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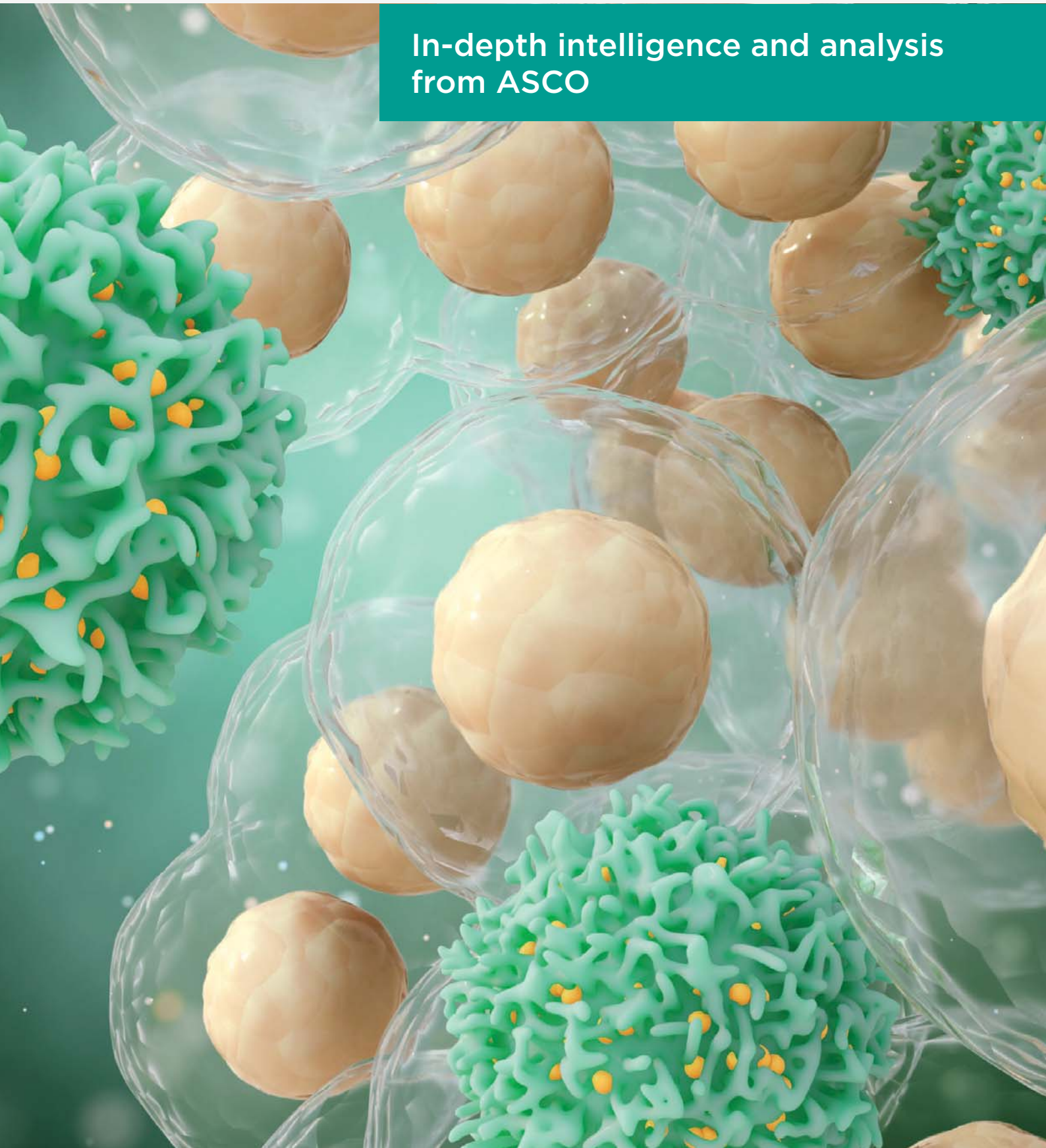

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TARGETS & MECHANISMS

Cancer's trajectory, as viewed by targets at AACR, ASCO and ASH

BY SANDI WONG, ASSISTANT EDITOR

Beyond the headliner presentations at 2019's three major cancer conferences were over a hundred posters and presentations showcasing new or emerging targets. A look at the identity of those targets reveals the growing diversity of approaches researchers are taking to manipulate the tumor microenvironment.

Between them, the American Association for Cancer Research (AACR), American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) meetings showcased 73 new therapeutic targets, defined as those with no active company programs against them and no entry in BioCentury's BCIQ database, and 70 emerging targets, those with a marked increase in mentions at 2019's conferences after appearing in two or fewer abstracts the previous year.

Not surprisingly, the immune component of the tumor microenvironment featured prominently among up-and-coming targets at all three meetings, with about half of the emerging targets expressed by immune cells.

Branching out from first-generation checkpoint and CAR T targets, proteins expressed by innate immune cells were especially on the rise, representing 11 of the 20 emerging immune targets (see "Emerging Immuno-oncology Mechanisms at ASH 2019").

The target with the biggest jump in mentions from AACR 2018 to 2019 was the receptor tyrosine kinase MERTK, which plays dual roles in regulating myeloid cell and cancer cell activity (see "Next-wave Targets at AACR 2019 Start Filling the Blanks in the Tumor Microenvironment").

ASH displayed several mechanisms that trigger phenotype switching of macrophages or T cells, turning them from immunosuppressive to proinflammatory (see "A View of Immune Reprogramming from ASH").

First-in-human data presented at ASCO and ASH also showed a concentration in immuno-onology.

Of the 22 first-in-human trials at ASCO, at least five had targets related to immunity in products with hot modalities including bispecifics and CAR Ts. At ASH, 10 of the 19 new-to-human therapies had immune-related targets, including two against BCMA, a target already in the spotlight that's in the midst of a modality showdown (see "Bispecifics and Allogeneics Steal the Spotlight from Autologous CAR Ts").

PROTEINS EXPRESSED BY INNATE IMMUNE CELLS WERE ESPECIALLY ON THE RISE.

Immune cells weren't the only components of the tumor microenvironment to make appearances at the conferences. Emerging targets also featured extracellular matrix proteins, such as MMP7 and CTSK7; cancer-associated fibroblast targets, including NTNG1; and the mitochondrial biogenesis regulator CEBPA, which controls macrophage polarization.

Other notable themes were metabolic pathways, gene regulation and transport proteins.

Targets with metabolic and transport functions accounted for nearly half of the 17 novel targets at ASH, while AACR's 26 new targets included two transporter proteins and several gene expression regulators, most of which were found in solid tumors.

ASCO's 31 new targets were dominated by 12 fusion proteins; 10 were novel ROS1 or NTRK fusions. Two drugs already have FDA approval for tissue-agnostic treatment of solid tumors with an NTRK gene fusion: Vitrakvi larotrectinib from Loxo Oncology at Lilly and Bayer AG (Xetra:BAYN), and Rozlytrek entrectinib from the Genentech Inc. unit of Roche (SIX:ROG; OTCQX:RHHBY) (see "ASCO 2019 Abstracts Show Solid Tumor Race Heating Up Among Bispecifics and CAR Ts"). bc

TARGETS

BCMA (TNFRSF17; CD269) - Tumor necrosis factor (TNF) receptor superfamily member 17
CEBPA - CCAAT enhancer binding protein alpha
MMP7 - Matrix metalloproteinase 7
NTNG1 - Netrin G1
ROS1 - c-ros proto-oncogene 1 receptor tyrosine kinase

TARGETS & MECHANISMS

Bispecifics and allogeneics steal the spotlight from autologous CAR Ts

BY LAUREN MARTZ, ASSOCIATE EDITOR

Standing out at this year's ASH meeting is a pair of growing threats to first-generation CAR T cell therapies: bispecific antibodies and allogeneic cell therapies. Gone are the days when autologous CAR Ts were the meeting's golden child. Now the task is to show what can improve on CAR Ts, and to demonstrate ways of fixing their flaws, or advancing competing technologies that can leapfrog them.

BioCentury's survey of the 4,780 abstracts from this year's American Society of Hematology (ASH) annual meeting, which takes place Dec. 7-10 in Orlando, identifies 42 new and emerging targets and 19 compounds with first-in-human data (see "Emerging Immuno-Oncology Mechanisms at ASH2019").

The survey uses a machine-learning algorithm to detect specific context-relevant terms followed by manual validation, and is coupled with analysis of the trends that emerge to present a picture of the state of preclinical and clinical research in blood cancers and other hematological disorders.

The strong showing of bispecific research continues the thread from this year's American Society of Clinical Oncology (ASCO) meeting, where abstracts focused on bispecifics showed the biggest year-on-year increase of all modalities (see "ASCO 2019 Abstracts Show Solid Tumor Race Heating").

Whereas ASCO highlighted a clinical showdown between bispecifics and CAR Ts, demonstrating bispecifics making inroads into solid tumors, ASH 2019 features several preclinical innovations to bispecific constructs that could help them compete with CAR Ts on efficacy and broaden their range of indications. ASH 2019 also has the next readouts in the BCMA story—a target in sights of CAR T cell and bispecific antibody developers that is touted as the next, best hope for expanding immunotherapy to tackle multiple myeloma (MM).

The last two years at ASH have seen a jump in activity in bispecifics, with abstract numbers more than doubling since BioCentury started analyzing the annual meeting in 2016 (see Figure: "Upward Momentum for Bispecifics at ASH").

Allogeneics, another competitor to first-generation CAR Ts, are also on the rise this year with a 45% increase over last year's count (see Figure: "Continued Rise of CAR T Cells at ASH").

The numbers this year—59 abstracts on bispecifics in cancer, 33 on allogeneics—are less notable than the contents and presenters, with a consistent engagement of industry in advancing the technologies.

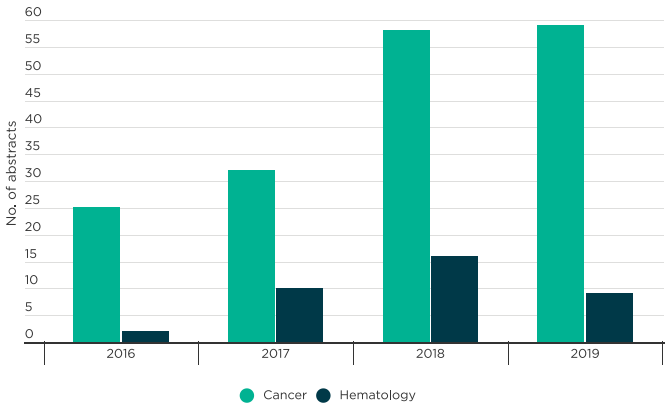
Upward momentum for bispecifics at ASH

CAR T cells remain one of the most heavily-studied modalities at the American Society of Hematology (ASH) meeting this year, but competing bispecific antibodies are also on an upward trend. Since BioCentury started analyzing the meeting in 2016, the number of abstracts covering bispecific antibodies has more than doubled, increasing from 27 in 2016 to 69 in 2019. Although the number of bispecific abstracts remained relatively flat this year, more targets are represented in this year's crop, including targets that aren't being pursued by CAR Ts in development.

Bispecific antibodies aren't limited to T cell-engaging antibodies for cancer. Each year, at least 7% of the bispecific antibodies are for other hematology indications, and most of those are bispecifics for hemophilia that bring together two coagulation factors to restore the normal cascade.

Although last year's abstracts included several trispecific T cell engaging antibodies, no trispecific constructs were counted at this year's meeting.

The chart includes the number of abstracts that discuss bispecific antibodies in a therapeutic context as determined by a machine learning algorithm and manual verification. *Source: ASH abstracts.*



This year, 19 different companies will present abstracts on bispecifics, down from 20 last year, with constructs that hit 14 targets (see Table: "Companies with Bispecific Antibodies at ASH 2019").

While bispecifics offer immediate advantages over CAR Ts, because they are cheaper and easier to produce, and simpler to administer, they have not met with the same fanfare. That is in part due to the single CAR T administrations that lead to very high response rates. In contrast, bispecifics require repeated infusions and have short half-lives. Bispecifics also carry some of the same toxicity baggage as CAR Ts.

At a cellular level, the end result of bispecific antibodies and CAR Ts is similar. They both activate tumor-specific T cells, triggering an antitumor immune response. Bispecifics do this by binding the T cell and the tumor cell to draw the two together. CAR Ts act by directly targeting a tumor antigen through an engineered receptor that causes the T cell to become active.

On display at ASH this year are technologies to minimize the toxicity of bispecifics, broaden them to targets beyond those addressed by CAR Ts in development, and expand immune cell engagement to cell types other than T cells.

Allogeneic CAR Ts could also solve some of the manufacturing and cost problems of the first-generation CAR T products, which are all autologous, but allogeneics have not yet broken through because they carry even more immunology risks. The added layers of genetic manipulation required to avoid those risks can compromise efficacy.

Allogeneic cell studies at ASH 2019 show some of the earliest clinical data from the class, highlight the benefits of different T cell phenotypes, and point to strategies that expand the therapies into different hematological malignancies. They also include two cell types that were absent last year, allogeneic Tregs and NK T cells, in addition to allogeneic T and NK cells, which feature both years (see Figure: "Allogeneics Beyond T cells, and Beyond Cancer at ASH").

Still, there's plenty of activity addressing the problems of autologous CAR Ts towards the creation of second-generation products. The total number of abstracts on CAR Ts continues to rise, reaching more than 200 this year, compared with 81 in 2016.

This year's abstracts contain at least 12 descriptions of CAR Ts that target multiple

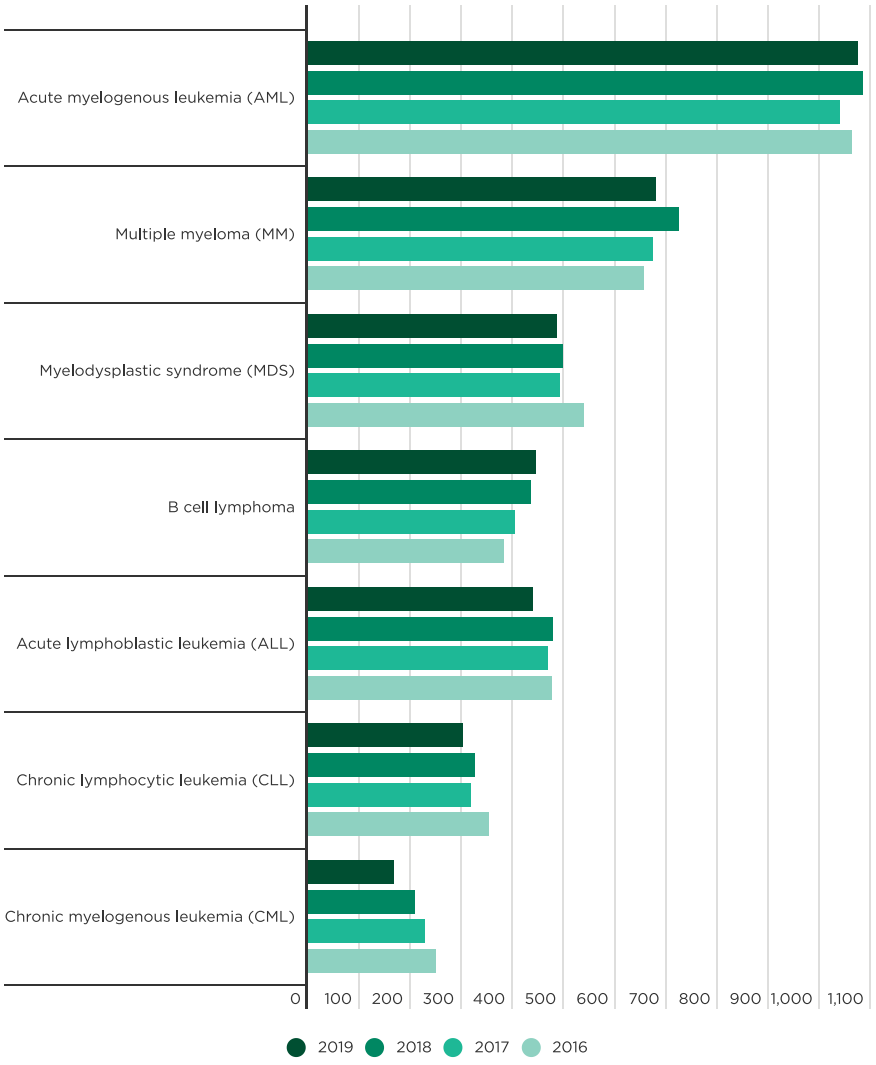
Cancer indications at ASH 2019

As the focus on CAR Ts and bispecific antibodies continues at the American Society of Hematology (ASH) meeting, it's no surprise that the number of abstracts discussing B cell lymphoma has risen year over year. Marketed CAR T cell therapies, and bispecific antibodies that direct T cells to tumor cells, are limited at the moment to B cell malignancies.

It's more surprising that research around multiple myeloma (MM) dipped this year despite the growing interest in BCMA-targeted CAR Ts, bispecific antibodies and antibody-drug conjugates, and especially given that the overall number of abstracts increased 10%.

While the number of abstracts on other indications has remained relatively flat year-over-year, chronic myelogenous leukemia (CML) has been showing a downward trend since 2016.

The chart includes the number of abstracts that mention each cancer indication in a therapeutic context as determined by a machine learning algorithm and manual validation. *Source: ASH abstracts.*



tumor antigens. Many of the dual-targeted CARs from both years hit CD19 and CD22, but dual-targeted CARs against BCMA are new this year and are represented in five abstracts.

The year of the bispecific

Bispecific abstracts feature one of the biggest attention grabbers at the meeting—the highly anticipated efficacy data from a Phase I/II trial of BCMA bispecific RGEN-5458 from Regeneron Pharmaceuticals Inc. (NASDAQ: RGEN). Among three patients treated at the initial dose level of 3 mg, one had a very good partial response, one had stable disease and a third progressed (No. 3176).

The preliminary results place RGEN-5458 at a lower efficacy than BCMA-targeted CAR Ts, which have seen objective response rates above 80% in relapsed or refractory MM, and antibody-drug conjugates (ADC), which come in with ORRs around the 60% range, although the initial Regeneron data only come from the lowest dose in the dose-finding study.

Another ASH abstract from Johnson & Johnson (NYSE:JNJ) and the Nanjing Legend Biotech Co. Ltd. unit of GenScript Biotech Corp. (HKSE:1548) confirms earlier efficacy results from the partners' anti-BCMA CAR T therapy JNJ-4528 (LCAR-B38M), with an ORR of 91% in 21 patients (No. 577).

Bispecifics also account for three of the 19 examples of first-in-human data on display at the conference (see Table: "First-in-Human at ASH").

These include another BCMA bispecific from Celgene Corp. (No. 143), a subcutaneously delivered CD20 bispecific from Genmab A/S (NASDAQ:GMAB) (No. 758), and a different CD20 bispecific from Xencor Inc. (NASDAQ:XNCR) (No. 4079). Celgene is now a unit of Bristol-Myers Squibb Co. (NYSE:BMY).

Over half of the abstracts discussing bispecifics feature constructs against the three most advanced CAR T targets: CD19, CD20 and BCMA.

They include 17 abstracts on CD19-targeting bispecifics, 12 covering CD20 and seven involving BCMA-directed bispecific antibodies. Whereas CD20 mostly overlaps with cancer types that express CD19, BCMA takes the technology into new indications.

Those studies include clinical data from approved drugs and therapeutic candidates including the first FDA-approved bispecific, Blincyto blinatumomab from Amgen Inc (NASDAQ:AMGN), and methods to predict response to the bispecifics. Blincyto targets CD19 on tumors and CD3 on T cells. (see Table: "Commercial Interest in Bispecifics Holds Steady").

Bispecific solutions

Despite their logistical advantages over CAR T cells, bispecifics have faced stability issues in the clinic and run many of the same safety risks, such as neurotoxicity and cytokine release syndrome (CRS).

At least two abstracts propose ways to minimize toxicity of bispecifics.

TeneoBio Inc. describes the screening method it used to design a bispecific antibody with a reduced risk of CRS and neurotoxicity. The company generated TNB-486 by screening a library of αCD3 antibodies for those that induced CD19-targeted lymphoma destruction while minimizing cytokine release.

In preclinical models, TNB-486 induced less cytokine release than a positive control antibody, while producing comparable lysis of CD19-positive lymphoma cells (No. 4070).

IGM Biosciences Inc. (NASDAQ:IGMS) presents an abstract describing a bispecific construct that merges the structures of standard IgG antibodies with IgM antibodies in a construct that allows strong binding to tumor antigens while preventing T cell over-stimulation.

IGM's CD20 bispecific IGM-2323 decreased cytokine release *in vitro* and *in vivo* in preclinical models, while maintaining T cell-dependent killing of CD20-expressing target cells (No. 1574).

Other abstracts branch out beyond the traditional CAR T cell surface targets, and extend the technology to different hematological malignancies (see Figure: "Cancer Indications at ASH 2019").

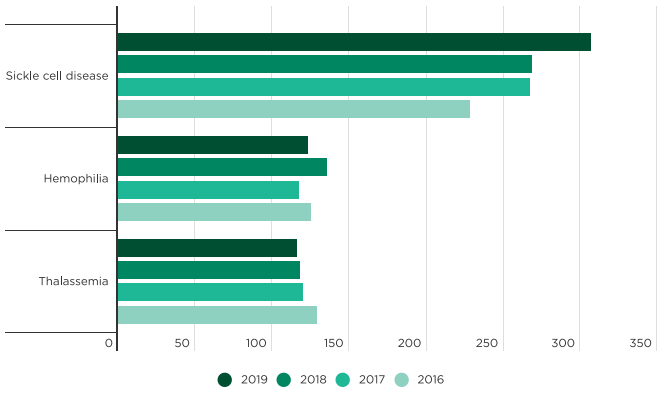
New CAR T designs that incorporate a TCR-like domain rather than an antibody domain are able to hit intracellular targets when presented by HLA molecules on the cell surface.

Hematology indications at ASH 2019

Activity in sickle cell disease continues to increase this year at the American Society of Hematology (ASH) meeting, as disease modifying therapies for the indication are advancing through the clinic. The clinical candidates are a mix of small molecules designed to reduce adhesion of sickled red blood cells and new modalities that boost fetal or engineered forms of fetal hemoglobin.

The same isn't true for hemophilia and thalassemia, however, which show steady or decreasing interest, although they also are the target of new modalities like gene editing and gene therapies.

The chart includes the number of abstracts mentioning each hematology indication in a therapeutic context as determined by a machine learning algorithm and manual verification. *Source: ASH abstracts.*



First-in-human at ASH

At least 19 abstracts to be presented at the 2019 **American Society of Hematology** meeting in Orlando contain the first efficacy data announced from first-in-human trials of new products. Most are in cancer indications — at least three abstracts for hematology products being presented contain safety data from healthy volunteers, but not response data in patients. Trials were identified by searching abstracts for the terms "first-in-human" or "first-in-man" and comparing resulting abstracts to data previously reported in company announcements or at other conferences, including the **American Society of Clinical Oncology** and the **American Association for Cancer Research** meetings. *Source: ASH abstracts as of Nov. 6*

Company	Product	Description	Indication	Results in abstract	Abstract
Amgen	AMG 673	Half-life extended anti-CD33/CD3 BiTE	Acute myelogenous leukemia (AML)	In 30 patients with relapsed or refractory AML, 50% of patients had grade 3 or worse treatment-related adverse events (TRAEs). 12 of 27 evaluable patients had blast reductions, while one patient had complete remission with incomplete hematologic recovery (CRi). Dose escalation was ongoing at data cutoff.	833
Aurora Bio	AUR01 (124 I-p5+14)	PET radiotracer	Amyloidosis imaging	In 10 patients with biopsy-confirmed systemic immunoglobulin light chain-associated amyloidosis, no serious adverse events (SAEs) were reported. Positron-emission tomography (PET) image analysis showed cardiac uptake and retention in 80% of patients who received ≥ 1 mCi 124I-p5+14, as well as retention in the liver (20%), spleen (40%) and kidney (60%).	3034
Autolus	AUTO2	CAR T cells targeting tumor necrosis factor (TNF) receptor superfamily member 17 (BCMA; TNFRSF17; CD269) and transmembrane activator and CAML interactor (TACI)	Multiple myeloma (MM)	In 11 patients who had received three to six prior lines of therapy, including a proteasome inhibitor or immunomodulatory agents, 82% developed ≥3 anemia and 73% ≥3 neutrophil count decrease. Five patients (45%) experienced grade 1 CRS. In seven patients receiving the three highest doses, the overall response rate (ORR) was 43% (28% partial responses (PRs) and 14% very good partial response (VGPRs)). One patient at the lowest dose had stable disease (SD) and was retreated at a higher dose, with SD continuing at the time of data cutoff.	3112

Company	Product	Description	Indication	Results in abstract	Abstract
Bayer	BAY 2599023	AAVhu37 containing single-stranded DNA genome encoding a B-domain deleted Factor VIII (FVIII)	Hemophilia A	Two patients received a single infusion of the gene therapy; no SAEs or TRAEs were reported at 15+ weeks of follow-up. Both patients showed evidence of FVIII expression, and one patient halted prophylaxis for 6 weeks while the other had no bleeds at 5.5 months post-treatment following 99 bleeds in the year prior to treatment.	4630
Bristol-Myers Squibb	CC-90009	Cereblon modulator	AML	In 45 patients with relapsed or refractory AML receiving CC-90009 on either days 1-5 or days 1-3 and 8-10 of a 28-day cycle, grade 3-4 TRAEs were reported in 23 patients (51%), including hypocalcemia (22%), hypotension (13%). AEs led to study discontinuation in two patients (4%), dose interruptions in 12 patients (27%) and dose reductions in two patients (4%). Three of 35 patients in the day 1-5 treatment group had responses; one each of complete remission (CR), morphologic CR with incomplete blood count recovery (CRi) and morphologic leukemia-free state (MLFS). Loss of the target protein, translation termination factor G1 to S phase transition 1 (GSPT1), in T cells and circulating AML blasts was dose dependent.	2547 232
Bristol-Myers Squibb	CC-93269	BCMA T-cell engager	MM	In 19 patients who had received 3-12 prior treatments, 17 patients (90%) developed CRS, with grade ≥3 CRS in one patient. One patient died "in the setting" of CRS, "with a potential infection as a contributing factor." There were no responses in seven patients treated with doses below 6 mg, but in 12 patients treated with doses ≥6 mg, ORR was 83%, with four stringent CRs, three PRs, and three VGPRs. Responses were ongoing for up to 4.7 months at data cutoff.	143

Company	Product	Description	Indication	Results in abstract	Abstract
City of Hope	64Cu-DOTA-Dara	Copper-64-Labeled daratumumab	MM imaging	Ten daratumumab-naïve patients with biopsy-confirmed MM received escalating doses of unlabeled daratumumab followed by 64CU-DOTA-Dara. PET and CT scanning of patients receiving 64CU-DOTA-Dara showed MM lesions which were not detected by fluorodeoxyglucose (FDG)-PET imaging, including discordant iliac crest lesions in two patients and bone lesions in the calvarium. One patient was positive for a pleural lesion with FDG-PET but negative on 64Cu-DOTA-Dara; a biopsy did not show recurrence of the lesion. Dose escalation to optimize unlabeled daratumumab dose was planned at data cuttoff.	4394
Eli Lilly	Loxo-305	Next-generation Bruton's tyrosine kinase (Btk) inhibitor	Chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL)	In 13 patients (9 CLL, 4 MCL) who received 2-6 prior therapies, including five who were intolerant to and five who relapsed on/after prior treatment with Btk inhibitor Imbruvica ibrutinib, no dose-limiting toxicities or SAEs were reported. In eight evaluable patients, ORR was 87.5%, including one PR and four partial response with lymphocytosis (PR-L) in five CLL patients and two PRs in three MCL patients. At data cutoff, 12 patients remained on therapy, with a duration of up to 5 months.	501
Eureka	ET019003	Next-generation anti-CD19 T cell therapy	Diffuse large B cell lymphoma (DLBCL)	In six patients with DLBCL which progressed or relapsed after 2-5 prior treatments, no grade ≥2 CRS was reported. One patient with lymphoma in the CNS had convulsions and cognitive disturbance which resolved within 24 hours after glucocorticoid treatment. ET019003 T-cell expandsion in vivo to a peak range of 26,000 - 348,240 per mL of blood (median 235,500) was observed in all patients. All patients had either a PR or CR when evaluated at one month.	2870

Company	Product	Description	Indication	Results in abstract	Abstract
Genmab	GEN3013	Bispecific anti-CD20/CD3 antibody	B cell non-Hodgkin lymphoma (NHL)	In 18 patients with CD20+ B-NHL, grade ≥3 anemia and neutropenia was reported in three patients each. Grade 1-2 CRS was observed in three out of eight patients before a modification to premedication with corticosteroids and six of 10 patients after; no patients had tumor lysis or neurological symptoms. One DLBCL patient treated at a higher dose had a complete metabolic response. Dose escalation was ongoing at data cutoff.	758
iCell	CD4 CAR	CAR T cells targeting CD4	Sezary syndrome	A single patient with over 50% leukemic blood cells at baseline showed complete remission by day 13 post-treatment, with leukemic blood cells eliminated. Percentage of CAR T and NK cells increased and skin symptoms of improved. Patient had grade 2 CRS.	2881
iCell	BCMA-CD19 cCAR	BCMA CAR fused to CD19 CAR by a self-cleaving P2A peptide	B cell acute lymphocytic leukemia (ALL)	A single patient with donor-specific anti-HLA antibodies (DSAs) too high for stem cell transplant showed CR and 80% reduction in DSAs two weeks after treatment. DSA reduction persisted at eight weeks.	38
Karus	KA2237	Oral PI3K p110β/δ Inhibitor	B cell lymphoma	In 21 patients, 43% of patients experienced a grade ≥3 TRAE, including rash, transaminitis and pneumonitis, with 29% of patients discontinuing treatment because of TRAEs. One patient died of treatment-emergent multifocal pneumonia. ORR in 19 evaluable patients was 37%, with four CRs and three PRs in patients across lymphoma subtypes. Two patients with DLBCL and CRs subsequently received autologous stem cell transplant.	4099

