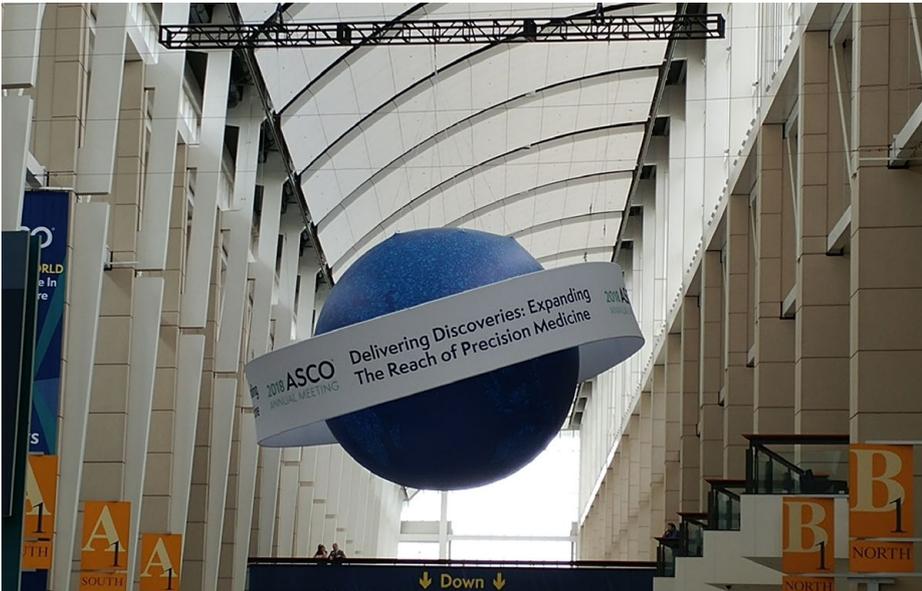


ASCO Annual Meeting Briefing



The theme of this year's ASCO meeting was "Delivering Discoveries: Expanding the Reach of Precision Medicine." Several facets of precision medicine were emphasized throughout presentations and discussions, including the many roles of big data, evolving standards of care, immunotherapy, and novel therapeutics. Challenges of rising costs and access to care were topics of focus throughout the meeting, and the need for research collaborations such as investigator-initiated, industry-supported studies was noted.

Hot Topic: Cost and Access

The rising cost of cancer therapies, particularly immunotherapies, was at the forefront of many discussions throughout the week. The highly-effective but expensive checkpoint inhibitors were often cited as an example, with annual per-patient costs in the hundreds of thousands of dollars. There was a great deal of concern about how to manage skyrocketing costs associated with increased use of precision therapies and with the trend toward combination immunotherapies such as the nivolumab/ipilimumab (Opdivo®/Yervoy®, Bristol-Myers

Squibb) combination approved for melanoma and renal cell carcinoma. Barriers to access (beyond cost) were also emphasized, with a number of presentations dedicated to access issues in developing countries, low-income countries, and underserved geographic areas and racial/ethnic groups. In addition to access facilitated through clinical trials and cancer foundations, compassionate use programs, national health programs, and collaborative efforts with industry were cited as possible solutions.

There was a great deal of concern about how to manage skyrocketing costs associated with increased use of precision therapies

Biosimilars received considerable attention throughout the meeting, with presenters discussing clinical and real world data on marketed biosimilars for filgrastim, trastuzumab, and rituximab and their implications for cancer care. Characterization studies for several biosimilars in development were also presented. Amgen, the maker of the first approved cancer biosimilar,

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Heather has over 5 years of experience in healthcare communications, working closely with clients in the pharmaceutical industry to ensure alignment of objectives, insights, and messaging. She has participated in several initiatives focused on identifying evidence needs, communication priorities, and scientific messages for key stakeholders, and on guiding clinical development for emerging therapeutics.

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bevacizumab-awwb (Mvasi[®]), delivered an industry expert presentation on what oncologists should know about biosimilars as they become more common in the cancer space.

