Clarion Perspectives from the

AACR 2019 Annual Meeting

Mar 29–Apr 3, 2019 • Atlanta, GA, USA

Prepared by Natalie Thovmasian and Dennis Chang

Immunotherapy Continues to Make Progress

Early clinical signals for hard-to-treat cancers

- **Pancreatic adenocarcinoma** sees unprecedented response rates in the frontline metastatic setting
  - CD40 agonist **APX005M** [Apexigen] **± nivolumab** (Opdivo) [BMS] **+ gemcitabine + nab-paclitaxel (Abraxane)** [Celgene] produced an ORR of 54% (n=24)[1], more than double the historical ORR for gem + Abraxane (23%)[2]
  - Vitamin D analog **paricalcitol + nivolumab + gem + Abraxane** had even more impressive results, with ORR 83% (n=23), mPFS 8.2 mo, and mOS 15.3 mo[3]. By comparison, gem + Abraxane had mPFS 5.5 mo and mOS 8.5 mo in its pivotal trial[2]. Paricalcitol may help address immunosuppression by myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs)[3]
- **Glioblastoma multiforme** (GBM) sees improved survival from antisense approaches
  - **IGV-001** [Imvax] is a personalized vaccine produced from autologous tumor cells treated with IGF1R antisense oligonucleotides, placed into 10–20 biodiffusion chambers, and then implanted into a patient's abdomen for 24–48 hours. Patients treated with IGV-001 post-surgery had significantly better survival than GBM patients previously given standard of care at the same institution: mOS = 17.3 mo. (n=35) vs 12.1 mo.[4]
  - TGFβR2 antisense **trabedersen (OT-101)** [Oncotelic] as a single agent was non-inferior to temozolomide, but adding trabedersen to chemo doubled the mOS vs chemo alone: 26.2 mo. (n=44) vs 13.1 mo. (n=18) in chemo-naïve patients[5]
- **Castrate-resistant prostate cancer** (CRPC) shows an early signal
  - Adenosine A2a receptor inhibitor **AZD4635 ± durvalumab** (Imfinzi) [AstraZeneca] produced 3 PR and 4 SD in 8 total CRPC patients; 1 PR and 2 SD were from AZD4635 monotherapy (n=4)[6]

Clinical updates on adding novel I-O agents to anti-PD1/PD-L1

- A TGFβ trap fused to anti-PD-L1, **bintrafusp alfa (M7824)** [EMD Serono/GSK] had previously reported promising data in 17 patients with HPV-associated/positive cancers (cervical, head and neck, and anal SCC)[7]. An updated analysis (n=43) continues to support efficacy, with ORR ~35% including delayed responses, median DoR not yet been reached, and 12-month OS ~60%[8]
- Class I HDAC inhibitor **entinostat** [Syndax] + **pembrolizumab** (Keytruda) [Merck] had previously reported efficacy in the post-anti-PD1/PD-L1 setting for both melanoma and NSCLC patients[9,10], and updated results reinforce the prior results and suggest potential monocyte-related biomarkers. In melanoma, ORR = 19% (n=53), and a reduction in circulating monocytic MDSCs or changes in related gene signatures correlated with response[11]. In NSCLC, ORR = 10% (n=72), and high baseline levels of monocytes correlated with response[12]
- ICOS agonist **vopratelimab (JTX-2011)** [Jounce/Celgene] ± nivolumab has modest efficacy in solid tumors in the ICONIC trial[13] . New analysis shows that patients in whom ICOS-high CD4-positive T cells increased post-treatment had better outcomes: mPFS ~6 mo. as compared to 2 mo. in the overall study population[14]

