Clarion perspectives from the

AACR Annual Meeting 2018: Driving Innovative Cancer Science to Patient Care

A Clarion team joined over twenty thousand attendees in Chicago at this year's AACR Annual Meeting, to learn about the latest advances in cancer science and clinical care, including these highlights:

I-O combinations in first-line NSCLC: And the winner is…

Non-small cell lung cancer often responds to immunotherapy, with multiple αPD-(L)1 approvals for distinct sub-indications. In the first-line metastatic setting, **pembrolizumab (Keytruda) [Merck]** is approved as a single agent for patients with PD-L1 tumor proportion score (TPS) ≥50%, and in combination with chemo for patients with nonsquamous NSCLC regardless of PD-L1 level. At AACR, new data was presented for **pembro + chemo**[1] and two competing I-O combinations: **atezo (Tecentriq) + bevacizumab (Avastin) + chemo [Roche]**[2] and **nivo (Opdivo) + ipilimumab (Yervoy) [BMS]**[3,4]. In the end, **pembro + chemo** remained on top, redefining standard of care:

- In **Keynote-189**, pembro + platinum chemotherapy + pemetrexed was superior to placebo + chemo in nonsquamous, ALK/EGFR wild-type NSCLC: mPFS 8.8 vs 4.9 mo (HR 0.52), mOS not reached vs 11.3 mo (HR 0.49). The advantage held up across all PD-L1 subgroups as well as subgroups based on age, sex, performance status, smoking status and presence of asymptomatic brain metastases.
- In **IMpower 150**, atezo + bev + carboplatin + paclitaxel also showed a PFS benefit vs chemo alone: mPFS 8.3 vs 6.3 mo (HR 0.62), and this trial included ALK+ and EGFR+ patients. However, mature OS results are not yet available. Furthermore, given that this is a 4-agent combination, even if it proves equivalent to the pembro 3-agent combination, it remains disadvantaged in terms of cost and safety/tolerability.
- In **CheckMate 227**, nivo + ipi vs chemo in squamous and nonsquamous NSCLC showed a PFS and preliminary OS advantage, but only in patients with high tumor mutational burden (TMB). Even in this biomarker-selected cohort, the magnitude of the benefit—mPFS 7.2 vs 5.4 mo (HR 0.58) and mOS 23.0 vs 16.4 mo (HR 0.79)—was less impressive than what was reported in Keynote-189.

This is not the end of the story; we await data for pembro + chemo in squamous NSCLC, pembro monotherapy (a low-toxicity option) in patients with TPS ≥1% rather than ≥50%, atezo + bev + chemo overall survival data, novel combinations, etc. For now, however, pembro + chemo is the regimen to beat in 1L nonsquamous NSCLC.

Sources: 1) CT075; 2) CT076; 3) CT077; 4) CT078

Novel mechanisms & combinations: The next wave

AACR is always a forum for showcasing diverse, innovative therapeutic approaches and hypotheses, some of which may lead to future transformative treatments. Just a few promising examples are highlighted here:

- **TLR9 agonists + αPD1:** Intratumorally injected **SD-101 [Dynavax] + pembro** shows durable efficacy in I-O naïve HNSCC (33% ORR) and melanoma (78% ORR; longer 12-mo PFS vs historical pembro data), and encouraging efficacy in melanoma patients who had received prior αPD1 therapy (ORR 15%, though n=13).[5,6] Similarly, **CMP-001 [Checkmate Pharma] + pembro** had an ORR of 22% (n=68) in melanoma patients with prior αPD1 therapy, and several responses have already lasted over a year.[7]
- **IL-15 agonist + αCD20: ALT-803 [Altor] + rituximab** produced an impressive CR rate of 43% in r/r indolent non-Hodgkin lymphoma (iNHL).[8] IL-15 may act via activation of NK cells, a key player in the antibody-dependent cellular cytotoxicity (ADCC) mediated by rituximab—which raises the intriguing possibility that IL-15 agonists could be broadly useful to enhance other ADCC-based mAb therapies.
- **RET inhibitor for RET-fusion cancers: BLU-667 [Blueprint Medicines]** produced a preliminary ORR of 45% in a mix of lung and thyroid cancers with fusions of the RET oncogene, and tumor shrinkage in >80% of those patients, showing again that drug development targeting oncogenic kinases can still bear fruit.[9]
- **siRNA:** An example on the very early, preclinical side is the use of C/G-rich short inhibitory RNA (siRNA) to attack cancer cells.[10] This approach is inspired by the observation that patients with Huntington's Disease—whose mutant gene encodes a C/G rich RNA—have an unusually low incidence of cancer, and is supported by preclinical studies showing that C/G-rich siRNAs are toxic to cancer cells.[11]

Sources: 5) CT098; 6) CT139; 7) CT144; 8) CT146; 9) CT043; 10) Peter #SY49-1; 11) Murmann 2018 EMBO Rep. 19(3).