In a dedicated clinical science symposium, panelists discussed the potential of biosimilars to address global cancer care challenges by offering lower-cost options and improved access compared with reference products. The HERITAGE trial of trastuzumab-dskt, which was conducted worldwide, and the PIONEER trial of filgrastim-sndz, which showed no significant differences among study subpopulations, were cited in support of the global applicability of biosimilars to heterogeneous populations, including underserved racial and ethnic groups not typically represented in clinical trials. Real-world EU5 data on use of biosimilar rituximab in clinical practice was used as an example of delayed but inevitable uptake of biosimilars. Cost was cited as a key appeal, but several questions about the future of this market remain to be answered:

- When new biosimilars enter the market, they will be priced lower than reference products, but how much lower?
- How will manufacturers of reference products respond to biosimilar entry?
- Will availability of multiple biosimilars for a given reference product create a different cost scenario?
- Will interchangeability, not currently a factor in the cancer space, become a driver of prescribing decisions?

Access to routine cancer care was also noted as an area of concern, with telemedicine approaches including phone- and video-conferencing as well as mobile apps touted as a key approach to increase access. One randomized study of genetic screening in a rural setting slightly enriched for low socioeconomic status demonstrated the value of telemedicine as a solution to genetic counseling access challenges. Among patients who received genetic testing, more than 75% of patients in the remote counseling arm proceeded with counseling, compared with only 6% in the usual care arm. Use of technology and hybrid cancer care services is expected to play a growing role in the future, and may provide another avenue to combat the rising costs of cancer care.

Hot Topic: Evolving Standards of Care

Throughout the meeting, presenters shared testimonials from patients, family members, and even themselves, emphasizing the impact that advances in cancer screening and treatment have had on their lives. With the ever-increasing number of precision therapies, outcomes are improving across nearly all cancer types (and subtypes). Advances were emphasized particularly heavily in lung cancer as well as in breast, prostate, colorectal, and hematologic malignancies, and standards of care are evolving rapidly to keep up with the availability of more-effective treatment options.

The plenary session focused on 4 studies deemed to be potentially practice-changing, including the heavily-anticipated Phase 3 TAILORX breast cancer study funded by the NCI. TAILORX demonstrated that chemotherapy can be spared in many patients with invasive hormone receptor-positive, HER2-negative breast cancer. Similarly, results of Pfizer's collaborative CARMENA trial conducted in Europe demonstrated noninferiority of the multi-targeted tyrosine receptor kinase inhibitor sunitinib, (Sutent[®]) compared with cytoreductive nephrectomy followed by sunitinib in metastatic renal cell carcinoma. Overall survival and progression-free survival rates were comparable between arms and median overall survival was improved in patients spared cytoreductive nephrectomy. The pace of change in the cancer landscape was highlighted in the CARMENA presentation, during which it was noted that the standard of care for renal cell carcinoma changed many times throughout the trial accrual period, ultimately incorporating immunotherapies as well as other small molecule therapies in the precision medicine armamentarium. These high-impact studies are only 2 of the many demonstrations of precision medicine replacing older cancer treatment approaches.

Standards of care are evolving rapidly to keep up with the availability of more-effective treatment options



Approaches for improving standards of care in geriatric and pediatric populations were also at the forefront. The importance of addressing the needs of these populations, both of which tend to be underrepresented in clinical trials, was evident in many presentations on diverse topics ranging from basic research to honoring patient preferences in clinical care. The focus on improving care for these patients is reflected in the evidence-based geriatric oncology guidelines recently released by ASCO and in the recent signing of the Childhood Cancer Survivorship, Treatment, Access, & Research (STAR) Act.

Hot Topic: Patient-reported Outcomes

There has been increasing recognition of the importance of patient-reported outcomes (PROs) in both clinical trials and routine cancer care. Use of PROs is becoming routine in providing complementary data on drug safety and efficacy, informing regulatory decisions (eg, as a component of patient experience data in FDA submissions), and supporting therapeutic value considerations beyond the traditional efficacy/cost demonstrations. PROs are also being harnessed to monitor patients' disease status, trigger treatment changes, and predict outcomes. Some early work presented indicated that cancer therapies that improve PROs can also reduce total costs and hospitalizations. If borne out in larger randomized trials and/or real world practice, observations such as these may be used to inform treatment decisions and could favorably influence reimbursement decisions.

