Clarion Perspectives on

Highlights at ASCO 2020

May 29-31, 2020 • Virtual Meeting

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Checkpoint inhibitors continue moving into frontline therapy – with setbacks

Urothelial carcinoma (UC): ICIs are redefining the 1L paradigm but fail in the adjuvant setting

- **Avelumab (Bavencio) [EMD Serono/Pfizer]** + best supportive care (BSC) improves survival (mOS 21.4 mo vs 14.3 mo for BSC alone) as maintenance therapy after 1L platinum-chemo in an interim readout of ph 3 JAVELIN Bladder 100.[1] This included both cisplatin-eligible and -ineligible patients and forces a rethinking of the 1L IO approach, although as previously reported at ASCO GU, the **enfortumab vedotin (Padcev) [SeaGen/Astellas] + pembrolizumab (Keytruda) [Merck]** combination also shines for 1L cisplatin-ineligible UC (ORR 73%, mPFS 12.3 mo, mOS not reached; n=45)[2]
- In contrast, adjuvant **atezolizumab (Tecentriq) [Roche]**, as announced earlier this year[3] did not improve DFS vs observation in high-risk muscle-invasive UC: mDFS 19 mo vs. 17 mo; even PD-L1 ≥ 5% patients did not benefit[4]

Hepatocellular carcinoma (HCC): Multiple ICI-based combinations set to face off in 1L

***Atezo + bevacizumab (Avastin) [Roche]** is now approved for 1L HCC[5] but will face competing ICI regimens. For example:*

- **Pembro + lenvatinib (Lenvima) [Eisai/Merck]** showed 46% ORR and 22 mo mOS in 1L HCC in ph 1 (n=100)[6], and is now in a phase 3 1L trial, LEAP-002
- A single high-dose primer of **tremelimumab** followed by **durvalumab (Imfinzi) [AstraZeneca]** showed 24% ORR with 18.7 mo mOS (n=75) in 1L-2L HCC[7] and this regimen also has a corresponding 1L ph 3 trial (HIMALAYA)

Pembrolizumab racks up 1L wins for MSI-H CRC and TNBC, but fails in SCLC

- For **microsatellite instability-high colorectal cancer (MSI-H CRC),** pembro is already approved 2L[8] but now shows positive 1L results in ph 3 Keynote-177: ORR 44% vs 33% and mPFS 16.5 mo vs 8.2 mo vs standard chemo[9]
- For 1L **triple-negative breast cancer (TNBC)**, pembro + chemo shows efficacy vs placebo + chemo in Keynote-355: mPFS was 9.7 vs 5.6 mo for PD-L1 CPS ≥10 (HR 0.65), and 7.5 vs 5.6 mo for PD-L1 CPS ≥1 (HR 0.74)[10]
- For **extensive-stage small-cell lung cancer (ES-SCLC)**, pembro is approved 3L[8], but, as previously reported[11], **pembro + etoposide + platinum-chemo** (EP) did not significantly improve OS vs EP alone (HR 0.80) in ph 3 Keynote-604; only PFS was significant (HR 0.73). [12] Thus pembro poses little threat to the **durva** and **atezo** combos approved for 1L ES-SCLC[13]

Sources: 1) ASCO 2020 Abstract #LBA1; 2) #5044; 3) Roche Press Release, 1/24/2020; 4) #5000; 5) FDA Press Release 5/29/2020; 6) #4519; 7) #4508; 8) Keytruda Product Label; 9) #LBA4; 10) #1000; 11) Merck Press release, 1/6/20; 12) #9001; 13) Imfinzi and Tecentriq Product Labels

IO expands its utility through new MoAs, combinations, and in new indications

New checkpoints show promise: TIGIT and LAG3

- **Anti-TIGIT tiragolumab + atezolizumab [Roche]** for 1L NSCLC with PD-L1 ≥1% in a ph 2 trial had a 5.6 mo mPFS (n=67) vs 3.9 mo mPFS for the placebo + atezo comparator (n=68).[1] This combination is now in 1L ph 3 trials for NSCLC and SCLC, though many other TIGIT inhibitor regimens are also in the pipeline
- **PD1 x LAG3 bispecific MGD013 + anti-HER2 margetuximab [MacroGenics]** in a ph 1 study for HER2-positive, 2L+ solid tumors (n=14) showed a 43% ORR (incl. 4 confirmed, 2 unconfirmed PRs), independent of PD-L1 and LAG3 expression[2]

Can anti-PD-(L)1 resistance be addressed with ICI+TKI combinations?

- **Atezo + cabozantinib (Cabometyx) [Exelixis]** in nonsquamous NSCLC after progression once on PD-(L)1 showed 27% ORR. Although response duration was limited at 5.7 mo (mDoR) and grade 3+ TRAE rate was 50%, this is some of the best data seen to date in the post-PD-(L)1 setting in lung cancer[3]
- **Pembro + Lenvatinib** continues to show strong efficacy post-PD-1 in renal cell carcinoma (RCC): ORR 52% (n=104)[4]

Early efficacy signals for anti-PD-(L)1 regimens in underserved rare tumors

- For **malignant pleural mesothelioma,** 1L **durvalumab + cisplatin + pemetrexed** shows ORR 56%, mPFS 6.7 mo, and mOS 20.4 mo (n=55), a strong improvement over historical 12 mo mOS for platinum-chemo[5]
- For **gestational trophoblastic tumor**, a tumor that develops in pregnancy, **avelumab** achieved normalization of the placental hormone hCG (the study's primary endpoint) for 53% of chemo-refractory patients (n=15); this marks an important step forward for these patients[6]

Sources: 1) ASCO 2020 Abstract #9503; 2) #3004; 3) #9610; 4) #5008; 5) #9003; 6) #LBA6008

