Clarion's Highlights from the

ASCO 2017 Annual Meeting

Clarion team members were among the ~40K attendees at this year's ASCO Annual Meeting, collectively viewing thousands of posters and talks. The following are just some of the key themes that emerged.

Building on PD1 Blockade Through Combinations

Anti-PD1/PD-L1 agents are established leaders in immuno-oncology (I-O) with FDA approvals in melanoma, NSCLC, renal cell carcinoma, head and neck cancer, bladder cancer, Hodgkin lymphoma, Merkel cell carcinoma, and MSI-H cancers. They now show single-agent activity in even more indications, such as cervical cancer (Hollebecque #5504; Schellens #5514), gastric cancer (Fuchs #4003), and mesothelioma (Kindler #8557; Scherpereel #LBA8507). However, in almost every cancer type, only a minority of patients respond, highlighting the need for combination approaches.

Nivolumab + ipilimumab ("nivo + ipi") is already standard of care in metastatic melanoma and has some compelling data in NSCLC and RCC (ASCO 2016, 2015). Nivo + ipi has continued to strengthen its dataset, showing robust responses against brain metastases (Long #9508) and activity in SCLC (Hellmann #8503) and sarcomas (D'Angelo #11007).

However, **epacadostat + anti-PD1** was the breakout story for I-O combinations this year. Epacadostat is Incyte's IDO1 inhibitor and has previously shown promising data in melanoma (e.g., at SITC in 2015), but now has a much more robust dataset, across multiple tumor types. Epacadostat + nivo had an ORR of ~63% in melanoma (Perez #3003), similar to nivo + ipi, and an impressive ORR of ~34% (including some CRs) in head and neck SCC (Hamid #6010), significantly higher than historical data with monotherapy. Epacadostat + pembrolizumab was active in NSCLC (Gangadhar #9014), bladder cancer (Smith #4503), and RCC (Lara #4515). All of this promising efficacy was achieved with a safety/tolerability profile very similar to single-agent anti-PD1. Further work is required to evaluate durability of response and the utility of biomarkers, but it seems likely that IDO + PD1 dual inhibition will play an important role in cancer immunotherapy.

Combining **anti-PD1 + other I-O mechanisms** continues to spark interest. Examples include TLR9 agonist SD-101 + pembro (Leung #9550), anti-LAG3 BMS-986016 + nivo in melanoma (Ascierto #9520), PEG-IL-10 AM0010 + nivo in RCC (Naing #4567), and a PD-L1 and TGF-β bispecific M7824 (Gulley #3006), but these are early findings with small samples. Further study is needed and eagerly awaited. Combining **anti-PD1 + targeted therapy** is also promising, with some striking data involving tyrosine kinase inhibitors: avelumab + axitinib had an ORR ~58% in RCC (Choueiri #4504), pembro + lenvatinib had an ORR ~50% in endometrial cancer (Makker #5598), and nivo ± ipi + cabozantinib had an ORR ~37% in bladder cancer (Apolo #4562). Combining **anti-PD1 + chemotherapy** may also be clinically meaningful (e.g., Bang #4012).

Anti-PD1/PD-L1 therapies are already major products on their own in certain cancer types, but combinations on an anti-PD1/PD-L1 backbone are starting to fulfill their promise to deepen and broaden the impact.

Additional Sources: FDA; Cowen & Co. Therapeutic Categories Outlook Feb 2017

Beyond PD1: Alternative I-O Targets

Non-PD1 I-O agents also continue to generate interesting data, not only in combination with anti-PD1/PD-L1, but also alone or in combination with other non-PD1 agents. For example, **CEA CD3 TCB**, a bispecific antibody targeting the tumor antigen CEA to T cells via CD3, produced monotherapy responses in microsatellite stable colorectal cancer (MSS CRC) (Tabernero #3002), a tumor type known to be resistant to PD1 blockade. **CPI-444**, an adenosine A2A receptor antagonist, produced high rates of disease control as monotherapy in PD1-pretreated NSCLC and RCC (Fong #3004). Adding anti-PD-L1 (atezolizumab) to either of these agents may improve their efficacy, but not dramatically, suggesting that they may be of interest as alternative mechanisms rather than (or in addition to) being combination partners for anti-PD1/PD-L1. In other studies, as has been reported previously, combining **oncolytic viruses + ipi** can more than double ipi's response rate in melanoma (Chesney #9509; Curti #3014), though the durability of those responses still requires verification.

CART (chimeric antigen receptor T cell) therapy has repeatedly outshone PD1 blockade in the treatment of hematologic malignancies. Multiple CART therapies targeting CD19 have shown compelling efficacy for ALL and for non-Hodgkin lymphomas (e.g., at ASH 2015, 2016). While CD19-targeted CART continues to be of interest, and has now shown some activity in multiple myeloma (Garfall #8517), the most dramatic results were for **CART therapy targeting BCMA** for multiple myeloma. Nanjing Legend's CART (LCAR-B38M) and bluebird bio's CART (bb2121) both showed 100% ORR (for bb2121, this excludes patients who received doses below 15 x 10^7) in heavily pretreated myeloma patients, with some responses proven to last a year or more, and safety/tolerability profiles that may be better than the CD19 CARTs (Fan #LBA3001; Berdeja #3010). These initial studies had small numbers of patients, but the early signal was so compelling that the conclusion is inescapable that BCMA-targeted CART will be important for myeloma treatment in the future.

