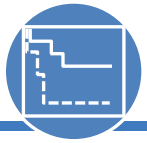
Clarion perspectives from the

ASCO-SITC Clinical Immuno-Oncology Symposium 2018

A Clarion team was among over 1,100 attendees at the 2nd annual ASCO-SITC joint symposium, to witness the readouts of clinical and translational research in immuno-oncology and implications for clinical care, including these highlights:

Confirmatory data updates: Following the survival curve



Immune checkpoint inhibitors have been the focus of thousands of presentations across dozens of conferences over the past several years, and yet we are still learning about the clinical profiles of these new therapeutic agents, how best to use them, and for which patients. One of the services that ASCO-SITC provides is a set of General Sessions that provide a review of the state of immuno-oncology for specific tumor types: melanoma, lung cancer, genitourinary cancers, hematologic malignancies, and head and neck cancers. The story of immunotherapy in each of these cancers is one of astonishing progress and dramatic responses.

Furthermore, this story continues to unfold, as new data analyses confirm in different sub-populations and settings that the "tail" of the survival curve flattens out, indicating durable disease control and—although continued follow-up is required to confirm it—potentially cures. Examples of such data at ASCO-SITC include:

- **Melanoma: Avelumab** joins the list of PD-1/PD-L1 axis inhibitors showing durable benefit in previously treated metastatic melanoma, with a 24-mo. OS of 47.7%[1].
- **Merkel cell carcinoma**: Follow-up of the **avelumab** registrational trial shows an 18-mo. OS of 40% and a plateau >30% extending beyond 30 mo[2].
- **Mesothelioma:** Updated data from the **avelumab** phase 1b trial shows 12-mo. OS of 45.9%[3].
- **NSCLC: Durvalumab** showed 24-mo. OS of 48% in 1L and 34% in 2L in the subset of patients with PD-L1 expression in ≥25% of tumor cells[4].
- **Brain metastases:** New data continues to support checkpoint inhibition in patients with brain mets[5].
- **Kaposi sarcoma: Anti-PD1** agents previously showed some modest activity against sarcomas[6-8]; now a study shows that **HIV+** Kaposi sarcoma may be highly sensitive to such agents, as 6 of 9 (67%) patients had an objective response (1 CR, 5 PR)[9].

Sources: 1) #191; 2) #192; 3) #166; 4) #169; 5) #214; 6) Tawbi, ASCO 2017 #11006; 7) Paoluzzi, ASCO 2016 #11047; 8) Schleinberg, ASCO 2017 #3060; 9) #63

New combinations and mechanisms: Expanding the toolkit

Anti-PD1 immunotherapies provide durable responses to only a small minority of cancer patients. Additional mechanisms and combinations are essential for realizing the full potential of immuno-oncology. Examples of new regimens with early data presented at ASCO-SITC 2018 include:

- **Anti-PD1 (spartalizumab; PDR001) + BRAF inhibitor (dabrafenib) + MEK inhibitor (trametinib)** triple combination **[Novartis]**: in BRAF-mutant, previously untreated advanced melanoma, 100% ORR and 33% CR was reported in the safety lead-in for the phase 3 COMBI-I trial[10], far exceeding historical data for either anti-PD1 alone or the dabrafenib + trametinib double combination[11].
- **Anti-PD1 (tislelizumab; BGB-A317) + PARP inhibitor (BGB-290) [Beigene]:** In a phase 1 trial, 20% ORR and 4% CR was reported across all tumor types, including both BRCA-wt and BRCA-mut patients. The ORR was >50% in the BRCA-mut subset[12]. Further study is warranted to evaluate this combination
- **PGE4 inhibitor (E7046) [Eisai]** may be a new approach to modulate myeloid cells and improve T cell infiltration. Although it remains to be seen whether it synergizes in combination with immune checkpoint inhibitors and radiation, as shown in preclinical studies, its phase 1 first-in-human trial showed promising changes in gene expression, cytokine release, and T cell infiltration[13].
- **Multi-cytokine therapy (IRX-2) [IRX Therapeutics]** may improve T-cell activation and infiltration. In a phase 2 neoadjuvant study in resectable HNSCC, patients with a higher level of TILs (≥35% vs <35%) post-treatment had significantly improved survival (5-yr OS: >75% vs. <20%)[14]. In a neoadjuvant study in early-stage breast cancer, pharmacodynamic responses were seen in gene expression, stromal TILs, peripheral T-cells, and PD-L1 expression, suggesting IRX-2 may synergize with other immunotherapies[15].

