Anti-PD1-Based Immunotherapy Pushes Forward

We saw some of the most significant advances for anti-PD1 based regimens in these tumor types:

- **Head and Neck Squamous Cell Carcinoma (HNSCC) frontline data expected to be practice-changing**
  
  - Pembrolizumab (Keytruda) [Merck] was previously approved for second line or later (2L+) HNSCC. Pembrolizumab now shows efficacy in frontline (1L) HNSCC, with improved 24-mo OS for pembrolizumab + platinum + FU (29%) and pembrolizumab alone (27%), vs the standard EXTREME regimen (19%). IO outcomes are even better in CPS ≥20 patients. This data led to FDA approval post-ASCO for pembrolizumab monotherapy in PD-L1+ (CPS ≥20) HNSCC, and for pembrolizumab + chemo regardless of PD-L1 expression.

- **Microsatellite Stable (MSS) colorectal cancer (CRC) may be IO-responsive when combined with TKI**
  
  - Few good options exist for MSS-CRC that has relapsed on frontline therapy, with ≤20% ORR in 2L and <10% in 3L+. Immunotherapy has historically had poor success in MSS-CRC, but an academic study in Japan combining the TKI regorafenib (Stivarga) [Bayer] + nivolumab (Opdivo) [BMS] showed striking results. ORR was 33%, and although median progression free survival was only 6.3 mo, the responses appeared durable.

- **Microsatellite Instability (MSI)-High CRC sees durable responses in frontline**
  
  - Nivolumab plus ipilimumab (Yervoy) [BMS] is approved for 2L+ MSI-H CRC. Data at ASCO showed that the combination in 1L achieved 58% ORR and strong durability (median duration of response not reached at 19.9 mo). This early data (n=45) suggest 1L nivolumab + ipilimumab may be a promising choice for the ~15% of CRC patients that are MSI-H.

- **Hepatocellular carcinoma (HCC) continues to see clinical benefit on anti-PD1; boosted by anti-CTLA4**
  
  - While 2L pembrolizumab failed to meet a stringent pre-specified endpoint, pembrolizumab will likely still be used in the clinic based on missing of median OS (13.9 mo) and OS HR (0.78) vs best supportive care. In an early study of 3 dosages, 2L nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) led to an impressive 22.8 mo median OS, 32% ORR and 8% CR (vs 18% ORR, 2% CR for pembrolizumab alone). At this dose, 20% of patients developed Gr3-4 hepatitis.

Advances for Novel Immunotherapy Mechanisms and Cell Therapies

Our view of the most promising early data for non-PD(L)1 mechanisms and cell therapies includes:

- **CD47**: At last year’s ASCO, the anti-CD47 agent Hu5F9-G4 [Forty Seven, Inc.] + rituximab showed promise in post-rituximab DLBCL. This year, Hu5F9-G4 posts more compelling data, now combined with azacitidine, achieving 64% ORR in frontline AML patients who are ineligible for standard induction chemotherapy. The combination also bridged 2 of 14 patients to transplant.

- **IL-15**: Preliminary Ph 2 results showed efficacy of the IL-15 receptor superagonist N-803 (formerly ALT-803) [NantCell] and BCG in BCG-unresponsive non-muscle invasive bladder cancer. Results were especially impressive in the high-risk carcinoma in situ subgroup, with 90% CR. Durability data are awaited.

- **Gene therapy: VB-111 [VBL Therapeutics]** is a viral gene therapy encoding a transgene to target angiogenic blood vessels. In platinum-resistant ovarian cancer, paclitaxel + high-dose VB-111 led to CA-125 response in 58% of patients. Paclitaxel + high-dose VB-111 also reached a median OS of 16.4 mo, vs only 5.7 mo for those on paclitaxel + a ‘sub-therapeutic’ VB-111 dose.

- **Autologous CART**: In r/r NHL, CD20-CD19 dual CAR-T [U. Wisconsin] achieved 82% ORR & 65% CR (n=17); importantly, point-of-care production allowed the cells to be given fresh with no freeze-thaw, which greatly improved cell viability. In r/r CLL with median 5 prior lines of therapy, anti-CD19 CART liso-cel (JCAR017) [Juno/Celgene] achieved 82% ORR and 46% CR/CRI.

  CART continues to gain traction in solid tumors with an updated 63% ORR for anti-mesothelin CART + anti-PD1 [MSKCC] in mesothelioma, and 33% ORR for Claudin 18.2 CART [CARsgen] in gastric and pancreatic cancers.

