Clarion Perspectives from the

ESMO Congress 2019

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PARP inhibitors continue to shine

PROfound efficacy in castration-resistant prostate cancer (CRPC)

- **Olaparib (Lynparza) [AstraZeneca/Merck]** was superior to physician's choice of androgen receptor-targeted agent (ARTA) **abiraterone (Zytiga) [J&J]** or **enzalutamide (Xtandi) [Astellas/Pfizer]** for mCRPC patients with homologous recombination (HR) pathway gene mutation(s) and prior progression on ARTA, in the phase 3 PROfound trial[1]
  - In the *BRCA* or *ATM*-mutant cohort, the mPFS for olaparib vs ARTA was 7.39 vs 3.55 mo., and the ORR was 33.3% vs 2.3%. The OS improvement of 18.5 vs 15.1 mo. was not significant (p = 0.0173), but the data were immature, and >80% of the control arm crossed over to olaparib upon progression[1]
  - It is worth noting that the molecular assay in PROfound (based on the **FoundationOne [Foundation Medicine]** CDx test) had a >30% failure rate, highlighting remaining need on the diagnostics front[2]
  - Moreover, **cabazitaxel (Jevtana) [Sanofi]** in the phase 3 CARD trial also doubled mPFS, also had ORR >30%, and sig. improved OS vs ARTA, all without the need for *BRCA*/HR mutation testing. It should be noted, though, that this study selected for patients who had relatively fast progression on ARTA, within 12 mo.[3]
- Other PARP inhibitors also report strong efficacy in phase 2 trials: in *BRCA*-mutant mCRPC, **niraparib (Zejula) [GSK/Tesaro]** had a 41% ORR in the GALAHAD study (interim analysis)[4], while **rucaparib (Rubraca) [Clovis]** had a 43.9% ORR in TRITON2[5]. All PARP inhibitors had lesser efficacy for non-*BRCA* HR mutations

Expanding roles in ovarian cancer

- Olaparib is approved as first-line (1L) maintenance therapy for ovarian cancer with *BRCA* mutation[7]. Now, **niraparib** and **olaparib + bevacizumab (Avastin) [Genentech]** report compelling phase 3 efficacy as 1L maintenance therapy regardless of *BRCA* mutation status: mPFS 21.9 vs 10.4 mo., HR 0.43 for niraparib vs placebo in the PRIMA study[8], and mPFS 22.1 vs 16.9 mo., HR 0.59 for olaparib + bev. vs bev. alone in PAOLA-1[9]. In both studies, efficacy was weaker for patients without any HR mutations

New competitors in different chemo combinations

- **Veliparib (ABT-888) [AbbVie]** + carboplatin + paclitaxel improved PFS vs placebo + the same platinum doublet for ovarian cancer in the VELIA study[10] and for *BRCA*-mutant HER2-negative breast cancer in BROCADE3[11]
- **Pamiparib (BGB-290) [Beigene]** reported phase 1 efficacy as a single agent[12] and combined with temozolomide[13]

1) ESMO 2019 #LBA12_PR; 2) #847PD; 3) #LBA13_PR; 4) #LBA50; 5) #846PD; 6) #LBA9; 7) FDA & EMA; 8) #LBA1; 9) #LBA2; 10) #LBA3; 11) #LBA9; 12) #451PD; 13) #452PD

Targeted therapies make progress versus old challenges

Early promise targeting RAS—though not in CRC

- **AMG 510 [Amgen]** reaffirmed phase 1 efficacy in KRAS G12C-mutant NSCLC (ORR 48% at all dose levels, n=23; 54% at 960 mg dose, n=13). However, the median duration of response was only ~15 weeks, and the response rate in CRC is far weaker (ORR 3% at all dose levels, n=29; 8% at 960 mg dose, n=12). Combinations will define the future of this compound; fortunately, the tolerability is excellent (7.9% grade 3, 0% grade 4/5 TRAEs)[1]
- A combination of Bcl-XL/Bcl-2 inhibitor **navitoclax (ABT-263) [AbbVie]** + MEK inhibitor **trametinib (Mekinist) [Novartis]** produced promising responses in *RAS*-mutant gynecologic cancers (ORR 31%, n=13; all 4 responses are still ongoing, with 3 already longer than 6 months). However, no responses were seen in CRC[2]