Company	Product	Description	Indication	Results in abstract	Abstract
Sanhome	SHC014748M	Phosphoinositide 3-kinase (PI3K) δ inhibitor	B cell lymphoma	In 38 patients who had received 1-8 prior treatments, grade ≥3 TRAEs included neutropenia (24%), pneumonia (13%), rash (8%) and diarrhea (5%). In 14 evaluable follicular lymphoma (FL) patients, ORR was 57% (8 PRs) with five patients with SD. In nine evaluable CLL or small lymphocytic lymphoma (SLL) ORR was 89%, with five PRs (56%) three PR-Ls (33%) and one patient with SD. One of three Waldenstrom macroglobulinemia (WM) patients had a PR (33%) while the other two had minor responses.	4000
Seattle Children's Hospital	T-APCs	T-cell antigen presenting cells (T-APCs) expressing truncated CD19	B cell ALL	T-APCS were administered after CD19 CAR T cell treatment in order to increase persistence of CAR T cells in patients with low CD19 antigen burden in the bone marrow prior to lymphodepletion and rapid contraction of CAR T cells, factors associated with early loss of persistence. In 11 patients, one had grade 3 febrile infusion reaction preventing further dosing, but no further grade 3 AEs or CRS was reported. In 10 patients with low CD19 antigen burden or rapid T cell contraction, eight (80%) had CAR T cell persistence beyond Day 63, and 50% had ongoing B cell aplasia, a marker of persistence, at data cutoff at a median follow-up of 8.8 months. Estimated 1-year leukemia free survival (LFS) is 69.2%.	223

Company	Product	Description	Indication	Results in abstract	Abstract
Synimmune	Flysyn	Fc-optimized FLT3 antibody	AML with minimal residual disease (MRD)	In 31 patients, one grade 3 TRAE or neutrophil decrease occurred on day 3, but resolved. Other TRAEs were grade 1-2. In 18 patients evaluable for response, six had bone marrow MRD negativity at some time point. One patient in the lowest dose group (n=3) had permanent MRD negativity in bone marrow (BM) until day 545 and one had temporary reduction in MRD at day 15. In the second group (n=3) one patient was MRD negative in bone marrow at day 22 but progressed on day 365. In the third dose cohort (n=3), two patients had MRD reduction in peripheral blood. In the fourth group (n=9), four patients had non-permanent MRD negativity in bone marrow. Six dose-escalation cohorts are planned.	3928
Tmunity	NYCE T cells	Autologous T Cells expressing cancer/testis antigen 1B (NY-ESO-1; CTAG1B) T cell receptor and CRISPR/Cas9 gene edited to eliminate endogenous TCR and PD-1	Multiple myeloma or myxoid round cell liposarcoma (MRCL)	Cells were manufactured with 89-96% viability for three patients. No neurotoxicity or CRS was reported in three infused patients. The first, a patient who had received eight prior therapies for MM, progressed at day 60. The second, a patient with MRCL relapsed after neo-adjuvant doxorubicin, surgery and radiation, had stable disease for over 90 days at data cutoff. The third patient was not yet evaluable.	49
Unum	ACTR087	Pharmacologically-controlled engineered T cell therapy	B cell lymphoma	In 26 patients with CD20-positive B cell lymphoma who received 1-9 prior therapies including at least an anti-CD20 antibody, there were four serious cases of CRS, including two grade 4 in patients who developed fatal sepsis, and two serious cases of neurotoxicity (one grade 5 and one grade 4 in a subject with fatal septic shock). ORR was 50%, with five CRs and five PRs in 20 evaluable patients.	244

Company	Product	Description	Indication	Results in abstract	Abstract
Xencor	XmAb13676	Bispecific anti-CD20/CD3 antibody	NHL, CLL	In 36 NHL patients who received one to nine prior treatments, four patients developed CRS, including one grade 4 CRS. 19 other ≥ grade 3 TRAEs were reported. Two patients with DLBCL had CRs and three had PRs, one patient with WM had a VGPR, and one patient with FL had a PR. In eight patients with CLL who received two to six prior treatments, one patient developed grade 3 CRS. Other SEAs included grade 3 hepatocellular injury and grade 2 jaundice cholestatic in one patient each. One of five patients treated at the highest dose had a CR.	4079

A study from Roche (SIX:ROG; OTCQX:RHHBY) describes a TCR-like T cell bispecific that bivalently recognizes a peptide fragment of the Wilms tumor antigen WT1, presented by HLA-A2, to treat acute myelogenous leukemia (AML). The bispecific killed cancer cells *ex vivo,* both from cell lines and patient samples, and *in vivo* in mice (No. 4450).

Immatics Biotechnologies GmbH highlights its bispecific T cell-engaging receptor (TCER), which is a fusion between a TCR and a humanized T cell recruiting antibody. A TCER targeting the intracellular tumor antigen PRAME has *in vitro* antitumor activity at low picomolar concentrations and inhibits growth in xenograft mouse models of PRAME-expressing tumor cells (No. 3368).

Other groups report new treatment strategies that combine bispecifics with T cell therapies.

A Memorial Sloan Kettering Cancer Center (MSKCC) team describes Ex Vivo Armed T cells (EVATs) cells, which are an adoptive T cell therapy co-incubated with bispecific antibodies targeting GD2 or HER2 (No. 1959). The arming step attaches the antibodies to T cell therapies before infusion to direct the cells to the tumor upon infusion.

Teams from The University of Texas MD Anderson Cancer Center and St. Jude's Children's Hospital describe adoptive T cell therapies for pediatric AML that secrete T cell-engaging bispecifics against CD123 and CD3. The potential benefits are improved tumor penetration and longer durations of action than antibodies with short half-lives (No. 4441; No. 3917).

Not all of the bispecifics discussed are designed to bind T cells.

A preclinical study from Compass Therapeutics LLC describes CTX-8573, an innate cell engager targeting BCMA. Rather than binding CD3 on T cells, it engages NK cells through antibody fragments that target the NKp30 NK cell receptor. It then recruits γδ T cells through an afucosylated Fc region of the anti-BCMA IgG domain that enhances engagement of CD16a (No. 3182).

Allogeneic growth

The focus on allogeneic cell therapies is also increasing. Among the 33 abstracts this year, 19 involve allogeneic T cells, and 16 of those involve allogeneic CAR Ts.

Allogeneic CAR T cells are created as off-the-shelf products, and therefore have lower associated costs than autologous CAR Ts. The problem is that the cells require genetic manipulation to prevent graft-versus-host disease (GvHD) and host-versus-graft reactions, often compromising the cells' fitness for purpose.

The earliest hints of allogeneic efficacy came from Cellectis S.A. (NASDAQ:CLLS), which started clinical testing of its first allogeneic CAR T cell therapy UCART19 in 2016 and UCART123 in 2017. However, the company faced initial setbacks with patient deaths due to CRS that led to clinical holds and protocol revisions including a dose decrease before the trials could resume, and efficacy data is just starting to emerge.

Cellectis will present preclinical data on UCART123 in primary blastic plasmacytoid dendritic cell neoplasm (BPDCN) at ASH (No. 2659).

Four abstracts present clinical data this year, including the first-in-human trial of PBCAR0191, a CD19-targeted allogeneic CAR T from Precision BioSciences Inc. (NASDAQ:DTIL).

In the Phase I/IIa trial of adult patients with relapsing-remitting non-Hodgkin's lymphoma (NHL) or relapsing-remitting B cell precursor acute lymphoblastic leukemia (ALL), initial 28-day data shows early PRs in two of the three patients treated at the first dose level. Both patients later progressed due to new lesions but there were no severe or dose-limiting adverse events (No. 4107).

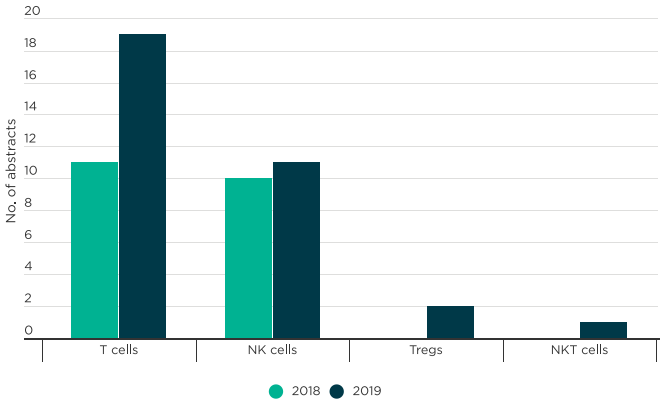
Allogeneics beyond T cells and beyond cancer at ASH

As the commercial challenges of first-generation CAR T cells are beginning to set in, interest in competing technologies that avoid those problems is rising. One of those is allogeneic CAR Ts, which could bring a simpler, off-the-shelf manufacturing process and lower costs of the cell therapy, if the added immunogenicity risks can be addressed.

The number of abstracts discussing allogeneic T cell therapies increased from 11 last year to 19 (73%) this year, and 16 of those are specifically on CAR T cells. The others describe allogeneic T cells with engineered T cell receptors and alternative T cell phenotypes such as cytokine-induced killer cells.

Abstracts discussing NK cells, which can be adoptively transferred from donors without the same level of modification, have remained relatively flat since last year, but two new allogeneic cell types come up at this year's meeting. NKT cells, a subset of immune cells that shares properties with NK and T cells, are mentioned in one abstract this year, and two abstracts describe allogeneic Tregs to induce immune tolerance for an autoimmune anemia and a transplant application.

The chart includes the number of abstracts that discuss bispecific allogeneic cell therapies as determined by a machine learning algorithm and manual verification. *Source: ASH abstracts.*



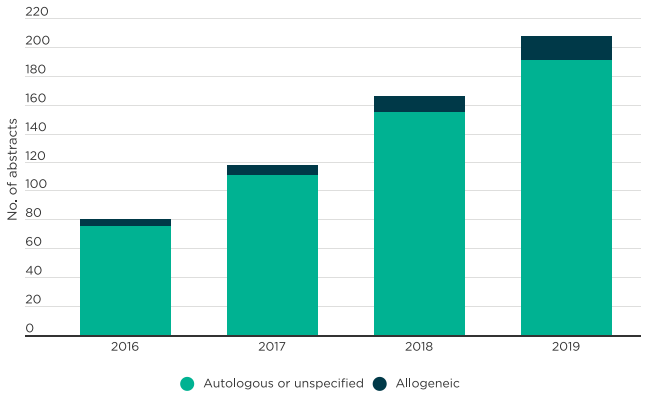
Continued rise of CAR T cells at ASH

CAR T cells are still on everyone's mind at the American Society of Hematology (ASH) meeting this year, along with increased interest in improving upon the modality and taking it into new indications to compete with other rising technologies. The abstract numbers have continued to grow year over year for CAR T cells since BioCentury began its analysis of the meeting in 2016.

The CAR T cell abstracts include effector and memory T cells, and cytokine-induced killer (CIK) cells, engineered to express chimeric antigen receptors.

The number of abstracts on allogeneic CAR T cells has also increased each year, from five in 2016 to 16 this year, indicating that off-the-shelf constructs are one improvement researchers are considering for the modality.

The chart reflects the number of abstracts that discuss CAR T cell therapies as determined by a machine learning algorithm and manual verification. *Source: ASH abstracts.*



Two academic groups from China will also report clinical results in relapsing-remitting AML patients. In one study, eight of 11 patients with p53 alterations who received autologous or allogeneic anti-CD19 CAR T cells achieved a molecular CR at 10 months (No. 3822).

In the other, 13 of 18 patients who received donor-derived anti-CD19 CAR T cells after allogeneic stem cell transplant failure achieved a CR (No. 4561).

A group from the University of Milan-Bicoc presents initial clinical data on another T cell subset. The group shows that cytokine-induced killer (CIK) cells engineered, via the non-viral Sleeping Beauty transposon system, to express a CD19-targeting CAR led to a CR or CRi in four of five B-ALL patients treated at the highest dose (No. 200). CIK cells share some properties with T and NK cells and are often considered an NKT cell subset. CRi is the term for CR with incomplete hematological recovery.

Preclinical abstracts on allogeneic T cell technologies span different types of T cell constructs and a range of indications.

For example, several studies suggest methods to treat T cell malignancies with allogeneic T cell therapies, which isn't possible with first generation cells due to fratricide. The problem is that CAR Ts designed to recognize T cell targets will ultimately kill themselves.

A University College London team uses base editing to prevent fratricide (No. 3219), while a Japanese group uses allogeneic γδ T cells expressing an αβ TCR against a virus that causes adult T cell leukemia and lymphoma (No. 3216).

GammaDelta Therapeutics Ltd. will present on a manufacturing strategy for its CAR-γδ T cells (No. 3321), and Fate Therapeutics Inc. (NASDAQ:FATE) will show preclinical data on its iPS cell-derived anti-CD19 CAR T cells (No. 4434).

Commercial interest in bispecifics holds steady

As bispecific antibodies are emerging as a threat to CAR T cells, companies are escalating their interest in the modality. At least 19 pharma and biotech companies at the 2019 American Society of Hematology (ASH) meeting are presenting abstracts on at least 25 bispecific antibodies.

The large majority (19) are T cell-directed bispecific antibodies that bind CD3 on T cells and a tumor antigen, but three others each bind two coagulation factors to treat hemophilia. The others include an antibody from Compass Therapeutics that attracts NK cells rather than T cells by binding NKp30.

The company list does not include supply/service companies. The list was generated by a scan of bispecific and multi-specific antibody abstracts at ASH that were identified through a machine-learning algorithm and manually verified. *Source: ASH abstracts.*

Company	Product	Targets	Study	Indication	Abstract #
Amgen	Blincyto blinatumomab	CD19xCD3	Expanded access	Pediatric acute lymphoblastic leukemia	1294
			Phase II	First-line diffuse large B-cell lymphoma (DLBCL), after Rituxan rituxumab	4077
			Nonclinical	Single cell RNA sequencing to analyze transcriptome of T cells before and after treatment	3886
Amgen	AMG 673	CD33xCD3	Phase I	Acute myelogenous leukemia (AML)	833
Amgen	AMG 701	BCMAxCD3	Preclinical	Multiple myeloma (MM)	135
Amphivena	AMV564	CD33xCD3	Phase I	Relapsed/refratory AML	834
Atum	T-Cell Engaging Antibody Circuits (TEACs)	CD123xCD33, others	Preclinical	AML	2653
Bristol-Myers Squibb	CC-93269	BCMAxCD3	Phase I	MM	143
			Preclinical	DLBCL	1580
Compass Therapeutics	CTX-8573	BCMAxNKp30	Preclinical	MM	3182
Genentech	Mosunetuzumab	CD20xCD3	Phase I/Ib	Non-Hodgkin lymphoma (NHL)	1285 1585 4728
Genentech / Roche	Emicizumab	Factor IX and Factor X (FIXxFX)	Phase III	Hemophilia A	626
Genmab	GEN3013	CD20xCD3	Phase I/II	B-cell NHL	758
			Preclinical	DLBCL, follicular lymphoma (FL), mantle cell lymphoma	4066
IGM	IGM-2323	CD20xCD3	Preclinical	NHL	1574

Company	Product	Targets	Study	Indication	Abstract #
IGM	IGM-2323	CD20xCD3	Preclinical	NHL	1574
Immatics	T Cell-Engaging Receptor (TCER) against PRAME	PRAMExCD3	Preclinical	PRAME-positive tumors	3368
Kymab	KY1049	FIXxFX	Preclinical	Hemophilia A	2410
Macrogenics	Flotetuzumab	CD123xCD3	Phase I/II	AML	460 733 1410
			Phase I	AML, combo with anti-PD1 antibody MGA012	2662
Molecular Partners	MP0250	VEGF-Ax HGF/SFxAlbumin (trispecific)	Phase II	MM	1899
Novo Nordisk	Mim8	FIXaxFX	Preclinical	Hemophilia A	96 2388 2631
Pfizer	PF-06863135	BCMAxCD3	Phase I	MM	1869
Regeneron	REGN1979	CD20xCD3	Phase II	FL	4007
			Phase I	Relapsed/refactory B-cell NHL	762
Regeneron	REGN5458	BCMAxCD3	Phase I	MM	3176
Roche	CD20-TCB (RG6026)	CD20xCD3	Phase Ib	B-cell NHL	1584 3799
			Phase Ib	B-cell NHL, combo with Tecentriq atezolizumab	2871
Roche	WT1-TCB	WT1xCD3	Preclinical	AML	4450
Sorrento	CD38/CD3 BsAb	CD38xCD3	Preclinical	MM, lymphoma	4463
Teneobio	TNB-383B	BCMAxCD3	Phase I	MM	1874
Teneobio	TNB-486	CD19xCD3	Preclinical	CD19-positive tumors	4070
Xencor Inc	XmAb13676	CD20xCD3	Phase I	NHL, chronic lymphocytic leukemia	4079

Sorrento Therapeutics Inc. (NASDAQ:SRNE) will present on a new antigen receptor design for its allogeneic cell therapies, which use standard T cells. It has two abstracts on Dimeric Antigen Receptor (DAR) T cells, which incorporate the complete antibody binding fragment of the parent antibody to more closely mimic the functional and biophysical properties of natural antibodies.

The DAR T cells target multiple myeloma (MM) antigens CD38 (No. 4444) and BCMA (No. 1942). In both cases, Sorrento shows anti-tumor activity *in vitro* and in mice.

Allogeneics beyond cancer

If the ASH abstracts are any indication of the future direction of allogeneic cell therapies, they point to the modality extending beyond T cells, and beyond cancer.

T cell therapies make up about 60% of the allogeneic cell therapy abstracts. The other 40% are split between NK cells, NKT cells and Tregs.

Allogeneic Tregs are new to the conference this year, and reflect a rising interest in the therapeutic potential of the cell type for autoimmune diseases.

Two abstracts describe allogeneic Tregs to treat autoimmune diseases or transplant with hematological consequences.

A study from an MD Anderson group suggests allogeneic cord blood-derived Tregs could help treat bone marrow failure syndromes such as aplastic anemia, and the group started a Phase I trial in nine patients (No. 1221).

Another MD Anderson group presents updated data from a Phase I trial evaluating allogeneic cord blood-derived Tregs to prevent GvHD in allogeneic stem cell transplant recipients. At a three and a half year follow up, five of six patients are alive and in complete remission; the sixth patient's death was unrelated to GvHD (No. 4547).

Other hematology indication drawing attention are sickle cell disease, β—thalassemia and hemophilia. (see Figure: "Hematology Indications at ASH 2019").

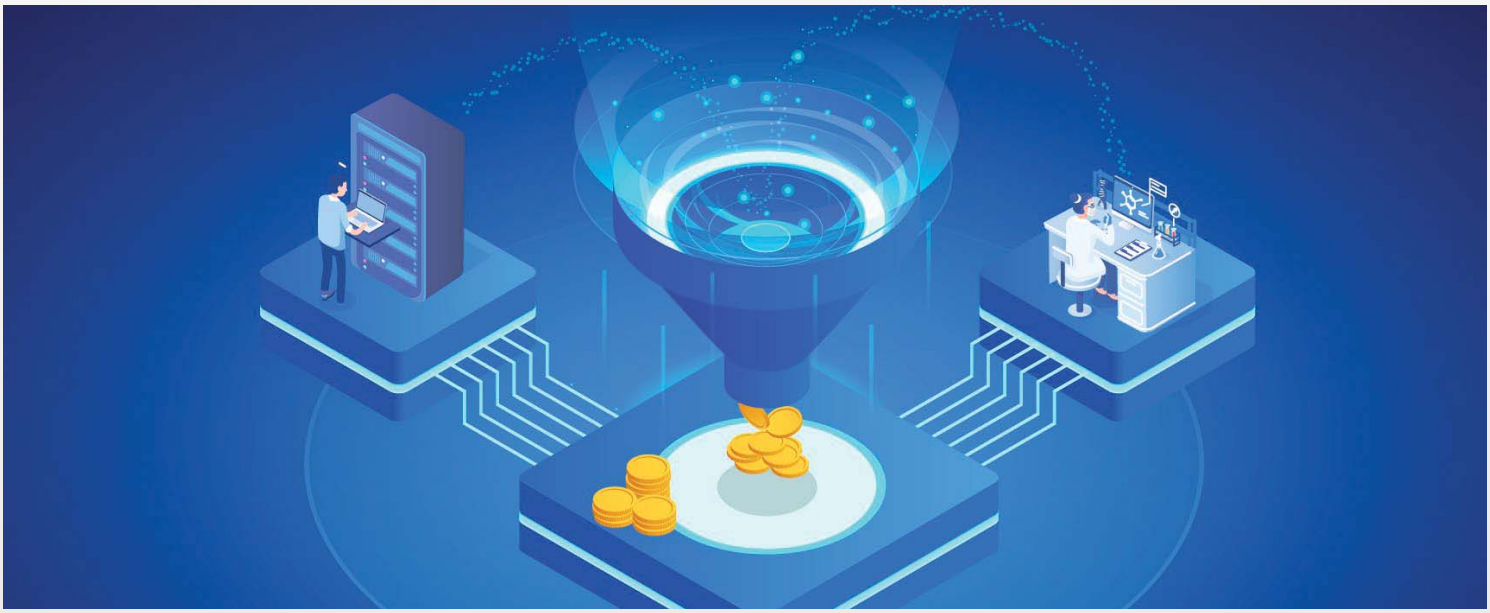
The growing interest in sickle cell disease is likely due to new modalities that offer potential cures, such as gene editing and gene therapy, though long-awaited breakthroughs may come sooner via traditional modalities (see "Sickle-Cell Disease Poised for Fresh Infusion").

The only representative of a hematology indication in the 19 first-in-human abstracts involves a gene therapy.

Bayer AG (Xetra:BAYN) reports Phase I/II data in two severe hemophilia A patients for BAY 2599023, an AAVhu37-based gene therapy that delivers DNA encoding a B-domain deleted Factor VIII. The patients achieved stable FVIII expression of 5% and 17% and both had early readouts of hemostatic efficacy (No. 4630).

TARGETS

BCMA (TNFRSF17; CD269) - Tumor necrosis factor receptor superfamily member 17
CD16a (FCGR3a; FGγRIIIa) - Fcγ receptor IIIa
CD33 (SIGLEC3)
CD123 - Interleukin-3 receptor α
GD2 - Ganglioside GD2
HER2 (EGFR2; ErbB2; neu) - Epidermal growth factor receptor 2
HLA-A2 - Major histocompatibility complex class I A 2
NKp30 (NCR3; CD337) - Natural killer p30 receptor
PRAME - Preferentially expressed antigen in melanoma
WT1 - Wilms tumor 1



BIOCENTURY & GETTY IMAGES

PRODUCT DEVELOPMENT

New reimbursement models are coming to cancer diagnostics

BY ERIN MCCALLISTER, SENIOR EDITOR

A newly proposed payment model aims to increase reimbursement for cancer diagnostics by incentivizing companies to produce more clinical utility data. However, to drive widespread adoption, companies may also need to look to risk-sharing deals with payers.

Molecular diagnostics and sequencing-based tests for cancer have been stuck in a negative loop.

Slow and inconsistent reimbursement practices coupled with a lack of data on health or economic benefits at launch often slows their uptake. This in turn hampers investment in new diagnostics, which are needed to guide treatment, reduce patient exposure to toxic or suboptimal therapies or identify patients at the greatest risk for adverse outcomes.

New payment models from various stakeholders are aiming to break that logjam.

One, from the American Society of Clinical Oncology (ASCO) and researchers at Duke University School of Medicine, proposes a framework that would tie different reimbursement levels to the amount and quality of clinical utility data generated for tumor biomarker tests.

Published in the *Journal of Clinical Oncology* in October, the model aims to help payers assess the value of new or existing diagnostics by categorizing the type of evidence that would support different levels of reimbursement. It could also serve as a road map for companies to understand the quality of evidence needed to gain greater reimbursement.

"There are poor quality tests out there, and good quality tests out there that aren't being reimbursed for very much or at all. At the same time, there's not a lot of incentive to invest in the creation and validation of good, tumor biomarker tests," said co-author Michaela Dinan. "What we posit is how can we create a value-based framework, where it could help companies understand the value of their test and have it be somewhat objective." Dinan is an associate professor of population health sciences at Duke University School of Medicine.

Two cancer diagnostic companies — Genomic Health Inc. and the Foundation Medicine Inc. unit of Roche (SIX:ROG; OTCQX:RHHBY) — agreed that a more standard framework for evidence generation and reimbursement such as the one proposed by ASCO is sorely needed.

However, in some cases, robust clinical utility data alone may not be sufficient to gain reimbursement and drive uptake.

"Ultimately you have to ask yourself 'What's in it for the payer?'" said Roger Longman, CEO of Real Endpoints LLC, a reimbursement consultancy.

To convince payers, companies may also need to demonstrate the economic value of their tests.

A second model, that would address how to generate health economics data, could come from a risk-sharing arrangement piloted last year by Harvard Pilgrim Health Care and Illumina Inc. (NASDAQ:ILMN).

Under this program, the payer reimburses a diagnostic, and the diagnostic company assumes responsibility for any added costs if use of the diagnostic does not reduce total costs to the payer.

Real Endpoints, which brokered the arrangement and tracked outcomes, is now working with an undisclosed diagnostics company on a similar arrangement, after early data from the pilot showed that these tests can be used to improve patient outcomes without increasing the cost burden on the health system.

"HOW CAN WE CREATE A VALUE-BASED FRAMEWORK, WHERE IT COULD HELP COMPANIES UNDERSTAND THE VALUE OF THEIR TEST AND HAVE IT BE SOMEWHAT OBJECTIVE?"

MICHAELA DINAN, DUKE

Setting data benchmarks

Dinan envisions that the ASCO framework could be used by payers to set baseline reimbursement rates for cancer biomarker tests. "It's a place to start and do things objectively to incentivize the promotion and propagation of tests that would benefit patients and the healthcare system," Dinan said.

Under the ASCO model, tumor biomarker tests would receive a baseline level of reimbursement for demonstrating analytic validity and minimum clinical utility, with increasing reimbursement contingent on additional data demonstrating that use of the test improves patient outcomes and reduces costs.

The authors do not propose specific baseline reimbursement amounts or increments by which payment for the tests should be increased. Instead, they outline the type and size of benefits that would need to be demonstrated to increase reimbursement.

At a minimum clinical utility threshold, the manufacturer would have to show some benefit of the test on patient response rates or progression-free survival (PFS) from an analysis of "convenience cohorts" to garner some amount of reimbursement. These data could include a retrospective analysis of historical outcomes data from patients who did not receive the biomarker-based test, compared with the outcome for patients who did receive the test.

The next level, which the authors considered "good" clinical utility data, would need to demonstrate a 10-20% improvement in PFS when validated as a secondary endpoint in a prospective clinical trial.

"Excellent" evidence, which would receive the maximum level of reimbursement, would include tests that show more than a 20% improvement over standard of care on overall survival or quality of life in a prospective randomized trial.

Getting to excellent

A handful of companies with tumor biomarker tests have already gained increased coverage by conducting prospective trials demonstrating clinical utility.

Genomic Health Inc., which was acquired by Exact Sciences Inc. (NASDAQ:EXAS) this month, has taken this approach with its Oncotype Dx test.

Genomic Health CSO Steven Shak told BioCentury that the company began generating clinical utility data in 2007 on Oncotype Dx in node-negative breast cancer patients, and has continued to build its evidence base, despite the cost of carrying out these trials.

"THIS PROVIDES A PREDICTABLE PATH FOR REIMBURSEMENT THAT COULD ENCOURAGE INVESTMENT AND SPEED DEVELOPMENT."

STEVEN SHAK, GENOMIC HEALTH

In June 2018, Genomic Health presented results from the Phase III randomized TAILORx trial in which 10,273 women with HR-positive, HER2-negative, axillary node-negative breast cancer were randomized to receive hormone therapy alone or in combination with chemotherapy. The study found that women with an Oncotype Dx recurrence score of 11-25 did not have any additional benefit from the chemotherapy, meaning that they could forgo the toxicity and added costs. Results were published in *The New England Journal of Medicine* and presented at the annual ASCO meeting last year.

"We were just proactive about generating this evidence at our own expense and with the hope that there would be a predictable path to reimbursement," Shak said.

Sales of Oncotype Dx have increased as it has generated new data. In 2018, sales grew nearly 15% to $358 million from $312 million in 2017, based in part on expanded private and Medicare coverage, according to a Genomic Health 10-K filing. Sales gains had been in the single-digit percentages for the previous four years.

Shak thinks that the framework proposed in *JCO* is a good step in helping other diagnostic companies gain reimbursement.

"Lack of a predictable reimbursement path slows development of tests and slows investment in those tests. This provides a predictable path for reimbursement that could encourage investment and speed development," he told BioCentury.

NGS feedback

While prospective randomized trials evaluating clinical utility are possible with tests like Oncotype Dx, which are designed to determine if a treatment can be avoided, these trials could be more challenging to design for NGS tests that help doctors decide between two different treatments.

To determine prospectively if the test produces better outcomes, the trial would have to include an arm that treats patients based on the results of NGS, and a control arm where the patient would receive whatever the standard therapy is without biomarker screening.

"Randomizing patients to different groups would be the gold standard, but it can't necessarily be done," Dinan said.

The trial would be unethical to conduct in a tumor type like non-small cell lung cancer (NSCLC) or metastatic breast cancer where screening for tumor mutations is SOC, but it could be carried out in other late-stage tumor types, particularly those where enrollment in a clinical trial is often the best available option, such as in previously treated metastatic pancreatic cancer or glioblastoma multiforme (GBM).

One alternative to a prospective trial could be to look at emerging real-world data across various tumor types, comparing treatment outcomes in patients who are receiving NGS and those who aren't. "There's enough patients now who are getting NGS that we will soon have critical mass to do this sort of study," Dinan said.

