Highlights From AACR Annual Meeting 2019

PD-1/L1 Resistance

Next-Gen Cell Therapies

TRKi

PD-1/L1 Resistance

- **PD-1/L1 resistance** has been an elusive issue with both cold and hot tumors. Limited success here has been attributed to the lack of optimal predictive biomarkers and the multitude of immunosuppressive factors in the tumor micro-environment.
- Myriad novel IO approaches are currently being investigated, though have modest data till date. Early-phase data in PD-1 resistant patients on two novel stimulatory immunotherapies (CD40 and ICOS) remains modest. Further updates for TLR9 and vaccines continued to build on their promise.
- Immune biomarkers such as ICOS high peripheral CD4 T cells, lymphoid aggregates were explored for patient selection, but need more research and validation in larger studies.

Next-Gen Cell Therapies

- Innovative technological solutions may address challenges seen with the first-gen CAR-Ts. Highlights include:
  (1) early activity of novel CAR-Ts in the clinic;
  (2) approaches to address two of the main challenges faced by adoptive cellular therapies in the clinic – loss of targeted antigen and exhaustion of CAR-T cells;
  (3) interesting CAR design strategies for improved efficacy and safety from the "bench."

TRKi

- Larotrectinib is the first TRKi that obtained a tumor agnostic approval in TRK fusion positive patients. However, its positioning is already being challenged by the next-gen TRKi given their potential applicability in resistant mutations.
- Presentations focused on approaches to overcoming resistance to first-gen TRKi, be it with next-gen TRKi or identifying some of the off-target resistant mutations.

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Resisting the IO Resistance

Research and clinical interrogation has progressively focused on mechanisms that drive PD-L1 resistance in both hot and cold tumors. The most promising approaches in IO progressors include antibody drug conjugates (nectin-4 in urothelial cancer and TROP-2 in NSCLC, bladder cancer), TKIs (Sitravatinib + PD-1i in NSCLC) and adoptive T-cell therapy (TILs in melanoma and cervical cancer). Other early attempts include a myriad of mechanisms such as epigenetic mechanisms (E.g., HDACi) and stimulatory approaches (E.g., TLR-9, CD122, IL-15 superagonist in combination with anti-PD-1i).

Considerable challenges resulting in such sub-optimal responses are due to:
- **Biomarkers** have had a low predictive value in determining the subset of patients likely to respond
- **Tumor immune microenvironment** of resistant patients is characterized by several immunosuppressive factors that have to be circumvented to demonstrate a clinical benefit

At AACR 2019, for the first time, early-phase data was presented with two novel stimulatory immunotherapies (CD40 and ICOS) and further updated for TLR9 and vaccines; exploratory immune biomarker analysis was also presented. However, this data needs to be replicated in larger studies (beyond ADC, TKIs, and TILs).

PD-1 Progressors in NSCLC and Melanoma
- Agonistic CD40 mAb acts by reversing T-cell exhaustion, making it more amenable for PD-1 resistant tumors to respond to PD-1 based and/or chemotherapy-based combinations[1]
  - APX005M, a potent CD40 agonist that activates tumor-specific CD8+ T cells by enhancing antigen processing and presentation, as well as providing co-stimulatory signals (CD80, CD86, and IL-12)
- APX005M + Nivolumab combination have early data in PD-1 refractory melanoma patients (progressive disease while on or within 3 months of anti-PD-1 therapy)[2]
  - Phase Ib: 20% PR in 5 patients; additional 2 patients had prolonged SD (>8 months)
  - Phase II of the study has currently enrolled 10 patients in the melanoma cohort – ORR 20% (2 PR); additional 2 patients had prolonged SD
- Preliminary biomarker analysis revealed high TILs and increased expression of IFN-γ inducible cytokines (CXCL9/CXCL10) while on treatment, corroborating with the mechanism of action of CD40[1]

Future Direction: Apexigen continues to enroll patients in Phase II of the study in an effort to validate data in larger patient subsets

- Intra-tumoral TLR9-agonist was implicated in reversing resistance to anti-PD-1 blockade via inducing interferon-alpha production which, in turn, activates NK cells, blocking tumor-mediated immune suppression, and promotes Th1 and CD8+ T cell homing into the tumor
  - Translational analysis has shown positive correlation of higher baseline plasmacytoid dendritic cell levels with responses – indicating potential as an enrichment biomarker
- Previous data with SD-101 + Pembrolizumab reported 19% RR and longer DoR (median not reached) in melanoma patients who had progressed on anti-PD-1 therapy[2]
  - Data was presented on novel TLR9-agonist DV-281 (via nebulizer) in NSCLC patients progressed on anti-PD-1 therapy
  - When combined with Nivolumab, DV-281 demonstrated dramatic clinical improvement and tumor shrinkage, demonstrating early signs of clinical activity