Sources: 10) #189; 11) FDA label; 12) #48; 13) #49; 14) Naylor, ASCO 2011 #5588; 15) #7

T cell-based therapies: Gaining steam

2017 was a landmark year for CAR-T with the FDA approvals of both Novartis's Kymriah (**tisagenlecleucel**) and Gilead/Kite's Yescarta (**axicabtagene ciloleucel**, "axi-cel")[16], but the range of presentations at ASCO-SITC shows that innovation in T cell-based therapies is just beginning to gain momentum. Some of the highlights include:

- **JCAR017 updated results continue to impress in NHL:** Hot on the heels of an impressive readout at ASH 2017[17] and news of Celgene's plan to acquire Juno Therapeutics[18], JCAR017 presented updated efficacy results of its CD19-targeted CAR-T therapy in DLBCL. A phase 1 trial reported 81% ORR and 63% CR, with a 50% CR rate at 6 mo[19]. These striking response rates were accompanied by low rates of severe CRS (1%) and neurotoxicity (12%). Evaluation in the pivotal cohort is currently ongoing.
- **TriCAR-T cells targeting CD19-negative B-ALL:** a preclinical study from Baylor demonstrated that tri-specific CAR-T cells targeting CD19, CD20, and CD22 effectively kill both CD19-positive and -negative primary ALL cells in an *in vitro* model and demonstrate superior serial killing comparing to monovalent CD19 CAR-T cells[20]. *In vivo* experiments are ongoing.
- **Viral-specific T cell (VST) therapy and associated combinations:** Cancers associated with viruses such as HPV (cervical cancer, head and neck cancers) and EBV (several lymphomas including Burkitt's, Hodgkin's, and others)[22] are prime targets for immunotherapies because of their multiple viral antigens. The meeting's final keynote presentation presented promising early data for generating an off-the-shelf T cell therapy using virus-infected cultured cells. For the relevant cancers, these multi-antigen VST therapies may be superior to TCR or CAR-T therapies based on single antigens, but may also be combined with CAR-T therapy or vaccines for greater effect[23].

Sources: 16) FDA; 17) Abramson, ASH 2017 #581; 18) Celgene press release Jan. 22, 2018; 19) #120; 20) #121; 22) McLaughlin-Drubin 2008 Biochim Biophys Acta 1782:127-50; 23) Brenner, Keynote

I-O biomarkers: Pursuing precision

Developing biomarker approaches to target the right immunotherapy to the right patients continues to be a high priority. Advances presented at this meeting include the following:

- **Integrating TMB into a combination biomarker approach for NSCLC:** Data analyses in an NSCLC study show that tumor mutational burden (TMB) is orthogonal to (independent of) PD-L1 expression or an IFNγ signature in predicting of response to anti-PD1 therapy[24].
- **9p24.1 as a new tumor agnostic biomarker for anti-PD1:** Pembrolizumab and nivolumab have previously shown high response rates across tumor types with high microsatellite instability or deficient mismatch repair (MSI-H/dMMR)[25]. At this meeting, amplification of the 9p24.1 locus (where the PD-L1 gene resides) was also linked to response to anti-PD1 in diverse solid tumors: 6 of 9 (67%) such patients responded. However, these amplifications are even rarer than MSI-H; they are found in only 0.7% of a set of >117,000 solid tumors[26].
- **Endogenous retrovirus (ERV) as a new biomarker in TMB-low tumors:** Analysis of clear cell RCC patients showed that expression of ERVs correlates with immune activation and checkpoint pathway upregulation, and may explain why ccRCC is so responsive to immunotherapy despite its relatively low TMB. One specific retrovirus, ERV3-2, was associated with response to anti-PD1 blockade in RCC and may be of interest as a biomarker across multiple cancer types[27].
- **β-catenin expression as a marker of resistance in NSCLC**: A study in NSCLC found β-catenin expression was associated with reduced CD8+ T cell infiltration. β-catenin–negative patients had significantly improved survival post-surgery (mOS: NR vs. 43.8 mo)[28]. This new data resonates with a study analyzing tumor samples from melanoma patients, linking β-catenin to immunotherapy resistance[29].

Sources: 24) Hellmann, GS6-2; 25) FDA; 26) #47; 27) #104; 28) #142; 29) Spranger 2015 Nature 523:231

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