Precision Oncology: Progress but hard lessons

The promise of precision medicine in oncology is tremendous. We are now or will soon be able to:

- **Target tumors with specific and often rare genetic markers, regardless of cancer type:** Pembro's approval for MSI-high cancers led the way in histology-agnostic approvals[12], larotrectinib [Loxo] for NTRK-fusions is coming soon[13], and immunotherapy for PD-L1 amplification seems likely to be another[14]. New evidence suggests that RET fusions and oncogenic HER2 mutations may continue the trend.[15,16]
- **Identify mechanisms or markers of immune resistance:** Many mechanisms of immune resistance are now known, including immune checkpoints, metabolic dysregulation, myeloid-derived suppressor cells, and others; mounting evidence shows that these mechanisms interact with each other and with molecular pathways such as β-catenin signaling, PI3K signaling, EMT, and epigenetic dysregulation.[17,18]
- **Detect residual or recurrent cancer with greater sensitivity:** New approaches like CAPP-Seq (cancer personalized profiling by deep sequencing) can detect very low levels of circulating tumor DNA (ctDNA) in blood, up to 5 months before radiographic progression in NSCLC.[19,20] Progress in colon (SafeSeqS) and bladder cancers (UroSEEK) underscores potential broad applicability in solid tumors.[20]

However, realizing that potential is challenging, as several sessions at AACR revealed:

- **TMB assays require harmonization:** A variety of assays assess TMB, such as Foundation Medicine and Illumina tests as well as academic lab-developed tests; however, they differ in sample requirements and preparation, the gene sets they sequence, the depth of coverage, definition of "mutation", cut-points, and other factors, raising concerns about reproducibility and complicating their interpretation.[21,22]
- **Interpreting NGS panels is resource-intensive:** Academic centers that implement broad NGS testing require regular discussions with a panel of multidisciplinary experts (called molecular tumor boards)[23,24] and/or robust, continually updated software tools to help clinicians interpret results.[25]
- **Microbiome studies still have not achieved consensus:** Studies agree that a patient's gut bacteria affect response to checkpoint blockade, but disagree on the specifics. For example, *Akkermansia muciniphila* correlates with good response and occurs commonly in patients in Paris, but neither is true in Houston.[26]
- **Some tumor-agnostic markers may not be completely tumor-agnostic:** IHC tests for mismatch repair deficiency (dMMR) vary in predictiveness depending on tumor site, more so than MSI-H assays.[27]

Sources: 12) FDA; 13) ; 14) ASCO-SITC 2018 #47; 15) CT043; 16) SY08-3; 17) Gajewski #SY13-02; 18) Zou #SY17-01; 19) Chaudhuri 2017 Cancer Discov 7:1394; 20) Chaudhuri #ED18; 21) Rimm, CT078 Discussant;22) "Shared Burden", BioCentury 15 Mar 2018; 23) Chinnaiyan #SY08-01; 24) Korn #SY08-02; 25) Solit #SY08-03; 26) RADT08; 27) RSP01

Novel preclinical models: Enabling the next wave of innovation

AACR is also a forum for new research tools and methods, including new preclinical models for drug testing:

- **Patient-derived xenografts** (human tumors implanted into mice) and **patient-derived organoids** (3D primary cell cultures) are already widely used but are now being assembled into large resource banks in the US (NCI's PDMR[27]; SEngine Precision Medicine[29,30]) and EU (EurOPDX EDIReX project[31]) so that researchers can access hundreds of existing patient "avatars" for drug testing.
- **Tumor explant cultures** such as the CANscript platform [Mitra Biotech][32] enable researchers to test multiple drug regimens on a single patient's tumor sample. By retaining the stroma and other non-tumor cells, such approaches may better test immunotherapy and other microenvironment-altering therapies. A key trade-off is that fresh patient samples must constantly be used for the cultures.

As we recently reported, only ~5% of cancer trials involve combinations of novel agents[33], and a 2018 study showed the success rate of oncology clinical trials is only 8%[34]. Better preclinical models may have multiplicative effects on the throughput and success rate of cancer drug development.

Sources: 28) #985; 29) #1619; 30) #582; 31) #986; 32) #LB346; 33) Scarlett 2016 Cancer Discov 6: 956; 34) Wong 2018 Biostatistics

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