Future Direction: Dynavax continues to plan for expansion cohorts evaluating DV-281 while pivotal SYNERGY-001 (KN-184) is ongoing for its flagship product SD-101

- Idera Pharmaceuticals presented data from ILLUMINATE-101 study concluding that TLR-9 agonist, Tilsotolimod induced changes in immune checkpoint gene expression in several tumors (melanoma, NSCLC, CRC, pancreatic, and others)[3]
  - NanoString analysis indicated rapid increase in dendritic cell activation and upregulation of IFN-alpha signaling, suggesting improved antigen presentation
  - Additionally, Tilsotolimod-induced upregulation of antigen presentation appeared to be tumor agnostic
  - Idera continues to evaluate Tilsotolimod + Ipilimumab combination in Phase II pivotal trial (ILLUMINATE-204) – data readout expected by the end of 2019
- JTX-2011 (Vopratelimab from Jounce Therapeutics) is an ICOS agonist antibody intended to stimulate primed CD4 T effector cells[4,5]
  - Clinical data was presented on its flagship product – ICOS agonist Vopratelimab (JTX-2011) in refractory solid tumor patients (ICONIC trial)

- Results from the trial showed possible emergence of a distinct and persistent population defined by the "ICOS high peripheral CD4 T cells," where Vopratelimab mono and combination with PD-1i demonstrated seemingly survival benefit as OS was not reached at 20 months vs. in that of ICOS low population; mPFS had tripled to 6.2 months
- Role of ICOS expression as potential biomarker, predictive of Vopratelimab response will be further validated
- Emergence of ICOS high peripheral CD4 T cells in evaluated patients did not have any trend with common markers such as PD-L1+, TMB-H, and MSI-High status, suggesting no association

Future Direction: To prioritize a combination with anti-CTLA-4, a mechanism known to upregulate and prime activated T cells and synergize with ICOS, in the dose expansion cohort targeting PD-1 progressors

Cold Tumors – Pancreatic Cancer
- Hypothesis being tested is that naturally non-immunogenic cancers, such as pancreatic, require at least two steps to induce an optimal immune response[6]
  - Reprogram immune responses following T-cell activation by stimulating T-cell agonists and inhibiting immunosuppressive signals; having best activated T cells is a key
  - Vaccines could address the first step to improve the effector T-cells infiltration in invasive pancreatic cancer followed by removing checkpoint blockade or mobilizing the immune response by using agonists
  - An observation of lymphoid aggregates was seen in the tumor biopsies suggesting T-cell infiltration with the administration of a neo-antigen vaccine a few years ago; it was followed by upregulation of PD-L1, the T-cell inhibitory signal
- Data is awaited from a neoadjuvant study of a vaccine, GVAX ± Nivolumab

Future Direction: New technologies are sensitive enough to predict early responders to immunotherapy, and will support personalized immunotherapy based on deep TME profiling, such as testing TCR repertoires, ahead of treatment

- Interim Phase Ib/II data readout from PRINCE study indicated promising antitumor activity with APX005M (agonistic CD40 mAb) + Nab Paclitaxel + Gemcitabine ± Nivolumab combination in frontline PDAC, a hard to treat tumor characterized by several immunosuppressive elements[7]
  - Promising ORR of 54% and DCR of 92% in 24 patients (across all cohorts) was observed
  - Baseline tumors were characterized by low immune infiltration, low CD8+ T cells
  - Decrease in KRAS variant allelic frequencies in ctDNA correlated with tumor shrinkage

Future Direction: Further immune profiling of samples and Phase II expansion cohort initiated

Sources: 1. Harriet Kluger et al, CT089/13, AACR 2019; 2. E. Garon et al, Abstract 8304 AACR 2019; 3. Hani M. Babikar et al, Abstract 4062 AACR 2019; 4. Timothy A. Yap et al, Abstract CT189 AACR 2019; 5. Harvey et al, Abstract 4053 AACR 2019; 6. Elizabeth M Jaffee Presidential Address, AACR 2019; 7. Harriet Kluger et al, CT089/13, AACR 2019

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Tracking TRK

The next generation TRKi are coming up quickly to challenge the initial positioning of Larotrectinib by targeting resistant TRK mutations. However, unlike historical precedence with other targeted therapies, the research is quickly evolving with next gen TRKi to circumvent resistance – upfront or in later lines. Of the several TRK related presentations at AACR, we selected four key presentations that focused on approaches to overcome resistance to first-gen TRKi such as Larotrectinib. Larotrectinib is the first TRKi that obtained a tumor agnostic approval in TRK fusion positive patients, with RR of 81% and mDOR not reached at 17.6 months.