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Targeted therapy highlights: Progress for new settings, agents, and mechanisms

EGFR inhibition as adjuvant therapy for NSCLC: Osimertinib outshines RADIANT

- Next-gen EGFR inhibitor **osimertinib (Tagrisso) [AZ]** resets the bar for adjuvant treatment of EGFR-mutant non-small cell lung cancer (NSCLC). Unblinded early, the ph 3 ADAURA trial showed mDFS NR vs. 28 mo for placebo (HR 0.21)[1] First-gen agent **erlotinib (Tarceva) [Roche/Astellas]** only had HR 0.61 for DFS in the EGFR-mutant subgroup of RADIANT[2]

HER2 inhibition continues its renaissance

- In the last 6 months, HER2+ breast cancer has seen the approvals of antibody-drug conjugate **trastuzumab deruxtecan (T-Dxd; Enhertu) [Daiichi/AZ]** and TKI **tucatinib (Tukysa) [SeaGen]** (+ **trastuzumab (Herceptin) [Roche]** + capecitabine)[3]. At ASCO 2020, both products showed efficacy for breast cancer patients with brain metastases[4,5]
- Moreover, AZ is not limiting T-Dxd to breast cancer, this year presenting positive data for HER2-positive 3L+ CRC (ORR 45%, mPFS 6.9 mo)[6], 2L+ NSCLC (ORR 62%, mPFS 14 mo)[7], and 3L+ gastric cancer (ORR 51%, mPFS 5.6 mo)[8]

Novel targeted mechanisms continue to emerge. Select examples include:

- HIF-2α inhibitor **MK-6482 [Merck]** showed 28% confirmed ORR (41% unconfirmed ORR) in 1L RCC driven by germline VHL mutations.[9] While germline VHL mutations are rare, 50% of clear cell RCCs are associated with VHL alteration[10]
- SLC6a8 inhibitor **RGX-202 [Rgenix]** showed preliminary efficacy for KRAS-mutant, 3L+ CRC: ORR 20%, DCR 60% (n=5) during dose escalation[11]

*Sources: 1) ASCO 2020 #LBA5; 2) J Clin Oncol **2015** 33(34): 4007; 3)FDA press release; 4) #1036; 5) #1005; 6) #4000; 7) #9504; 8) #4513; 9) #5003; 10) Nature **2013** 499(7456): 43; 11) #3504*

Hem-onc highlights: Continued progress for new mechanisms & combinations

Myeloma sees updates for BCMA CAR-T and first-in-human data for a new class of protein degrader

- CAR-T cell therapies targeting BCMA continue to show promise: **JNJ-4528 [J&J/Legend]** had 100% ORR (n=29) in CARTITUDE-1, and the 11.5 mo median follow-up shows durability and deepening of responses[1]. **Orvacabtagene autoleucel (orva-cel) [BMS/Juno]** shows similarly high ORR (92%, n=62) in EVOLVE, with a similar deepening of responses over time[2]. **Idecabtagene vicleucel (ide-cel) [BMS/bluebird]** in pivotal trial KarMMa shows lower ORR (73%) and more limited durability (mDoR 10.7 mo, mPFS 8.8 mo), but with a more mature dataset (n=128)[3]. All of these studies were in heavily pretreated MM patients and had low (<10%) rates of grade 3+ CRS and neurotoxicity
- Cereblon E3 ligase modulator (CELMoD) **CC-92480 [BMS/Celgene]** mediates proteasomal degradation of Ikaros and Aiolos, transcription factors involved in myeloma proliferation. CC-92480 + dexamethasone in heavily pretreated MM achieved ORR 21.1% (54.5% at the recommended ph2 dose) with manageable toxicity in ph 1 (n=76)[4]

Positive results for CD47 inhibition and IDH1 + BCL2 inhibition in AML/MDS

- Anti-CD47 **magrolimab [Gilead/Forty Seven]** + azacitidine confirms the compelling data presented at ASH 2019 in MDS and AML, achieving ORR 91% (CR 42%) with responses that deepen over time (6-mo CR 56%)[5] Another anti-CD47, **TTI-622 [Trillium]**, achieved only ~11% ORR in r/r DLBCL, but impressive responder case studies support target validity[6]
- A ph 1b/2 trial combining IDH1i **ivosidenib (Tibsovo) [Agios]** + BCL-2i **venetoclax (Venclexta) [Roche/AbbVie]** ± azacitidine in IDH1-mutant AML and high-risk MDS achieved 90% ORR (50% MRD negative), mPFS 9.4 mo, mOS NR (2 yr follow-up)[7]

Sources: 1) ASCO 2020 #8505; 2) #8504; 3) #8503; 4) #8500; 5) #7507; 6) #3030; 7) #7500

COVID-19: The toll on cancer patients

As the coronavirus pandemic ravages the globe, oncologists are taking a hard look at the toll taken on cancer patients. Calls to action raised in March via social media led to the formation of consortia to aggregate and share real-world clinical data. Data from the two largest studies to date were presented at ASCO

- **CCC19: The COVID-19 and Cancer Consortium** spans 106 centers, most in the US, and reported data for 928 patients with any cancer and confirmed COVID-19 infection[1]. **TERAVOLT: Thoracic Cancers International COVID-19 Collaboration** spans 26 countries and reported data for 400 patients with thoracic cancers and diagnosed or suspected COVID-19 infection[2]
- Both studies showed high hospitalization (50–78%) and mortality rates (13–35%), and found that along with performance status, age, and comorbidities, **active cancer/chemotherapy is an independent predictor of mortality**[1,2]. The findings affirm the importance of using telemedicine and other measures to minimize on-site patient visits and lower infection risk

Sources: 1) ASCO 2020 #LBA110; 2) #LBA111

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