Several presentations focused on the feasibility and clinical value of technological solutions to collection of PROs, including use of smartphone apps and wearables, symptom assessment by remote lay health workers, and use of web-based apps such as MoovCare™ to monitor symptoms as surrogate indicators of disease progression.

Presentations demonstrating improved PROs in clinical trials represented a variety of therapies and cancer types. Roche's Phase 3 IMmotion151 trial of combined atezolizumab/bevacizumab has demonstrated an improvement in progression-free survival compared with sunitinib in patients with previously untreated metastatic renal cell carcinoma. New PRO data indicated less-severe symptoms and better quality of life with the combination therapy vs sunitinib. Similarly, PRO data from KEYNOTE-189 demonstrated that a pembrolizumab/chemotherapy combination maintained global health status/quality of life in patients with nonsquamous non-small cell lung cancer whereas these scores decreased in patients who received chemotherapy alone. Both abstracts concluded that, combined with previously reported efficacy data, their PRO data support first-line use of the investigational regimens.

Spotlight on Genomic Screening, Big Data, and Health Technology Solutions in Precision Medicine

Big data, including enormous genomic datasets, is playing an ever-expanding role in oncology, from informing basic research to

facilitating enrollment in clinical trials. The value of genomic screening is evident in the FDA's first tissue/site-of-origin agnostic drug approval for pembrolizumab (Keytruda®, Merck) and in the shift of clinical trials toward basket designs in which many types of cancer are included based on a common molecular profile. There are numerous mutations and molecular characteristics for which patients can be screened in a targeted manner. Next generation sequencing (NGS) of the genome provides broad coverage and can identify alterations that may otherwise be missed, and is becoming increasingly common.

One of this year's first sessions was a point/counterpoint discussion focused on next generation sequencing and which patients should be screened. The session was not a debate, as both discussants agreed that genetic and genomic screening is now an intrinsic part of cancer care and drug development, and emphasized the many successes of precision therapies made possible by molecular profiling. Instead, discussions centered on when in the disease and treatment course patients should be profiled, what type of biopsy (solid tissue or liquid) is appropriate, which of several approved tests should be used, and where the cost burden should lie.

Genetic and genomic screening is now an intrinsic part of cancer care and drug development

Current guidance from the US Center for Medicare & Medicaid Services seems to indicate that serial testing



would not be reimbursed, but this policy fails to address patients who develop new mutations with disease progression or in response to therapy and who would be candidates for rescreening. Discussants made a case for drug manufacturers/study sponsors to cover costs of NGS, with the caveat that sponsors should not have sole control of the resulting data. During several presentations, audience members questioned the necessity and value of such large volumes of data and whether existing data are sufficient to inform cancer diagnosis and treatment. The response from researchers and oncologists was consistent – even more data are needed. Targeted therapies have revolutionized cancer treatment and outcomes, particularly in breast and non-small cell lung cancer. However, there are many malignancies for which actionable targets have not yet been discovered. Further, many patients with actionable targets for which precision therapies exist do not respond to these treatments, and the underlying reasons for treatment resistance are often unknown. Malignancies may harbor or develop resistance mechanisms in the form of additional mutations, bystander effects in heterogeneous tumors, etc. Multifactorial profiling, accounting for DNA, RNA, and protein alterations, tumor histology, prior therapy, and patient characteristics, was proposed as an approach to increase therapeutic success rates.

Several academic, government, and commercial health technology solutions are working to aggregate, integrate, and curate cancer data, and many of these combine molecular profiling with real-world data such as treatment decisions and survival. Research-focused examples from meeting presentations included NIH's ClinGen, NCI's SEER program, ASCO's

CancerLinq database, AACR's GENIE, and the Flatiron Health database. Many companies have developed proprietary platforms designed to help inform diagnosis and treatment decisions, including Allscripts' 2bprecise, IBM's Watson, and Oncompass's RealTime Oncology Treatment Calculator.

The National Comprehensive Cancer Network suggests that participation in clinical trials is the best way for patients to access therapy, but many speakers noted the challenges of trial accrual, including low rates of enrollment and slow accrual with passive methods. The FDA and ASCO are working together to relax eligibility criteria for clinical trials to eliminate irrelevant but restrictive criteria and increase access.