Next Generation TRKi

Data was presented at AACR 2019 with three next gen TRKi that are currently in clinical development – LOXO-195, Repotrectinib and PBI-200 in resistant mutations and are positioning themselves subsequent to the first-gen TRKi (Larotrectinib and Entrectinib). Structural improvements for tighter binding of the next gen TRKi to the ATP pocket binding and avoiding steric clashes make them clinically active in resistant mutations.

LOXO-195 is a second-gene TRKi that is known to be active in all types of resistant mutations – solvent front (SFM), gatekeeper (GK) and xDFG mutations. SFM appear to be the most type of resistant mutation (~45%) acquired with a first-gen TRKi. Another 30% of patients harbor GK, XDFG and other bypass mutations.[1] Approximately 20% of patients had unknown mutations.

- 45% of patients with TRK resistant mutations had responded to LOXO-195, though data in specific subsets of TRK resistant mutations needs to be demonstrated; also, as expected, LOXO-195 was not effective in patients with TRK independent resistant mutations.

Repotrectinib is one such low molecular weight next gen TRKi that claimed activity in patients with diverse resistant mutations.[2]

- When compared to LOXO-195 (second-gen TRKi), it was 10 times more potent against solvent front (SFM, common form of resistance to first-gen TRKi), 100 times more potent against gatekeeper mutations and the only TRKi till date active in compound mutations.

- PR was observed in two Repotrectinib treated patients (metastatic salivary gland tumor and cholangiocarcinoma), who had previously received first-gen TRKi (Entrectinib or Larotrectinib).

PBI-200, as developed by Pyramid Biosciences is moving into the clinic, and is a second-gen TRKi.[3]

It demonstrated higher activity in G595R, G639R, G623R solvent front resistant mutations as compared to first-gen TRKi, Larotrectinib and Entrectinib, besides working in both WT and mutant TRK fusions. Permeability into the BBB has been an issue with Larotrectinib and less with Entrectinib. However, PBI-100 demonstrated several fold increase in brain penetration as compared to the first-gen TRKi and some of the second-gen TRKi such as LOXO-195 and Repotrectinib.

Off-Target Resistant Mutations

It has also been observed that TRK independent mechanisms maybe driving resistance to TRKi. Data from a study, supported by Loxo Oncology, presented some bypass resistant mechanisms that manifested in 6 TRK fusion + GI cancer patients treated with first or second-gen TRKi. These were primarily BRAFV600E mut, KRASG12a or D mutations, MET amp that notably converged on the ERK signaling pathway.[4]

- Preclinical study in the PDX models (derived from patients with BRAFV600E mutations) with LOXO-195 and Trametinib (MEKi) combination was effective in tumor growth inhibition and also the growth of resistant mutant cell lines.

Future Direction:

- The rapid evolution of the next gen TRKi shows potential to form a continuum of care for TRK fusion patients progressing on first-gen TRKi. Rational TRKi combination therapies in TRK dependent and independent resistant mutations should be explored further.

Sources:

1. Hyman David, Abstract CT127, AACR 2019
2. Drilon Alexander, Abstract 442, AACR 2019
3. Pal Kollol, Abstract 2198, AACR 2019
4. Cocco Emiliano, LB-118, AACR 2019

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Advancements in Adoptive Cell Therapies

Despite the recent CAR-T approvals in select hematologic malignancies and the remarkable expansion of CAR-T clinical trials for a wide range of heme and solid tumors—many challenges remain. The chief among them are identifying tumor-restricted antigens to minimize on-target, off-tumor toxicities, enhancing tumor-killing effect, improving T-cell persistence and developing strategies to ameliorate CAR-T associated toxicities, such as cytokine release syndrome (CRS) and CAR-T-related encephalopathy syndrome. At AACR 2019, an array of presentations described innovative technological solutions to address these challenges. The highlights were (1) early activity of novel CAR-Ts in the clinic, (2) approaches to address two of the main challenges faced by adoptive cellular therapies in the clinic – loss of targeted antigen and exhaustion of CAR-T cells, and (3) interesting CAR design strategies for improved efficacy and safety from the "bench."

Early clinical results of CAR-Ts:

Early promising data was presented on Mesothelin-targeted CAR-T cells in malignant pleural mesotheliomma, Her2-targeted CAR-T cells in advanced sarcomas, and CD19/CD22 bispecific CAR in B-cell malignancies

a. A Phase I study reported that the humanized mesothelin targeted CAR (iCasM28z CAR), when intrapleurally administered as a single dose followed by PD-1 checkpoint blockade, resulted in durable responses (72% response rate) in 15 mesothelioma patients. No CRS or neurotoxicity was observed in any patient. The hypothesis is that the mesothelin-targeted CAR-T-cell therapy transforms the tumor microenvironment (TME) to a more "immune hot" signature, thus making the tumors more susceptible to PD-1 blockade. A clinical trial specifically analyzing the combination of CAR-T cells and anti-PD-1/L1 agent is planned to start later in 2019.[1]