Advances treating cholangiocarcinoma by targeting molecular subtypes

In advanced cholangiocarcinoma, 2L chemotherapy has marginal efficacy; targeting oncogenic drivers may provide meaningful improvement:

- IDH1 inhibitor **ivosidenib (Tibsovo) [Agios]** in the phase 3 ClarIDHy study had a minimal ORR (2%) but high DCR (58% vs 23% for placebo) for *IDH1*-mutant, previously treated cholangiocarcinoma. The mPFS was 2.7 vs 1.4 mo. with placebo, and PFS at 12 mo. was 22% vs 0% for placebo[3]
- FGFR inhibitor **pemigatinib [Incyte]** in the phase 2 FIGHT-202 study had an impressive ORR (35.5%) and DCR (82%) in previously treated cholangiocarcinoma FGFR2-fusion/rearrangement[4]

1) ESMO 2019 #446PD; 2) #447PD; 3) #LBA10_PR; 4) #LBA40

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Anti-PD(L)1 immunotherapy continues to move earlier

Immunotherapy in the neoadjuvant/adjuvant settings

- For stage IIA–IIIB triple-negative breast cancer (TNBC) patients, **pembrolizumab (Keytruda) [Merck]** combined with standard neoadjuvant chemo sig. improved the pCR rate vs for placebo + chemo: 64.8% vs 51.2% in the phase 3 Keynote-522 trial. Pembro was continued as single-agent adjuvant therapy post-surgery; survival data remain immature, but there is a favorable trend for event-free survival even at 18 months (HR=0.63)[1]
- For stage IIIB–IVM1a melanoma, neoadjuvant **talimogene laherparepvec (Imlygic or T-VEC) [Amgen]** produced a pCR rate of 17.1%, and sig. improved relapse-free survival (RFS) and OS vs surgery alone: after correcting for a high rate of unresectable patients, 2-year RFS was 50.5% vs 30.2%, HR=0.66; 2-year OS was 88.9% vs 77.4%, HR=0.49[2]. However, T-VEC faces formidable competition from neoadjuvant **nivolumab (Opdivo) + ipilimumab (Yervoy) [BMS]** which produces a pCR rate of 65–80%[3], 3-year RFS of 80%, and 3-year OS of 90%[4]. Nivo + ipi is also strongly efficacious in the adjuvant setting, with 2-year RFS of 70%[5], and 3-year OS of 70%[4]
- For resectable stage III/IV cutaneous squamous cell carcinoma, **cemiplimab (Libtayo) [Sanofi/Regeneron]**, already approved in the advanced/metastatic setting, reports a pCR rate of 55% (n=20) as neoadjuvant therapy[6]

First immunotherapies for first-line treatment in non-MSI-high GI cancers

- For 1L hepatocellular carcinoma (HCC), **nivolumab** was tested versus standard-of-care **sorafenib (Nexavar) [Bayer]** in Checkmate 459. Nivo did not meet the predefined statistical significance threshold, but nevertheless seems to provide clinically meaningful benefit over sorafenib: ORR 15% vs 7%, 2-year PFS 14% vs 6%, mOS 16.4 vs 14.7 mo.[7] In the GO30140 study, **atezolizumab (Tecentriq) [Genentech] + bevacizumab** showed an ORR of 36% (n=104), mPFS of 7.3 mo., and mOS of 17.1 mo., comparing very favorably to historical controls[8]
- For 1L esophageal squamous cell carcinoma, **nivolumab** had superior OS to chemo in the phase 3 ATTRACTION-3 study: mOS 10.9 vs 8.4 mo., HR 0.77, p=0.019. However, both ORR and mPFS were numerically worse. Given the unmet need and the superior safety profile of nivo, it is likely nivo will still become a 1L option[9]

