Clarion perspectives from the

SITC 2017 Annual Meeting

In November, Clarion team members attended the Society for Immunotherapy of Cancer (SITC) annual meeting. As cancer Immunotherapy has grown from an intriguing possibility into a transformative reality, the SITC meeting has also grown from an intimate gathering into a major clinical conference with hundreds of posters and oral presentations plus two days of pre-conference programs. Below are some highlights.

A window into the future of cell-based immunotherapies

2017 has been a landmark year for CAR-T (chimeric antigen receptor T cell) therapy. The SITC meeting's Keynote Address[1] celebrated FDA approvals of the first CAR-T therapies, Novartis's Kymriah (tisagenlecleucel) and Kite's Yescarta (axicabtagene ciloleucel), and their extraordinary clinical efficacy against certain leukemias and lymphomas. However, there remains room for improvement, especially in applying the technology to new indications. Dozens of posters and talks throughout the conference offered a glimpse into innovations still to come for CAR-T and other adoptive cell transfer (ACT) therapies. Although it is too early to judge which specific approaches will succeed, the volume and diversity of development activity presage an exciting future.

- **Enhancing efficacy through drug combinations:** Attempts to overcome mechanisms of immune resistance by combining CAR-T therapies with appropriate drugs include addressing resistance to BCMA-targeted CAR-T through cleavage of BCMA using a gamma secretase inhibitor[2], T cell exhaustion using anti-PD1 therapy[3], metabolic immune resistance using an IDO1 inhibitor[4], and insufficient T cell infiltration of tumors using a tumor penetrating peptide[5] or IL-15 agonist therapy[6].
- **Targeting solid tumors through novel receptors:** Efforts to develop CAR-T therapies for solid tumors include targeting FGFR4 for rhabdomyosarcoma[7], HER2 for breast cancer[8], and chlorotoxin—added to bind glioma cells—for glioblastoma[9]. Some groups are using bispecific receptors instead of conventional CARs[10,11,12], while others are using TCRs[13, 14] or modified TCRs[15] targeting mesothelin or other antigens.
- **New genetic engineering approaches:** CAR-T and TCR therapies depend on genetic engineering for their targeting receptors, but additional genetic manipulations may improve T cell activity[16,17], overcome resistance mechanisms such as TGFβ signaling[18], or increase tumor tropism by adding a chemokine receptor[19,20,21]. They may also lead to "off-the-shelf" ACTs (rather than modifying a patient's own cells); one potential approach involves CRISPR-mediated deletion of the TCRα gene (TRAC) and B2M[22].
- **NK cell therapies:** Multiple groups are also developing/exploring ACTs based not on T-cells but on natural killer (NK) cells[23,24,25,26]. The potential importance of NK-based approaches was illustrated by data showing that HLA-E upregulation—which has been implicated in NK cell evasion—is associated with resistance to T cell-targeting immune checkpoint blockade in Merkel cell carcinoma[27].

Sources: 1) Grupp, SITC '17, "The CAR T Revolution in Leukemia"; 2) O10; 3) P316; 4) P199; 5) P206; 6) P309; 7) P196; 8) P517; 9) P201; 10) P198; 11) P214; 12) P207; 13) P161; 14) P166; 15) P171; 16) P168; 17) P205; 18) P187; 19) P180; 20) P184; 21) P504; 22) P181; 23) P167; 24) P188; 25) P176; 26) P266; 27) O27.

Building on immune checkpoint blockade with novel combinations

As the anti-PD1, PD-L1, and CTLA4 immune checkpoint inhibitors (ICIs) continue to solidify their importance and expand their clinical applications—with 11 new FDA approvals in just the first 10 months of 2017—their limitations have also become increasingly clear. Only a minority of cancer patients can hope to benefit from these drugs when they are administered as single agents. Accordingly, hundreds of clinical studies have been initiated to explore different drug combinations on an ICI backbone. SITC attendees were treated to some promising early data for several of these novel combinations.

- **NKTR-214 + nivolumab:** The cytokine IL-2 was launched a quarter-century ago as Proleukin (aldesleukin). Nektar's NKTR-214 is IL-2 altered so that it stimulates effector T cells (Teffs) much more than regulatory T cells (Tregs), and has been pegylated for improved pharmacokinetics. The combination of NKTR-214 + the BMS anti-PD1 nivolumab seems to have an ORR at least as good as historical data for nivo + ipilimumab ("nivo+ipi") in anti-PD1-naïve melanoma, NSCLC, and RCC, but with better safety/tolerability.[28] The number of patients in this dataset is still small, so the field eagerly awaits further development.