Early studies of novel immunotherapy mechanisms

- With a few exceptions (e.g., AZ5458 above), single-agent, non-PD1-based immunotherapies have minimal efficacy. Anti-TIM3 **MBG453** [Novartis], and IL-15 agonist **NIZ985** [Novartis] are just the latest agents to report a 0% ORR in phase 1 studies of solid tumors. Clinical synergy with anti-PD1 remains inconclusive[15,16]
- Preclinical studies provide evidence for a vast number of potential I-O mechanisms and I-O combinations (with and without PD1/PD-L1 inhibitors). Just a few examples follow.
  - *Examples of New Mechanisms:* **anti-SIRPα ADU-1805** [Aduro] to induce macrophage-mediated killing of cancer cells[17], **anti-TIGIT YH29143** [Yuhan] as a new immune checkpoint inhibitor, and **anti-MERTK RGX-019** [Rgenix] to address macrophage-mediated immune evasion[19]
  - *Examples of New Combinations:* **IL-15 + STING** agonists to augment NK cell activity[20], **anti-CEACAM6 BAY-1834942** [Bayer] **+ anti-PD1** or **+ anti-TIM3** to target CEACAM6-expressing adenocarcinomas[21], and **DPP8/9** inhibitor **BXCL701** [Bioxcel] + **anti-PD1 + OX40 agonist** to bridge innate and adaptive immune responses[22]

1) AACR 2019 #CT004; 2) Abraxane product label; 3) AACR 2019 #CT152; 4) #CT038; 5) #5029; 6) #CT026; 7) ASCO 2018 #3007; 8) AACR 2019 #CT075; 9) ASCO 2018 #9530; 10) ASCO 2018 #9036; 11) AACR 2019 #CT072; 12) #CT041; 13) ASCO 2018 #3000; 14) AACR 2019#CT189; 15) #CT183; 16) #CT082; 17) #1203; 18) #4844; 19) #LB-277; 20) #4070; 21) #LB-075; 22) #LB-077

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617-757-7850 • dchang@clarionhealthcare.com

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I-O Biomarkers Continue to Undergo Exploration

Combining PD-L1 with TMB and/or other markers

PD-L1 IHC already guides immune checkpoint inhibitor (ICI) use in NSCLC, bladder, cervical, and gastric cancers[1] but retrospective analyses suggest that other biomarkers combined with PD-L1 may have greater utility. For example:

- The **BMS 4-gene signature** assesses PD-L1, CD8A, LAG3, and STAT1 expression in tumors by RNA-seq. This combination seems to be more predictive for **nivo** responses than PD-L1 alone in hepatocellular carcinoma[2]
- **Tumor mutation burden (TMB)** seems to be predictive of **durvalumab (Imfinzi) + tremelimumab** [AZ] responses in NSCLC, independent of PD-L1; TMB and PD-L1 combined may be even more predictive[3]
- **TMB combined with the BMS 4-gene signature** is more predictive of **nivo + ipi (Opdivo + Yervoy)** [BMS] responses in melanoma than either alone[4]

Examples of continued exploration of other I-O markers

- Systemic inflammation markers in the **IL-6/CRP** axis are associated with worse response to **atezolizumab (Tecentriq)** [Genentech] in triple-negative breast cancer (TNBC)[5]
- Loss of function mutations of **STK11** (a.k.a. **LKB1**) are associated with worse responses to ICI in NSCLC[6]
- Gain of function mutations of **Notch1/2/3** are associated with better responses to ICI in NSCLC[7]
- **High TMB combined with low copy number alteration (CNA)** is associated with better responses to ICI in a pan-cancer analysis of the MSK-IMPACT dataset[8]
- **TCR repertoire in TILs**—specifically high mean ratio of shared clones—may predict ICI efficacy[9]
- **Microbiome** studies correlate bacterial species with ICI response, albeit with limited concordance[10,11]. Fecal transplantation studies suggest that the microbiome may be used as a therapeutic, not just a diagnostic[12]

Engineered Cell Therapy Sees New Insights and Improvements

Predicting durability in CD19-targeted CAR-T therapy

- **Tisagenlecleucel** (Kymriah) [Novartis]: CAR transgene levels in the blood are too variable to be predictive[1], but minimal residual disease (MRD) may be a signal of favorable response at least in ALL[2]
- **Axicabtagene ciloleucel** (Yescarta) [Gilead]: pretreatment Immunoscore may predict response in DLBCL[3]