- **Allogeneic cell therapy**: The engineered cell therapy HS-110 [Heat Biologics] is designed to secrete the heat shock protein / adjuvant gp96 to induce an immune response. In patients with NSCLC who failed a prior checkpoint inhibitor, HS-110 + nivolumab achieved 15% ORR—among the best data seen to-date in this setting.
Targeted Therapy Makes Major Strides

We saw targeted therapy make major strides, with new data for agents targeting key pathways:

PARP inhibitors go broad – beyond BRCA1 or BRCA2 mutant ovarian cancer

- **BRCA wild-type ovarian cancer**: In the platinum-resistant setting, *olaparib* (Lynparza) [AstraZeneca] produced an ORR of 13% (n=53), more than double that of the chemo comparator arm

- **BRCA wild-type breast cancer**: In HER2-negative disease with non-BRCA homologous recombination pathway mutations (*PALB2, CHEK2*, etc.), *talazoparib* (Talzenna) [Pfizer] produced an ORR of 31% (n=13)

- **Prostate cancer** with DNA damage repair mutations (*BRCA1/2, PALB2, ATM, CDK12, and others*): *Olaparib* produced a RECIST/PSA ORR of 35% (n=92) overall, 80% (n=30) in the *BRCA1/2* mutant cohort

- **Pancreatic cancer** with germline BRCA mutation (4–7% of pancreatic cancers): *Olaparib* as maintenance therapy after first-line platinum chemotherapy almost doubled the mPFS vs placebo, 7.4 vs 3.8 mo. *Veliparib* (ABT-888) [AbbVie] added to FOLFOX or FOLFIRI also shows promising efficacy signals

Drugging KRAS at last?

- **AMG 510** [Amgen] inhibits G12C mutant KRAS through elegant chemistry acting on the aberrant cysteine. In a Ph 1 study, AMG510 monotherapy showed an impressive 50% ORR (n=10) in NSCLC. At least a couple of these patients had progressed after prior treatment with anti-PD1 therapy. No responses were seen in CRC (n=19)

- Competitor **MRTX849** [Mirati] is also in a Ph 1/2 trial of KRAS G12C-mutant solid tumors

Refinement & innovation of targeted therapy for breast cancer

- **CDK4/6 inhibitors** for HR+ breast cancers: *Ribociclib* (Kiqlai) [Novartis] + endocrine therapy has updated survival data for premenopausal women: 42-mo OS is 70% vs 46% for endocrine tx alone. *Palbociclib* (Ibrance) [Pfizer] + exemestane + leuprolide shows early efficacy in premenopausal patients

- **PI3K pathway inhibitors** for HR+ breast cancers: PI3Kα inhibitor *alpelisib* (Piqray) [Novartis] + fulvestrant, approved for 2L treatment of HR+ breast cancer harboring *PIK3CA* mutations, shows patient-reported QoL was maintained, similar to fulvestrant alone. AKT inhibitor *capivasertib* (AZD5363) [AstraZeneca] doubled mPFS vs fulvestrant alone (10.3 vs 4.8 mo) and extended mOS (26 vs 20 mo) in a Ph 2 trial, without the need for biomarker selection, but with some toxicity: 1/3 of patients required dose reduction

- **HER2**: Biosimilar *trastuzumab-dkst* (Ogivri) [Mylan] showed long-term survival is equivalent to *trastuzumab* (Herceptin) [Roche]. A next-gen anti-HER2, *margetuximab* [Macrogenics] was superior to trastuzumab, but only modestly: mPFS was 5.8 vs 4.9 mo for each agent, respectively, in combination with chemo. *Neratinib* (Ner lynx) [Puma] was superior to *lapatinib* (Tykerb) [Novartis] in combination with capecitabine in 3L+ (mPFS 8.8 vs 6.6 mo). *Pyrotinib* (Hengrui) is another emerging small-molecule, and antibody-drug conjugate (ADC) *trastuzumab deruxtecan* (DS-8201) [AZ/Daichi] is in a Ph 3 trial

Novel mechanisms continue to emerge

- **Targeting oncogenic fusions**: *Entrectinib* [Roche] has activity against pediatric tumors with NTRK, ALK, or ROS1 fusions as well as ALK mutations, *LOXO-292* [Loxo] has efficacy in RET-fusion pediatric cancers, while competitor *BLU-667* [Blueprint] has efficacy data for RET-fusion lung and thyroid cancers. **Repotrectinib** (TPX-0005) [Turning Point] has excellent efficacy in ROS1-fusion NSCLC, but a death on study raises concerns