CLARION | Healthcare, LLC

One Financial Center, Suite 1610 Boston MA 02111 Ph: 617.757.7850, www.clarionhealthcare.com

Clarion's Highlights from the

ASCO 2017 Annual Meeting

The Arrival of Tissue-Agnostic Drug Development

ASCO is always a venue for sharing readouts of major clinical trials that will change the practice of specific tumor types (e.g., the LATITUDE and STAMPEDE trials of abiraterone + ADT in hormone-sensitive prostate cancer (Fizazi #LBA3, James #LBA5003), but those conventional achievements were outshone this year by work that defines new cancer indications—not by their tissue of origin, but by their molecular features.

Pembrolizumab in MSI-H cancers: In May, the FDA issued the first cancer therapy approval for a tissue-agnostic indication for Merck's pembrolizumab in microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors. Pivotal data pooled from 5 trials (n=149) showed a 39% ORR, with 78% of responses lasting at least 6 mo. While CRC comprised over half of enrolled patients, the efficacy was similar across 10 other tumor types, paving the way for this landmark approval (Diaz #3071). Surprisingly, the accelerated approval was granted without a companion diagnostic, leaving clinicians wondering how and when should test for MSI or dMMR, particularly outside of CRC. Should PCR tests for MSI-H status or IHC tests for dMMR be used? Which kits/reagents/protocols are appropriate? Merck has committed to develop companion diagnostics for MSI-H and dMMR; these are eagerly awaited.

Larotrectinib in NTRK-fusion positive tumors*:* The other big story for tissue-agnostic therapy was from Loxo Oncology. Their NTRK targeted therapy larotrectinib, shows remarkable efficacy—ORR 78%—in NTRK-fusion positive patients across 17 tumor types, regardless of age, tumor type, NTRK gene variant, or fusion partner (Hyman #LBA2501). With an NDA submission planned for later this year, larotrectinib is on track to become the next therapy to receive a tissue-agnostic approval, and it will have a companion diagnostic. However, NTRK fusions are exceedingly rare: occurring in only 1,500–5,000 cancer diagnoses in the US per year, across many tumor types, including ultra-rare histologies.

More is yet to come: Preliminary results from the I-PREDICT study showed that these two trailblazers are not alone: patients that were matched to a targeted therapy as part of treatment via genomic profiling had a 33% CR/PR rate compared to 0% ORR in unmatched patients in fatal malignancies (Sicklick #2512). NCI's ongoing massive MATCH trial (n=6,452 pts) is testing genotype-matched therapy across 19 distinct trial arms. Defining cancer indications by molecular markers is thus a growing trend, though defining cancers by histology will remain important. As Dr. Keith Flaherty put it in one session, "Lineage matters". For example, BRAF inhibitors have much poorer efficacy in CRC than in melanoma. Furthermore, broad testing of molecular markers remains a challenge; thus economics matters, too. As the field evolves, the utility, value, and implementation of biomarker tests will be carefully considered by clinicians, payers, and regulators.

Additional Sources: FDA.gov https://tinyurl.com/ya2u3ard, Onclive.com https://tinyurl.com/y7t776y6, www.loxooncology.com, Garber 2017 Nat Biotechnol 35:297-8; ASCO '17: TPS2624, TPS2599, TPS10583, Kelly "Immunotherapy for Esophageal and Gastric Cancer"

MACRA-Economic Pressures on Oncology Practices

ASCO primarily focuses on clinical aspects of cancer treatment, and the newsfeeds tend to be dominated by excitement over new therapies. However, this excitement must be tempered by the economic realities which have caused hundreds of US oncology practices to close in the last year and hundreds more to be acquired by hospitals, even while the national cost of cancer care continues to rise at an unsustainable rate. Accordingly, ASCO held multiple sessions (e.g., "Practicing Oncology in the MACRA world", "Practice Realities in a Shifting Policy Landscape", "What Can We Learn from the International Experience?") to review the challenges that practicing oncologists face in the trenches.

MACRA (Medicare Access and CHIP Reauthorization Act) loomed large given that the metrics that practices report this year will help determine Medicare payments in 2019 under the Merit-based Incentive Program System (MIPS). MACRA has noble intentions: to align payment with quality of care while reducing costs, i.e., shifting the US from volume-based to value-based reimbursement. However, the experiences of both academic and community practices show that major investments—such as new personnel and new software—are necessary to meet all the requirements. MACRA allows alternative payment models besides MIPS, such as the CMS Oncology Care Model, but the requirements are equally stringent. Moreover, the financial risk for practices will be unprecedented: under the current plan, MACRA will penalize practices if they report worse outcomes vs prior benchmarks, but in a given practice, the patients vary so much from year to year that penalties may be assigned by random chance. As Dr. Barbara McAneny showed, in a two-sided risk model, a particularly bad string of luck one year could be "practice-ending". The ASCO sessions mentioned some options (e.g., grants) to partially mitigate the cost burden, but even so, the economic challenges for oncology practices will almost certainly intensify.

Additional Sources: ASCO 2017 State of Cancer Care in America; COA 2016 Community Oncology Practice Impact Report; Kaufman et al.2017 J ImmunoTher Cancer 5:38

Prepared by Dennis Chang, Jesse Wolinsky, Natalie German, and Bigyan Bista

CLARION | Healthcare, LLC

One Financial Center, Suite 1610 Boston MA 02111 Ph: 617.757.7850, www.clarionhealthcare.com