New first-line I-O + chemo options

- For extensive-stage, small-cell lung cancer (ES-SCLC): **durvalumab (Imfinzi) [AstraZeneca]** + etoposide + platinum chemo was superior to chemo alone in the phase 3 CASPIAN study: mOS 13.0 vs 10.3 mo., HR=0.73[10]. This regimen will be competitive with the approved **atezo** + etoposide + carboplatin combination, which has mOS 12.3 vs 10.3 mo. for chemo alone, HR = 0.76, in IMpower133[11]
- For urothelial bladder: **atezolizumab** + gemcitabine + platinum has superior PFS to placebo + chemo: mPFS 8.2 vs 6.3 mo., HR=0.82, p=0.007. OS shows a favorable trend but is not yet mature. The study population included both cisplatin-eligible and ineligible patients[12]

1) ESMO 2019 #LBA8; 2) #LBA66; 3) #LBA75; 4) #1313PD; 5) #LBA67; 6) #LBA74; 7) #LBA38; 8) #LBA39; 9) #LBA11; 10) #LBA89; 11) #1736O; 12) #LBA14

TMB or not TMB?

In NSCLC, TMB might be predictive for anti-PD(L)1 monotherapy, but not for I-O combinations

- For **pembro** monotherapy in a pooled analysis, higher TMB levels seem to be predictive of clinical response[1]
- For **atezo** monotherapy in the B-F1RST study, blood-based TMB was associated with higher response rates, but due to the lack of a control arm, it is unclear whether it was predictive or prognostic[2]
- TMB lacked utility for first-line treatment with **pembro** + chemo[3,4] or with **nivo + ipi**[5]

TMB may still define immunotherapy-responsive populations in diverse solid tumors

- In basket study Keynote-158, **pembro** efficacy is higher for TMB-high (≥10 mutations/Mb, assessed using FoundationOne CDx) than TMB-low, across diverse tumor types: ORR 30.3% vs 6.7%, 2-yr PFS 18.9% vs 6.5%[6]
- This study is consistent with previous reports on the predictive potential of TMB for ICI, for example from MSKCC (using MSK-IMPACT)[7] and UC San Diego (in partnership with Foundation Medicine)[8]

Next steps

- It seems that to make TMB a practical companion diagnostic for immunotherapy, we need to harmonize the assays, define the right cut-points for different tumor types, and combine with other I-O biomarkers

1) ESMO 2019 #LBA79; 2) #LBA83; 3) #LBA80; 4) #LBA82; 5) #LBA4; 6) #1192O; 7) Samstein 2019 Nat Genet 51:202; 8) Goodman 2017 Mol Cancer Ther 16:2598

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The next I-O combinations

The predominant use of immune checkpoint inhibitors thus far has been as monotherapy or combined with cytotoxic chemotherapies, but their full potential will involve more sophisticated combinations

Anti-PD1 + anti-CTLA4 is still the leader among I-O + I-O combinations…

- **Nivo + ipi** reaffirms its benefit in its original indication, advanced melanoma, with updated survival data—52% OS at 5 years![1]—and intracranial efficacy data (ORR 51%, 3-year PFS 43%)[2]. Nivo + ipi may also (finally) play a role in 1L NSCLC, specifically in the PD-L1 <1% population where it seems competitive with pembro + chemo[3], and also shows strong efficacy for cervical cancer with ORR ranging from 23% to 46% depending on the line of therapy and dosing schedule[4]
- **Durvalumab + tremelimumab [AstraZeneca]** shows an early efficacy signal in heavily pretreated CRPC: ORR 16% (n=37) in contrast to 0% with durvalumab alone[5]