Foundation Medicine, which markets the FoundationOne pan-companion NGS diagnostic, declined to comment on how it could design a prospective study that assessed the clinical utility of the test over no screening.

FoundationOne received a National Coverage Determination (NCD) from the Centers for Medicare & Medicaid Services in February 2018, which opened up reimbursement for the test to the entire Medicare population.

NGS is still not the norm for the majority of cancers, including NSCLC (see "Success in Lung Cancer Niches Will Hinge on Access to Next-gen Sequencing").

"Commercial payers have been slow to broadly adopt coverage for comprehensive genomic profiling panels, even when FDA-approved and Medicare-covered," a Foundation spokesperson told BioCentury.

The company said it continues to work with members of the healthcare system to improve access to FoundationOne, conduct clinical trials and gather real-world data. But it believes a model that provides a more standard approach to evidence generation and reimbursement is needed.

"We've seen a lot of advancements in this area, which are encouraging, but there is no standard right now and that's where we need to move collectively," the spokesperson said.

Foundation Medicine and Genomic Health agreed that widespread adoption of any model would also be critical.

"The success or failure of any proposed coverage model hinges on health plan adoption on a broad scale," Foundation's spokesperson said.

"This will require large scale adoption to provide incentives to power the cycle of investment in high quality tumor biomarker development," Shak said, adding that it's not enough to improve adoption in the U.S. "It's also an issue globally."

"THE SUCCESS OR FAILURE OF ANY PROPOSED COVERAGE MODEL HINGES ON HEALTH PLAN ADOPTION ON A BROAD SCALE."

FOUNDATION MEDICINE

One more piece of the puzzle

Clinical utility data only satisfy part of the problem. Companies may also need to demonstrate the economic benefits of a test to the healthcare system.

"The idea of tiering levels of payment to evidence is great, and frankly, clever," said Real Endpoints' Longman.

The Harvard Pilgrim-Illumina pilot, a first-of-its-kind risk-sharing deal announced in February 2018, could serve as a model for how companies can gather this type of evidence.

Illumina had already established the clinical utility of its non-invasive prenatal tests (NIPTs), but the lack of health economic data was stalling reimbursement.

Under Illumina's deal with Harvard Pilgrim, the payer reimbursed the cost of the company's NIPTs for all pregnancies. The partners, with Real Endpoints' help, tracked the total cost of screening tests including NIPTs, serum-based tests, ultrasound and invasive follow-up tests for low- and average-risk pregnancies.

If after one year the total screening costs were higher than the historical costs Harvard Pilgrim incurred for low- and average-risk pregnancies, when NIPT was not used, Illumina had to make up the difference. If the costs were lower, Harvard Pilgrim kept the savings.

The partners also collected real-world evidence on costs and outcomes that Illumina can use to support reimbursement of its tests by other payers (see "De-risking Risk Reduction").

Longman said that incorporating Illumina's NIPTs into prenatal screening led costs to increase by "a tiny bit" and improved patient outcomes. An economic model of the risk-sharing arrangement suggested that costs could increase by as much as $304,000 (18%), according to data presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)-Europe earlier this month. However, the full economic analyses, including additional cost offsets that may have been achieved due to increased screening, are expected next year.

Risk-sharing could be the next step in securing reimbursement for tumor biomarker tests like NGS to help doctors decide which high-cost cancer treatment is best for a patient. "I think a risk-sharing arrangement seems more reasonable when you're trying to demonstrate the health economic utility," said Jane Barlow, EVP and chief clinical officer at Real Endpoints.

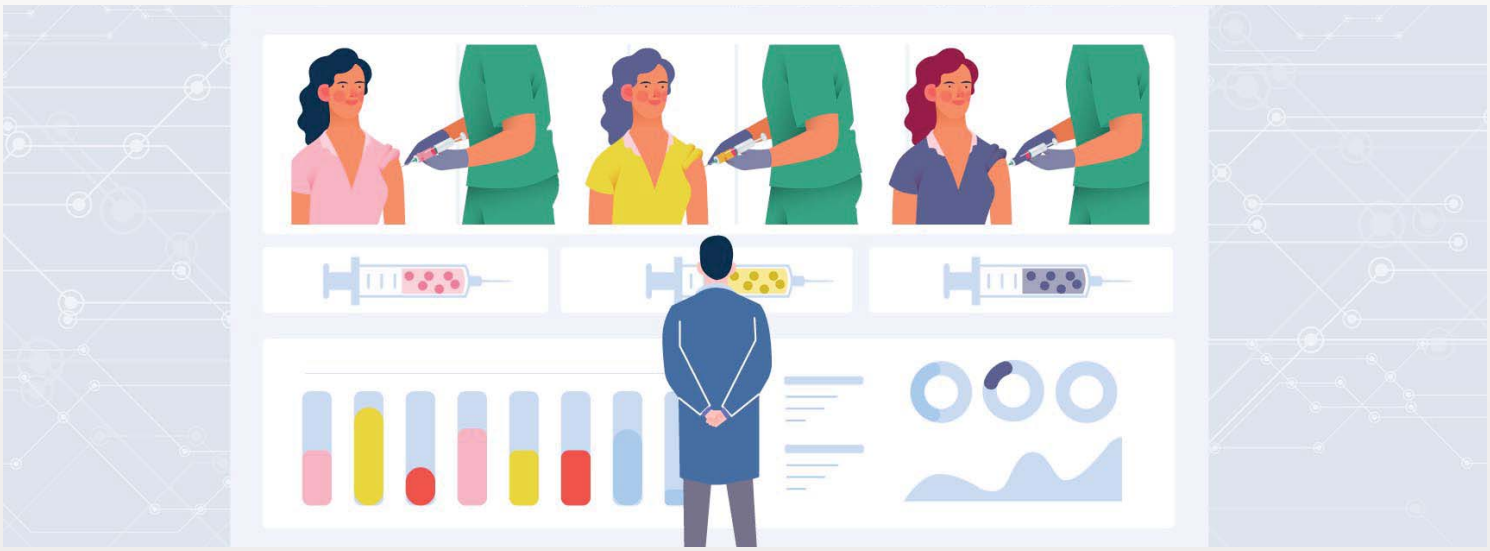
The challenge with a test like FoundationOne is that its effect on costs isn't as obvious as a test like Oncotype Dx, which identifies patients who don't need additional treatment. FoundationOne and other NGS-based tests for treatment selection identify the optimal treatment to produce the greatest benefit. The treatment on top of the costs for the test would likely represent an incremental increase in costs.

Longman doesn't think that there will be a one-size-fits-all approach to cancer diagnostics reimbursement, but believes risk-sharing could be one piece of the model.

Real Endpoints is working with an undisclosed company on a screening test that includes a clinical trial, a patient registry and a risk-sharing arrangement. "The issue is that it's going to be very expensive if it's used as it should be. It may lower costs over time, but it may not lower costs for the payer while that beneficiary is with them," Longman said. "You only want to do risk-sharing arrangements when there is significant medical impact and significant economic impact."

TARGETS

HER2 - Epidermal growth factor receptor 2 (HER2; EGFR2; ErbB2; neu)



BIOCENTURY & GETTY IMAGES

PRODUCT DEVELOPMENT

Reading into the first wave of neoantigen results

BY KAREN TKACH TUZMAN, ASSOCIATE EDITOR

The first clinical data from neoantigen vaccine companies have started to answer questions about the best way to quickly gauge whether patients are responding. The lessons include how to design combination trials that point to efficacy beyond checkpoint inhibition, and how to increase the rigor of *ex vivo* assays.

The idea that mutations from a patient's own tumor could be harnessed to treat cancer has been gaining steam for the last six years, with more than a dozen companies announcing personalized neoantigen vaccine programs. Each player has developed its own strategies for identifying neoantigens in tumors and delivering them as peptides, nucleic acids, or in microbial vectors (see "Neo Wave").

At least six have reported signals from Phase I trials. The results indicate the vaccines are capable of stimulating T cell responses in patients, but in the absence of long-term overall survival (OS) data, the connection between those responses and therapeutic benefit remains unclear.

"If you immunize, and there are pre-existing T cells there, it should be easy to see them straight away out of the blood," said Pact Pharma Inc. CEO Alex Franzusoff. "That doesn't mean that the T cells you got from immunization are actually relevant to the tumor."

Part of the challenge will be separating out the vaccines' effects from those of checkpoint inhibitors, given that the majority of Phase I programs are planned as single-arm combination studies.

"It's a non-trivial problem, particularly in early stage trials," said Gritstone Oncology Inc. (NASDAQ:GRTS) CEO Andrew Allen, noting that eschewing checkpoint inhibitors leaves companies open to an obvious mechanism of resistance. "The concern is, even if you make great neoantigen-specific T cells, they could get shut down by checkpoints."

Companies are tackling the problem by looking for big jumps in progression-free survival (PFS) relative to historical checkpoint monotherapy data, or by targeting tumors that are largely insensitive to checkpoint inhibition.

Other hurdles to gauging progress include variability in how companies conduct ELISPOT cytokine production assays, an *ex vivo* method widely used to assess responsiveness of patients' immune cells to neoantigens, and the limited ability of standard RECIST criteria to predict how the therapies will affect OS. RECIST criteria were designed for chemotherapies and center on tumor mass reduction, and don't account for the long response timelines and immune infiltration commonly seen in immunotherapy (see "Rethinking RECIST for Immunotherapies").

Neon Therapeutics Inc. (NASDAQ:NTGN) CEO Hugh O'Dowd said investors "struggle" to interpret data showing widespread neoantigen responses without consistent reduction in cancer mass. He thinks histology data will be key for assessing benefit, because they can reveal the composition of the tissue mass, and said Neon's histology data suggests these masses are being depleted of viable tumor cells and filling up with immune and fibrotic cells.

"When we see this evidence on the immune side, we think for the randomized trials, leveraging this biology in a variety of formats will ultimately bear this out," O'Dowd said.

Checking efficacy

Companies have shared Phase I neoantigen vaccine data via a handful of papers and presentations, ranging from top-line Phase Ib data to case studies of single patients (see Figure: "Personalized Progress").

Although most companies' results capture preliminary single-agent activity, every company moving forward on the back of disclosed clinical data is incorporating checkpoint inhibitors into its long-term strategy.

Neon has disclosed the field's largest clinical dataset so far.

In July, Neon announced results from a Phase 1b study of its personalized neoantigen peptide vaccine NEO-PV-01 in combination with the anti-PD1 mAb Opdivo nivolumab from Bristol-Myers Squibb Co. (NYSE:BMY) in 82 patients with checkpoint-naive metastatic melanoma, non-small cell lung cancer (NSCLC) or bladder cancer.

To tease out NEO-PV-01's contribution from Opdivo's effects, Neon compared its PFS results to historical studies of checkpoint inhibitor monotherapy in patients with similar baseline characteristics. For each indication, the single-arm study showed longer PFS than previously reported for Opdivo alone.

"Given this is a single-arm trial, there are caveats, but what we were excited about was the consistency across all three tumors," said CSO Richard Gaynor.

Neon is planning a randomized Phase II study of its vaccine in combination with checkpoint inhibitor therapy in a biomarker-defined population of first-line metastatic melanoma patients. Timelines and biomarkers for the study are undisclosed.

BioNTech SE, whose 2017 *Nature* study of 13 melanoma patients was among the first to suggest PFS benefit from neoantigen cancer vaccines, is now moving forward with a Phase II randomized control study of its mRNA neoantigen vaccine candidate RO7198457 in combination with the anti-PD1 Keytruda pembrolizumab from Merck & Co. Inc. (NYSE:MRK), providing the field's first head-to-head comparison with checkpoint inhibitor monotherapy.

Like Neon, BioNTech and its partner, the Genentech Inc. unit of Roche (SIX:ROG; OTCQX:RHHBY), are also testing their neoantigen vaccine and anti-PD1 combo in first-line advanced melanoma, where the latter is approved. The study launched in January, and aims to enroll 132 patients.

RO7198457 is also in a Phase I solid tumor study alone and in combination with Genentech's anti-PD-L1 Tecentriq atezolizumab. The German biotech declined to discuss either study, citing a quiet period ahead of its IPO.

Genocea Biosciences Inc. (NASDAQ:GNCA), Agenus Inc. (NASDAQ:AGEN), Advaxis Inc. (NASDAQ:ADXS) and Aduro Biotech Inc. (NASDAQ:ADRO) have each presented single-agent data from their neoantigen vaccine programs in five or fewer patients. These case studies have primarily captured vaccine immunogenicity using ELISPOT assays.

"THAT DOESN'T MEAN THAT THE T CELLS YOU GOT FROM IMMUNIZATION ARE ACTUALLY RELEVANT TO THE TUMOR."

ALEX FRANZUSOFF, PACT PHARMA

Genocea uses its ATLAS platform — a combination of bioinformatic analyses and cell-based screens — to find candidate neoantigens that stimulate immune responses in patient blood pre-treatment. Empirically screening for pre-existing immunity increases the company's chances of selecting neoantigens that drive productive responses, said CMO Tom Davis. "We're getting immune responses to nearly all the targets we've been putting into patients."

Aduro has deprioritized its *Listeria* vector-based neoantigen vaccine program, and Agenus and Advaxis did not return requests for comment on their respective peptide- and *Listeria*-based products.

Companies that kicked off single-arm combination neoantigen trials this year are leveraging differences in checkpoint inhibitor sensitivity across tumor types to optimize detection of vaccine responses.

Allen said Gritstone is focusing on cancers where the drugs have had little effect, such as microsatellite stable (MSS) colorectal cancer.

Personalized progress

At least six neoantigen companies have reported Phase I data from their personalized vaccine products. All six have demonstrated they can induce neoantigen-specific T cell responses in patients using ELISPOT *ex vivo* cytokine production assays.

In July, **Neon Therapeutics Inc.** (NASDAQ:NTGN) presented top-line data, including progression free-survival (PFS) and objective response rate (ORR) based on RECIST v1.1 criteria, from its peptide vaccine **NEO-PV-01** plus the anti-PD1 Opdivo nivolumab from **Bristol-Myers Squibb Co.** (NYSE:BMY) in 82 patients with melanoma, bladder cancer or non-small cell lung cancer (NSCLC). The company also presented ELISPOT and histology data from a subset of melanoma patients at the American Association for Cancer Research meeting in March.

BioNTech SE published a 2017 study of its mRNA vaccine **IVAC mutanome** in 13 melanoma patients, among which eight were tumor-free after 23 months, and all of which showed neoantigen responses. Since launching its partnership with the Genentech Inc. unit of **Roche** (SIX:ROG; OTCQX:RHHBY), BioNTech changed the name of its neoantigen vaccine program to **RO7198457**.

Together with **Immatics Biotechnologies GmbH**, BioNTech co-led the Glioma Actively Personalized Vaccine Consortium (GAPVAC), which in 2018 published a paper showing neoantigen responses in eight out of 10 glioblastoma patients who received a sequential combination of **APVAC1**, a peptide vaccine of unmutated antigens shared across multiple patients, and **APVAC2**, a peptide vaccine comprised of personalized neoantigens. Both BioNTech's 2017 and 2018 studies were published back-to-back with similar studies in melanoma and glioblastoma patients, respectively, from academic teams led by Neon's scientific founders.

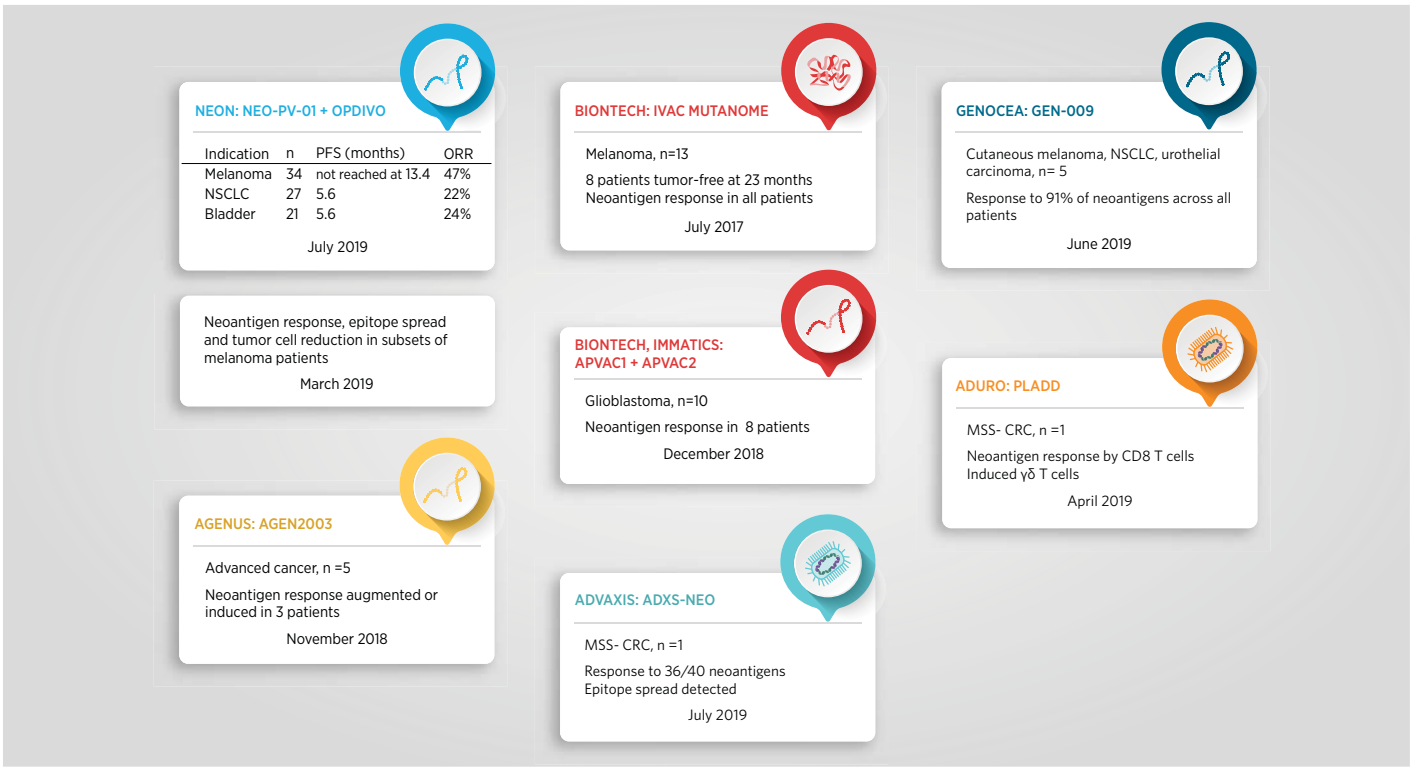
Genocea Biosciences Inc. (NASDAQ:GNCA) presented a poster at the June 2019 meeting of the American Society of Clinical Oncology (ASCO) showing responses to 91% of the neoantigens in its **GEN-009** peptide vaccine across five patients with cutaneous melanoma, NSCLC or urothelial carcinoma.

Agenus Inc. (NASDAQ:AGEN) presented a poster at the November 2018 meeting of the Society for Immunotherapy of Cancer (SITC) showing responses to neoantigens in its **AGEN2003** peptide vaccine were increased or induced *de novo* in three out of five patients with a range of advanced solid tumors. The company has an ongoing Phase 1a study of a modified version of the vaccine, **AGEN2017**.

Advaxis Inc. (NASDAQ:ADXS) announced preliminary data in July showing immune responses to 36 out of 40 neoantigens in a patient with microsatellite stable colorectal cancer (MSS-CRC) treated with **ADXS-NEO**, an attenuated *Listeria monocytogenes* strain engineered to secrete personalized neoantigens.

Aduro Biotech Inc. (NASDAQ:ADRO) presented data at the European Neoantigen Summit in June showing its *L. monocytogenes*-based vaccine **pLADD** induced neoantigen-specific CD8 T cell and γδ T cell responses in a patient with MSS-CRC. The company has deprioritized the program.

PD-1 (PDCD1; CD279) - Programmed cell death 1



"DEMONSTRATING DELTA IS HARD IF TUMORS HAVE A HIGH BACKGROUND RESPONSE RATE."

ANDREW ALLEN, GRITSTONE

"Demonstrating delta is hard if tumors have a high background response rate" to checkpoint inhibition, he said.

Gritstone launched Phase I/II studies of its two vaccine candidates, the personalized neoantigen therapy GRANITE-001 and the shared neoantigen therapy SLATE-001, in February and July, respectively. Both vaccines deliver neoantigens via a prime/boost approach using a viral vector followed by self-amplifying mRNA, and both are being tested in combination with anti-CTLA-4 and either anti-PD-1 or anti-PD-L1.

In July, Pact began testing its engineered neoantigen-specific TCR therapy NeoTCR-P1 in cancers with high, medium or low sensitivity to checkpoint inhibitors: melanoma and bladder cancer, MSS colorectal and ovarian cancer, and prostate and hormone receptor-positive breast cancer, respectively.

The company uses beads coated with tetramers of HLA complexes bound to predicted neoantigen peptides to isolate neoantigen-specific T cells from patient blood, and then expresses the TCRs from those cells in fresh autologous T cells (see "Highly Personal").

Spot test

While companies wait for the long-term data needed to show an OS benefit, they are parsing histology and cell culture data to understand how their vaccines affect patients' immune systems and tumors.

Gaynor thinks Neon's most important readouts are tumor histology data suggesting NEO-PV- 01 is triggering killing of cancer cells in tumor masses, leaving behind a scaffold of fibrotic stromal cells and immune cells.

"Just because you see a mass after therapy with the vaccine, that doesn't always equate to tumor," he said. "We can say for the melanoma cohort post-vaccine, in the majority of patients, we don't see viable tumor."

He thinks RECIST criteria don't capture the vaccine's therapeutic benefit, and suggested the amount of cell-free DNA (cfDNA) released from tumors could provide a more accurate indicator of response. Researchers are increasingly using circulating tumor DNA to monitor responses to therapy (see "ctDNA Inches Toward New Applications").

Neon is collaborating with sequencing company Natera Inc. (NASDAQ:NTRA) to monitor cfDNA in an ongoing Phase I study testing NEO-PV-01 plus Keytruda and chemotherapy in NSCLC.

On the cell culture front, *ex vivo* ELISPOT assays comparing pre- and post-treatment T cell responses have emerged as a major workhorse in the neoantigen field. These tests don't say what is happening in the tumor, but they do provide insight into how responsive the patient's immune cells are to the vaccine.

ELISPOT assays involve exposing immune cells from patients' blood to the neoantigens in the personalized vaccines they were given, and counting how many colonies of cells produce cytokines in response, typically IFNγ. The goal is to see an increase in responses to neoantigens compared with baseline.

But companies are increasingly recognizing that to interpret these assays, the devil is in the details. In particular, how long cells are cultured before staining for IFNγ, and whether they're cultured with immunostimulatory factors like IL-2, likely impact the sensitivity of the assay.

"If you don't see anything there, you can keep adding cytokines for days or weeks," said Allen.

The field has not been consistent in its definitions of ELISPOT assay protocols, Genocea CSO Jessica Flechtner told BioCentury. "The data might not be as representative as what people expect."

Flechtner said infectious disease researchers typically perform what she called "*ex vivo* ELISPOTs," where cells are stimulated directly out of the body for up to 22 hours. In contrast, the cancer vaccine field has historically performed, and neoantigen studies have reported, "cultured ELISPOTs" where cells are incubated with peptides and cytokines for days or weeks.

For example, a pair of 2018 glioblastoma studies from Neon's academic founders and from a BioNTech and Immatics Biotechnologies GmbH-led consortium used cultured ELISPOTs lasting up to 21 days and

12 days, respectively, and included IL-2 (see "Neo Opportunities for Glioblastoma").

The discrepancy with infectious disease protocols comes from the fact that cancer vaccines were traditionally generated against tumor antigens that weren't mutated, so they were recognized by the immune system as "self." But companies are increasingly realizing that because neoantigens are mutated "non-self" proteins, analogous to infectious pathogens, infectious disease protocols are appropriate for the class, Flechtner said. "The field is coming full circle."

"JUST BECAUSE YOU SEE A MASS AFTER THERAPY WITH THE VACCINE, THAT DOESN'T ALWAYS EQUATE TO TUMOR."

RICHARD GAYNOR, NEON

Flechtner said Genocea performs both *ex vivo* and cultured ELISPOT assays, in order to make apples-to-apples comparisons with the rest of the field. In addition, she thinks the assays could be providing different layers of information. "It may be the cultured ELISPOT picks up some more of the memory T cells that are circulating, whereas the *ex vivo* assay picks up effector cells."

Allen thinks variability in how often ELISPOT assays are done, and what types of cells are represented, is also making it difficult to interpret results. "If you treat 10 patients, show me 10 ELISPOTs, and show the CD8 responses."

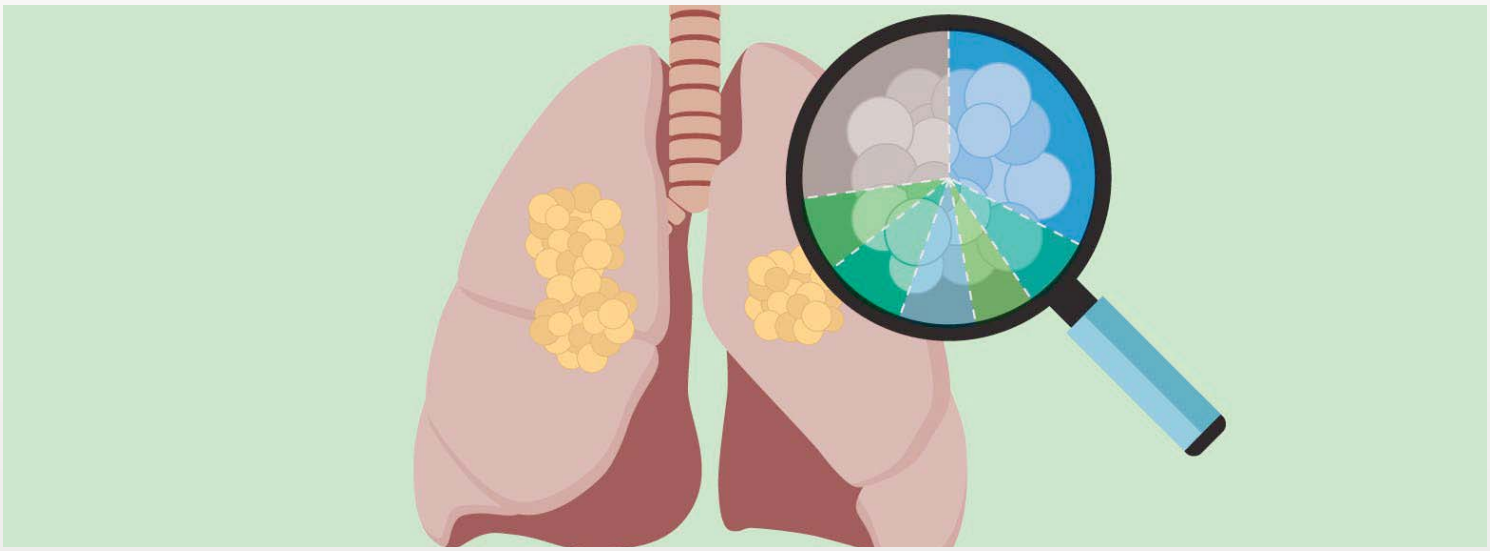
Gaynor said Neon doesn't add cytokines to its ELISPOT assays, and cultures cells between one and five days. The company also tests the specificity of T cell responses by checking that the cells respond to only the mutant and not wild-type forms of the antigens, and performs additional assays such as gene expression profiling to gauge the quality of responding cells.

Neon is also using ELISPOTs to measure epitope spreading, a phenomenon in which vaccine-induced tumor killing exposes a patient's immune system to additional neoantigens beyond those in the vaccine, extending the response. Neon tests for epitope spreading by assessing the emergence of T cell responses against neoantigens that were identified by the company's discovery platform but not included in the vaccine.

Flechtner said Genocea is also using its ATLAS platform to screen all of each patient's mutant peptides for epitope spreading. "Epitope spread is a secondary indicator that you're actually killing your tumor." bc

TARGETS

CTLA-4 (CTLA4; CD152) - Cytotoxic T-lymphocyte associated protein 4
PD-1 (PDCD1; CD279) - Programmed cell death 1
PD-L1 (B7-H1; CD274) - Programmed cell death 1 ligand 1



BIOCENTURY & GETTY IMAGES

PRODUCT DEVELOPMENT

Success in lung cancer niches will hinge on access to next-gen sequencing

BY ERIN MCCALLISTER, SENIOR EDITOR

New targeted lung cancer therapies against RET, KRAS and c-MET are all outperforming standard of care in the clinic, including checkpoint inhibitors. But whether these therapies see uptake will likely depend more on whether next-generation sequencing becomes embedded in routine care than the small differences between them.

Four of the therapies are poised to enter the market within the next year, targeting narrow slices of the non-small cell lung cancer (NSCLC) patient population not yet served by tumor-targeted agents.

Selpercatinib from Eli Lilly and Co. and pralsetinib from Blueprint Medicines Co. are both designed for RET fusion-positive tumors; Merck KGaA's tepotinib and Novartis AG's capmatinib target cMET-positive tumors. These mutations make up 2% and 3% of NSCLC patients, respectively.

A third drug class could be on the market within the next two years, targeting KRAS g12c mutated NSCLC, which accounts for about 13% of patients. Amgen Inc.'s AMG 510 is the only program that has read out. Competitor Mirati Therapeutics Inc. is set to announce data from MRTX849 next quarter.

The five programs with data have shown response rates ranging from 50% to 68%, a big jump from the 11%-33% typically seen with standard of care, which, in some cases, includes checkpoint inhibitors.

But given the small numbers of patients and no clear efficacy advantage within each class, the ability to gain a foothold will boil down to whether patients and their physicians are aware of the new treatment options and have access to the diagnostic tools.

