Clarion Perspectives from the

ASCO 2019 Annual Meeting

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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[1]. 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[2]
- **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[3]
- **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)[4]. This early data (n=45) suggest 1L nivolumab + ipilimumab may be a promising choice for the ~15% of CRC patients that are MSI-H[5]
- **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 its safety profile, median OS (13.9 mo) and OS HR (0.78) vs best supportive care[6]
  - 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 pembro[6]). At this dose, 20% of patients developed Gr3-4 hepatitis[7]

1) ASCO 2019 #6000; 2) Merck Press Release 11 Jun 2019; 3) ASCO 2019 #2522; 4) #3521; 5) Fam Cancer. 2016; 15: 405–412; 6) ASCO 2019 #4004; 7) #4012

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[1]. 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[2]
- **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[3]
- **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[4]
- **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[5]. 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[6]

  CART continues to gain traction in solid tumors with an updated 63% ORR for **anti-mesothelin CART** + **anti-PD1 [MSKCC]** in mesothelioma[7], and 33% ORR for **Claudin 18.2 CART [CARsgen]** in gastric and pancreatic cancers[8]
- **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[9]

1) ASCO 2018 #7504; 2) ASCO 2019 #7009; 3) #4561; 4) #5542; 5) #2510; 6) #7501; 7) #2511; 8) #2509; 9) #9109

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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[1]

- ***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[2]
- ***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)[3]
- **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[4]
- **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[5]. **Veliparib (ABT-888) [AbbVie]** added to FOLFOX or FOLFIRI also shows promising efficacy signals[6,7]

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)[8]
- Competitor **MRTX849 [Mirati]** is also in a Ph 1/2 trial of *KRAS* G12C-mutant solid tumors[9]

Refinement & innovation of targeted therapy for breast cancer

- **CDK4/6 inhibitors** for HR+ breast cancers: **Ribociclib (Kisqali) [Novartis]** + endocrine therapy has updated survival data for premenopausal women: 42-mo OS is 70% vs 46% for endocrine tx alone[10]. **Palbociclib (Ibrance) [Pfizer]** + exemestane + leuprolide shows early efficacy in premenopausal patients[11]
- **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[12]. 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[13]
- **HER2 inhibitors:** Biosimilar **trastuzumab-dkst (Ogivri) [Mylan]** showed long-term survival is equivalent to **trastuzumab (Herceptin) [Roche]**[14]. 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[15]. **Neratinib (Nerlynx) [Puma]** was superior to **lapatinib (Tykerb) [Novartis]** in combination with capecitabine in 3L+ (mPFS 8.8 vs 6.6 mo)[16]. **Pyrotinib [Hengrui]** is another emerging small-molecule [17], and antibody-drug conjugate (ADC) **trastuzumab deruxtecan (DS-8201) [AZ/Daiichi]** is in a Ph 3 trial[18]

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[19]. **LOXO-292 [Loxo]** has efficacy in RET-fusion pediatric cancers[20] while competitor **BLU-667 [Blueprint]** has efficacy data for RET-fusion lung and thyroid cancers[21, 22]. **Repotrectinib (TPX-0005) [Turning Point]** has excellent efficacy in ROS1-fusion NSCLC, but a death on study raises concerns[23]
- **Targeting tyrosine kinases:** The EGFR × cMET bispecific **JNJ-61186372 [Janssen]** had 28% ORR in EGFR-mutant NSCLC resistant to prior TKIs[24]. The HER3 inhibitor **CDX-3379 [Celldex]** + anti-EGFR **cetuximab (Erbitux) [Eli Lilly]** produced a CR in cetuximab- and anti-PD1-resistant HNSCC[25]. FGFR inhibitors in development, including **infigratinib [QED]** and **vofatamab [Rainier],** may address FGFR3-mutant urothelial cancers[26, 27], though cancers of the urothelial tract may be more susceptible than the bladder[28]
- **Other targets: Enfortumab vedotin [Astellas/Seattle Genetics]**, an ADC targeting Nectin-4, has ORR 44% and mOS 11.7 mo. for 2L+ bladder cancer[29]. Nuclear export inhibitor **selinexor [Karyopharm]** has early single-agent activity for glioblastoma—ORR 10% at the highest dose—which supports further study[30]

1) Product labels for Lynparza, Rubraca, Zejula, Talzenna; 2) ASCO 2019 #5507; 3) #3006; 4) #5005; 5) #LBA4; 6) #4014; 7) #4015; 8) #3003; 9) TPS3161; 10) LBA1008; 11) #1007; 12) #1039; 13) #1005; 14) #1021; 15) #1000; 16) #1002; 17) #1001; 18) TPS1102; 19) #10009; 20) #10045; 21) #9008; 22) #6018; 23) #9011; 24) #9009; 25) #6025; 26) #2410; 27) #4511; 28) #4510; 29) LBA4505; 30) #2005

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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[1]. The accuracy depends on the gene frequency, tumor volume, other tumor factors[2], and test stringency[3], but certain blood tests (e.g., **OncoBEAM [Sysmex]** or **Guardant360 [Guardant]**) are >90% concordant with tissue tests[4,5]
- **Detecting resistance mutations:** Liquid biopsy tests can also detect the emergence of new mutations as mechanisms of therapy resistance[2]. Examples include detecting secondary ALK mutations in NSCLC using an **Inivata** test[6], or *ESR1* (estrogen receptor) and *HER2* mutations in breast cancer using **Guardant360**[7]

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)[8] and PD-L1-expressing exosomes[9] 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[10,11]. 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[12]
- **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[13,14]
- **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%[15]. Further validation and refinement is eagerly awaited

1) FDA; 2) ASCO 2019 #1075; 3) #4565; 4) #3542; 5) Corcoran, ASCO 2019, "cfDNA in colorectal cancer: Ready for prime time?"; 6) #3055; 7) #1036; 8) e13163; 9) #9517; 10) #3518; 11) #3602; 12) #3507; 13) #9510; 14) #9548; 15) #3049

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[1]. 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[2]. 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[3]
- **Clinical practice:** Implementation science studies ways to improve evidence-based practice, and is an essential component of reducing care disparities[4]. 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[5]
- **Clinical research:** There is also a need to improve the representation of racial minorities in clinical trials[6], e.g., with clinical trial screening tools[7], 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[8]

1) NCI: https://www.cancer.gov/about-cancer/understanding/disparities; 2) ASCO 2019 #LBA1; 3) #6563; 4) Rapport 2018 J Eval Clin Pract 24:117; 5) #6508; 6) #e18128; 7) #e14587; 8) #5035

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