- **A cytokine revival:** The Nektar product is actually only one of several cytokine-based approaches in development. For example, Armo Biosciences has AM0010, a pegylated IL-10 agent which shows promise in combination with nivo or pembrolizumab ("pembro")[29]; Altor Bioscience has ALT-803, an IL-15 "superagonist"[30]; and OncoSec Medical has tavokinogene telsaplasmid, an IL-12 plasmid therapy with intriguing data in combination with pembro for melanoma[31].
- **IDO1 + PD1 dual inhibition:** Earlier this year, Incyte presented compelling early data for IDO1 inhibitor epacadostat + nivo or pembro. New IDO1 inhibitor regimens are also emerging, such as BMS-986205 + nivo[32], which showed early efficacy in urothelial cancer similar to epacadostat + pembro[33].
- **IMO-2125 + ipilimumab:** While multiple anti-PD1-based combinations are efficacious for anti-PD1-naïve patients in immunogenic tumors, treatment of anti-PD1-resistant or refractory patients remains an unmet need. Many regimens are being tested in this setting, including Idera's TLR9 agonist IMO-2125 in combination with ipi: 5 of 10 melanoma patients responded[34]. Although the sample size was small, 50% would represent the best ORR seen to date post-anti-PD1.
- **Many others:** Additional combination partners for ICIs range from OX40 agonists[35] to adenosine A2A receptor antagonists[36] to anti-CSF1R[37] to HDAC inhibitors[38] and others. Testing a range of approaches is important because immunotherapy will not be a one-size-fits-all solution. Different combinations will be needed to address distinct mechanisms of resistance: tumor microenvironment (TME) immuno-suppression, immune cell exclusion, and lack of immune activation (the "immune desert" phenotype).

Sources: 28) O20; 29) O12; 30) O25; 31) P524; 32) O41; 33) ASCO 2017 #4503; 34) O18; 35) O17; 36) O4; 37) O42; 38) O19.

Mapping the way towards precision immuno-oncology

As the number of potential I-O regimens explodes, biomarkers to guide their use become increasingly vital. Accordingly, SITC held a cross-functional, pre-conference event dedicated to this topic ("Immuno-Oncology Biomarkers: Today's Imperatives for Tomorrow's Needs"), and included over 160 posters and talks with a major biomarker component. Key findings and perspectives include the following:

- **Multiple biomarkers are better than one:** The context in which immunotherapies must act involves a complex choreography of host, tumor-intrinsic, and TME factors, each with multiple molecular pathways and cell types[39]. Accordingly, diagnostics companies are starting to develop composite IO tests, such as the HalioDx *Halioseek* test for PD-L1 and CD8 multiplex immunohistochemistry (IHC)[40], and the OmniSeq *Immune Report Card* panel combining over 5 distinct assay types[41].
- **Mechanism-specific biomarkers:** PD-L1 IHC can enrich for responses to anti-PD(L)1 treatment[39], and LAG3 IHC enriches for responses to anti-LAG3 + anti-PD1 therapy[42]. Similarly, a NanoString assay for A2AR and CD73 expression enriches for clinical benefit to Corvus's A2A inhibitor CPI-444 ± Roche's anti-PD-L1 agent atezolizumab—with greater predictivity than either marker alone[36]. These mechanism-specific markers are likely to be validated and become commercially available in the near term.
- **Tumor mutational burden:** Assays for TMB also offer near-term potential for clinical utility. For example, the FoundationOne panel sequences only 1.5% of the genes in the exome, and yet measures TMB with robustness comparable to whole exome sequencing[43], and may soon be applied to blood-based tests[39,44]. Neither mechanism-specific biomarkers nor TMB is likely to be sufficient as a single biomarker, but both hold potential as components of larger biomarker panels tailored to individual tumor types.
- **Many other IO biomarkers under exploration,** including measures of gene expression, gut microbiome, and TCR/T-cell repertoire, but their clinical validation may take considerable time and effort. To illustrate: three different studies of the microbiome of melanoma patients each identified different bacteria as predictive of immunotherapy response: *Faecalibacterium*[45], *Bifidobacterium*[46], and *Akkermansia*[47].

Sources: 39) Hegde, Pre-conference; 40) Hermitte, Pre-conference; 41) Morrison, Pre-conference; 42) ASCO 2017 #9520; 43) Szustakowski, Pre-Conference; 44) P96; 45) O30; 46) P394; 47) Routy 2017 Science

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