In clinical trials, eligible patients were identified for these therapies via NGS. This is still not the norm in routine cancer care, however, despite the availability of multiple sequencing tests that can assess underlying tumor mutations to guide treatment decisions (see "Why Tissue Agnostic Drug Development Needs NGS to Go Mainstream").

Lilly, Amgen, Blueprint and Merck agreed that education about testing will be critical to success. Some of these companies are also hoping that simply having more effective targeted treatments on the market will urge oncologists to adopt NGS.

In the meantime, the companies have started to delineate clinical programs for these molecules, either testing them in earlier treatment settings or with different combination partners, that could influence how oncologists choose among them over the long term.

Nailing down NGS

With clear benefit over SOC, the biggest barrier to uptake of these therapies will be physician's lack of usage of NGS to profile tumor mutations.

The companies are counting on a mix of physician education and an "if you build it they will come" mentality to fix the problem.

According to Jake Van Naarden, COO of the Loxo unit of Lilly, about 20%-30% of NSCLC patients get NGS testing to identify tumor mutations and guide treatment decisions. Lilly gained selpercatinib via its $8 billion acquisition of Loxo Oncology Inc. in February.

He and Amgen's VP of global development and oncology therapeutic area head Gregory Friberg believe that as more drugs targeted to select mutations become available, the evolving armamentarium could drive uptake of NGS.

"In many ways this the result of the fact that there haven't been as many tools in the toolkit when they find these rare mutations. But I believe that we're reaching a tipping point in lung cancer," Friberg told BioCentury.

"The more and more biomarkers we have, the more that will happen and it could drive a step change," added van Naarden. With efficacy in the 70% range for agents such as selpercatinib, "it will really start to shift

Lilly has separate partnerships with Illumina Inc. and Thermo Fisher Scientific Inc. to develop companion diagnostics. Illumina is developing the NGS-based pan-cancer companion diagnostic TruSight Tumor 170 and added RET mutations to the multi-gene panel through a 2018 partnership with Loxo.

Blueprint said in an emailed statement to BioCentury that it is building a precision medicine field-based team "to raise awareness of testing standards and help connect healthcare providers, multidisciplinary teams, including pathologists, and testing laboratories to ensure the testing is actionable and timely."

These approaches are essentially taking a leaf from the rare disease playbook, where companies often engage in extensive outreach to physicians and patient communities to raise disease awareness and facilitate proper diagnosis (see "Pharmas Learn from Rare Disease Units").

"I BELIEVE THAT WE'RE REACHING A TIPPING POINT IN LUNG CANCER."

GREGORY FRIBERG, AMGEN

care and the odds that a majority of the population is going to benefit," he said.

There are already drugs approved in NSCLC to treat four different molecularly defined subgroups — EGFR, ALK, ROS1 and BRAF. The approval of this next tranche of targeted agents would nearly double the number of therapies targeting genetic subgroups. The new therapies have response rates at least as good as the first batch.

Still, companies are realistic that showing efficacy isn't enough for assuring uptake.

"Obviously this molecule works, and so now the goal is to make sure that physicians identify patients with RET alterations. A key part of our launch will be to guide testing," said Anne White, SVP and president of Lilly Oncology.

van Naarden said that education would also extend to pathologists. "We also want to be sure pathologists are aware and ensure they know what high-quality testing looks like," he said.

Another challenge is that NGS is frequently only available at academic centers where much of the clinical trial research is conducted. A June collaboration announced by Amgen would expand clinical trials to community settings (see "Amgen Looks to Identify More KRAS-Mutant Patients").

The partnership could have the twin benefits of identifying larger numbers of KRAS patients and raising awareness of NGS and AMG 510.

Neck and neck in RET and c-Met

Data presented at medical conferences this year have set the stage for a tight race across the different molecular subgroups in NSCLC. All have come from single-arm studies, but they show response rates that exceed historical data for SOC.

The latest tranche were revealed this past week at the International Association for the Study of Lung Cancer's World Conference on Lung Cancer (WCLC) in Barcelona.

Data from Lilly's selpercatinib have set the bar for response rates in RET fusion-positive NSCLC.

The selpercatinib data were from the pivotal Phase II portion of the LIBRETTO-001 trial in 105 previously treated RET fusion-positive NSCLC patients.

Selpercatinib's 68% ORR was identical to the Phase I results presented from the program at the same meeting the previous year, and slightly higher than the 60% ORR of Blueprint's pralsetinib (see "Lilly Presents RET Data").

Blueprint presented its data at the American Society of Clinical Oncology (ASCO) meeting in June (see "Blueprint Presents RET Data").

Currently, when NSCLC patients are identified as RET fusion-positive, which happens rarely due to the poor uptake of NGS tests, oncologists treat them with off-label Cabometyx cabozantinib from Exelixis Inc. Cabometyx is a multi-kinase inhibitor that hits RET along with c-MET, VEGFR-1, VEGFR-2 and VEGFR-3. In an open-label trial in previously treated NSCLC patients, Cabometyx had an ORR of 28%. The drug is approved to treat renal cell carcinoma and hepatocellular carcinoma.

"We sort of know that patients with RET fusion-positive lung cancer don't seem to get a lot of benefit out of PD-1 therapies or in combination with chemotherapy," said Loxo's Van Naarden.

In treatment experienced patients, checkpoint inhibitors such as Opdivo nivolumab have shown response rates of 20%; chemotherapies such as docetaxel perform at around 10%. Opdivo is marketed by Bristol-Myers Squibb Co.

Lilly plans to file an NDA for selpercatinib this year and Blueprint expects a filing for pralsetinib in 1Q20, putting the two molecules' potential launches just months apart.

Based on the LIBRETTO data, Lilly thinks selpercatinib could be the go-to treatment option for this molecular subgroup. "I think what you see with that dataset puts selpercatinib in the company of what we think are best-in-class therapeutics for other genomically-defined lung cancers with a high response rate, a high CNS response rate and an emerging durability signal showing that when patients go into a response, they stay in response for a very long time," Van Naarden told BioCentury.

The company also believes the molecule's safety profile could be differentiating, with 1.7% of patients discontinuing due to treatment-related toxicity vs. 3% for pralsetinib.

Blueprint argues that differences between the trials make it difficult to discern which agent is best-in-class. Specifically, all of the responses reported for pralsetinib in the Phase I/II ARROW trial were confirmed, whereas two partial responses in LIBRETTO had yet to be confirmed. There was also a slightly higher proportion of patients in ARROW with brain metastases, 40% vs. 35% for LIBRETTO, which could result in a lower ORR because these patients often have a worse prognoses.

The c-Met race is equally tight.

Novartis and Merck KGaA each presented data at ASCO in June from c-Met inhibitors. In the Phase I/II trials, Novartis reported an ORR of 68% among treatment-naïve patients receiving capmatinib monotherapy and 41% in previously treated patients. Merck KGaA reported an ORR of 50% across all treatment lines in c-Met positive patients for tepotinib.

Patients with c-Met mutations are sometimes treated off-label with Pfizer Inc.'s Xalkori crizotinib, a c-Met and ALK inhibitor, or Cabometyx.

Data from a 13-patient trial presented at ASCO in 2016 showed that Xalkori had an ORR of 33%.

Novartis plans to file an NDA this year for capmatinib, and Merck is planning an NDA for tepotinib in 2020.

Novartis and Merck declined to say how they see their therapies differentiating. Merck said in an emailed statement to BioCentury: "We believe we have a clinically differentiated investigational product that in clinical trials has shown encouraging activity."

Novartis noted capmatinib could change SOC for patients with cMET mutated NSCLC.

Alex Spira, a medical oncologist and director of the Virginia Cancer Specialists Research Institute, does not think the differences between these programs are meaningful.

> **"NOW THE GOAL IS TO MAKE SURE THAT PHYSICIANS IDENTIFY PATIENTS WITH RET ALTERATIONS."**
>
> ANNE WHITE, ELI LILLY

"To me, these are all very similar to each other. They're all best-in-class," said Spira.

Carving out KRAS' benchmark

In KRAS, the what constitutes best-in-class could start to become clear later this year when Mirati reports its first data. For now, Amgen's AMG 510 data presented at WCLC puts the response rate to beat at 54%.

In the Phase I open-label dose ranging study, seven of the 13 evaluable NSCLC patients treated with the high dose of 960 mg achieved a partial response. That's well above the 20% ORR seen with patients who receive Opdivo as second-line therapy, which is administered regardless of tumor marker status. Amgen said it's still gathering natural history data to understand how KRAS-positive patients respond to the PD-1 inhibitor. According to Spira, KRAS patients tend to progress sooner and generally have a worse prognosis.

The patients in the AMG 510 trial had received a median of 3.5 prior therapies, ranging from 1 to 8.

"We're still in the early days, but we're feeling enthusiastic about this given that these are heavily pretreated patients and we're seeing these types of responses," said Amgen's Friberg.

AMG 510's nearest competitor is MRTX849 from Mirati, which declined to be interviewed. MRTX849 is in a Phase I/II trial for solid tumors. MRTX849 irreversibly locks KRAS in an inactive GDP-bound state by covalently binding to cysteine 12 in the protein's inducible switch II pocket.

At the American Association for Cancer Research (AACR) meeting in March, Mirati presented preclinical data from tool compound MRTX1257. In xenograft-bearing mice given oral doses of 100 mg/kg MRTX1257 daily for 28 days, some mice had complete responses that were maintained for more than 120 days after treatment was stopped. The molecule also showed over 50% tumor shrinkage in mouse models. Mirati noted in the AACR poster that MRTX849 and MRTX1257 have demonstrated "comparable selective activity in KRAS-mutant disease models."

According to a presentation at AACR, AMG 510 also covalently binds KRAS, occupying a previously unknown "cryptic pocket" induced by side-chain motion of the His95 residue of KRAS.

AMG 510 may have set the response rate to beat in KRAS-mutant NSCLC, but it's unclear if it will be best-in-class.

Looking at other molecularly targeted NSCLC agents is one way to shape expectations.

The RET inhibitors have shown rates approaching 70%. Among EGFR inhibitors, AstraZeneca plc.'s Tagrisso osimertinib is considered to be best-in-class to treat EGFR T790M-positive NSCLC and showed an ORR of 65% among 279 patients in a Phase III trial of 419 previously treated patients harboring this mutation.

Friberg cautioned against these parallels, stating that patient populations with some of these mutations are likely more homogeneous than the KRAS-mutated population and their biology better characterized.

"KRAS hasn't been as well understood. We're still in unchartered territory and given that these mutations aren't as rare as say a RET, we would expect to see some biologic diversity," he told BioCentury.

AMG 510 has been in the clinic for just over a year and Friberg said that as Amgen gains more experience with the molecule, it will look at the underlying biological diversity tied to treatment response to see if there are specific subgroups within the KRAS mutant population who benefit more than others.

Nonetheless, Spira was impressed by the results.

"A 54% response rate in lung cancer is great," he told BioCentury.

Amgen has already started enrolling patients in a Phase II single-arm monotherapy trial of AMG 510 and expects to report data next year. The biotech has said the trial is pivotal and it could file an NDA for the molecule based on the Phase II data.

Path to differentiation

Over the long run, the companies aim to generate clinical data that better differentiate these compounds, and they are taking different tacks, primarily via combination studies.

Amgen has an ongoing Phase I trial that is testing AMG 510 plus Merck & Co. Inc.'s Keytruda pembrolizumab in KRAS-mutated NSCLC patients. Friberg said the biotech is also exploring combinations with SHP-2 and MEK inhibitors.

A poster presented at AACR suggested that Mirati may explore combinations of MRTX849 with SHP-2 inhibitors, CDK4/6 inhibitors or mTOR inhibitors.

Lilly has a preclinical next-generation RET inhibitor that it thinks could address resistance to selpercatinib and other first-generation inhibitors such as Blueprint's pralsetinib.

Merck KGaA and Novartis are both testing their c-Met inhibitors in combination with approved EGFR inhibitors, though they've selected different partner molecules which could affect how the agents are used. Merck KGaA is testing tepotinib with Tagrisso and has a separate study with first-generation EGFR inhibitor Iressa gefitinib from AstraZeneca. Novartis is testing capmatinib with Roche's Tarceva erlotinib and Iressa, as well as its own investigational third-generation EGFR inhibitor nazartinib (EGF816). bc

COMPANIES AND INSTITUTIONS MENTIONED

American Association for Cancer Research (AACR), Philadelphia, Pa.
American Society for Clinical Oncology (ASCO), Alexandria, Va.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
AstraZeneca plc (LSE:AZN; NYSE:AZN), Cambridge, U.K.
Blueprint Medicines Co. (NASDAQ:BPMC), Cambridge, Mass.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Exelixis Inc. (NASDAQ:EXEL), South San Fransisco, Calif.
Illumina Inc. (NASDAQ:ILMN), San Diego, Calif.
Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
Merck KGaA (Xetra:MRK), Darmstadt, Germany
Mirati Therapeutics Inc. (NASDAQ:MRTX), San Diego, Calif.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Thermo Fischer Scientific Inc. (NYSE:TMO), Waltham, Mass.
Virginia Cancer Specialists Research Institute, Fairfax, Va.

TARGETS

ALK - Anaplastic lymphoma kinase
c-MET - c-Met receptor tyrosine kinase (c-MET; MET; HGFR)
EGFR (ErbB1; HER1) - Epidermal growth factor receptor
KRAS - K-RAS
mTOR - Mammalian target of rapamycin
RET - Ret Proto-oncogene
SHP-2 (SHPTP2; PTPN11) - Src homology protein tyrosine phosphatase 2
FLT1 (VEGFR-1) - VEGF receptor 1
FLT4 (VEGFR-3) - VEGF receptor 3
VEGFR-2 (KDR/Flk-1) - VEGF receptor 2
PD-1 (PDCD1; CD279) - Programmed cell death 1

EMERGING COMPANY PROFILE

Impact casting a wide synthetic lethality net

BY ELIZABETH S. EATON, STAFF WRITER

After laying the foundation with its PARP inhibitor, Impact plans to build a comprehensive synthetic lethality pipeline across known DNA damage repair targets and new ones outside of DDR to address a wider range of cancer mutations than other synthetic lethality companies.

The principle of synthetic lethality is that while cancer cells can tolerate or even benefit from losing one regulator of DNA damage repair, simultaneous inhibition of a second DDR protein causes overwhelming genetic damage that triggers cell death.

PARP inhibitors are the prime example, producing synthetic lethal interactions in patients with mutations in DDR pathway proteins BRCA1 and BRCA2.

Shanghai-based Impact Therapeutics Inc.'s lead program is PARP inhibitor IMP4297, and CEO Jun Bao told BioCentury the company plans to develop drugs against five more known DDR targets before moving into novel target discovery in the broader field of synthetic lethality.

"We wanted to be able to use a validated target to set a foundation, to build discovery and development capabilities," said Bao, who joined Impact in October 2018 from Beijing Shenogen Pharma Group Ltd., where he was EVP and CBO.

Previously, Bao was director of global business development and head of China BD at GlaxoSmithKline plc.

IMP4297 is slated to enter two pivotal Chinese trials in ovarian cancer by year end, and begin Phase II trials for prostate and small cell lung cancer by 2022.

AstraZeneca plc markets the lone PARP inhibitor approved in China, Lynparza olaparib, to treat ovarian cancer. Impact presented clinical data at this year's American Society of Clinical Oncology meeting showing that IMP4297 led to fewer toxicities and trial discontinuations than Lynparza, suggesting it could have a better safety and tolerability profile. Impact also has internal preclinical data that show that the company's candidate was 15-20 times more potent than Lynparza in BRCA-mutated cancer cells.

An AstraZeneca spokesperson said Impact's compound is still far off from reaching the market and pointed to Phase III data of Lynparza showing efficacy in ovarian, pancreatic, breast and prostate cancers, including data reported this month of the PARP inhibitor plus Avastin bevacizumab as first-line maintenance therapy in ovarian cancer. The combination had no safety signals outside of Lynparza's known profile.

Bao said Impact does not plan to seek approval of IMP4297 in the U.S. because there are already four marketed PARP inhibitors.

IMPACT THERAPEUTICS INC.
Shanghai, China

Technology: Compounds that modulate synthetic lethality and the DNA damage repair pathway

Disease focus: Cancer

Clinical status: Phase I

Founded: 2009 by Ye Tian and Shuixiong Cai

University collaborators: N/A

Corporate partners: CStone Pharmaceuticals Co. Ltd.

Number of employees: 24

Funds raised: $46 million

Investors: Lilly Asia Ventures, Decheng Capital, China Summit Capital, WuXi Healthcare Ventures, HaiBang Ventures, Sungent bioVenture, Yuexiu Fund

CEO: Jun Bao

Patents: 16 issued covering pipeline compounds, including PARP and Hedgehog pathway inhibitors

Next in line in Impact's pipeline is IMP7068, a WEE1 inhibitor that is expected to enter clinical testing in the U.S. and China by YE20 in p53-mutated cancers. WEE1, another DDR target, has synthetic lethal interactions with p53 mutations.

According to BioCentury's BCIQ database, AstraZeneca is the only company with a clinical WEE1 inhibitor; its AZD1775 is in Phase II testing for ovarian cancer.

Bao said Impact has internal preclinical data suggesting IMP7068 is more selective than AZD1775, which could lead to fewer off-target effects and fewer overlapping toxicities when testing combinations.

While several large pharmas, including AZ, Bayer AG and Merck KGaA, are developing one or more DDR-targeting compounds, Bao said Impact's goal is to have the most comprehensive synthetic lethality pipeline, allowing it to test a range of synthetic lethal combinations internally and address a wider range of cancers than competitors.

Impact has internal programs in discovery against other DDR targets including ATR, ATM, Chk1 and DNA-PK.

Bao said Impact is also in talks with an undisclosed Seattle company to discover a broad range of synthetic lethality targets outside of DDR.

Data presented at ASCO suggest targets in the ATR pathway are lining up behind PARP as the next drivers of synthetic lethal cancer killing.

Upon detecting DNA damage and replication stress, ATR transmits signals through Chk1 and WEE1, leading to cell cycle arrest. ATM performs a similar function through Chk2, but largely detects double-stranded breaks, whereas ATR can respond to a wider set of DNA lesions (see "Following PARP, ATR Axis is Next in Line to Expand Synthetic Lethal Drug Class").

Impact has raised $46 million in venture financing, including a $30 million series C round in August 2018 led by Decheng Capital.

Bao said Impact plans to close a $75 million series D by 1Q20, which should give the company runway into 2022 and enable it to complete pivotal trials of IMP4297, start Phase I testing of its ATM inhibitor IMP08 and conduct IND-enabling studies of its ATR, Chk1 and DNA-PK programs.

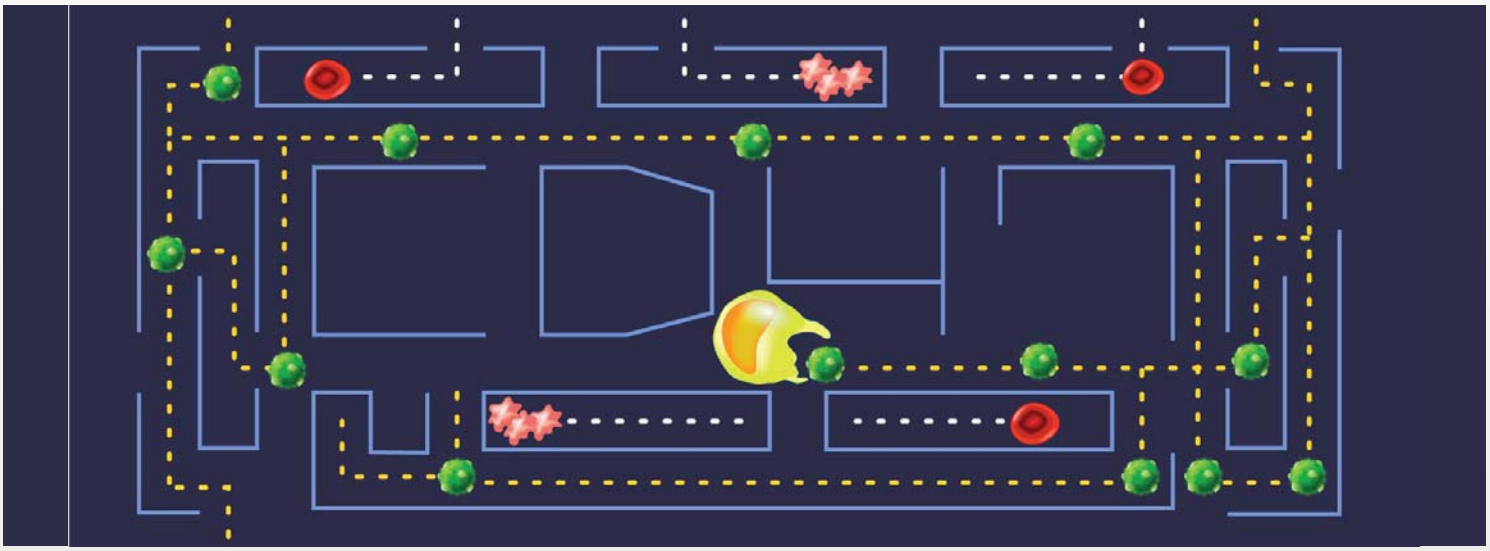
The company hopes to list on the Hong Kong stock exchange or NASDAQ in 2022. bc

COMPANIES AND INSTITUTIONS MENTIONED

American Society of Clinical Oncology, Alexandria, Va.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Bayer AG (Xetra:BAYN), Leverkusen, Germany
Beijing Shenogen Pharma Group Ltd., Beijing, China
Impact Therapeutics Inc., Shanghai, China
Merck KGaA (Xetra:MRK), Darmstadt, Germany

TARGETS

ATM - Ataxia telangiectasia mutated
ATR (FRP1) - Ataxia telangiectasia and Rad3 related
BRCA1 - Breast cancer 1 early onset
Chk1 (CHEK1) - Checkpoint kinase 1
DNA-PK - DNA-dependent protein kinase
PARP - Poly(ADP-ribose) polymerase
WEE1 - WEE1 tyrosine kinase



BIOCENTURY & GETTY IMAGES

PRODUCT DEVELOPMENT

Eat this, don't eat that: CD47 companies' first hurdle

BY KAREN TKACH TUZMAN, ASSOCIATE EDITOR

The rush to drug CD47 shows no signs of abating, with five companies launching clinical programs for cancer this year and three moving forward on the back of encouraging Phase I data. The differentiator may be in which company develops the cleverest strategy to tell macrophages which cells to eat and which to leave alone.

Having briefly occupied the limelight as the next PD-1, CD47 is moving to the harsh light of day as companies work out how to capitalize on its broad potential in cancer, without falling foul of the safety issues that have already downgraded at least one candidate.

Interest in the target was kicked off by findings from Irv Weissman's lab at Stanford University, which demonstrated anti-tumor effects of blocking CD47, a "don't eat me" signal that prevents cells from being engulfed by macrophages. The idea is that preventing the interaction between CD47 on tumor cells and SIRPA, its binding partner on macrophages, would relieve a blockade on innate antitumor immunity, similar to the way PD-1 inhibitors release the brakes on antitumor T cells (see "Forty Seven and Counting").

Weissman co-founded Forty Seven Inc. in 2015. Since then, at least 11 other companies have announced CD47 programs, and at least 24 compounds are in development targeting CD47 or SIRPA, according to BioCentury's BCIQ database.

Weissman, a professor of pathology and developmental biology, is also director of the Institute of Stem Cell Biology and Regenerative Medicine at Stanford.

However, early clinical studies, in particular by Surface Oncology Inc., have revealed dose-limiting hematological toxicity to be a sticking point for the target.

Surface saw two neutropenia-related dose-limiting toxicities at a lower than expected dose in an all-comer Phase I trial of its anti-CD47 mAb SRF231, and has deprioritized its program. Celgene Corp. terminated a Phase I trial of its anti-CD47 mAb CC-90002 in myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML), but has not disclosed data. A separate Phase I trial in combination with Rituxan rituximab to treat hematologic neoplasms is ongoing.

Other companies have also reported toxicity due to excessive elimination of red blood cells (RBCs), platelets or neutrophils.

The problem is that because CD47 is ubiquitously expressed, healthy cells act as antigen sinks that soak up anti-CD47 mAbs, which means high doses are needed to target tumors. But those high doses also suppress the "don't eat me signal" on blood cells, prompting macrophages to engulf them and causing hematological toxicity.

According to Surface CEO Jeff Goater, animals haven't been a viable testing ground to tease out differences in toxicity.

"You have a set of antibodies all more or less looked similar from a preclinical perspective. You moved them into the clinic, and they all look very different," said Goater.

Forty Seven, Trillium Therapeutics Inc. and ALX Oncology Ltd. have each reported clinical data they see as proof-of-concept for their compounds (see Table: "CD47's Clinical Report Card"). The next two years should see more results from the latest wave of entrants to the clinic.

All ten companies with clinical-stage compounds have disclosed strategies to solve the toxicity, with a common theme being addition of a second component that creates a tumor-specific "eat me" signal. This leverages the fact that binding to CD47 alone is not enough to induce cancer killing; it needs to be coupled with active stimulation of phagocytosis from an anti-CD47 mAb's Fc domain or another source, either of which can be delivered separately, in a more tumor-specific fashion.

Surface has not completely abandoned its program. The company testing whether lower, more frequent dosing could reduce the neutropenia risk, and sees an opportunity for the compound in transplant conditioning.

CD47's clinical report card

At least three companies have reported clinical efficacy and toxicity data from antibodies or fusion proteins against CD47. Adverse event rates represent sums across all grades of toxicity. **Trillium Therapeutics Inc**. (TSX:TRIL; NASDAQ:TRIL) data is from IV administration of TTI-621. Two more companies have reported issues with their programs, but not detailed data. **Celgene Corp**. (NASDAQ:CELG) terminated a Phase I trial of CC-90002 in patients with acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) when "preliminary monotherapy data in relapsed/refractory AML and high-risk MDS did not offer a sufficiently encouraging profile for further dose escalation/expansion." A separate Phase I trial in combination with Rituxan rituximab is ongoing. **Surface Oncology Inc.** (NASDAQ:SURF) said it would not open dose expansion cohorts for SRF231 after seeing two hematologic dose-limiting toxicities in the first 18 patients treated in a Phase I trial; the trial in solid and hematological cancer patients is ongoing to test other dosing schedules.

ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease; ALT = alanine aminotransferase, increase associated with liver damage; NR = not reported; (A) Forty Seven reported Complete Remission with Incomplete Hematologic Recovery (CRi), morphologic leukemia-free state (MLFS)/ marrow complete response and hematologic improvement (HI) in its calculation of overall response rates *Source: company presentations and announcements, ClinicalTrials.gov*

Forty Seven Inc. (NASDAQ:FTSV)	5F9	Ph I/II	Rituxan rituximab (n=115)	14%	29%	19%	NR	Diffuse large B-cell lymphoma (DLBCL) (n=59)	36%	15%	20%	12%
								Indolent lymphoma (n=38)	61%	24%	37%	24%
		Ph I/II	Monotherapy (n=10)	0%	20%	0%	0%	Acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) (n=10)	10%	0%	0%	70%
			Vidaza azacitadine (n=36)	25%	37%	26%	12%	AML (n=14)	64%	36%	0%	36%
								MDS (n=9)	100%	55%	0%	0%
ALX Oncology Ltd.	ALX148	Ph I	Herceptin trastuzumab (n=30)	7%	7%	13%	NR	HER2+ gastric and and gastroesophageal junction cancer (n=18)	22%	0%	22%	28%
			Keytruda pembrolizumab (n=52)	4%	8%	8%	14%	Squamous cell carcinoma of the head and neck (SCCHN) (n=19)	16%	0%	16%	32%
								Non-small cell lung cancer (NSCLC) (n=18)	0%	0%	0%	44%
Trillium Therapeutics Inc. (TSX:TRIL; NASDAQ:TRIL)	TTI-621	Ph I	Monotherapy (n=179)	7%	11%	25%	NR	Mycosis Fungoides (n=24)	17%	0%	17%	NR
								Sézary Syndrome (n=5)	20%	20%	0%	NR
								Peripheral T-cell Lymphoma (n=11)	18%	0%	18%	NR
								DLBCL (n=8)	25%	13%	13%	NR
			Rituxan (n=24)	NR	NR	NR	NR	DLBCL (n=24)	25%	4%	21%	NR

At least three companies with clinical-stage CD47 inhibitors are also developing candidates against SIRPA, whose narrower expression profile reduces tox risk (see Sidebar: "The Eater's Side").

Weighing independence

What strategy a company chooses will determine whether it can pursue the product as a monotherapy, or whether its candidate will require a partner compound. Competitors run the spectrum, with some prioritizing single agent activity at the cost of more limited dosing or indication options, and others entirely focused on combos for greater flexibility on both counts (see Figure: "Restrictive Diet").

ALX's approach only works as a combination. Its ALX148 contains an inactive Fc domain, and requires co-delivery of antibodies against tumor antigens to provide macrophages with Fc receptor-driven "eat me" signals.

"The antibody provides that activating signal in a tumor-specific way, which leads the macrophage only to the cancer cell," said CMO Sophia Randolph.

Forty Seven's anti-CD47 mAb 5F9 uses an IgG4 Fc domain, which CEO Mark McCamish said triggers phagocytosis but not antibody-dependent cellular cytotoxicity (ADCC), making it less likely to cause off-tumor toxicity. While the company has seen some single agent activity, it is banking on combinations with tumor-targeting mAbs, chemotherapy or checkpoint inhibitors to maximize efficacy.

"The signal we got from monotherapy, from an FDA registration approach, was not adequate," said McCamish. "We had to come up with ways to augment the pro-phagocytic signals on the tumor itself."

Trillium is aiming to create a monotherapy. Its lead candidate TTI-621 uses an IgG1 Fc domain, which strongly induces killing of tumor cells but is more prone to killing platelets, in particular. The company is tuning dosing and delivery to mitigate toxicity.