Many initiatives are using advanced informatics approaches to match patients with molecularly selected clinical trials. This both increases patient access to precision therapeutics and facilitates clinical trial accrual. Several trial matching solutions in development were presented, including

- Perthera's cloud-based virtual tumor board that ranks the strength of patient/trial matches by scoring molecular rationale, disease relevance, and patient history, and accounts for geographical distance to study sites, and
- PRECISE, an automated system that tracks patients based on molecular and clinical profiles and uses artificial intelligence and machine learning to match patients to clinical trials of appropriate targeted therapies.

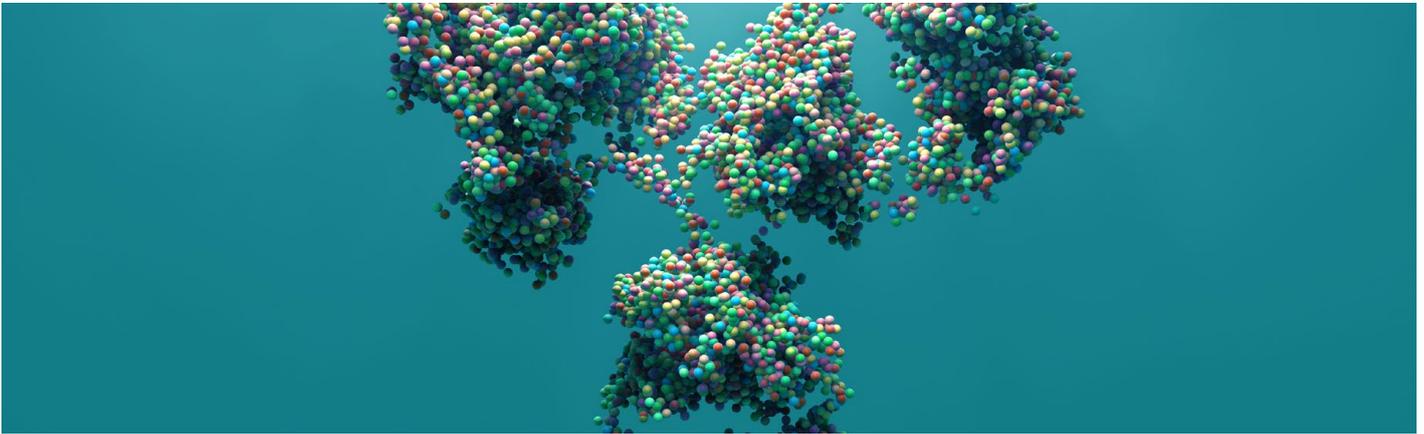
A feasibility study of PRECISE demonstrated that the platform prospectively identified 44% of patients

who subsequently enrolled in 42 clinical trials, facilitating accrual of a variety of molecular profiles and tumor types for precision medicine studies.

The nearly 40-arm NCI MATCH signal-finding study in patients with solid tumors, lymphoma, or myeloma, was showcased in multiple presentations, demonstrating modest results to date. For example, Roche's PI3-K inhibitor tasisib failed to achieve any objective responses in heavily pretreated patients with activating mutations in the catalytic subunit of PI3-K, although some tumor regression was observed. Ongoing efforts of MATCH and other public and commercial initiatives will continue to refine matching algorithms as the understanding of cancer profiles evolves, and will likely play an increasing role in clinical trials evaluating the potential benefit of targeted therapies. Pediatric MATCH, including patients aged 1–21 years, is also on the horizon.

In addition to identifying candidate therapies suitable for further development, these efforts may also shed light on mechanisms underlying treatment failure in those therapies that do not demonstrate sufficient activity in certain cancers, informing future drug development efforts. The degree of concordance among outputs of the many health technology solutions using big data for research, diagnosis, treatment decisions, and clinical trial matching remains to be seen.