… but new I-O + I-O approaches continue to emerge. For example:

- Adenosine receptor ($A_{2a}R$ and $A_{2b}R$) inhibitor **AB928 [Arcus]** shows promising efficacy in combination with pembro + carboplatin + pemetrexed in NSCLC patients: 3/3 patients have responded thus far[6]
- Arginase inhibitor **INCB001158 [Incyte]** + pembro produced an ORR of 7% and DCR of 30% in heavily pretreated, microsatellite-stable (MSS) CRC, which is notoriously unresponsive to immunotherapy[7]

Combining I-O + kinase inhibitors or antibody-drug conjugates (ADCs) can have powerful efficacy

- **Pembro + lenvatinib (Lenvima) [Eisai/Merck]** was approved in 2L endometrial cancer shortly before ESMO started, and report updated data: ORR 38.3%, mPFS 5.4 mo., mOS 16.4 mo. in non-MSI-H patients[8]
- **Avelumab (Bavencio) [EMD Serono/Pfizer] + axitinib (Inlyta) [Pfizer]** was approved in 1L renal cell carcinoma (RCC) earlier this year. Subgroup analyses show that the combination is superior to sunitinib across patients receiving cytoreductive nephrectomy[9], those with sarcomatoid RCC[10], and those in Japan[11]
- **Pembro + enfortumab vedotin [Seattle Genetics]**, an anti-Nectin-4 ADC, produced a compelling ORR of 71% (n=45) in 1L, cisplatin-ineligible urothelial cancer in the phase 2 EV-103 study[12]
- **Nivolumab + dabrafenib (Tafinlar) [Novartis] + trametinib** in BRAF-mutant melanoma shows an outstanding ORR of 91% (n=26), although the mPFS was only ~8 months. In patients with prior immune checkpoint inhibitor (ICI) treatment, the ORR was 83% (n=16)[13]

Could targeted therapy-based approaches be the way forward after ICI failure?

- In renal cell carcinoma (RCC) after progression on prior ICI, **pembro + lenvatinib** reported an ORR of 64% (n=33)[14] and CXCR4 inhibitor **mavorixafor (X4P-001) [X4 Pharma] + axitinib** reported an ORR of 61% (n=18)[15]. However, it is unclear without a control arm how much the I-O component contributed to the efficacy
- In urothelial carcinoma after progression on platinum chemo and ICI, **sacituzumab govitecan [Immunomedics]**, a Trop-2 ADC, reported an ORR of 29% (n=35)[16]

Cell therapies for solid tumors show more early signals

The latest examples:

- **NY-ESO-1**-targeted TCR-T cell therapy **TBI-1301 [Takara Bio Inc.]** produced responses in synovial sarcoma patients: ORR 33% (n=9)[1]. All responders had the highest level of NY-ESO-1 expression (>75% by IHC) in their tumors. Thus far, only synovial sarcoma patients have responded, out of four tumor types initially tested[2]
- **MART-1**-targeted TCR-T cell therapy **[Netherlands Cancer Institute]** produced responses in hard-to-treat melanoma patients: ORR 18% (2/12), with one responder in the post-anti-PD1 setting and one responder with uveal melanoma[3]
- Fibroblast activating protein (**FAP**)-targeted CAR-T therapy **[Univ. Hosp. Zürich]** shrank lesions with minimal toxicity in 3/3 mesothelioma patients[4]

1) ESMO 2019 #LBA68; 2) #1311O; 3) #LBA4; 4) #LBA62; 5) #LBA51; 6) #1206P; 7) #440O; 8) #994O; 9) #908PD; 10) #910PD; 11) #956P; 12) #901O; 13) #1312O; 14) #1187PD; 15) #1186PD; 16) #LBA55

1) ESMO 2019 #1182PD; 2) #1183PD; 3) #1184PD; 4) #1226P

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