b. Another Phase I study (HEROS) evaluated autologous HER2-targeted CAR-T cells in patients with advanced HER2+ sarcomas, after lymphodepleting chemotherapy. These cells additionally express CD-28, which make the T cells persist longer when stimulated. Two of the 10 patients treated on the protocol, experienced long-term complete responses (CRs) and 3 patients had stable disease. Although a majority of patients treated developed CRS, these events were resolved within 5 days by supportive care. This study uses a CD-28 modified, Her2-targted CAR and follows an earlier trial which analyzed the efficacy/safety of just the Her2-targeting component and achieved an mOS of 10.3 months in 19 patients.[2]

Combating antigen escape and T-cell exhaustion that drive tumor resistance:

Antigen low relapses limit the long-term durability of response following CAR therapies.

a. Although CD19-targeted CAR Ts have received approvals in some heme malignancies, relapses with loss or diminished surface expression of CD19 are increasingly recognized as a cause of treatment failure. CD22-targeted CAR-T cells are poised to address leukemia resistant to anti-CD19 immunotherapy, demonstrating that resistance to immunotherapy via antigen loss can be overcome by treatment with CAR-T cells targeting an alternative antigen, opening the way to dual targeted CAR therapies. CD19/CD22 bispecific CAR-T cells have begun to show efficacy along with a good safety profile in relapsed/refractory B-cell malignancies. One CR and 2 PRs were noted in 5 DLBCL patients treated and 5 CRs and 1 PR among 7 B-ALL patients treated.[3,4]

T-cell exhaustion occurs commonly in CAR-T cells and is a major factor limiting success, especially in solid tumors.

b. In one study, c-Jun overexpression in the engineered CAR-T cells demonstrates increased efficacy in controlling even low-antigen disease in in vivo preclinical models. Additionally, transcription factors belonging to the bZIP/IRF family were identified as key components contributing to the T cell exhaustive signature using whole genome analyses. New CAR-T cell designs focused on including modulation of bZIP/IRF-motif proteins (such as c-Jun) can potentially enhance treatment efficacy while resisting CAR-T cell exhaustion.[5]

CAR-T Cell Design/Engineering Strategies:

Improved therapeutic T cells have multiple sensors that recognize combinations of tumor antigens, allowing the cells to assess their environment and make more precise decisions on when to activate.

a. Universal Immune Receptor using SpyCatcher enables covalent attachment of targeting ligands (SpyTag) to the T-cell surface receptors and allows for dose-dependent cytokine secretion and specific lysis of antigen-expressing tumor cells. In a preclinical study, cell populations that expressed both Her2 and EGFR were demonstrated to be specifically selected using this technology. Although early in development, an array of different antigens (e.g., Her2, EGFR, EpCAM, and CD20) can be recognized by Spy-T cells, either simultaneously or sequentially, thus broadening the possibility of response against tumors with heterogenous antigen expression.[6]

b. Combining induced pluripotent stem cells (iPSC) and genome editing technologies, iCAR-T cells have been designed such that tumor-targeted T cells can arise from a single clone of iPSC. This technology could achieve 100% accuracy in the genome editing of the target using CRISPR technology, without off-target effects. One study disrupts the diacylglycerol kinase proteins (DGKα and DGKζ) and demonstrates enhanced persistence and improved anti-tumor activity of iCAR-T cells in in vivo tumor models. DGKs are membrane-bound kinases that modulate multiple pathways including ERK, VEGF, c-Met, mTOR, and others. In immune cells, DGK inhibition boosts T-cell activation by increasing Ras/Erk pathway activity, which, in turn, drives IL-2 receptor expression and T-cell proliferation.[7]

1. Prasad Adusumilli, AACR 2019, A phase I clinical trial of malignant pleural disease treated with regionally delivered autologous mesothelin-targeted CAR T cells: Safety and efficacy.

2. Shoba Navai, AACR 2019, Administration of HER2-CAR T cells after lymphodepletion safely improves T cell expansion and induces clinical responses in patients with advanced sarcomas.

3. Crystal Mackall, AACR 2019, Next-generation CAR-T cells designed to overcome tumor resistance.

4. Kendarian Saad, AACR 2019, CAR-T cells in the clinic: Strategies to enhance efficacy and reduce toxicity.

5. Crystal Mackall, AACR 2019, Next-generation CAR-T cells designed to overcome tumor resistance.

6. Nicholas Minutolo, AACR 2019, Dose control of CAR-like T cell activity through post-translational covalent loading of ligands to a universal immune receptor.

7. Tatsuki Ueda, AACR 2019, Enhanced effector responses of regenerated CAR-T cells derived from genome edited iPSCs.