Many initiatives are using advanced informatics approaches to match patients with molecularly selected clinical trials



Spotlight on Immunotherapy

Antibody-based Approaches

In the opening session, Dr. Bruce Johnson commented in his president's address that immunotherapy has come of age. The checkpoint inhibitors nivolumab and pembrolizumab, which have demonstrated efficacy in nearly 20 tumor types, were practically omnipresent throughout this year's meeting, including numerous posters, oral abstract sessions, and clinical science symposia. Their success was noted by Dr. Johnson, who pointed out that some patients receiving nivolumab for non-small cell lung cancer are maintaining responses and surviving beyond 3 years. He also cited a 40% improvement in survival in lung cancer patients receiving pembrolizumab, which is approved as first-line therapy for non-small cell lung cancer patients with PD-L1 expression $\geq 50\%$. Bristol-Myers Squibb's exhibit booth emphasized nivolumab's efficacy in previously treated cancers (eg, non-small cell lung cancer, squamous cell carcinoma of the head and neck, urothelial cancer, melanoma, renal cell carcinoma). In contrast, Merck focused on their first-line status.

The Phase 3 KEYNOTE-042 study, presented by Dr. Gilberto Lopes during the plenary session, evaluated pembrolizumab as first-line monotherapy for advanced or metastatic non-small cell lung cancer in patients with tumor proportion score (TPS) of at least 1%. Regardless of TPS, pembrolizumab significantly improved overall survival compared with platinum-based chemotherapy, and patients receiving pembrolizumab exhibited longer duration of response.

There was a greater benefit in patients with TPS of 50% or greater, who comprised almost half of the study population. Median survival in these patients was nearly twice as long with pembrolizumab compared with chemotherapy (20 versus 12 months). As is evident from this study, checkpoint inhibitors like pembrolizumab are likely to continue driving a shift in cancer care paradigms, reducing reliance on chemotherapy in the first-line setting and delivering improved patient outcomes.

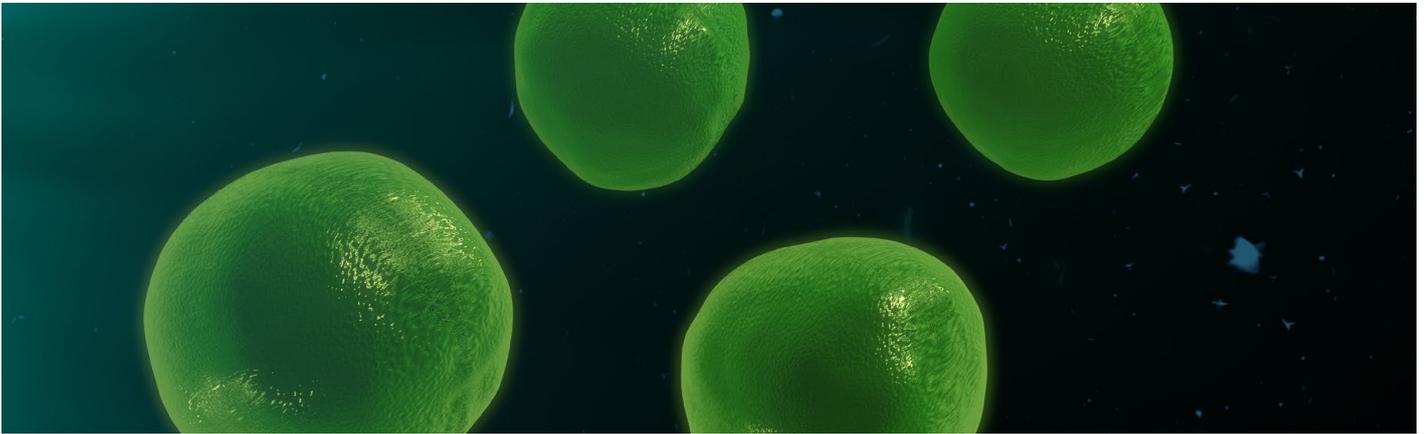
Immunotherapy combinations were also in the spotlight, particularly in 2 clinical science symposia exploring combinations of checkpoint inhibitors with:

- Other immunotherapies
- Epigenetic modifiers
- PARP inhibitors
- Chemotherapy
- Radiation therapy

While many immunotherapy-based combinations have demonstrated efficacy, some unsuccessful approaches were noted. This included the combination of pembrolizumab with the indoleamine inhibitor epacadostat for melanoma, which failed to provide a benefit beyond the 12-month overall survival rate of 74% conferred by pembrolizumab alone. Many companies are pursuing development of novel immunotherapies and immunotherapy combinations. Continued exploration of combination immunotherapies is certain as the understanding of checkpoint inhibitor resistance mechanisms and tumor complexity increases.