"We've made no secret of the fact that we think the IgG1-bearing CD47 blockers are the highest likelihood for monotherapy activity, so we're continuing to pursue that with TTI-621, both intratumorally and intravenously," said CEO Bob Uger.

Forty Seven's compound is a mAb against CD47, while ALX's and Trillium's compounds are bivalent SIRPA fusion proteins.

ALX wants company

ALX thinks that the advantage of ALX148 is that it separates blockade of "don't eat me" signals from instigation of "eat me" signals. "When you have an asset that has those two functional ends on the same molecule, you lose your specificity," Randolph said.

The company has shown that swapping an active Fc domain into ALX148 induces anemia and thrombocytopenia in preclinical models. "The hematological toxicity is not a class effect, it's a molecule effect," said Randolph.

The eater's side

Blocking the macrophage side of the CD47-SIRPA interaction could offer a safer way to promote tumor phagocytosis.

While CD47 is expressed ubiquitously, SIRPA is primarily expressed on macrophages. As a result, SIRPA inhibitors could have more limited effects on off-target cells, and avoid the need to overcome the "antigen sink" phenomenon that has pushed up dosing of anti-CD47 therapies.

Two anti-SIRPA mAbs began Phase I testing this year.

OSE Immunotherapeutics S.A. and Boehringer Ingelheim GmbH are testing the SIRPA inhibitor BI 765063 in solid tumors as a monotherapy and in combination with Boehringer's anti-PD1 mAb BI 754091.

OSE Immunotherapeutics CSO Nicolas Poirier told BioCentury BI 765063 overcomes resistance to checkpoint inhibition in preclinical models by modulating macrophage activity and allowing more T cells to enter the tumor microenvironment.

He said OSE has patented selective blockade of SIRPA but not SIRPG, which contributes to antitumor T cell responses.

Celgene Corp. is one of at least three companies developing both CD47 and SIRPA inhibitors.

The company is testing CC-95251 alone and in combination with anti-CD20 mAb rituximab or anti-EGFR mAb cetuximab in hematological malignancies and solid tumors, respectively.

Forty Seven Inc. President and CEO Mark McCamish believes the biotech's preclinical anti-SIRPA mAb FSI-189 will induce less anemia than its lead CD47 inhibitor 5F9, and sees opportunities for FSI-189 in transplant conditioning and infectious disease.

He thinks FSI-189 won't show single-agent activity in cancer, but could be used in combination regimens.

Arch Oncology Inc. presented preclinical data on a range of anti-SIRPA mAbs at this year's American Association for Cancer Research (AACR) meeting.

President and CEO Julie Cherrington said the company has not selected a lead compound, but is prioritizing agents that bind the most prevalent SIRPA variants, induce phagocytosis both as a single agent and in combination with the company's CD47 inhibitor AO-176, and do not suppress T cell activity, regardless of their ability to bind SIRPG.

— Karen Tkach Tuzman

A Restrictive diet for CD47

Companies with clinical **CD47** inhibitors are using an array of construct design and combination strategies to stimulate potent **macrophage** phagocytosis of **tumor cells** by simultaneously blocking the cancer's "don't eat me" signals and increasing "eat me" signals, all while avoiding engulfment of healthy hematological cells like red blood cells (**RBC**s).

Each competitor is using its biologic against CD47 to block the "don't eat me" interaction between CD47 on tumor cells and **SIRPA** on macrophages. The companies vary in how they deliver tumor-selective "eat me" signals via **FCGR**, a receptor on macrophages that binds the biologic compounds' long stalks, known as Fc domains. Fc domains derived from **IgG1** (**green**) antibodies trigger the strongest killing response, which can lead to more effective tumor killing but also greater toxicity; those derived from **IgG4** (**orange**) or **IgG2** (**pink**) have weaker killing effects.

1) ALX Oncology Ltd. is developing **ALX148**, a fusion protein against CD47 with an inactive Fc domain **(gray)**. To deliver "eat me" signals through FCGR, the compound must be combined with a tumor-specific biologic with an active Fc domain, like the anti-**HER2** IgG1 mAb herceptin.

2) Forty Seven Inc. (NASDAQ:FTSV), **Trillium Therapeutics Inc.** (NASDAQ:TRIL; TSX:TRIL) and **Innovent Biologics Inc.** (HKEX:1801) are developing **5F9**, **TTI-622** and **IBI188**, respectively. These compounds moderately activate FCGR via their IgG4 Fc domains; Forty Seven and Trillium are combining their compounds with additional pro-phagocytic signals like the anti-**CD20** IgG1 mAb rituximab, which targets B cell cancers. Innovent has not disclosed its strategy.

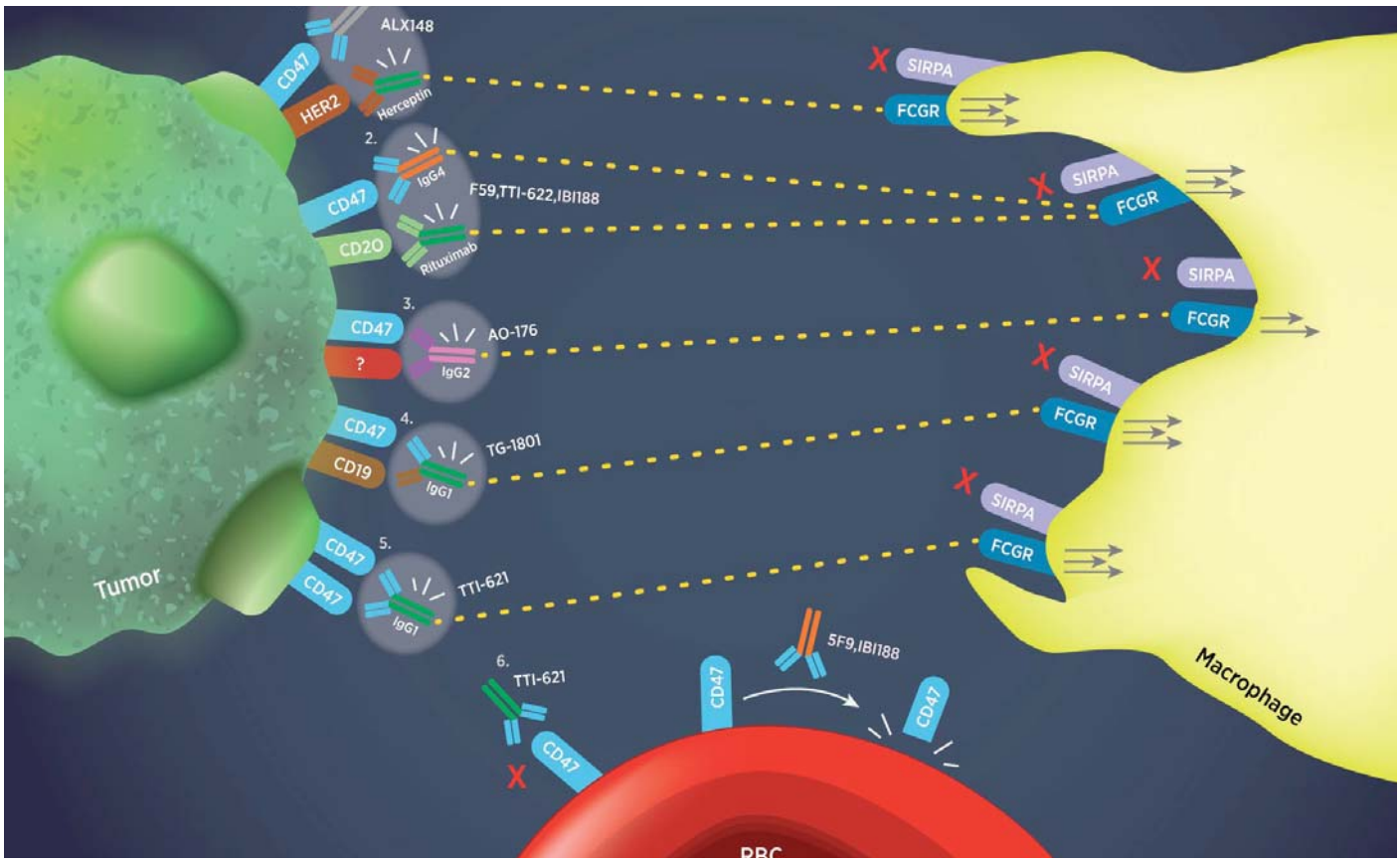
3) Arch Oncology Inc. is developing **AO-176**, a mAb that selectively targets CD47 in the presence of undisclosed tumor-specific proteins. The compound activates FCGR moderately via its IgG2 Fc domain, and induces direct tumor killing via a programmed cell death pathway.

4) TG Therapeutics Inc. (NASDAQ:TGTX) is developing **TG-1801**, an IgG1 bispecific antibody that weakly binds CD47 and strongly binds the B cell cancer antigen **CD19**, making CD47 blockade dependent on the presence of CD19.

5) Trillium's lead compound **TTI-621** is a fusion protein that requires CD47 clustering to bind the target and activates FCGR strongly via its IgG1 domain.

6) Trillium has shown TTI-621 is not effective at binding RBCs because CD47 is difficult to cluster on RBC membranes. Forty Seven and Innovent are administering their anti-CD47 mAbs at low priming doses before giving higher therapeutic doses; the priming dose cleaves CD47 from the surfaces of RBCs, reducing anemia induction by the subsequent therapeutic dose.

FCGR - Fc gamma receptor (FCGR); HER2 (EGFR2; ErbB2; neu) - Epidermal growth factor receptor 2 ; IgG1 - Immunoglobulin G1; IgG2 - Immunoglobulin G2; IgG4 - Immunoglobulin G4; SIRPA (CD172a; SHPS-1) - Signal regulatory protein α



She says its strategy could open indications that would be challenging for a CD47-targeting agent alone. "In the solid tumor space, we can dose higher, and not be limited by hematological toxicity."

She also believes ALX148 will be better positioned for use in earlier rounds of therapy and in combinations with other agents known to have hematological toxicity.

Randolph added ALX has looser clinical trial enrollment criteria than competitors with regards to pre-treatment hemoglobin levels and prior transfusions.

In a Phase I study, ALX combined its product with the anti-HER2 mAb trastuzumab or Merck & Co.'s anti-PD1 mAb Keytruda pembrolizumab.

According to Randolph, the ALX148/trastuzumab combo acts by triggering Fc-dependent phagocytosis, whereas the ALX148/Keytruda combo recruits macrophages and T cells into tumor, and possibly induces M1 macrophage polarization in an Fc cell-independent manner. In a Phase I study presented at the 2019 American Society of Clinical Oncology (ASCO) meeting, the compound induced single digit rates of anemia and neutropenia and an 8-13% rate of thrombocytopenia when dosed at 10 mg/kg per week in combination with standard regimens of trastuzumab in patients with HER2-positive gastric and gastroesophageal junction cancer, or Keytruda in patients with squamous cell carcinoma of the head and neck (SCCHN) or non-small cell lung cancer (NSCLC).

Forty Seven ways to detox

Forty Seven is minimizing 5F9-induced anemia using a priming dose of 1 mg/kg to clear the CD47 from RBC surfaces before delivering higher doses capable of targeting the tumor.

"Within about two hours of the initial dose, the binding of our molecule to CD47 on red blood cells causes a cleavage — what we call pruning — of CD47 on all red blood cells, old and new," said McCamish. FortySeven presented the priming strategy at last year's American Society of Hematology (ASH) meeting, and is continuing to investigate the mechanism.

The company has patented the dosing strategy in the U.S., Europe and Japan. "The priming dose is something we patented early on, and that's the crux of this. We do believe it will be on the label, which will be a key part of the patent protection, because it is a safety issue," McCamish said.

Forty Seven is testing combinations with the anti-CD20 mAb rituximab, which provides an extra 'eat me' signal via its IgG1 Fc receptor, and the chemotherapy azacitidine, which the company believes promotes upregulation by the tumor of endogenous eat-me signals like calreticulin.

At June's Congress of the European Hematology Association (EHA) meeting, the company reported data from a Phase I/II study of its rituximab/5F9 combo in non-Hodgkin lymphoma (NHL), and a Phase Ib study of its monotherapy and azacitidine combo in AML and MDS patients.

CBO Craig Gibbs told BioCentury the compound's safety profile is now "well-established," with experience in 290 patients of doses up to 45 mg/kg, and some patients treated for more than two years. The company is in discussions with FDA about accelerated approval for 5F9 plus azacitidine for MDS and 5F9 plus rituximab for diffuse large B cell lymphoma (DLBCL), a type of NHL, based on single arm studies with historical controls.

The compound is also in Phase I or I/II testing for other hematological cancers and solid tumors, and FortySeven is exploring preclinical combinations with newer agents like CD24 inhibitors (see "Combo Opportunities for Weissman's Latest 'Don't Eat Me' Signal").

> **"ALL MORE OR LESS LOOKED SIMILAR FROM A PRECLINICAL PERSPECTIVE. YOU MOVED THEM INTO THE CLINIC, AND THEY ALL LOOK VERY DIFFERENT."**
>
> JEFF GOATER, SURFACE ONCOLOGY

Trillium takes two

To minimize the risk profile of TTI-621, Trillium is taking a "cautious" dosing strategy for its IV studies, and focusing on indications where the compound can be delivered intratumorally, said Uger. He said intratumoral delivery "gets us around the systemic exposure issue, and gets a lot of drug locally to where we want it to be."

Intratumoral TTI-621 is in Phase I/II testing for solid tumors and mycosis fungoides, a type of cutaneous T cell lymphoma (CTCL), both as a monotherapy and in combination with checkpoint inhibitors or IFNα. Trillium presented data on its intratumoral monotherapy for CTCL at a January T-Cell Lymphoma Forum, and Uger said the company is in discussions with FDA about a registrational path for early stage disease.

The IV form of the compound is in Phase I/II testing to treat four forms of lymphoma as a monotherapy, or in combination with checkpoint inhibitors or rituximab. According to Uger, Trillium stuck to a low dose of 0.2 mg/kg in response to grade four thrombocytopenia events, but recently raised the dose to 0.5 mg/kg following discussions with FDA after it became clear that platelet counts rebounded within a week and the compound did not cause bleeding.

"We've seen single agent activity with our drug across a number of heme indications," said Uger. "We're encouraged by that, because frankly, we believe we've been underdosing."

He said the company has developed an assay to measure receptor occupancy in tumor microenvironment, rather than the more commonly tested bloodstream, which he said will be key "to better define how far up in dose we need to go."

Trillium has developed a second compound, TTI-622, with an Fc domain from IgG4 instead of IgG1; the agent is in Phase I testing alone and in combination with rituximab, checkpoint inhibition or a proteasome inhibitor regimen. "We are under no illusions that TI-622 is going to have significant monotherapy activity. For us, it's a combination play," Uger said.

He argues TTI-621 and TTI-622 will have a lower risk of anemia than competitors because the Trillium molecules don't bind CD47 on RBC surfaces. The company has biochemical data suggesting the compounds require bivalent interactions with clustered CD47 molecules for high avidity binding, and CD47 molecules on RBCs are less capable of clustering because they are embedded in stiff cytoskeletal networks.

Next in line

Companies entering the clinic have made it clear that tackling the target's toxicity will be their priority.

Arch Oncology Inc. CEO Julie Cherrington told BioCentury its anti-CD47 IgG2 mAb AO176 preferentially targets tumor cells because it selectively binds CD47 in the presence of undisclosed proteins that are specifically expressed on cancer cells.

The company presented data at this year's meeting of the American Association for Cancer Research (AACR) showing the compound preferentially bound cancer cells over T cells, epithelial cells or RBCs, and exhibited a clustered binding pattern on tumor cell surfaces not seen for Forty Seven's 5F9, which bound tumor cell surfaces uniformly. The data also show AO176 is capable of directly killing tumor cells, which the company believes occurs via a programmed cell death pathway.

In March, Arch announced $50 million in series B funding to advance AO176 in the clinic; the compound is in Phase I testing to treat solid tumors. Formerly known as Tioma Therapeutics Inc., Arch raised $86 million in its 2016 series A round.

TG Therapeutics Inc. has TG-1801, a bispecific IgG1 antibody targeting CD47 and CD19 licensed from Novimmune S.A. last year, in Phase I testing for B cell lymphoma. Because the compound binds CD47 weakly and CD19 strongly, it preferentially binds CD47 on cells expressing the B cell marker CD19.

"Our drug would be essentially useless for any other diseases other than B cell malignancies, which is the focus of our company, but in those diseases, it's the ideal manifestation of a CD47 inhibitor," CEO Michael Weiss told BioCentury. He anticipates TG-1801 will have single-agent activity, but sees opportunities to combine the compound with ublituximab, the company's glycoengineered anti-CD20 mAb in Phase III testing for chronic lymphocytic leukemia (CLL) and multiple sclerosis (MS).

The CD47 space has also seen a flurry of activity in China.

Innovent Biologics Inc. has initiated U.S. and Chinese Phase I studies of its anti-CD47 IgG4 mAb IBI188 in advanced malignant cancers. The company has described IBI188 as having "stronger receptor blocking ability than similar drugs."

In an email to BioCentury, CEO Michael Yu said the company is managing toxicity via a priming dose strategy. Though the dosing plan is similar to Forty Seven's approach, Yu said Innovent has a developed a new delivery strategy "to make sure that we respect their IP and have our own freedom of operations."

In June, I-Mab Biopharma began U.S. Phase I testing of its anti-CD47 mAb TJC4 for multiple cancers. The company identified the mAb via a screening strategy that selected for clones that bound CD47 with high affinity, but seldom or minimally bind RBCs. I-Mab also plans to initiate Chinese Phase I trials for AML and NHL.

ImmuneOnco Biopharma Co. Ltd. has IMM001, an Fc fusion protein targeting CD47, in Phase I testing for leukemia in China. The company disclosed it resubmitted its IND to China's National Medical Products Administration (NMPA) after the agency asked for additional preclinical data showing the compound had "good safety" against human RBCs and platelets.

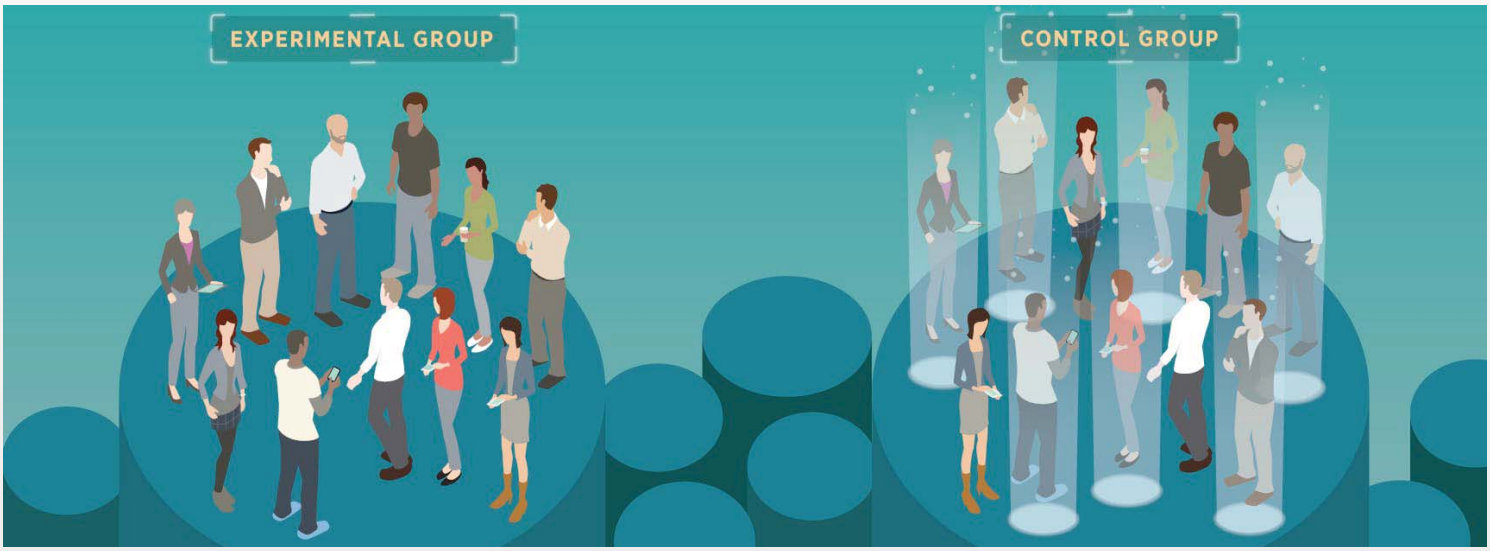
I-Mab and ImmuneOnco did not comment in time for publication.bc

COMPANIES AND INSTITUTIONS MENTIONED

ALX Oncology Ltd., Dublin, Ireland
American Association for Cancer Research (AACR), Philadelphia, Pa.
American Society of Clinical Oncology (ASCO), Alexandria, Va.
American Society of Hematology (ASH), Washington, D.C.
Arch Oncology Inc., Brisbane, Calif.
Boehringer Ingelheim GmbH, Ingelheim, Germany
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
European Hematology Association (EHA), the Hague, the Netherlands
Forty Seven Inc. (NASDAQ:FTSV), Menlo Park, Calif.
I-Mab Biopharma, Shanghai, China
ImmuneOnco Biopharma Co. Ltd., Shanghai, China
Innovent Biologics Inc. (HKEX:1801), Suzhou, China
Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
National Medical Products Administration, Beijing, China
Novimmune S.A., Plan-les-Ouates, Switzerland
OSE Immunotherapeutics S.A. (Euronext:OSE), Nantes, France
Stanford University, Stanford, Calif.
Surface Oncology Inc. (NASDAQ:SURF), Cambridge, Mass.
TG Therapeutics Inc. (NASDAQ:TGTX), New York, N.Y.
Trillium Therapeutics Inc. (NASDAQ:TRIL; TSX:TRIL), Toronto, Ontario
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

TARGETS

IFNα - Interferon α
IgG1 - Immunoglobulin G1
IgG2 - Immunoglobulin G2
IgG4 - Immunoglobulin G4
HER2 (EGFR2; ErbB2; neu) - Epidermal growth factor receptor 2
PD-1 (PDCD1; CD279) - Programmed cell death 1
SIRPA (CD172a; SHPS-1) - Signal regulatory protein α
SIRPG (CD172g) - Signal regulatory protein γ



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TOOLS & TECHNIQUES

Broadening role for external control arms in clinical trials

BY KAREN TKACH TUZMAN, ASSOCIATE EDITOR

External control arms are moving from theory to practice as drug developers begin to use them to make internal go/no-go decisions for clinical programs and to support regulatory applications. The field is largely split between those drawing on past clinical trials versus real-world data, and at least one company is pushing the approach further by simulating artificial patients to augment control arms in complex, chronic indications like Alzheimer's disease.

Randomizing patients into experimental and control arms is critical to building confidence that the benefits observed in patients treated with a drug are due to the drug itself, and not the patients' baseline characteristics. But the prospect of being assigned to a control group leads many patients to opt out of the clinical trial process all together, and filling control groups in rare and severe diseases is often infeasible or unethical.

External control arms offer a way to reduce the number of study participants treated with placebo or standard of care, decreasing trial size, duration and cost and incentivizing patient participation.

The idea is to replicate traditional randomization using control data from past clinical trials or real-world data (RWD) from electronic health records (EHRs) and other sources. RWD goes beyond natural history data because it can include patients undergoing treatment in real time and provides more detailed information at the level of individual patients.

At a Friends of Cancer Research meeting in November, FDA officials voiced cautious optimism for external control arms, identifying single-arm trials as the setting where the approach has the clearest benefit. The agency has already made a handful of regulatory decisions supported in part by external control data.

Examples include the 2017 approval of PD-L1 inhibitor Bavencio avelumab from Pfizer Inc. and Merck KGaA for Merkel cell carcinoma, where short patient survival times precluded recruitment of a prospective control group. The control arm used data from electronic medical records obtained in community and academic centers.

Another was the April label extension for breast cancer drug Ibrance palbociclib from Pfizer to include men with hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer. The expansion was supported by data from Pfizer's global safety database, IQVIA claims data and EHRs from the Flatiron Health unit of Roche.

Pfizer Chief Development Officer Chris Boshoff said that for external control arms to go mainstream, they will have to build credibility through repeated use in guiding internal go/no-go decisions, like whether to advance a candidate to Phase II.

While some see any departure from prospective randomized control trials (RCTs) as dangerous, there is growing support for the idea that industry should make as much use of available data as possible to at least

augment traditional approaches, particularly in settings that where RCTs are unattainable.

The approach is gaining visibility through company partnerships, pre-competitive workshops and conference presentations, including recent ones by FDA's Project Switch, a program launched last year to study external controls derived from legacy trial data (see "Clinical Trial and Regulatory Efficiency at ASCO19").

The most established strategies populate external control arms using previously collected data, taking care to match the baseline characteristics of the patients in the external dataset to those in the new study using a method known as propensity scoring (see Sidebar: "Random by Design").

Unlearn.AI Inc. is going a step further, using data from historical trials and patient registries to build algorithms that simulate artificial patients. Its simulations have not yet been used to augment control arms in trials.

New simulations

Unlearn.AI simulates patient trajectories in neurodegenerative and inflammatory diseases based on control group data from dozens of trials. The method learns the probability distributions underlying the historical training data, and uses those distributions to generate new data.

CEO Charles Fisher said Unlearn.AI chose to focus on Alzheimer's and inflammatory conditions like rheumatoid arthritis and multiple sclerosis because the complexity of the indications is a good match for its machine learning tools, and because it was able to access sufficient historical data through non-profits like Vivli and Transcelerate Biopharma Inc.

Unlearn.AI's simulations are being used to guide trial design by simulating hypothetic outcomes under different study conditions. In collaboration with an undisclosed pharma, the company has used its model to "ask questions about trial design, size and inclusion criteria" for Alzheimer's, said Fisher.

The company aims to use its simulations to supplement control arms, and is preparing to seek guidance from regulatory agencies on using its platform to run synthetic controls for Alzheimer's trials.

Unlearn.AI also hopes to generate "digital twins" of individual patients in experimental arms. "We can ask, what would have happened to this person if they had received the placebo," said Fisher.

For input data, the company sticks to commonly collected clinical and demographic parameters such as neurological exam scores, APOE mutation status and background medication, but is keeping an eye on newer molecular biomarkers of disease. "We definitely are interested in including those as they become more popular, but we have to see which ones end up becoming adopted," Fisher said.

The two-year old company has raised a $4.2 million seed round from DCVC Bio, Data Collective, Mubadala Ventures and angel investors.

Random by design

The first step in populating an external control arm is finding patients who meet the inclusion/exclusion criteria of the new study. But that alone is not enough to ensure the balance in patient characteristics one would expect from an RCT, said Ruthanna Davi, VP of data science in the Acorn AI unit of Medidata Solutions Inc.

"They still vary in parameters like age and ECOG score," she said. "We have to go farther, and match on those kinds of prognostic factors."

Companies developing external control arms use a statistical method known as propensity scoring to match the baseline characteristics of historical patients to those in the present study. Propensity scores estimate the likelihood that a patient would be enrolled a given trial.

Medidata uses algorithms to repeatedly sample patients from its criteria-matched historical control studies until it gets a distribution of propensity scores that closely resembles those in the new study's experimental group. The analysis is blinded to the patients' outcomes.

In contrast, Concerto HealthAI employs experienced oncology nurses to randomize patients from its RWD platform into control groups based on their case reports, just as if they were randomizing prospectively recruited patients. The company then uses propensity scores to check the experimental and control groups are balanced.

Researchers are evaluating their methodologies by comparing the survival curves and hazard ratios of prospectively recruited control groups from past clinical studies to those of matched external control arms.

A Friends of Cancer Research working group including Davi co-authored a white paper that performed this type of analysis for a non-small cell lung cancer (NSCLC) case study, and found good concordance between the results generated by its external control arm versus the original control group. The study, also presented at this year's American Society of Clinical Oncology (ASCO) meeting, was co-authored by researchers from FDA, Bristol-Myers Squibb Co., Daiichi Sankyo Co. Ltd. , the LUNGevity Foundation, Johns Hopkins University and Fred Hutchinson Cancer Research Center.

FDA's Project Switch presented two similar studies at ASCO: one in NSCLC, where the all four test cases were concordant, and one in multiple myeloma, where only two out of four were. Unlike in the FOCR-backed study, however, the Project Switch studies swapped in external control groups from other clinical trials wholesale without propensity matching; the FDA authors said future studies could include seeing whether propensity matching improved concordance.

— Karen Tkach Tuzman

Unlearn.AI also brings in revenue by offering data standardization as a service, and uses that data to further train its models.

Trials redux

External control arms based on control data from previous trials have the advantage of providing high quality, directly measured endpoint and covariate data from extensively monitored global sites, said Ruthanna Davi, VP of data science in Medidata Solutions Inc.'s Acorn AI unit. "These trials are designed to be used for regulatory purposes in the first place."

These types of external controls are best suited for well-studied diseases where the standard of care has remained constant over time and outcomes are predictable, said Antoine Yver, EVP and Global Head of Oncology R&D at Daiichi Sankyo Co. Ltd.

An example is small cell lung cancer (SCLC), the focus of Project Data Sphere LLC's external control arms program. Following a 2018 symposium with FDA, the oncology-focused non-profit put out calls to pharmas for SCLC control data; it has received six data sets so far from Amgen Inc., Bayer AG, Eli Lilly & Co. and the Alliance for Clinical Trials in Oncology, and is due to receive another four by the end of the year.

Project Data Sphere is starting to make this external control data available to trial sponsors through its data sharing platform.

Program Manager Dave Handelsman said a team led by Dana-Farber Cancer Institute researchers has been standardizing the data, which is due to be published this fall. Project Data Sphere plans to discuss the data with FDA, and Handelsman hopes the conversations will provide greater clarity on how FDA thinks companies should deploy external control arms.

Medidata, which has stored and analyzed data from more than 17,000 clinical trials over the last 20 years, provides drug developers with external control data from previous trials in a range of indications.

The company offers its external control arms as a guide for internal go/no-go decisions, and believes they could eventually play a role in regulatory submissions.