Addressing acquired resistance due to antigen loss

- CD22 CAR-T [NCI] continues to show efficacy after failure of CD19 CAR-T, but also shows significant toxicity[4]
- In preclinical models, CARs targeting both CD19 & CD22 may pre-empt antigen loss and lower relapse risk[5]
- In myeloma, GPRC5D is independent of BCMA and thus an alternative/2nd antigen for CAR-T[6] or bispecifics[7]

Off-the-shelf vs point-of-care

- **Off-the-shelf CAR-T:** Allogene/Servier/Cellectis remain at the forefront with **UCART19** in phase 1[8] and **ALLO-501** to begin phase 1 by mid-year[9], but **FT-819** [Fate Therapeutics] may not be far behind[10]
- **Off-the-shelf NK cell therapies** include **PNK-007** [Celularity], which showed promising phase 1 efficacy for multiple myeloma[11], though efficacy was weak in AML[12]; and **FT-519** [Fate], a preclinical CD19 CAR-NK[13]
- **Point-of-care cell therapy: F1 Oncology** has a novel vector that may enable same-day apheresis & infusion[14]

Progress towards solid tumor cell therapies

- **Mesothelin CAR-T iCasM28z** [MSKCC] **+ anti-PD1** produced responses in 8 of 11 patients with malignant pleural disease[15], the best efficacy yet for solid-tumor CAR-T. **HER2 CAR-T** [Baylor] induced CRs in 2 of 10 children with HER2+ sarcomas[16]
- Other antigens include ASPH[17], CD70[18,19], glypicans[20,21], ICAM[22,23], MUC1[24] (CARs); AFP[25] and MAGE[26] (TCRs)
- Other efforts include seeking to address exhaustion/improve persistence[27,28], augment cell killing by secreting BiTEs[29], or encode Boolean logic into the cells using a combinatorial, modular platform[30]

1) Product labels for Keytruda and Tecentriq; 2) AACR 2019 #2675; 3) #CT074; 4) #CT037; 5) #CT001; 6) #SY42-02; 7) #4011; 8) #4522; 9) #3222; 10) #1991; 11) Gong 2019 Clin Transl Med 8:9; 12) #CT042

1) AACR 2019 #CT237; 2) CT077; 3) CT153; 4) LB-146; 5) Sadelain, "Mechanisms of tumor escape…"; 6) Smith 2019 Sci Transl Med 11:eaau7746; 7) DDT02-03; 8) ASH 2018 #0896; 9) press release 2019-3-8; 10) #LB-073; 11) CT108; 12) CT079; 13) 3207; 14) 2327; 15) CT036; 16) LB-147; 17) 2306; 18) 3184; 19) 3716; 20) 2309; 21) 2311; 22) 2322; 23) 4696; 24) 2323; 25) 3183; 26) 2313; 27) Symposium "Immune exhaustion…"; 28) Klebanoff, "T cell therapy 2.0…"; 29) 2328; 30) Lim, "Engineering smarter CAR T…"

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Targeted Therapies Extend to New Settings and Indications

Addressing acquired resistance

- **EGFR-mutant NSCLC** treatment improved significantly with approval of front-line **osimertinib** (Tagrisso) [AstraZeneca] in 2018[1], but resistance and disease progression eventually occur. The TATTON study showed that patients with MET alterations may benefit from a combination of **osimertinib + savolitinib** (a MET inhibitor) [AZ][2,3,4]. TATTON also showed efficacy of **osimertinib + selumetinib** (a MEK inhibitor) [AZ] for patients without MET alterations, though most patients in this arm were osimertinib-naïve[5].
- **FLT3-mutant AML** may be treated front-line with **midostaurin** (Rydapt) [Novartis] + chemo, and in the r/r setting with **gilteritinib** (Xospata) [Astellas], which was approved in Nov 2018 based on an interim analysis of the ADMIRAL trial[1]. Final analysis of ADMIRAL reports EFS and OS benefit, thus reaffirming gilteritinib as the standard of care in the r/r setting[6]. Competitor **quizartinib** [Daiichi] is still under FDA review[7]
- **NTRK-fusion solid tumors: Larotrectinib** (Vitrakvi) [Bayer/Loxo Oncology] was just approved for this subpopulation in November 2018[1], but already there are 3 clinical-stage competitors presenting data at AACR: NTRK/ROS1 dual inhibitors **entrectinib** [Genentech][8] and **repotrectinib** [TP Therapeutics][9], as well as Loxo's own next-generation NTRK inhibitor, **LOXO-195** [Loxo][10]. The latter two drugs have activity even when NTRK has mutations that produce resistance to larotrectinib.