Bispecific antibodies may provide one way to combat resistance. These antibodies are engineered for dual specificity to a T-cell antigen (CD3) and a tumor-specific surface antigen, thereby providing a physical link between cells to overcome immune evasion mechanisms. Several preclinical and first-in-human studies using engineering platforms and antibody technology from Amgen (BiTE), Zymeworks (Azymetric), and Glenmark (BEAT) were presented. Bispecific antibodies are gaining traction, with 2 (catumaxomab and blinatumomab) already on the market and many more in clinical development. During the meeting, Amgen announced 2 new collaborations with MD Anderson focused on their BiTE technology in hematologic cancers.

Continued exploration of combination immunotherapies is certain as the understanding of checkpoint inhibitor resistance mechanisms and tumor complexity increases



Cell-based Approaches

Gene-modified cell-based therapies such as chimeric antigen receptor (CAR)-T cell therapy represent the intersection of state-of-the-art precision medicine and truly personalized medicine. The last year saw approval of the first 2 CAR-T cell therapies, Kymriah® (tisagenlecleucel, Novartis) and Yescarta® (axicabtagene ciloleucel, Kite Pharma/Gilead Sciences), with both indicated for hematologic malignancies in relapsed or refractory patients. These CD19–targeting CAR-Ts are providing game-changing efficacy in B-cell malignancies; in fact, the Novartis booth exhibited their clinical data under a header describing the therapy as “a potentially definitive treatment.” A handful of presentations discussed immunogenicity, value, and dosing of Kymriah®, whereas Kite/Gilead presented clinical data from their pivotal trial, ZUMA-1, as well as from ZUMA-3. They also announced plans for a Phase 3, randomized clinical trial comparing Yescarta® with standard of care for diffuse large B-cell lymphoma (ZUMA-7).

Several additional CAR-T cell therapies, aimed at CD19 and other targets such as BMCA and ROR1, are in development for hematologic malignancies as well as solid tumors and were highlighted throughout the meeting. BMCA is enriched on plasma cells, some subsets of mature B-cells, and plasmacytoid dendritic cells; as a result, targeting BMCA has the potential to limit off-target effects in hematologic malignancies. Bb2121 (Bluebird Bio/Celgene), which targets human-specific BMCA and uses a 4-1BB costimulatory domain, was described as “the optimal BMCA CAR-T cell design” in a much-anticipated presentation of Phase 1

results. Bluebird’s data demonstrated an impressive overall response rate of 96% and a high complete response rate in heavily pretreated multiple myeloma patients, 30% of whom were pentarefractory and 40% of whom had high-risk features. Robust responses were observed regardless of high versus low BMCA expression, and the safety profile appeared to be favorable, with no neurotoxicities and only 2 cases of serious cytokine release syndrome reported. A companion poster presented data suggesting that early achievement of minimal residual disease–negative status may predict deeper responses.

A well-attended immunotherapy education session focused on cytokines, immunoepigenetics, and cell therapies. Dr. Carl June presented long-term follow-up data on the first leukemia patients treated with CAR-T and demonstrated that CAR-T cells can persist and provide long-term immunosurveillance, supporting his description of this therapy as “a living drug.” He also discussed the potential

advantages combining CAR-T cell technology with bi-specific antibodies, which could actively traffic T-cell–bound antibodies to poor-penetration areas such as the brain. The concept of “armored CARs” was introduced as an approach for increasing the efficacy of CAR-T cell therapy for solid tumors, where the microenvironment and immune checkpoints can be more active and cause rapid T-cell inhibition or exhaustion. A presentation of early data suggested that armoring approaches such as incorporating dominant-negative TGF- β onto PSMA-targeting CAR-T cells for prostate cancer can reduce local inhibitory effects on CAR-T anti-tumor activity. These TGF- β –modified CAR-T cells are being evaluated in a Phase 1 trial of metastatic or castrate-resistant prostate cancer.