Co-founder and president Glen de Vries told BioCentury the company is investing in methods to standardize data across trials at scale, including machine-learning based approaches.

However, Yver cautioned that submitting past clinical trial data for FDA review as an external control arm to a new study is not as straightforward as it sounds.

FDA requires sponsors to submit patient-level data, but sponsors only have permission to share this past trial data with FDA in aggregate because patients did not consent to having their data used outside of the original study.

"WE CAN ASK, WHAT WOULD HAVE HAPPENED TO THIS PERSON IF THEY HAD RECEIVED THE PLACEBO."

CHARLES FISHER, UNLEARN.AI

"It seems very trivial, but it's actually very real," he said, adding that work to de-identify control data and make it available for FDA analyses is ongoing.

Keeping it real

In cases where there is limited clinical trial experience with a disease or disease subtype, RWD may be a more fruitful source for external controls.

"So many studies are aimed at rare mutations that may not even have been tested for before the last two years. So all my clinical trial data from more than two years ago is irrelevant," said Edward Stepanski, SVP and COO of Concerto HealthAI. He said RWD also better captures the baseline characteristics of patients treated in community practices, which can be substantially different from those of patients in clinical trials.

The concern is that variability in data quality and in reporting of endpoints and covariates could confound analyses.

CEO Jeff Elton said Concerto HealthAI focuses on mining unstructured oncology data from EHRs, including physicians' notes and genetic data, which he said is key to achieving the same rigor as RCTs. "Most datasets that most people use are composed of the structured fields alone."

The company has undisclosed projects underway using external control arms to support regulatory submission. In March and April, Concerto HealthAI announced deals with Bristol-Myers Squibb Co. and Pfizer

Inc., respectively, to conduct external control arm and prospective real-world outcomes studies in cancer.

Flatiron Health has already used RWD-based external controls to support regulatory submissions. Its platform combines curated oncology EHR data with tumor mutation profiling data from Roche's Foundation Medicine unit.

In addition to supporting FDA's label extension for Ibrance, standard-of-care data from Flatiron's platform helped parent company Roche gain speedier European market access from health technology assessment authorities for its cancer drug Alecensa alectinib in ALK-positive advanced non-small cell lung cancer (NSCLC) in patients who failed or were intolerant to crizotinib.

In 2017, Alecensa gained conditional approval in the indication in Europe based on Phase II data from 225 patients treated with the drug and RWD from 77 patients treated with ceritinib.

Roche acquired Flatiron in 2018 for $1.9 billion (see "Accelerating Flatiron").

Flatiron was not available to comment in time for publication.

monARC Bionetworks is building RWD-based external control arms for rare diseases like idiopathic pulmonary fibrosis by reaching out to patients directly. The company builds disease-specific patient research networks via advocacy groups, health systems and social media.

"We provide them tools to aggregate all of their health records" and track their symptoms, said CEO and founder Komathi Stem. "They also want to participate in research. Either they want to be matched to a potential trial, or they just want to share their data."

She said monARC's longitudinal database can incorporate data from any marketed test, and in the future could include inputs from wearables like sleep monitors. The company can also leverage its direct patient interactions to do prospective studies, such as surveys on patient-reported outcomes (PROs), said Stem.

monARC has not announced external control arm partnerships with drug developers.

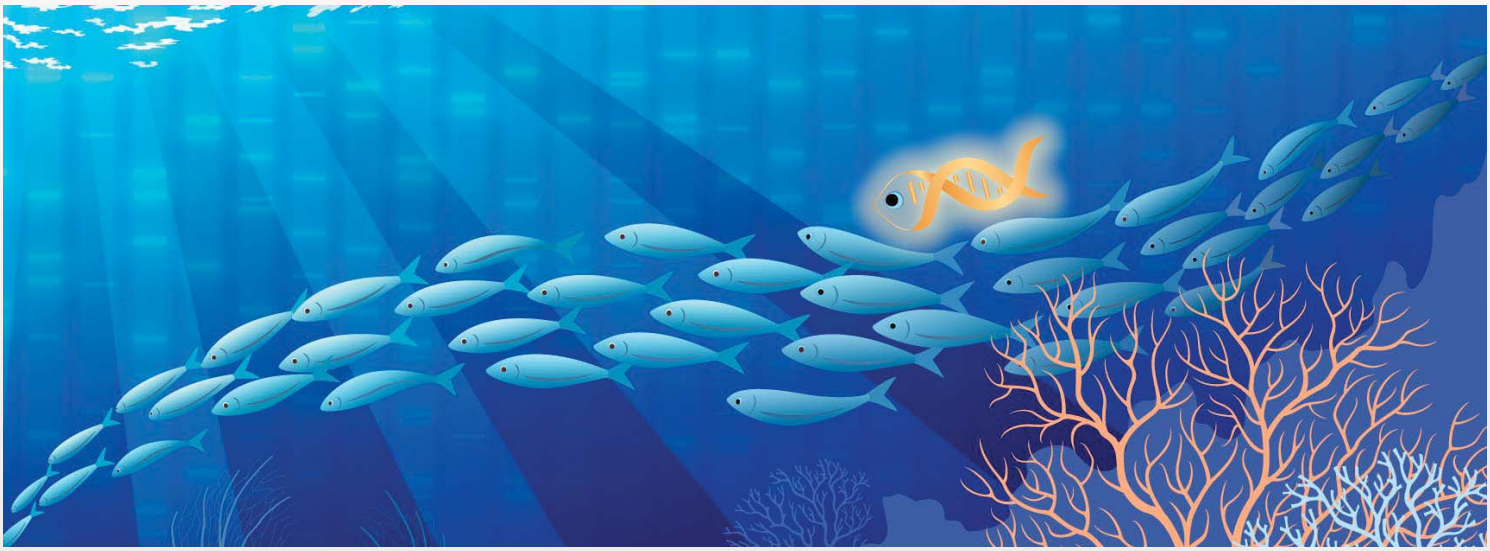
Yver thinks RWD-based external controls will be important for settings where patients frequently cross over from the control group into a new line of treatment, because patients in real-world settings are less likely to confound the study by switching away from standard-of-care than patients in clinical trials. bc

COMPANIES AND INSTITUTIONS MENTIONED

Alliance for Clinical Trials in Oncology, Boston, Mass.
American Society of Clinical Oncology, Alexandria, Va.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Bayer AG (Xetra:BAYN), Leverkusen, Germany
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Concerto HealthAI, Boston, Mass.
Daiichi Sankyo Co. Ltd. (Tokyo:4568), Tokyo, Japan
Dana-Farber Cancer Institute, Boston, Mass.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Friends of Cancer Research, Washington, D.C.
IQVia Holdings Inc. (NYSE:IQV), Durham, N.C.
Medidata Solutions Inc. (NASDAQ:MDSO), New York, N.Y.
Merck KGaA (Xetra:MRK), Darmstadt, Germany
monARC Bionetworks, Redwood City, Calif.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Project Data Sphere LLC, Cary, N.C.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
TransCelerate BioPharma Inc., Conshohocken, Pa.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.
Unlearn.AI Inc., San Francisco, Calif.
Vivli, Cambridge, Mass.

TARGETS

APOE4 - Apolipoprotein E epsilon 4



BIOCENTURY & GETTY IMAGES

PRODUCT DEVELOPMENT

Why tissue-agnostic drug development needs NGS to go mainstream

BY ERIN MCCALLISTER, SENIOR EDITOR

Next-generation sequencing is emerging as the rate-limiting factor for how fast and broadly tissue-agnostic drug development will take off in drug development. By engaging community oncologists, some companies hope to spread the word and enable more patients access to trials earlier in their disease.

This month saw the third agent approved based on its molecular target rather than the cancer's tissue of origin, when Japan's Ministry of Health, Labor & Welfare granted approval to Roche's Rozlytrek entrecitinib to treat NTRK-positive cancer.

Rozlytrek joins Bayer AG's Vitrakvi larotrectinib, also approved for NTRK-positive cancers, and Merck & Co.'s Keytruda pembrolizumab, which was approved in May 2017 to treat MSI-H or mismatch repair deficient tumors.

"This has become a more viable approach to drug development now that we have this regulatory precedence," said Kate Haviland, COO at Blueprint Medicines Inc.

But better efficiency in finding the right mutations to target, and the patients who carry them, is critical for wider adoption. There is still a patchwork integration of NGS in practice. How companies access and deploy the technology will shape the way tissue-agnostic drug development takes hold in cancer care.

"It's one thing to test 100 patients to identify one who might benefit, but if you can test 10 or 15 patients and identify different mutations, then it becomes critically important," said Alan Sandler, SVP, global head of product development oncology at the Genentech Inc. unit of Roche.

Some early adopters have taken advantage of the tumors where NGS is commonly used -- "anchor indications" -- and found driver mutations that are targeted by a marketed drug. That drug can then be tested in tissue-agnostic settings on patients with other tumors harboring the same mutation.

Others have used NGS data from patients who have exhausted all options, where oncologists may be trying to enroll them in a clinical trial or exploring off-label opportunities. Mutations that match compounds in development can guide companies towards trials for a tissue-agnostic indication.

The larger but harder opportunity lies in designing programs from the get-go for tissue-agnostic drug development, which means finding mutations that will serve as drivers across multiple cancer types. The challenge is in obtaining enough patient data to catch the rare mutations, and finding the mutations early enough to enroll the patients in trials or treat them once these agents are on the market.

Companies are turning to community settings to integrate NGS more routinely in clinical practice, which requires introducing more oncologists to the importance of tumor profiling early in the treatment paradigm. This could reduce the disconnect between test availability and access to trials and also improve uptake after the drugs are approved.

"Trials are concentrated at high volume centers but most patients are being treated in the community. They don't have access to the testing or the trial and this leads to a breakdown in clinical development," said Scott Tomlins, CMO and lab director at Strata Oncology Inc.

Anchors first

Blueprint chose to develop its RET inhibitor BLU-667 first in lung and thryoid cancers because NGS is more commonly used in those indications. It plans to follow this with a tissue-agnostic approach for other solid tumors that harbor a RET mutation.

The mutation is present in about 1-2% of NSCLC tumor types and is expected to have roughly the same prevalence across other solid tumors. In thyroid cancer, however, the prevalence of RET mutations is about 90%.

"Given that lung cancer is already so widely tested, and even thyroid patients tend to be well identified, there are footholds in these indications that allow us to move quickly," said Haviland.

The strategy should allow Blueprint to move its asset faster to registration while it gets patients enrolled in the tissue-agnostic cohort, she said.

Blueprint is allowing the centers to use their own methods to identify RET-positive patients for the tissue-agnostic cohort in its Phase II trial of BLU-676.

Therapies targeting several mutations are now available for treating NSCLC, a factor Sandler says is behind the "very high" level of NGS testing in the disease.

Use of NGS to find mutations and guide treatment decisions may eventually replace the need for individual companion diagnostics. That efficiency has been the major selling point for Roche with its Foundation One pan-companion diagnostic, obtained through the acquisition of Foundation Medicine Inc.

For example, with a finite quantity of biopsied tissue, the test can assess the presence of driver mutations addressed by marketed treatments for NSCLC.

Roche is using its internal businesses, including Foundation Medicine and Flatiron Health, to improve uptake of NGS, and identify cancer mutations and subsequent therapies that could follow a tissue-agnostic approach.

Last line opportunity

Boehringer Ingelheim GmbH discovered that its marketed tyrosine kinase inhibitor Gilotrif afatinib might be effective in patients with an NRG1 fusion mutation based on outcomes reported for patients who received the drug under compassionate use, whose tumors had been analyzed by NGS.

Gilotrif binds the kinase domains of EGFR, HER2 and EGFR4 and is marketed to treat NSCLC.

According to Victoria Zazulina, corporate VP, global head of oncology at Boehringer, the evidence started to emerge over the past two years via case report forms from compassionate use. "These patients had no other options," Zazulina said, but those who harbored NRG1 gene fusions were having positive responses to the drug.

The fusion occurs in less than 1% of cancers, making it difficult to detect without testing a large number of patients.

> **"THIS HAS BECOME A MORE VIABLE APPROACH TO DRUG DEVELOPMENT NOW WE HAVE THIS REGULATORY PRECEDENCE."**
>
> KATE HAVILAND, BLUEPRINT MEDICINES

Zazulina said that without access to NGS, it's unlikely the identification would have been made.

Boehringer is now working with the American Society of Clinical Oncology (ASCO) to enroll patients in the group's Targeted Agent and Profiling Utilization Registry (TAPUR) study.

TAPUR is enrolling patients with advanced solid tumors, B cell non-Hodgkin's lymphoma or multiple myeloma for whom there are no standard treatment options. Physicians will choose the appropriate therapy based on genomic screening for relevant mutations performed by any CLIA-certified laboratory.

Based on outcomes, Boehringer can decide whether to seek an sNDA, conduct additional studies or take other steps with the molecule.

Zazulina said the pharma decided to make use of the TAPUR platform because it's an established trial with protocols in place to identify and test these patients.

"ASCO has helped establish that, and that is what is needed to be able to identify these rare types of tumors," she told BioCentury.

TAPUR doesn't specify which NGS platform PIs must use. "We allow the sites to use whatever test is available," said Richard Schilsky, CMO of ASCO.

Bayer and partner Loxo Oncology Inc. used the same strategy in the development of Vitrakvi where they used site-selected NGS tools to screen patients for NTRK-fusion status.

Rather than wait for the companies to develop a validated companion diagnostic, FDA granted Vitrakvi accelerated approval in November with the development of a test as part of the post-marketing commitments.

Loxo was acquired by Eli Lilly and Co. in February.

Broadening NGS integration

Companies such as Strata Oncology Inc., Tempus Labs Inc. and others are starting to reach out to community cancer centers to embed NGS earlier in the treatment paradigm, and to work with companies to quickly identify patients for clinical trials.

Strata partners with healthcare systems and companies to pair NGS testing with clinical trial recruitment.

"It's a real barrier to order the test, read the test and then only find out that they're not a candidate or they are a candidate for a trial but they have to fly halfway across the country," said Scott Tomlins, CMO, lab director at Strata.

"We partner with healthcare systems and bring them a portfolio of biopharma-sponsored trials, in particular those looking for specific molecular subgroups of patients," he added.

There is no cost to the patient for the testing and, because NGS is often used in later-stage patients where there may be limited biopsied tissue remaining, Strata has developed an NGS test that can find molecular markers with very little material.

"What we've found is that about half of the samples we receive are smaller than the minimum tissue requirements for comprehensive tests recommended in NCCN guidelines, which sets up a problem of where they often don't have sufficient tissue, but we've seen more than a 95% success rate in tissue samples as small as 1-2 millimeters," Tomlins said.

"YOU DON'T ORDER A TEST UNLESS YOU'RE GOING TO DO SOMETHING WITH THE RESULTS. IF YOU HAVE A TREATMENT, IT REALLY STARTS TO FUEL TESTING."

ALAN SANDLER, GENENTECH

The National Comprehensive Cancer Network sets therapeutic treatment guidelines that most oncologists follow and payers use to set formularies.

"We are matching the testing to the population that can benefit from this and also have the ability to drive enrollment in clinical trials," he added. Strata has partnerships with 19 healthcare systems.

According to a presentation at a May Friends of Cancer Research meeting, Strata was one of the companies that provided NGS testing to help enroll patients in trials for Vitrakvi.

On June 3, Tempus launched its Tempus Integrated Molecular Evaluation (TIME) trial service. It uses Tempus' platform, which analyzes genetic information and real-time patient clinical data to match patients to clinical trials and academic and community cancer centers (see "Computing Care").

The TIME service includes over 40 provider networks and 1,800 oncologists and expects to be able to match over 70% of patients to a biomarker-driven trial, including tissue-agnostic studies.

Roche is deploying its access to real-world evidence via its Flatiron Health unit and molecular tumor characterization from its Foundation Medicine unit to improve uptake of NGS in the community and find new molecular markers that could drive future tissue-agnostic approaches.

"We are uniquely positioned with our real-world evidence platform that gives us prevalence information and the molecular genetics information from Foundation One to identify opportunities and new targets," for a tissue-agnostic approach, Sandler told BioCentury.

Roche's NTRK inhibitor Rozyltrek is under review in the U.S. with an Aug. 18 PDUFA date. In the meantime, it's working with its Foundation Medicine unit to develop a companion diagnostic for Rozyltrek.

Sandler believes that one reason physicians don't readily perform NGS after diagnosis is because in many cancer types outside of NSCLC, there aren't as many drugs available to treat specific molecular subgroups. "The other key element is not just the test but having an effective therapy where if you merge the two, and build it, they will come, and it will be beyond just academic evaluations," Sandler told BioCentury.

"You don't order a test unless you're going to do something with the results. If you have a treatment, it really starts to fuel testing," Sandler said.

Bayer's Scott Fields agreed, and thinks that the availability of drugs like Vitrakvi will improve the integration of NGS into clinical practice. "We already know in lung cancer that there is rationale to do this kind of testing, but not every tumor type has this rationale. Now that you have drugs that are quite active in specific molecularly-defined populations, I think people are going to have to really think about the consequence of not testing," Fields said.

Fields is SVP, head of pharmaceutical development for oncology at Bayer.

Blueprint is also addressing the issue of access to NGS. Haviland said that as the company gets closer to market with BLU-676, it will increase its educational outreach to oncologists to make sure they are aware of RET alterations and are proficient in reading tumor profiling reports.

"We need diagnostics that are interpretable, accessible and actionable. We are focused on 'actionable' right now, but as we look to file our NDA and build our commercial team, we will be addressing the interpretability and accessibility issue," Haviland said. bc

COMPANIES AND INSTITUTIONS MENTIONED

American Society of Clinical Oncology (ASCO), Alexandria, Va.
Bayer AG (Xetra:BAYN), Leverkusen Germany
Blueprint Medicines Corp. (NASDAQ:BPMC), Cambridge, Mass.
Boehringer Ingelheim GmbH, Ingelheim, Germany
Friends of Cancer Research, Washington, D.C.
Genentech Inc., South San Francisco, Calif.
National Comprehensive Cancer Network (NCCN), Plymouth Meeting, Pa.
Roche (SIX:ROG; OTCQB:RHHBY), Basel, Switzerland
Strata Oncology Inc. Ann Arbor, Mich.
Tempus Labs Inc., Chicago, Ill.

TARGETS

EGFR (ErbB1; HER1) - Epidermal growth factor receptor
EGFR4 (HER4; ErbB4)- Epidermal growth factor receptor 4
HER2 (EGFR2) - Epidermal growth factor receptor 2
NRG1 (HRG1)- Neuregulin 1
NTRK - Neurotrophic tyrosine kinase receptor
RET - Ret-proto-oncogene

BIOCENTURY & GETTY IMAGES

PRODUCT DEVELOPMENT

ASCO 2019 sessions provide guidance on expanding patient pools for clinical trials

BY ALLISON JOHNSON, STAFF WRITER

Two sessions at this year's American Society of Clinical Oncology meeting gave drug developers a glimpse of how to match more patients to clinical trials by broadening eligibility criteria and encouraging trial enrollment in community settings.

Both measures could increase patient enrollment, especially in rare indications or those where enrollment at academic centers is competitive, and they could increase access to patients who better reflect the diversity in the real world.

According to ASCO presenters and panelists, more than 80% of patients live near a community hospital or practice, but only about 3-5% of them enroll in a clinical trial compared with 7-10% of patients living near an academic hospital.

"Community is a very, very viable option. Pharmas should not necessarily go back to the same well over and over again hoping that the patients show up," Carla Balch, CEO of Inteliquet Biopharma, told BioCentury. Inteliquet, which uses real-world data to find and match patients with clinical trials, presented at a separate ASCO session.

"Sponsors need to choose sites based on the data -- where are the patients? We know where the patients are," said Balch.

Balch was previously CEO of Altos Solutions, which Flatiron Health acquired in 2014 for its oncology-specific medical record system, OncoEMR.

While the panelists at the two sessions were largely from community hospitals and ASCO working groups, pharmas have started demonstrating movement on these topics in the last year, through partnerships with community hospital networks and digital health companies designing site-less trials.

FDA is on board with both ideas and has taken steps to support broadening of inclusion criteria and research in community clinics.

In a March statement, former FDA Commissioner Scott Gottlieb said, "Some eligibility criteria have become commonly accepted over time or used as a template across trials without a clear scientific or clinical rationale or justification. In other cases, eligibility criteria can be deliberately restrictive, even though it is not clinically merited."

FDA published five guidance documents in March and another on June 6 to expand eligibility criteria for trials. Only one of these is final (see "FDA Looks to Broaden Cancer Trial Eligibility").

Also this year, FDA announced a working group to explore decentralized trials, in part to give patients living far from academic research sites the option to participate in clinical trials without the financial and time burden of travel. The group includes members from Amgen Inc., Roche, Roche's Genentech Inc. Unit, Science 37 Inc. and IQVIA Holdings Inc.

Retrospective data at ASCO suggest the broader inclusion criteria outlined by FDA could double the number of potential enrollees.

But to realize the goal of reaching more patients this way, companies will need to decide which enrollment criteria they are willing to budge on and by how much.

And many community hospitals don't have the infrastructure to conduct clinical research, which could lead to delays in trial starts, resulting in patients progressing and become ineligible. Tapping into the community may mean forming partnerships with companies designed to deliver that infrastructure.

Taking a broader view

Retrospective studies presented at ASCO make the case that broadening eligibility criteria, including those in the FDA guidances, could nearly double the number of potential trial participants.

One issue the study ran into, which will likely affect others like it, was that the electronic health records did not hold all the information the researchers wanted about the patients and what they'd been treated with.

For example, the authors had wanted to evaluate the inclusion criteria of "patients with brain metastases that had responded to treatment and/or were stable," but the records did not give information on the treatment or stability of the metastases. Instead, the group had to change its criteria to include all patients with brain metastases.

Inteliquet is solving this problem by collecting and integrating information from several sources including electronic health records, lab information systems, molecular diagnostics, and in some cases, the practice's management systems, registries and biobanks.

"PHARMAS SHOULD NOT NECESSARILY GO BACK TO THE SAME WELL OVER AND OVER AGAIN HOPING THAT THE PATIENTS SHOW UP."

CARLA BALCH, INTELIQUET

A group that included presenter R. Donald Harvey, director of Phase I clinical trial selections and associate professor at the Winship Cancer Institute of Emory University, as well as authors from FDA, ASCO and Concerto HealthAI, applied broadened eligibility criteria to 10,500 non-small cell lung cancer (NSCLC) patients in ASCO's CancerLinQ database.

Using electronic health records in CancerLinQ, the group tabulated the number of patients who were excluded from a trial because they did not meet one of three criteria used in most trials: a previous cancer diagnoses in a different tissue; brain metastases; and creatine clearance ≤ 60 mL/min.

They found that including all patients in the first two categories, and those with creatine clearance ≥ 30 mL/min, would have enabled 5,005 (47.7%) more subjects to be enrolled in a trial.

The company thinks some eligibility criteria should be conditional, rather than a hard yes or no. These include measures like platelet counts that can change on a day-to-day basis, where one day the results make a patient eligible and the next, they don't.

At ASCO, the company presented a retrospective study in which it identified 53 patients that could have been eligible for at least one of 16 trials. Five of those patients were deemed ineligible based on platelet count, but two of them only missed the cutoff by 10%. Balch thinks these patients should be considered for a trial.

Balch said Inteliquet consistently finds that about 40% of patients are deemed ineligible based on a handful of narrowly missed conditional criteria.

Inteliquet analyzes these measures in real-time to match patients to trials, and sends hard and conditional criteria results to physicians. For patients who would be eligible save for a conditional criterion, the

TO REALIZE THE GOAL OF REACHING MORE PATIENTS THIS WAY, COMPANIES WILL NEED TO DECIDE WHICH ENROLLMENT CRITERIA THEY ARE WILLING TO BUDGE ON AND BY HOW MUCH.

physician can work directly with the pharma sponsor or the CRO to decide whether or not to include that patient in the trial, Balch said.

While the decision to include patients who narrowly miss a conditional criterion belongs to the sponsor and is out of Inteliquet's hands, Balch said "we'd like to open the discussion more with pharma to look at the number of patients who were right on the border, but never approached for the trial."

Need for speed and infrastructure

Running clinical trials requires staff, money and laboratories, but often community hospitals do not have dedicated research departments with those resources, which can create delays in trial starts.

For companies looking to enroll trial participants in community hospitals, one option is to partner with groups such as the Clinical Research Alliance (CRA) that are designed to bring trial infrastructure to the community setting.

CRA is an independent consortium of medical oncologists in New York that provides community hospitals in the region with the research and regulatory staffing required to run trials.

In an ASCO presentation on June 2, CRA founder Francis Arena described how the independent consortium of medical oncologists is tackling this problem. "We have said to the individual practices that have joined the Clinical Research Alliance that we will send to you a clinical research nurse to be a part of your staff, though you don't have to pay a nickel for her or him, and we're going to help manage these trials for you," said Arena, who also is a clinical professor in the department of medicine at New York University Medical College, and medical director at NYU Langone Arena Oncology.

According to Arena, CRA's community sites were the first to enroll patients in Phase II and Phase III studies testing BeiGene Ltd.'s selective Btk inhibitor zanubrutinib (BGB-3111) to treat non-Hodgkin lymphoma (NHL).

CRA can open trials in 2-4 weeks, he said.

Tempus Labs Inc. also can help sponsors start trials in about two weeks, according to Senior Director of Operations Amy Franzen.

On June 3, Tempus announced the launch of its Tempus Integrated Molecular Evaluation (TIME) Trial. The program will analyze patient sequencing data, then match the patients to trials in a closed network that comprises community and academic centers.

To achieve speedy enrollment, Tempus is going beyond matching patients to providing resources to needed to get trials going. Franzen said Tempus has designed standardized clinical trial and budget agreements that trial sites and sponsors agree to up front, eliminating a major source of delay. Tempus also uses a centralized IRB review to speed up the process.

Inteliquet offers speed in a different way, by beginning to track patients at first diagnosis and first treatment, then forecasting when those patients will progress on first-line treatment, requiring a second-line therapy. Inteliquet can relay those forecasts to pharma sponsors planning second-line trials, to help sponsors choose the most promising locations for opening trials.

A handful of pharmas have started tapping groups like CRA, Tempus and Inteliquet to reach patients in the community.

Amgen is forging partnerships with groups like U.S. Oncology Research to conduct trials in community practices (see "Following Promising ASCO readout for AMG 510, Amgen Looks to Identify More KRAS-mutant Patients").

And Novartis AG, UCB S.A. and Sanofi have started to adopt technologies enabling site-less trials through partnerships with companies including Science 37 and TrialSpark (see "A Year of Digital Progress at Novartis").

But ASCO presenter Edward Kim, chair of the department of Solid Tumor Oncology at the Levine Cancer Institute, cautioned trials should be matched carefully with community hospitals.

"You have to decide what your program is. You should not be a jack of all trades. You cannot run Phase I, Phase II, Phase III, retrospective studies. You need to assess what your system is capable of and focus there," said Kim.

For example, trials testing targeted agents will make the most sense at community hospitals with a genomics department, he said.bc

COMPANIES AND INSTITUTIONS MENTIONED

American Society of Clinical Oncology, Alexandria, Va.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
BeiGene Ltd. (NASDAQ:BGNE; HKSE:6160), Beijing, China
Clinical Research Alliance, New Hyde Park, N.Y.
Concerto HealthAI, Boston, Mass.
Emory University, Atlanta, Ga.
Inteliquet Biopharma, Memphis, Tenn.
IQVIA Holdings Inc. (NYSE:IQV), Durham, N.C.
Levine Cancer Institute, Charlotte, N.C.
New York University Langone Medical Center, New York, N.Y.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Sanofi (Euronext:SAN; NASDAQ:SNY), Paris, France
Science 37 Inc., Culver City, Calif.
Tempus Labs Inc., Chicago, Ill.
TrialSpark, New York, N.Y.
U.S. Food and Drug Administration, Silver Spring, Md.
UCB S.A. (Euronext:UCB), Brussels, Belgium

TARGETS

Btk - Bruton's tyrosine kinase

FIRSTSIGNAL/ISTOCK/GETTY IMAGES

TARGETS & MECHANISMS

Following PARP, ATR axis next in line to expand synthetic lethal drug class

BY KAREN TKACH TUZMAN, ASSOCIATE EDITOR

Promising ASCO readouts suggest targets in the ATR pathway are lining up behind PARP as the next drivers of "synthetic lethal" cancer killing.

Biomarker and combination strategies presented at the American Society of Clinical Oncology meeting indicate the thinking may need to go beyond simple two-way synthetic lethal interactions like PARP-BRCA, which involve one inhibitor plus one mutation.

ASCO data on the ATR pathway gave fuel to an emerging idea that synthetic lethality combinations can also be created via a drug plus another drug, or even triple combinations of drugs plus mutations.

Once the first PARP inhibitor showed proof of concept, the question became what other pairings could yield new cancer drugs. The four approved PARP inhibitors are marketed to breast and/or ovarian cancer, and are being tested in a growing number of indications, most recently metastatic pancreatic cancer (see "Broadening the PARP Playing Field"; "Lynparza shows PFS benefit of 3.6 months in pancreatic cancer").

The principle of synthetic lethality is that while cancer cells can tolerate or even benefit from losing one regulator of DNA damage repair (DDR), such as BRCA1, simultaneous inhibition of a second DDR protein, such as PARP, causes overwhelming genetic damage that triggers cell death.

Scores of preclinical studies have characterized synthetic lethal DDR interactions beyond PARP and BRCA, including the replication stress sensor ATR and its downstream targets Chk1 and WEE1 (see "Meeting the Burden").

At ASCO, Bayer AG presented data from a first-in-human Phase I trial of its ATR inhibitor BAY-1895344, in which all responders in the dose-escalation cohort were retrospectively shown to lack function of the kinase ATM. The findings support a long-standing hypothesis from preclinical studies that ATM acts as ATR's synthetic lethal partner. These patients survived for a year or more.

