Clarion Perspectives from the

ASCO GI Congress 2020

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A New Age of Cancer Care – Innovation Goes Beyond New Agents

Patient reported outcomes (PROs) are increasingly receiving the attention they deserve

"Only OS and QoL matter, anything else is a surrogate" —Dr. Ian Tannock (Univ. of Toronto [Emeritus])[1]

- **PROs enhance survival:** A keynote lecture at ASCO GI cited a study at MSKCC showing that app-based, continuous PRO monitoring led to a gain in mOS of up to 5 mo[2], an effect comparable to many successful phase 3 drug trials[3]
- **QoL metrics fiercely debated:** The Ph3 BEACON study reported QoL for **cetuximab (αEGFR) [Lilly] + encorafenib (BRAFi) ± binimetinib (MEKi) [Pfizer/Array]** on BRAF V600E mCRC in 2L, but was criticized for the approach[4]
  - Data shows increased time to definitive QoL deterioration; critics think endpoint selection may artificially inflate benefit
  - Triplet showed no better QoL than doublet – and only the doublet will be filed with the FDA

New clinical trial paradigms may help bring new therapies to challenging-to-treat indications

- **ASCO's TAPUR study** showed that HER2-overexpressing r/r mCRC responded well to dual HER2 targeting with **pertuzumab + trastuzumab [Roche]** (25% ORR, n=28)[5]
  - TAPUR spans many drugs and tumor types; its goal is to evaluate outcomes of FDA-approved agents in off-label indications
  - The findings of HER2-targeting in CRC confirm results from the previously reported TRIUMPH study[6]
- A keynote lecture showcased **Precision Promise,** a highly innovative **adaptive trial** is seeking to eliminate inefficiencies in the search for new therapies for pancreatic cancer, where unmet need is notoriously high[7]
  - **Overseen by PanCan,** the trial involves **many industry partners** contributing drugs to be tested in parallel and in combinations
  - Machine learning and other dynamic design elements make patients **more likely to receive better performing regimens**, update biomarker selection criteria in real time based on NGS data, and automatically close arms or expand to Ph3 if warranted
  - **Novel design features** include **re-randomization** so patients may receive two experimental treatments in the same trial

Successes and Setbacks Among GI Cancer Trials

Anti-PD1 + Lenvatinib [Eisai/Merck] combinations continue to shine across indications

- **Pembrolizumab [Merck] + lenvatinib** have 69% ORR and 7.1 mo mPFS in 1/2L GEC in the Ph2 EPOC1706 trial (n=29)[8]
- **Nivolumab [BMS] + lenvatinib** deliver 66.7% ORR (8.3% CR) in 1L HCC, with 7.4 mo mPFS in a Ph1b (n=24)[9]

Anti-PD-L1 combinations also show promise for 1L in CRC and HCC

- **Avelumab [Pfizer/EMD Serono] + cetuximab + FOLFOX** in 1L RAS/BRAF wt mCRC hit 81% ORR and ~80% OS at 24mo in the Ph2 AVETUX trial[10]
- **Atezolizumab + bevacizumab [Roche]** show additional PRO data from Ph3 IMbrave150 in 1L HCC: QoL remains high for 11.2 mo vs. 3.6 mo with sorafenib, in addition to OS benefit of the combo over SoC reported in November[11]

Pancreatic cancer: Multiple failures underscore the importance of efforts like Precision Promise

- **Veliparib [AbbVie] (PARPi) + gemcitabine + oxaliplatin** in 1L gBRCA/PALB2 PDAC (Ph2, n=50) does not improve efficacy vs chemo alone, but increases hematologic toxicities[12]. This contrasts with the success of PARPi in the maintenance setting, leading to approval of **olaparib [AZ]**[13]
- **Pegilodecakin (PEG-IL-10) [Lilly] + FOLFOX** vs. FOLFOX alone in 2L PDAC hits a 1.0 HR in OS (n=567) in the Ph3 SEQUOIA study and didn't improve PFS or ORR either[14]

How we define PD-L1 positivity matters – and the right approach may differ across tumor histologies

- **CPS vs TPS? Avelumab** for 1L maintenance in gastric cancer missed its endpoint in the Ph3 JAVELIN gastric 100 trial[15]
  - The regimen flunked in both ITT and PD-L1 "positive" patients as defined by TPS (% tumor cells positive for PD-L1). Unlike in NSCLC, CPS may have been a better metric for gastric cancer, as it assesses PD-L1 not only on tumor cells, but also immune cells
- **What threshold? Pembro** in gastric/GEJ cancers missed its endpoint in the prespecified CPS≥1 subgroup but reanalysis of KN-059/61/62 results in the CPS≥10 subgroup may show a potential benefit over SoC across 1L through 3L[16]

1) Ian Tannock; ASCO GI 2020 Meeting Abstracts; 2) Keynote: What's next after precision oncology?; 3) E.g., multiple inidcations on the Keytruda label, including esophageal cancer, NSCLC, and others; 4) ASCO GI 2020 #8; 5) #132; 6) ESMO2019 #526PD; 7) Keynote: Adaptive Platform Trial Design: The New Horizon for Pancreas and Other Cancers; 8) #374; 9) #513; 10) #96; 11) #476; 12) #639; 13) Lynparza product label; 14) #637; 15) #278; 16) #427

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