New approaches for hard-to-treat cancers

- **BRCA1/2 or PALB2-mutant pancreatic cancer:** Prior exploratory studies have shown that this subgroup of pancreatic cancer may benefit from PARP inhibitors[11]. The latest results for platinum chemotherapy + **rucaparib** (Rubraca) [Clovis Oncology] maintenance therapy continue to show promise[12]
- **KRAS-mutant cancers:** KRAS has long been considered "undruggable", but progress continues to be made specifically targeting the G12C mutation. No less than 3 compounds have promising preclinical activity against KRAS G12C: **AMG 510** [Amgen][13,14,15], **MRTX1257** [Mirati Therapeutics][16], and **ARS-1620** [Wellspring Biosciences][17], though they may be best used in combination with inhibitors of signaling kinases. Other combination strategies that extend beyond G12C include inhibition of SHP2 + MEK ± CDK4/6i[18,19].

1) FDA; 2) AACR 2019 #CT032; 3) #CT033; 4) #4897; 5) CT034; 6) CT184; 7) Daiichi Sankyo press releases; 8) #CT131; 9) #442; 10) #CT127; 11) Ohmoto 2019 Int J Mol Sci 20:561; 12) AACR 2019 #CT234; 13) #3090; 14) #4455; 15) #4484; 16) #LB-127; 17) #4228; 18)#954; 19) #1322

New Technologies May Enable or Accelerate Future Breakthroughs

New preclinical models

I-O involves not only tumor cell biology but also tumor microenvironment and host immune interactions. Thus, conventional in vitro, xenograft, and organoid models fall short, but newer approaches include:

- **Co-culture of human tumor & immune cells** by AIM Biotech[1], InSphero[2,3], and BioDuro[4]
- **Mice with humanized immune systems** at MD Anderson, for use with patient-derived xenografts[5]
- **Patient tissue explant systems** that preserve TME architecture and diverse cell types
  - **Mitra Biotech**'s CANscript system is the most advanced; the platform was originally validated with chemo-therapies, but is being used now to study a wide range of I-O and non-I-O regimens[6,7,8]
  - **Nilogen Oncosystem**'s 3D-EX platform is similar[9,10], but does not include autologous host blood
  - **Fred Hutch**[11] and **AstraZeneca**[12] have also started to test immunotherapies in tumor slice cultures

New applications of digital technology

- The meeting opened with a highly engaging session called **"Physicist vs Physician: Digitizing clinical assessment and using it for evidence-based prediction of outcomes"** in which Peter Kuhn and Jorge Nieva reviewed various ways cancer can be digitized, including their collaborations on more accurately measuring performance status, which has the potential to improve treatment and clinical outcomes[13]
- Many other sessions and presentations focused on digital applications, including molecular profiling of tumors and the immune system for translational research, and machine learning for regulatory science[14]

1) #47; 2) #52; 3) #57; 4) #4970; 5) #4984; 6) #3205; 7) #3212; 8) #5009; 9) #34; 10) #42; 11) #1099; 12) #1190; 13) PL01-01; 14) E.g., major symposia SY36, SY05, SY11, and "Artificial intelligence and machine learning for regulatory science and drug development applications"

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Dennis Chang, PhD *Principal*
dchang@clarionhealthcare.com
One Financial Center • Boston, MA 02111
617-757-7850