Other companies developing ATR inhibitors are encouraged by the results, which could be leveraged for a biomarker strategy in patient recruitment. "We see an opportunity for ATR to be linked directly to patient populations," said Michael Zinda, CSO of Repare Therapeutics Inc., a preclinical-stage synthetic lethality company founded by Versant Ventures in 2016.

Presentations on compounds from KGaA, Sierra Oncology Inc. and AstraZeneca plc provided evidence for using different combinations of mutations and pharmacological compounds to induce synthetic lethality via the ATR pathway.

Andree Blaukat, head of translational innovation platform oncology at Merck KGaA, thinks finding reliable synthetic lethal interactions for ATR pathway inhibitors will require biomarker and combination strategies more complex than the classical one mutation, one inhibitor paradigm. "I believe the synthetic lethality in this case is much more context dependent."

Sierra CSO Christian Hassig agreed, noting that even for PARP inhibitors, the presence of a BRCA mutation doesn't guarantee a patient will respond, because other mutations and non-genetic alterations can also play a role.

"The field has been a little misguided in thinking there was going to be an easy, repetitive synthetic lethal story," he said. "There are other factors at play, and it requires time to deconvolute that and identify the optimal areas to deploy these agents."

Fatal ATRaction

The ATR pathway's primary role is to preserve genomic integrity in cells undergoing stress during replication by delaying mitosis until the stress is relieved, preventing the accumulation of further DNA damage.

Upon detecting DNA damage and replication stress, ATR transmits signals through Chk1 and WEE1, leading to cell cycle arrest. ATM performs a similar function through Chk2, but largely detects double-stranded breaks, whereas ATR can respond to a wider set of DNA lesions (see Figure: "Taking a break").

Taking a break

Clinical data from ASCO support the pairing of targets in the ATR and ATM pathways for inducing synthetic lethality. In response to DNA damage and replication stress, the ATR and ATM pathways transmit signals to arrest the cell cycle, avoiding replication catastrophe and cell death.

At least 10 companies have active programs targeting ATR or ATM pathway proteins for cancer.

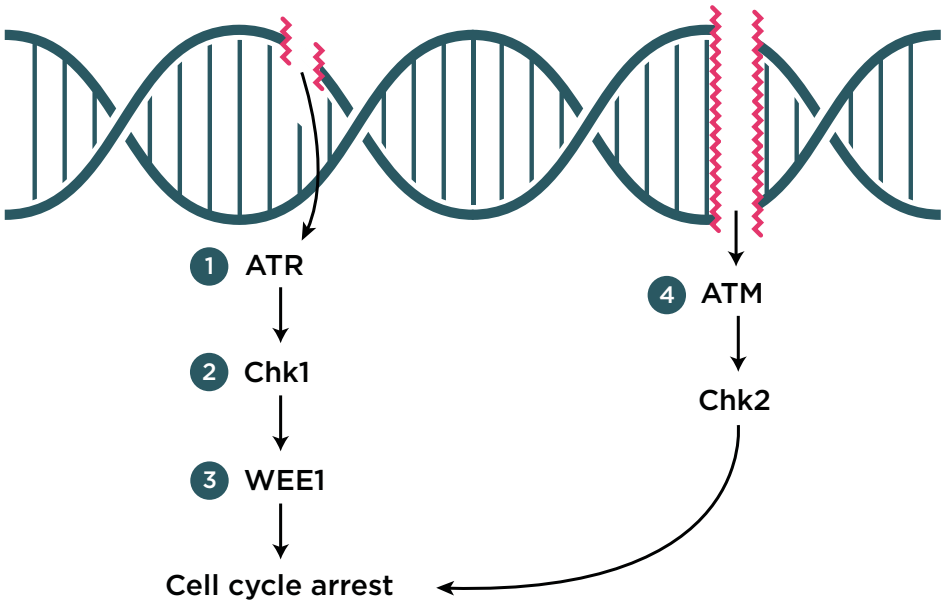
1. **ATR inhibitors. Merck KGaA** (Xetra:MRK) has M6620 in Phase II testing for ovarian cancer, bladder cancer and other solid tumors, and M4344 in Phase I testing for solid tumors. **AstraZeneca plc** (LSE:AZN; NYSE:AZN) has AZD6738 in Phase II testing for gastric cancer and in Phase I testing for head and neck cancer and other solid tumors. **Bayer AG** (Xetra:BAYN) has BAY1895344 in Phase I testing for solid tumors and lymphoma, and in preclinical testing for prostate cancer. **Atrin Pharmaceuticals LLC**'s ATRN-119 and ATRN-212 are in preclinical testing.

2. **Chk1 inhibitors. Sierra Oncology Inc.** (NASDAQ:SRRA) has SRA737 in Phase I/II testing for colorectal cancer, head and neck cancer, non-Hodgkin lymphoma (NHL), non-small cell lung cancer (NSCLC), ovarian cancer, prostate cancer and other solid tumors. In preclinical development are CASC-578 from **Seattle Genetics Inc.** (NASDAQ:SGEN), VER250840 from **Cumulus Oncology Ltd.**, and V158411 from the Vernalis Research unit of **Ligand Pharmaceuticals Inc.** (NASDAQ:LGND).

3. **WEE1 inhibitors.** AstraZeneca's AZD1775 is in Phase II testing for ovarian cancer and other solid tumors, and **Debiopharm Group**'s Debio 0123 is in preclinical testing.

4. **ATM inhibitors.** AstraZeneca has AZD1390 in Phase I testing for brain cancer. Merck KGaA has M-3541 and **Shuttle Pharmaceuticals Inc.** has a bi-functional HDAC inhibitor and ATM activator in preclinical testing.

ATM - Ataxia telangiectasia mutated; ATR (FRP1) - Ataxia telangiectasia and Rad3 related; Chk1 (CHEK1) - Checkpoint kinase 1; Chk2 (CHEK2) - Checkpoint kinase 2; WEE1 - WEE1 tyrosine kinase



Inhibitors of these DDR regulators can drive genomically unstable cancer cells into a "replication catastrophe" that triggers cell death. The key will be finding the right conditions, either in tumor molecular profiles or via pharmacological combinations, to tip the balance without unacceptable toxicity to normal cells.

Bayer's presentation at ASCO puts ATM aberrations "at the top of the list" of settings in which ATR inhibitors could succeed, said Oren Gilad, CEO of Atrin Pharmaceuticals LLC. Atrin has three ATR inhibitors in preclinical development, which it plans to take into the clinic later this year or early in 2020.

Scott Fields, SVP and head of pharmaceutical development oncology at Bayer, said the BAY-1895344 dose-escalation study was enriched for patients with DDR mutations, but the association between therapeutic response and ATM mutation or silencing was found retrospectively.

The pharma has launched an expansion phase of its Phase I study that includes five patient cohorts: four defined by tumor tissue of origin, and the fifth defined by ATM status. Because the early data show therapeutic effects in a range of cancers including breast, appendix and endometrial tumors, Fields thinks ATM aberrations have the potential to become tissue-agnostic companion biomarkers for ATR inhibitors.

Seven out of 11 patients with ATM aberrations did not respond to the compound, indicating the synthetic lethal effect varies across different types of ATM aberrations and genetic backgrounds. Fields said the company plans to examine differences between responders and non-responders with ATM aberrations in retrospective molecular profiling studies.

Blaukat thinks ATM function will be less predictive of ATR inhibitor response than BRCA mutations have been for PARP drugs, and that other tumor mutations will substantially influence sensitivity. "ATM loss of function is a great first step to develop ATR inhibitors, but it may be more complex," he said.

Merck KGaA is identifying synthetic lethal interactions for its DDR inhibitors via CRISPR-based screens with academic partners and molecularly profiled patient-derived xenograft models. The company is investigating two ATR inhibitors, an ATM inhibitor and a DNA-PK inhibitor.

These experiments supported the company's decision to pursue DDR drug combinations as an alternative to looking for drug-mutation pairings. "I believe it's possible to combine DDR inhibitors in order to create synthetic lethality pharmacologically," Blaukat said.

At ASCO, Merck KGaA presented data on the combination of its ATR inhibitor M6620, Abbvie Inc.'s Phase III-stage PARP inhibitor veliparib and cisplatin, showing two partial responses and 22 cases of stable disease out of 34 evaluable patients with advanced solid tumors, most of whom had previously undergone platinum chemotherapy. Stable disease was maintained for up to 11 21-day cycles, with a median of four cycles.

M6620 is in Phase II testing for bladder cancer and ovarian cancer.

Atrin is also investigating the combination of ATR and PARP inhibitors in preclinical models. Gilad thinks it may be necessary to triangulate DDR combinations with tumor profiling to activate synthetic lethal interactions involving more than two targets.

"The field is going toward pairing combinations of two, or maybe more, drugs to a tumor type based on the genetic makeup of that tumor," he said.

"WE SEE AN OPPORTUNITY FOR ATR TO BE LINKED DIRECTLY TO PATIENT POPULATIONS."

MICHAEL ZINDA, REPARE THERAPEUTICS

Pathway progress

In some hard-to-treat cancers, companies are exploiting chemotherapies that induce DNA damage as partners for targets in the ATR pathway.

Sierra presented two Phase I/II studies of its Chk1 inhibitor SRA737 in advanced solid tumors: a first-in-human dose-escalation study of the compound on its own, and a trial of its effects in combination with low doses of the DNA synthesis inhibitor gemcitabine.

Both studies were conducted in patients whose cancers had mutations in tumor suppressor genes, oncogenic drivers or DDR proteins. "Our aim for the study was to identify, either by indications or genetics, patient subgroups that were particularly sensitive to Chk1 inhibition," said Chief Development Officer Barbara Clencke.

Sierra reported higher disease control rates in patients whose tumors had mutations in PI3K pathway genes, or in a gene network known as the Fanconi anemia/BRCA pathway, which includes ATR, CDK12 and FANCA. Mutations in the latter pathway were enriched in anogenital cancers, in which three out of 10 patients had partial responses.

The most common adverse events for Sierra's SRA737 were gastrointestinal. Gilad credited the sub-therapeutic dose of gemcitabine and compound's selectivity for Chk1. "It's a much cleaner molecule," he said. In contrast, the top adverse events for other ATR axis inhibitors at ASCO were hematological toxicities.

Sierra has designed a Phase II study of Chk1 plus low dose gemcitabine in second line metastatic HPV+ anogenital squamous cell carcinomas, and plans to investigate genetic markers of response in this population. Hassig thinks stratifying patients based on genetic factors alone could exclude patients whose synthetic lethal interactions occur on the basis of histone methylation or other non-genetic changes.

Two presentations at ASCO suggested AstraZeneca's WEE1 inhibitor AZD1775 could make a difference in platinum-resistant ovarian cancers when combined with chemotherapies.

In a Phase II placebo-controlled study, AZD1775 plus gemcitabine increased progression-free survival (PFS) from 3 to 4.6 months and overall survival (OS) from 7.2 to 11.5 months compared with gemcitabine alone. Another Phase II trial evaluated different regimens of AZD1775 plus chemotherapy, among which combination with carboplatin was most potent, resulting in a mean PFS of 10.1 months.

Both studies showed the combos induced high frequencies of hematological toxicity, but these could be tamped down with prophylactic GM-CSF treatment, said Susan Galbraith, head of oncology in AstraZeneca's IMED Biotech unit, said.

She said the investigators behind the placebo-controlled trial are in the process of analyzing tumor samples for predictive biomarkers of response.

"I BELIEVE IT'S POSSIBLE TO COMBINE DDR INHIBITORS IN ORDER TO CREATE SYNTHETIC LETHALITY PHARMACOLOGICALLY."

ANDREE BLAUKAT, MERCK KGAA

AstraZeneca and Sierra have clinical and preclinical programs, respectively, investigating the combination of their ATR pathway compounds with PARP inhibitors.

COMPANIES AND INSTITUTIONS MENTIONED

AbbVie Inc. (NYSE:ABBV), Chicago, Ill.
American Society of Clinical Oncology, Alexandria, Va.
AstraZeneca plc (LSE:AZN; NYSE:AZN), Cambridge, U.K.
Atrin Pharmaceuticals LLC, Doylestown, Pa.
Bayer AG (Xetra:BAYN), Leverkusen, Germany
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
KGaA (Xetra:MRK), Darmstadt, Germany
Repare Therapeutics Inc., St-Laurent, Quebec
Sierra Oncology Inc. (NASDAQ:SRRA), Vancouver, B.C.

TARGETS

ATR (FRP1) - Ataxia telangiectasia and Rad3 related
ATM - Ataxia telangiectasia mutated
BRCA1 - Breast cancer 1 early onset
Chk1 (CHEK1) - Checkpoint kinase 1
Chk2 (CHEK2) - Checkpoint kinase 2
CDK12 - Cyclin dependent kinase 12
DNA-PK - DNA-dependent protein kinase
FANCA (FA) - Fanconi anemia complementation group A
GM-CSF (CSF2) - Granulocyte macrophage colony-stimulating factor
PARP - Poly(ADP-ribose) polymerase
PI3K - Phosphoinositide 3-kinase
WEE1 - WEE1 tyrosine kinase

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PRODUCT DEVELOPMENT

ASCO 2019 abstracts show solid tumor race heating up among bispecifics and CAR Ts

BY ALLISON JOHNSON, STAFF WRITER

While strong progress in CAR T therapies will again feature at this year's ASCO meeting, bispecific antibodies are having a moment — making more inroads into solid tumors than CAR Ts and branching out via new strategies.

BioCentury's fourth annual survey of abstracts at the American Society of Clinical Oncology (ASCO) meeting presents a snapshot of clinical research in cancer, according to a machine learning-based analysis of 4,627 abstracts for mentions of products, indications, targets, modalities or other hot topic terms.

The 2019 analysis documents 31 novel targets and 22 products in first-in-human trials presented at the meeting, as well as trends in two technologies to improve clinical trials and regulatory decisions (see Table: "ASCO 2019 New Targets" and "Clinical Trial and Regulatory Efficiency Get Help from ctDNA, RWE at ASCO19").

New modalities continue to advance, with nine of the first-in-human products outside of traditional small molecule and antibody modalities (see Table: "ASCO 2019 First-in-Human Abstracts").

Bispecific antibodies threaten to steal the show. Though the total number of abstracts mentioning bispecifics — including one tetraspecific compound — is still less than some other new modalities, the class showed a substantial surge in activity this year over last (see Figure: "ASCO 2019 Modalities").

CAR T cell therapies saw the second biggest increase. The dominance of bispecifics indicates a resurgence of activity for a modality that has been largely eclipsed by CAR Ts, in particular since Novartis AG's Kymriah tisagenlecleucel became the first FDA-approved CAR T in 2017.

THE NEXT STEP FOR BOTH MODALITIES IS ACHIEVING EFFICACY IN SOLID TUMORS, AND THE ASCO ABSTRACTS SUGGEST BISPECIFICS COULD TAKE THE LEAD.

The first bispecific antibody to receive FDA approval was Amgen Inc.'s Blincyto blinatumomab, in 2014, but the modality has been dogged by stability and toxicity issues.

Despite the headstart for bispecifics, both modalities have two products on the market, and all four are approved for liquid tumors.

Last year's American Society of Hematology (ASH) meeting suggested the bispecific dam may finally be breaking, at least in blood cancers (see "Intermittent Move Beyond Blincyto").

ASCO 2019 first-in-human abstracts

The first efficacy data from at least 22 first-in-human trials are being presented at this year's American Society of Clinical Oncology meeting in Chicago. The therapies span 21 targets and seven modalities.

Although the total number of abstracts mentioning ADCs fell this year compared with 2018, the modality appears to be advancing, with companies presenting first-in-human data from four candidates. The list includes HuMax-AXL-ADC from **Genmab A/S** (CSE:GEN;Pink:GMXAY) and **Seattle Genetics Inc.** (NASDAQ:SGEN), and ABBV-085 from **AbbVie Inc.** (NYSE:ABBV). Both therapies are in development for sarcoma, among other solid tumor types. According to BioCentury's BCIQ database, only one other ADC is in the clinic for sarcoma.

For bispecific antibodies and CAR T cell therapies, solid tumors are the next frontier, and both modalities are represented in first-in-human solid tumor abstracts. These include bispecifics pasotuxizumab from **Amgen Inc.** (NASDAQ:AMGN) and partner **Bayer AG** (Xetra:BAYN), KN046 from **Suzhou Alphamab Co. Ltd.** spinout **Alphamab Oncology Ltd.**, and a mesothelin-targeted CAR T therapy from **Memorial Sloan Kettering Cancer Center**.

Miltenyi Biotec GmbH and collaborators will present first-in-human data from a CAR T to treat non-Hodgkin lymphoma (NHL).

Multiple small molecules on the list are designed to inhibit historically difficult targets. For example, Amgen Inc. will present the first data from AMG 510, an inhibitor that selectively targets the G12C mutant form of KRAS.

And a fresh crop of three pan- or family member-specific BET inhibitors are among the small molecules with first-in-human data. Though BET bromodomain proteins are longstanding targets, no therapies against them are on the market, and the class has had to contend with a lack of biomarkers for predicting who will respond, and non-durable responses from those who do.

Trials were identified by searching abstracts for the terms "first-in-man" and "first-in-human" and comparing resulting abstracts to previously reported data in the BCIQ: BioCentury Online Intelligence database, PubMed and company websites. *Source: ASCO abstracts as of May 15*

Company	Product	Description	Indication	Results in abstract	Abstract
AbbVie Inc. (NYSE:ABBV)	ABBV-085	ADC against leucine-rich repeat containing 15 (LRRC15)	Solid tumors including sarcomas	Safety data in 78 patients; in 27 sarcoma patients 4 confirmed (15%) and 2 unconfirmed (7%) PR; 8 (30%) SD	3004
AbbVie Inc. (NYSE:ABBV)	Mivebresib (ABBV-075)	Pan-inhibitor of BET bromodomain proteins	Acute myelogenous leukemia (AML)	Safety data as monotherapy in 19 patients and 22 in combo with Venclexta venetoclax; median best % bone marrow blast change for 26 evaluable patients was -20% (range, -98% to +300%); median OS 2.6 months	7030
Amgen Inc. (NASDSAQ:AMGN)	AMG 510	Small molecule G12C-mutant K-Ras (KRAS) inhibitor	Sold tumors	Safety data in 22 patients; in 9 evaluable patients 1 PR in NSCLC (11%); 6 SD (67%) median duration 9.7 weeks	3003
Amgen Inc. (NASDAQ:AMGN) / Bayer AG (Xetra:BAYN)	Pasotuxizumab (BAY 2010112)	Bispecific T cell engager (BiTE) antibody against prostate-specific membrane antigen (PSMA)	Castration-resistant prostate cancer (CRPC)	Safety data in 16 patients; dose-dependent PSA decline; 3 patients with PSA declines ≥50%; 1 patient with complete regression of soft tissue metastases and "marked" regression of bone metastases	5034
Apogenix AG / AbbVie Inc. (NYSE:ABBV)	ABBV-621	Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-receptor agonist fusion protein	Solid tumors	Safety data in 57 patients; PR for 20 weeks 1 pancreatic cancer patient; SD in 27 patients (47%), 6 >12 weeks	3013
AstraZeneca (LSE:AZN; NYSE:AZN)	AZD5153	Small molecule inhibitor of bromodomain containing 4 (BRD4)	Solid tumors and lymphoma	Safety data in 28 patients; dose-dependent changes in expression of target genes	3085
Bayer AG (Xetra:BAYN)	BAY 1895344	Oral ataxia telangiectasia and Rad3-related (ATR; FRP1) inhibitor	Solid tumors	Safety data in 18 patients; 31% ORR in 13 patients with and without DNA damage repair defects	3007
Celgene Corp. (NASDAQ:CELG)	CC-90010	Oral BET bromodomain proteins inhibitor	Solid tumors and non-Hodgkin lymphomas (NHL)	Safety data in 69 patients; PR in 1 astrocytoma and 1 endometrial cancer patient (3%); SD in 7 (10%) patients	3015

Company	Product	Description	Indication	Results in abstract	Abstract
Daiichi Sankyo Co. Ltd. (Tokyo:4568)	DS-1001b	Isocitrate dehydrogenase 1 (IDH1) inhibitor	IDH1-mutant gliomas	Safety data in 45 patients; 1 CR (3%), 3 PR (10%) and 10 (34%) SD in 29 contrast-evaluable patients	2004
Daiichi Sankyo Co. Ltd. (Tokyo:4568)	DS-1062a	ADC against tumor-associated calcium signal transducer 2 (TROP2; TACSTD2; EGP-1)	Non-small cell lung cancer (NSCLC)	Safety data in 22 patients; 1 PR (6%) and 8 SD (44%) in 18 evaluable patients	9051
Eisai Co. Ltd. (Tokyo:4523)	MORAb-202	ADC against Folate receptor 1 (FOLR1; FR-alpha; FOLR)	FRα-positive solid tumors	Safety data in 16 patients; 38% ORR including 1 CR in ovarian cancer and 5 PR	5544
Eli Lilly and Co. (NYSE:LLY)	LY3214996	Inhibitor of MAP kinase 1 (MAPK1; ERK-2) and MAPK3	Solid tumors	Safety data in 51 patients; tumor regression in 7 BRAF/non-BRAF mutant patients; 4 SD > 4 months	3001
Genmab A/S (CSE:GEN;Pink:GMXAY) /Seattle Genetics Inc. (NASDAQ:SGEN)	Enapotamab vedotin (HuMax-AXL-ADC)	ADC against AXL receptor tyrosine kinase (AXL; UFO)	Solid tumors	Safety data in 47 patients; PR in 1 patient with NSCLC and 2 patients with ovarian cancer (6%)	2525
Medical College of Wisconsin / University of Wisconsin / Miltenyi Biotec GmbH	CAR-20/19-T	Bispecific anti-CD19, anti-CD20 CAR T cells	NHL	Safety data in 11 patients; 82% ORR at day 28; 6 CR (55%) and 3 PR (27%)	2510
Memorial Sloan Kettering Cancer Center	iCasp9M28z T cell infusions	Mesothelin-targeted CAR T cells	Malignant pleural mesothelioma (MPM), metastatic lung and breast cancers	Safety data in 20 patients; in 14 MPM patients receiving anti-PD-1 therapy, 2 complete metabolic response (14%), 5 PR (36%) and 4 SD (29%)	2511
Merck & Co. Inc. (NYSE:MRK)	MK-4166	Antibody against glucocorticoid-induced tumor necrosis factor receptor (TNFR)-related protein (GITR; TNFRSF18)	Solid tumors in dose-escalation cohort; melanoma expansion cohort	Safety data as monotherapy in 48 patients and in combo with Keytruda pembrolizumab in 65 patients; 9% ORR in dose escalation; 69% ORR in checkpoint-naive melanoma patients	9509
Pellficure Pharmaceuticals Inc.	PCUR-101	Synthetic plumbagin	CRPC	Safety data in 12 patients; PSA declined ≥50% in 1 patient; stopped trial to reformulate to allow higher dosing	e16517
Sierra Oncology Inc. (NASDAQ:SRRA)	SRA737	Checkpoint kinase 1 (Chk1; CHEK1) inhibitor	Solid tumors	Safety data in 55 patients; "clinical activity" in anal, cervical and rectal cancer patients	3095
Alphamab Oncology Ltd. / Suzhou Alphamab Co. Ltd.	KN046	Bispecific antibody against PD-L1 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4; CTLA4; CD152)	Solid tumors	Safety data in 10 patients; CR in 1 NSCLC patient at high dose (33%); SD in 1 triple-negative breast cancer patient and 1 renal cell carcinoma patient at mid-dose (66%)	2554
Taiho Pharmaceutical Co. Ltd.	TAS-119	Aurora kinase A (AURKA; Aurora-A) kinase inhibitor	Solid tumors	Safety data in 74 patients; 38% SD but no CR or PR	3063
University of Michigan	Ad-hCMV-TK + Ad-hCMV-Flt3L	Adenoviral vectors expressing Human herpes simplex type 1 (HSV-1) thymidine kinase UL23 and FMS-like tyrosine kinase 3 ligand (FLT3LG)	Newly diagnosed, resectable glioma	Safety data in 18 patients; increased infiltration of inflammatory cells; "may provide a clinically significant survival"	2019
YooYoung Pharmaceutical Co. Ltd.	YYB101	Anti-hepatocyte growth factor/ scatter factor (HGF/SF) mAb	Solid tumors	Safety data in 39 patients; 1 PR (3%) for 14 months in patient with sebaceous carcinoma; 17 SD (44%)	3104

New targets at ASCO 2019

At least 19 abstracts describe 31 new targets or biomarkers at the 2019 **American Society of Clinical Oncology** meeting. New targets are defined as those not previously reported on by BioCentury or included in its BCIQ database. They were identified using software to search abstracts for key words or phrases indicative of new targets, then manually searching the abstracts for targets not in BCIQ. Among the new targets, a dozen are oncogenic fusion proteins, and another, CCDC6, is a binding partner of RET fusion proteins. (A) When multiple academic institutions were listed on an abstract, only the first is shown; all biopharma companies are shown. *Source: ASCO abstracts as of May 16*

Target	Indication(s)	Description	Presenting Institution (A)	Abstract
B Melanoma Antigen (BAGE)	Colorectal cancer	Expression of cancer-testis gene BAGE decreased 2.4-fold in tumor tissues compared to normal tissues	**Rostov Research Institute of Oncology**	e14233
CD161 (KLRB1)	Prostate cancer	CD161 is expressed on natural killer (NK) cells; C-type lectin domain family 2 member D (CLEC2D) antibodies inhibited CD161-CLEC2D interaction leading to NK cell mediated cytotoxicity in cell lines	**Zumutor Biologics Inc.**	e14222
Coiled-coil domain containing 6 (CCDC6)	Solid tumors	CCDC6 was a RET proto-oncogene (RET) upstream partner in 24.2% of RET fusions	**University of Texas MD Anderson Cancer Center**	3106
Discoidin, CUB and LCCL domain-containing protein 2 (DCBLD2); V-set and immunoglobulin domain containing 10 (VSIG10)	Lung cancer	Whole genome gene expression microarrays showed VSIG10 overexpression in lung adenocarcinoma and large cells, but not other cancer types; DCBLD2 was overexpressed in non-small cell lung cancer (NSCLC) samples, but not small cell lung cancer (SCLC)	**R.G.C.C. International GmbH**	e14656
Capping actin protein of muscle Z-line subunit α 2 (CAPZA2)	Non-small cell lung cancer (NSCLC), gastric adenocarcinoma	Researchers identified 17 MET kinase domain rearrangements (KDRE) with 5′ partner genes from tissue and blood-based circulating tumor DNA samples; CAPZA2 was the most common KDRE	**Beijing Cancer Hospital**	3078
Glutathione S transferase μ 1 (GSTM1)	Anthracycline-induced cardiac dysfunction (ACD) in childhood cancer survivors	GSTM1 is involved in detoxification of anthracyclines; GSTM1 null genotype was associated with an increase in ACD	**University of Alabama at Birmingham**	10030
Histone cluster 2 H2B family member F (HIST2H2BF)	Solid tumors and lymphoma	AZD5153 is a bromodomain containing 4 (BRD4) inhibitor; in a Ph I trial, it caused a dose-dependent change in target genes, including HIST2H2BF	**Sarah Cannon Research Institute**; **AstraZeneca plc** (LSE:AZN; NYSE:AZN)	3085
MIER1 transcriptional regulator (MIER1); microRNA-454-3p (miR-454-3p)	Colorectal cancer (CRC)	MIER1 is downregulated and associated with poor response in CRC patients; miR-454-3p regulated MIER1 and was associated with poor survival in CRC patients	**Fudan University**	e15108
Oral cancer-associated serum protein 1 (OASEP1)	Oral cancers	OASEP1 protein was expressed in 74.4% of patient samples; siRNA targeting OASEP1 significantly suppressed growth of oral cancer cell lines	**University of Tokyo**	e14627
Phosphodiesterase 4D interacting protein (PDE4DIP)	Melanoma	Deleterious events in PDE4DIP, a negative regulator of mammalian target of rapamycin complex 1 (mTORC1), were associated with non-response to checkpoint inhibitors	**Duke University Medical Center**	3086
Pyridoxal phosphatase (PDXP; CIN)	Glioma	PDXP and cofilin-1 (CFL1) expression were positively correlated with elevated phosphoglycerate kinase 1 (PGK1), suggesting it plays a role in resistance to radiotherapy, and PDXP knockout decreased radioresistance	**Nanjing Medical University**	e14631
RAS-like estrogen regulated growth inhibitor (RERG)	Breast cancer	Knockdown of RERG promoted Ras and signal transducer and activator of transcription 3 (STAT3) signaling pathways in cell lines and enhanced mobility of cancer cells, making them intractable to selective estrogen receptor modulators (SERM)	**National Defense Medical Center, Taipei**	e14638

Target	Indication(s)	Description	Presenting Institution (A)	Abstract
Solute carrier family 45 member 3 (SLC45A3)	Prostate cancer	In cell lines, a small molecule modulator of the CH1 domain of E1A binding protein p300 (EP300; p300)/CREB binding protein (CBP) inhibited the p300-dependent androgen receptor (AR) related transcriptional response as demonstrated by downstream response of genes including SLC45A3	**Inthera Bioscience AG**	3015
Transforming growth factor β receptor 3 (TGFBR3)	Ovarian cancer	High expression of TGFβ pathway genes including TGFBR3 is associated with worse survival outcomes	**Cleveland Clinic**	e14262
Zinc fingers and homeoboxes 2 (ZHX2); serine protease 8 (PRSS8)	Colorectal cancer (CRC)	Protein and mRNA levels of ZHX2 were significantly increased in CRC, correlating with poor outcomes and recurrence; ZHX2 may regulate PRSS8	**Jining Medical University**	e15010
ST6 beta-galactoside α-2,6-sialyltransferase 1 (ST6GAL1; CD75s)	B cell lymphoma, multiple myeloma	Tetravalent antibody EBU-141 Tetra bound to ST6GAL1 on mature B cell lymphoma and myeloma plasma cells, increasing antibody-dependent cellular cytotoxicity (ADCC) over conventional chimeric antibody chEBU-141 IgG1	**University of Kiel**	e14004
Fusion proteins				
FGFR1-TACC1 oncogenic fusion protein	Pediatric brain tumors	Targeted exome sequencing identified activation of FGFR pathway with fibroblast growth factor (FGF) receptor 1 (FGFR1; CD331)/transforming acidic coiled-coil containing protein 1 (TACC1) oncogenic fusion protein and activating mutation as a targetable marker of high-risk cancers	**Translational Genomics Research Institute** (TGen)	e21516
PAX7-FOXO1 oncogenic fusion protein	Rhabdomyosarcoma	Paired box gene 7 (PAX7) - Forkhead box O1 (FOXO1) fusion gene is associated with alveolar rhabdomyosarcoma, but fusion status was not associated with differences in outcomes in adults	**Lunenfeld-Tanenbaum Research Institute**	e22525
TPR-TrkA; EML1-TrkB; KANK1-TrkB; EML4-TrkC; ETV6-TrkC; EEF1G-ROS1; GOPC-ROS1; TFG1-ROS1; DCTN1-ALK; KIF5B-ALK oncogenic fusion proteins	Pediatric central nervous system (CNS) tumors	Each gene fusion is a target aberration in neurotrophic tyrosine kinase receptor 1 (TrkA; NTRK1), TrkB, TrkC, c-ros proto-oncogene 1 receptor tyrosine kinase (ROS1) or anaplastic lymphoma kinase (ALK), the targets of entrectinib; in a Ph I trial, the gene fusions were associated with response	**St. Jude Children's Research Hospital**; **Roche** (SIX:ROG; OTCQX:RHHBY)	10009

The next step for both modalities is achieving efficacy in solid tumors, and the ASCO abstracts suggest bispecifics could take the lead, as they are covering more targets and being tested in a wider range of solid tumor indications.