CAR-T cell therapy is still at an early stage, particularly for solid tumors. Potential avenues of future commercial CAR-T cell therapy development were topics of great interest.



These included identification of novel targets, methods to improve cell expansion and persistence, and incorporation of anti-resistance mechanisms. As with many state-of-the-art therapies, cost, access, and scalability challenges were highlighted. Despite the high costs of the 2 currently marketed CAR-T cell therapies, ICER has determined these treatments to be cost-effective based on their clinical benefit, and one presenter hypothesized that technology solutions such as automation may drastically reduce costs over time.

Potential avenues of future commercial CAR-T cell therapy development were topics of great interest

Vaccine-based Approaches

Therapeutic vaccines represent another high-tech immuno-oncology treatment approach in its early stages but receiving mention at ASCO. Provenge® (sipleucel-T, Dendreon), indicated for castrate-resistant prostate cancer, is currently the only therapeutic vaccine on the market. There were a few presentations of first-in-human data for virus-, bacteria-, and dendritic cell-based vaccines in development, mainly for prostate cancer and glioblastoma. PROSTVAC (riliimogene galvacirepvec/riliimogene glafolive, Bavarian Nordic), did not meet the primary endpoint of overall survival in the updated interim analysis of the Phase 3 PROSPECT trial intended to confirm positive results of a previous Phase 2 study. Promising results in glioblastoma were presented for the personalized, dendritic cell-based GAPVAC101 and the bacteria-based VMX01. Although results

reflected only a small number of patients, both vaccines demonstrated manageable safety and biological activity. Based on Phase 1 results, a pilot study of combined VMX01/anti-PD-L1 therapy is planned.

Emerging Drugs: Focus on 2 Promising Candidates

As the number of actionable targets and potential MOAs continues to rise, the cancer space is seeing an explosion in pipeline activity, and the success of highly effective marketed therapies such as kinase and checkpoint inhibitors has not dampened excitement over development of new drug candidates.

LOXO-292, the selective RET inhibitor in development by LOXO Oncology, was one of several success stories presented during ASCO. Results of the Phase 1, first-in-human LIBRETTO 001 trial conducted in heavily pretreated patients with locally advanced or metastatic RET-altered solid tumors were presented in a session dedicated to identifying and directing therapies at actionable targets. LOXO-292 demonstrated a confirmed response rate of 70% or higher for fusion-positive cancers such as non-small cell lung cancer and a 33% confirmed response rate for RET mutant cancers. For RET fusion-positive cancers, there were no differences in efficacy among cancer types, RET fusion partners, or prior lines of therapy (including multikinase inhibitor therapy). A substantial effect on brain and lung metastases was also noted.

The potential of cytokine therapies to augment the effectiveness of checkpoint inhibitor therapies in “cold” tumors was another area of interest. Novel combinations using cytokines

with immune checkpoint inhibitors and other immune modulating agents may provide yet another advancement in the cancer treatment landscape.

The success of highly effective marketed therapies such as kinase and checkpoint inhibitors has not dampened excitement over development of new drug candidates

The Nektar Therapeutics CD122-biased cytokine, NKTR-214, was a topic of multiple posters. Preliminary results of the Phase 1/2 PIVOT trial of NKTR-214 in combination with nivolumab for advanced solid tumors received quite a bit of attention. The combination therapy showed sustained response as well as deepening response with longer duration of treatment. Updated data for urothelial cancer, renal cell carcinoma, and melanoma demonstrated that a large proportion of patients in each subgroup achieved pre-specified efficacy criteria. Overall response rates were favorable in these patients – for example, in the melanoma subgroup, overall response rate was 85% in patients meeting efficacy criteria versus 50% in the whole group. Of note, the NKTR-214/nivolumab combination was effective in PD-L1-positive and PD-L1-negative patients.

To speak with an ICON expert and gain further insight into these latest developments and trends, please contact us at enquiries@iconplc.com

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