- **Targeting tyrosine kinases**: The EGFR × cMET bispecific JNJ-61186372 [Janssen] had 28% ORR in EGFR-mutant NSCLC resistant to prior TKIs. The HER3 inhibitor *CDX-3379* [Cellxide] + anti-EGFR *ceftarab* (Eributix) [El Lilly] produced a CR in cetuximab- and anti-PD1-resistant HNSCC. FGFR inhibitors in development, including *infrafinitib* [QED] and *vofatamab* [Rainier], may address FGFR3-mutant urothelial cancers, though cancers of the urothelial tract may be more susceptible than the bladder

- **Other targets**: *Enfortumab vedotin* [Astellas/Seattle Genetics], an ADC targeting Nectin-4, has ORR 44% and mOS 11.7 mo. for 2L+ bladder cancer. Nuclear export inhibitor *selinexor* [Karyopharm] has early single-agent activity for glioblastoma—ORR 10% at the highest dose—which supports further study
Liquid Biopsy: Prime Time and the Pipeline

A set of blood-based liquid biopsy tests are ready for prime time in cancer care:

- **Companion diagnostics (CDx) for targeted therapy:** Marketed examples include the cobas EGFR Mutation Test V2 [Roche Diagnostics] for EGFR-mutant NSCLC, and the therascreen PIK3CA RGQ PCR Kit [Qiagen/Neogenomics] for PIK3CA-mutant breast cancer. The accuracy depends on the gene frequency, tumor volume, other tumor factors, and test stringency, but certain blood tests (e.g., OncoBEAM [Sysmex] or Guardant360 [Guardant]) are >90% concordant with tissue tests.

- **Detecting resistance mutations:** Liquid biopsy tests can also detect the emergence of new mutations as mechanisms of therapy resistance. Examples include detecting secondary ALK mutations in NSCLC using an Inviva test, or ESR1 (estrogen receptor) and HER2 mutations in breast cancer using Guardant360.

The following are some of the most promising novel uses for liquid biopsy presented at ASCO:

- **Actionable IO biomarkers** such as blood-based tumor mutation burden (TMB) and PD-L1-expressing exosomes show promise but remain experimental.

- **Prognostic evaluation** based on circulating tumor DNA (ctDNA) detectability post-treatment is a promising application, for example in resected CRC. Another use is risk stratification based on circulating tumor cells (CTC) detectability, for example for choosing more aggressive regimens such as FOLFIRINOX + bevacizumab (Avastin) [Roche] in CRC.

- **Monitoring for early signs of progression,** for example an increase in ctDNA, shows promise in melanoma patients after dabrafenib + trametinib (Tafinlar + Mekinist) [Novartis] or other treatments.

- **Early disease screening** through liquid biopsies is a potential disruptive innovation that could dramatically shrink cancer mortality. Grail is developing an assay to screen for cancer-specific methylation patterns in ctDNA; the sensitivity at 99% specificity was outstanding for certain stage IV tumor types (e.g., 100% for breast, ovarian, gastric, esophageal, and hepatobiliary). Sensitivity (at 99% specificity) for stage I–III disease was an encouraging ~69%.

Racial Disparities in Cancer Care: Closing the Gap

Certain minority racial groups are at greater risk of cancer-related morbidity and mortality, and much of the disparity is due to preventable factors such as access to and quality of care. The following is our take on key insights to the inequities and how to address them:

- **Federal payer policy:** The Affordable Care Act (ACA) may be a controversial piece of legislation, but its expansion of Medicaid funding is associated with a significant reduction of the disparity between African Americans and whites in terms of time to treatment: from 4.8% to 0.8% fewer patients receive treatment within 30 days of diagnosis. This observational study does not prove causation, but other studies also connect improved access with lower disparity. E.g., within the equal-access Military Health System, there is no racial disparity in CRC time to treatment or adherence to guidelines.

- **Clinical practice:** Implementation science studies ways to improve evidence-based practice, and is an essential component of reducing care disparities. For example, a program at MassGeneral Hospital to institute same-day breast biopsy (instead of scheduling a follow-up visit) eliminated the racial disparity in time to breast cancer diagnosis.

- **Clinical research:** There is also a need to improve the representation of racial minorities in clinical trials, e.g., with clinical trial screening tools, to reveal differences that may inform care decisions. For example, real-world data showed that prostate cancer vaccine sipuleucel-T (Provenge) [Dendreon] has better efficacy in blacks than in whites, whereas there were too few blacks in the Ph 3 trials to make this conclusion.