Bispecific push in solid tumors

Among 27 abstracts featuring bispecifics, 16 (59%) list one or more solid tumor types as the primary indication, vs. five out of 51 (10%) of CAR T abstracts. The ASCO abstracts show bispecifics being explored in 13 solid tumor indications, and CAR Ts in seven (see Figure: "Bispecifics Outpace CAR T Cells in Solid Tumors").

Drug developers that see more promise in bispecifics than CAR Ts for solid tumors cite the tendency of CAR Ts to become ineffective due to the immunosuppressive environment in solid tumors. In contrast, bispecifics can penetrate the tumor to activate or reactivate the T cells already there (see "Solid Hopes for T Cell Bispecifics").

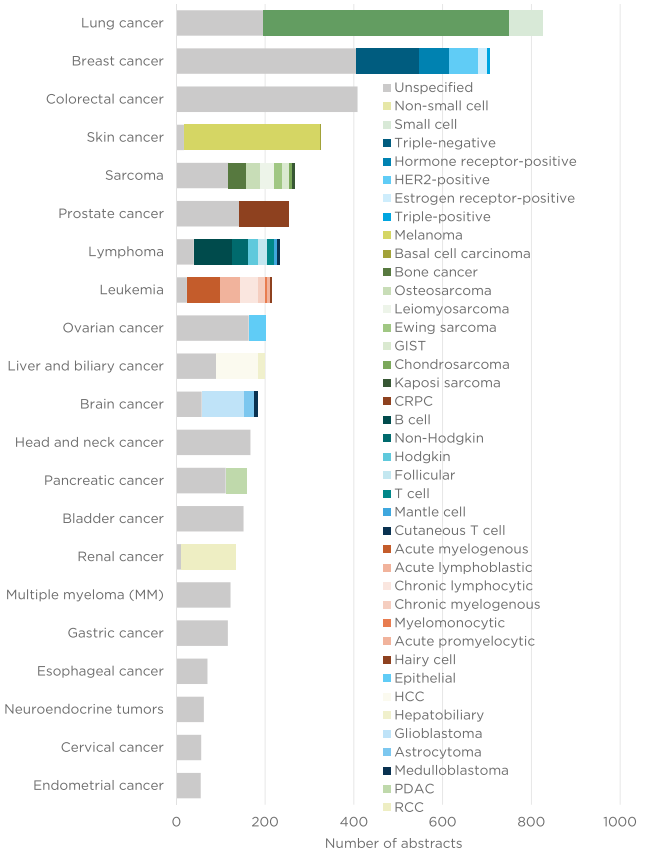
At least 14 companies and institutions will present a bispecific construct for solid tumors at the meeting, and no two of these therapies target the same pair of antigens, suggesting the field is casting a wide net rather than piling onto the same targets.

Amgen Inc. is following up Blincyto with additional bispecific T cell engagers (BiTEs). It will present Phase I therapy AMG 757, which targets the tumor antigen DLL3 and CD3 for small cell lung cancer (SCLC), and AMG 596, an EGFRvIII and CD3 BiTE for glioblastoma. Neither abstract indicates trial data will be discussed. In both therapies, the CD3-binding arm targets the T cell, and the other arm targets the tumor (TPS8577; TPS2071).

Johnson & Johnson will present Phase I data from the EGFR-c-MET bispecific antibody JNJ-61186372 to treat non-small cell lung cancer (NSCLC). Both of its targets are on the tumor. The compound is partnered with Genmab A/S, although Genmab authors are not on the abstract (9009).

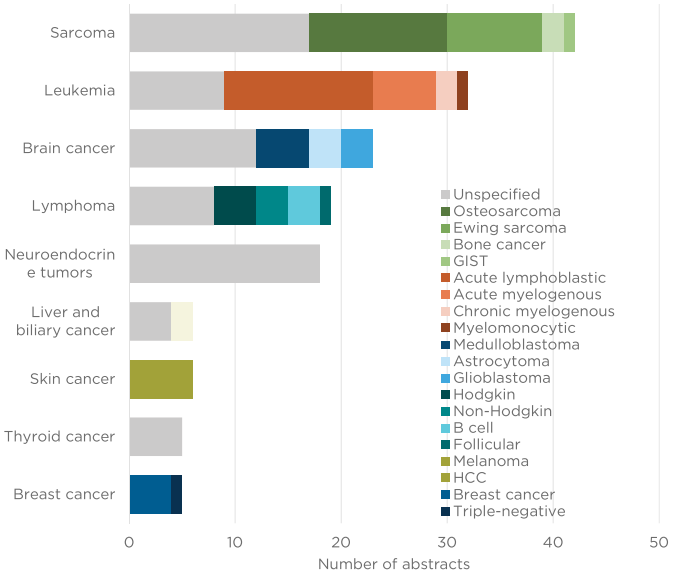
Top indications at ASCO 2019

The top five indications at ASCO 2019 remained the same as in 2018. The chart shows indications that were mentioned in at least 50 abstracts. The analysis included 4,627 abstracts, of which 4,089 mentioned at least one cancer indication. The analysis excluded abstracts in tracks related to survivorship and supportive care. Indications were assigned by a machine-learning algorithm designed by BioCentury; double counting was allowed for abstracts that mentioned more than one cancer subtype. *Source: ASCO abstracts as of May 16 Source: ASCO abstracts as of May 15*



Pediatric indications at ASCO 2019

Once again in 2019, sarcomas were the most common cancer type in **American Society of Clinical Oncology** (ASCO) meeting abstracts concerning children with cancer, despite leukemias and brain cancers being more common in pediatric patients. Pediatric abstracts were compiled by adding abstracts assigned to ASCO's Pediatric Oncology track to abstracts in other tracks that contained the words pediatric, adolescent or child. The analysis excluded abstracts assigned to tracks related to survivorship, supportive care and symptom management. *Source: ASCO abstracts as of May 15*



Other companies are presenting bispecifics in which both arms bind to T cells, or that marry bispecifics with another modality.

Immunocore Ltd., for example, will present three abstracts for tebentafusp (IMCgp100), a cell therapy engineered to express a bispecific TCR targeting CD3 and the melanoma antigen SILV (9592; 9530; 9523).

One of the tebentafusp abstracts is a retrospective analysis of the therapy in uveal melanoma patients, showing it sensitized them to treatment with immune checkpoint inhibitors. The finding aligns with the idea that bispecifics can activate existing T cells in the tumor microenvironment. The compound is in a pivotal Phase I/II trial for the indication.

One group is going beyond dual specificity to tetra-specific antibodies.

A preclinical study from the Chinese PLA General Hospital described an antibody targeting PD-1, CD47, VEGF and TGFβ to treat NSCLC. The authors say the antibody is more efficacious than a combination of all four mono-specific parent antibodies (e14002).

Doubling down on checkpoints

Five of the bispecific abstracts describe antibodies against two different checkpoint proteins. In each case, one arm binds PD-1, PD-L1, or CTLA4 while the other binds CTLA-4 or one of three next-generation checkpoints: TIM3, LAG3 or OX40.

Individual mAbs against these newer checkpoints will also be presented at ASCO. Among the immuno-oncology targets, TIM3 and LAG3 are mentioned most frequently behind the standard trio of PD-1, PD-L1

and CTLA-4. LAG3 appears in 27 abstracts and TIM3 in 13. OX40 appears in seven.

Some companies that are testing dual checkpoint bispecifics are also testing combinations of single agents against the same targets.

Eli Lilly and Co., for example, is running two Phase I trials of a combination of an anti-TIM3 and an anti-PD-L1 antibody, and will present at ASCO a Phase I trial of LY3415244, its anti-TIM3, anti-PD-L1 bispecific for advanced solid tumors (TPS2654).

A common rationale cited in the bispecific checkpoint abstracts is that these developers want to capture in a single molecule the synergistic effects of combining mono-targeted checkpoint antibodies, while improving the safety profile.

The goal is to simplify dosing, tie together the agents' PK/PD, and provide a bigger therapeutic window to boost efficacy.

Other companies presenting dual checkpoint bispecifics at ASCO include MacroGenics Inc., Alligator Biosciences AB, F-Star Biotechnology Ltd. and Alphamab Oncology Ltd (TPS2661; TPS2653; TPS2652; 2554).

In Alphamab's Phase I trial to treat solid tumors, the high dose of its anti-PD-L1 and anti-CTLA-4 bispecific KN046 led to a complete response (CR) in one NSCLC patient, and the mid-dose led to stable disease (SD) in one patient with triple-negative breast cancer (TNBC) and another with renal cell carcinoma (RCC).

Alphamab designed KN046 with a CTLA-4 binding arm that it thinks will have a better safety profile than anti-CTLA-4 antibody Yervoy ipilumumab, which causes autoimmune reactions that limit its dosing in combination regimens.

The other companies' abstracts did not detail clinical data.

Solid competition

The ASCO abstracts show CAR T cells and bispecifics competing in at least six solid tumor indications, although largely with different targets.

Only one target overlaps between the CAR T and bispecific therapies at ASCO, and both candidates are Amgen's. CAR T therapy AMG 119 and bispecific AMG 757 both target DLL3 and are in Phase I testing for SCLC. Amgen has not indicated data for either will be presented at the meeting (TPS8576).

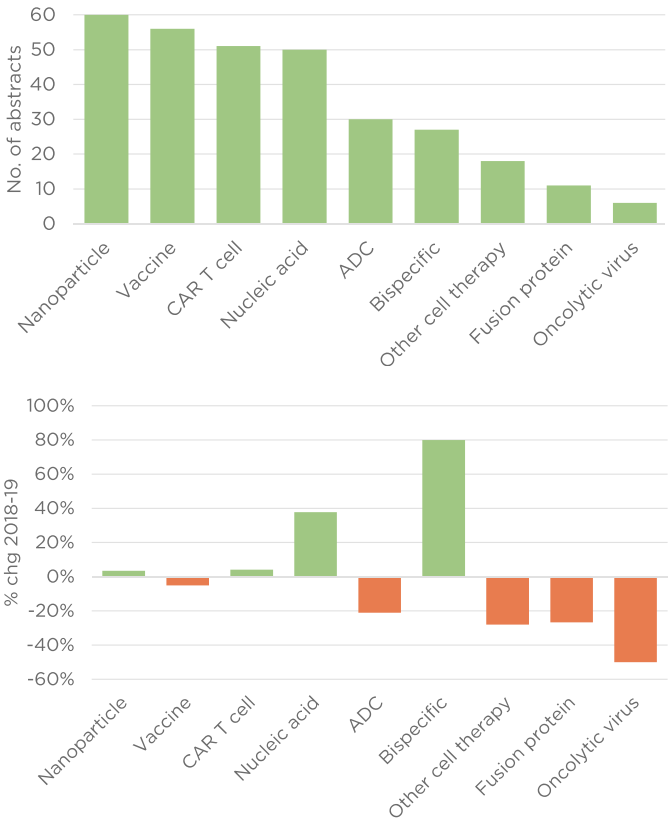
Bellicum Pharmaceuticals Inc., CARsgen Therapeutics Co. Ltd. and a group from Memorial Sloan Kettering Cancer Center (MSKCC) led by Michel Sadelain will also present Phase I data from CAR T therapies in solid tumors. Sadelain was a scientific co-founder of CAR T cell company Juno Therapeutics, which was acquired by Celgene Corp. in 2018.

Bellicum's CAR targets PSCA to treat prostate cancer; CARsgen's targets the tumor antigen claudin 18.2 to treat advanced gastric and pancreatic adenocarcinoma; and MSKCC is targeting mesothelin for pleural mesothelioma, lung and breast cancers (2536; 2509; 2511).

ASCO 2019 modalities

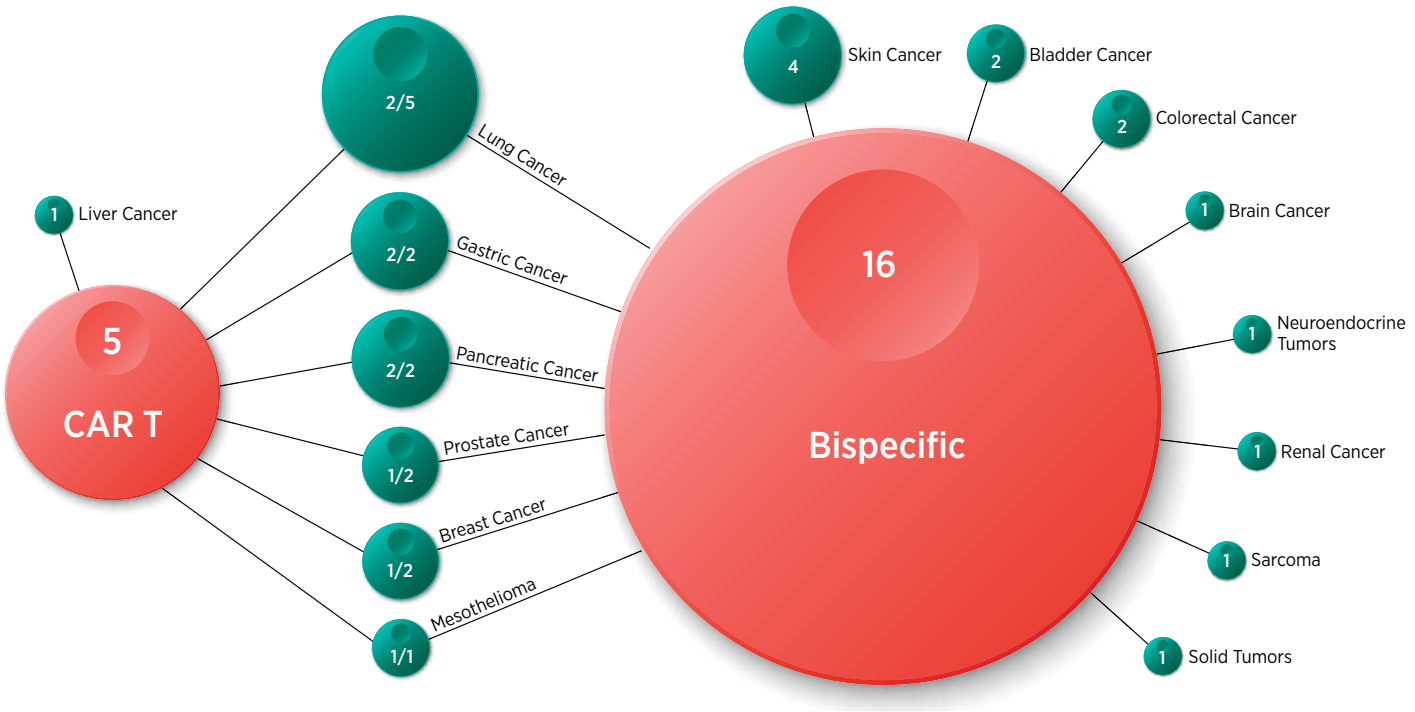
New modalities continue to be well represented at this year's **American Society of Clinical Oncology** (ASCO) meeting. Though bispecific antibodies rank sixth for the number of mentions in abstracts, the class saw the biggest rise over 2018 among the new modalities, followed by CAR T cell therapies. Top graph shows the number of abstracts in 2019; bottom graph shows percent change from 2018. While the number of ADC abstracts fell this year, four products will have first-in-human data presented.

Modalities were identified using a machine learning-based text search of abstracts assigned to any of ASCO's presentation tracks related to clinical, preclinical or basic research. Exosomes and liposomes were categorized as nanoparticles, and include liposomal chemotherapy formulations. The vaccine category includes DNA, neoantigen, peptide and RNA vaccines. The nucleic acid category includes antisense oligonucleotides, siRNA, shRNA, microRNA (miRNA), long noncoding RNA (lncRNA) and small activating RNA (saRNA). The bispecific category contains one abstract describing tetraspecific antibodies. The other cell therapy category includes all cell therapies minus CAR T cells. mAbs and small molecules were excluded from this analysis. The analysis also excluded abstracts assigned to tracks related to survivorship, supportive care and symptom management. *Source: ASCO abstracts as of May 15*



Bispecifics outpace CAR T cells in solid tumors

Five CAR T cell therapies and 16 bispecific antibodies in this year's ASCO abstracts list one or more solid tumor indications. The figures in green circles represent the number of abstracts that mention a particular indication; where two figures are shown they represent the number of CAR T/bispecific abstracts, respectively. Bispecifics include bispecific antibodies, one tetraspecific antibody, and bispecific T cell engagers. Six indications overlap between CAR T and bispecific therapies, including lung cancer, which had the most mentions across the two modalities. *Source: ASCO abstracts as of May 15*



Liver cancer is the only solid tumor type mentioned in a CAR T abstract and not in any bispecific abstracts. A group at Baylor College of Medicine describes the design of a Phase I trial for GPC3-targeted CAR T cells to treat pediatric liver tumors (TPS2647).

Fortifying CARs

Much of the progress in CAR T therapies is still in the realm of blood cancers and centers on avoiding checkpoint repression or antigen escape, themes that were observed at last year's ASH meeting as well (see "Souped-Up CARs at ASH 2018").

Solving either problem should help the modality in solid tumors.

Researchers from Zhejiang University will present Phase I data from CD19 CAR T cells expressing an engineered PD-1 molecule in which the intracellular signaling domain is replaced with the stimulatory CD28 domain. The effect is to turn PD-1 into a activator rather than repressor (7557).

Alpine Immune Sciences Inc. presented preclinical data at last year's ASH meeting on a similar approach.

Innovative Cellular Therapeutics Co. Ltd. is fortifying CD19 CAR T cells against checkpoint repression by engineering a dominant negative PD-1 protein into the cells. The idea is to express an engineered version of PD-1 that out-competes endogenous PD-1 for ligand binding, but does not generate an inhibitory signaling cascade in the presence of its ligands. The company will present Phase I data at ASCO (e19028).

Researchers at Huazhong University of Science and Technology and Miltenyi Biotec GmbH are tackling the problem of antigen escape in blood cancers.

Antigen escape is a type of drug resistance that occurs when a tumor stops expressing the CAR T therapy's target. Targeting more than one antigen makes antigen escape less likely.

The Huazhong University team's abstract contains updated data from its pilot trial delivering a cocktail of CD19- and CD22-targeted CAR Ts to B cell non-Hodgkin lymphoma patients (2534).

Miltenyi will present Phase I data from a bispecific CAR T therapy that targets CD20 and CD19 and is in testing to treat B cell NHL (2539). bc

COMPANIES AND INSTITUTIONS MENTIONED

Alligator Bioscience AB (NASDAQ:OMX; SSE:ATORX), Lund, Sweden
Alphamab Oncology Ltd., Suzhou, China
Alpine Immune Sciences Inc. (NASDAQ:ALPN), Seattle, Wash.
American Society of Clinical Oncology, Alexandria, Va.
American Society of Hematology (ASH), Washington, D.C.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Baylor College of Medicine, Houston, Texas
Bellicum Pharmaceuticals Inc. (NASDAQ:BLCM), Houston, Texas
CARsgen Therapeutics Co. Ltd., Shanghai, China
Chinese PLA General Hospital, Beijing, China
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
F-star Biotechnology Ltd., Cambridge, U.K.
Genmab A/S (CSE:GEN; Pink:GMXAY), Copenhagen, Denmark
Huazhong University of Science and Technology, Wuhan, China
Immunocore Ltd., Abingdon, U.K.
Innovative Cellular Therapeutics Co. Ltd., Shanghai, China
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
MacroGenics Inc. (NASDAQ:MGNX), Rockville, Md.
Memorial Sloan Kettering Cancer Center (MSKCC), New York, N.Y.
Miltenyi Biotec GmbH, Bergisch Gladbach, Germany
Zhejiang University, Hangzhou, China

TARGETS

c-MET (MET; HGFR) - c-Met receptor tyrosine kinase
CTLA-4 (CTLA4; CD152) - Cytotoxic T-lymphocyte associated protein 4
DLL3 - Delta like canonical Notch ligand 3
EGFR (ErbB1; HER1) - Epidermal growth factor receptor
EGFRvIII - Epidermal growth factor receptor variant III
GPC3 - Glypican 3
LAG3 (CD223) - Lymphocyte-activation gene 3
OX40 (TNFRSF4; CD134) - Tumor necrosis factor receptor superfamily member 4
PD-1 (PDCD1; CD279) - Programmed cell death 1
PD-L1 (B7-H1; CD274) - Programmed cell death 1 ligand 1
PSCA - Prostate stem cell antigen
SILV (PMEL17; GP100; PMEL) - Silver homolog
TGFβ - Transforming growth factor β
TIM3 (HAVCR2) - T cell immunoglobulin and mucin domain 3
VEGF - Vascular endothelial growth factor

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PRODUCT DEVELOPMENT

Clinical trial and regulatory efficiency get help from ctDNA, RWE at ASCO19

BY ALLISON JOHNSON, STAFF WRITER

This year's crop of ASCO abstracts show companies are going full bore on pre- and post-market technologies that can speed up development and regulatory timelines.

In BioCentury's analysis of 4,627 abstracts, over 500 feature circulating tumor DNA or real-world evidence, and they showcase how companies, institutions and regulatory agencies are applying the technologies.

The survey uses a machine learning-based analysis of abstracts published ahead of the American Society of Clinical Oncology meeting, for mentions of products, indications, targets, modalities or other hot topic terms (see "ASCO 2019 abstracts show solid tumor race heating up among bispecifics and CAR Ts").

DNA shed from tumors into circulation carries information about the cancers' mutations, and companies' first use of the technologies has been in identifying patients for trials.

The ASCO 2019 abstracts indicate that ctDNA is being increasingly deployed to determine patient response, with companies measuring the abundance of a specific mutation in ctDNA over time.

In this setting, ctDNA promises faster answers than traditional imaging-based outcome measures, saving time both for drug developers and patients (see "ctDNA Inches Towards New Applications").

Like ctDNA, real-world data also can guide patient selection, making trial populations more representative of real-world diversity, and accelerating recruitment through broader enrollment criteria or the need for fewer patients.

One way real-world data can do both of those things is through deployment of synthetic control arms in clinical trials, and three retrospective studies presented at ASCO suggest use of real-world evidence to design these control arms is getting closer to implementation.

Synthetic control arms use previously collected data from a comparable patient population treated with the same control the trial is employing, or would employ if it had one. Their use could cut the number of patients needed for randomized control trials by as much as 50%.

In the post-market setting, real-world evidence can help determine if off-label drug use supports expanded approvals or trials in new indications.

All of these concepts are themes in this year's abstracts.

ctDNA points the way

At ASCO 2019, ctDNA is mentioned in 238 abstracts, across at least 32 indications and 228 targets.

Eleven abstracts describe use of ctDNA levels as a secondary (1/11) or exploratory (10/11) endpoint in a clinical trial, and dozens more describe correlating ctDNA levels with therapeutic response by analyzing serial samples from baseline to disease progression.

AstraZeneca plc sponsors two of the trials with ctDNA endpoints. The pharma is measuring changes from baseline in EGFR-mutant ctDNA

IN BIOCENTURY'S ANALYSIS OF 4,627 ABSTRACTS, OVER 500 FEATURE CIRCULATING TUMOR DNA OR REAL-WORLD EVIDENCE.

as a secondary endpoint in the Phase II SAVANNAH trial of EGFR inhibitor Tagrisso osimertinib and c-MET inhibitor savolitinib to treat non-small cell lung cancer (NSCLC) (TPS9119).

In the Phase III FLAURA trial testing Tagrisso vs. SOC EGFR inhibitors, AZ will measure changes from baseline in EGFR mutant ctDNA as an exploratory endpoint (9020).

AZ and Roche market the Cobas EGFR Mutation Test v2 as a diagnostic for tissue or liquid biopsies. The test was the first liquid biopsy diagnostic approved by FDA.

EGFR was the most common target mentioned in abstracts that featured ctDNA, appearing in 66 abstracts. Also in the top five targets for ctDNA abstracts were TP53 (65 mentions), BRAF (43), KRAS (42) and HER2 (31), suggesting the technology is being used in genetically defined patient populations and patients being treated with targeted therapies.

RWE takes on clinical trials

Among the 254 real-world data abstracts is a basket of those intended to inform clinical trial decisions spanning which patients to recruit to whether a new trial is warranted.

Data from these studies were derived from institution or hospital-specific, online or regional registries, in addition to databases from companies like Roche's Flatiron Health Inc. unit and IQVIA Holdings Inc.

In one abstract, Flatiron argues real-world data should be used to inform patient selection for control arms in randomized control trials (RCTs) (6540).

Flatiron researchers found that across 15 RCTs for metastatic breast, advanced NSCLC, metastatic renal cell carcinoma (RCC), multiple myeloma (MM), and advanced urothelial cancer, the SOC comparator used in the trials rarely reflected the SOC patients would have received outside of the trial setting, with the median real-world relevance 37%.

A handful of abstracts examine whether real-world data can and should expand patient eligibility criteria for clinical trials, including a late-breaking abstract from FDA, ASCO and other partners that will be presented on June 3 (LBA108).

Others are using RWE to identify new indications for an approved therapy.

Sema4 is hoping response to treatment with off-label therapies can support clinical trials in new indications.

One abstract from the company describes an analysis of 145,000 cancer patient records from Mount Sinai Hospital. It found many instances of off-label treatment with targeted therapies and checkpoint inhibitors with varying degrees of therapeutic response, measured using time to treatment discontinuation as a surrogate endpoint (e20642).

Pfizer Inc. will present an abstract relaying the real-world approach it used to secure FDA approval in April of CDK4/CDK6 inhibitor Ibrance palbociclib to treat men with breast cancer, a patient population rare enough to make RCT enrollment challenging (1055).

Synthetic solutions

Synthetic control arms, created from historical trial data or real-world data, could obviate the need for placebo arms in RCTs, speeding recruitment and clinical completion timelines.

At this year's ASCO, three abstracts describe creating and retrospectively testing a synthetic control arm.

Two of those abstracts are from FDA's Oncology Center for Excellence (OCE), which will present results from Project: Switch. The project's goal is to create synthetic control arms that can help evaluate an approved drug in a new setting, or be deployed in RCTs of investigational therapies for rare diseases with poor prognoses.

In one abstract, the FDA authors find they can switch the docetaxel control arms of five second-line metastatic NSCLC trials without affecting the outcomes of the individual trials. The studies' investigational therapies included immunotherapies and an anti-VEGF treatment (9105).

The results of a similar switching experiment are less clear. In a second abstract, the FDA researchers apply the same methodology to create

synthetic control arms from four MM trials, where the control was lenalidomide plus dexamethasone. The switched arms only replicated two of the four trial results. The authors did not describe the experimental therapies tested in the trials, but said the different therapeutic classes, or the line of treatment, could have affected the results (8047).

Daiichi will present the third synthetic control arm abstract. Its goal is to support accelerated approvals with confirmatory trials that use a synthetic control arm.

The Japanese pharma uses a test case of an undisclosed NSCLC trial to show a synthetic control arm can replicate the overall survival outcomes observed in the trial (9108). bc

COMPANIES AND INSTITUTIONS MENTIONED

American Association for Cancer Research, Philadelphia, Pa.
American Society of Clinical Oncology, Alexandria, Va.
AstraZeneca plc (LSE:AZN; NYSE:AZN), Cambridge, U.K.
Daiichi Sankyo Co. Ltd. (Tokyo:4568), Tokyo, Japan
IQVIA Holdings Inc. (NYSE:IQV), Durham, N.C.
Mount Sinai Hospital, Toronto, Canada
Pfizer Inc. (NYSE:PFE), New York, New York
Roche (SIX:ROG; OTCQB:RHHBY), Basel, Switzerland
Sema4, New York, N.Y.
U.S. Food and Drug Administration, Silver Spring, Md.

TARGETS

c-MET (MET; HGFR) - c-Met receptor tyrosine kinase
CDK4 - Cyclin dependent kinase 4
CDK6 - Cyclin dependent kinase 6
EGFR (ErbB1; HER1) - Epidermal growth factor receptor
HER2 (EGFR2; ErbB2; neu) - Epidermal growth factor receptor 2
TP53 - p53
KRAS - K-Ras
VEGF - Vascular endothelial growth factor

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