Clarion Perspectives from the

ESMO 2018 Congress

Oct. 19–23, 2018 • Munich, Germany

Breast Cancer Sees First Movers for Novel Mechanisms

Atezolizumab (Tecentriq [Genentech]) to be the first I-O therapy for breast cancer

Supported by the IMpassion130 phase 3 trial of anti-PD-L1 atezo + nab-paclitaxel (Abraxane [Celgene]) vs placebo + nab-pacli. for first-line (1L) adv. triple-negative breast cancer (TNBC):

- Atezo had a positive albeit modest benefit in all-comers—mPFS 7.2 vs 5.5 mo., mOS 21.3 vs 17.6 mo., ORR 56% vs 46%—and stronger benefit in PD-L1+ patients: mPFS 7.5 vs 5.0 mo., mOS 26.0 vs 15.5 mo., ORR 59% vs 43% (CR rate 10% vs 1%)[1]
- These long-awaited results confirm the promise seen in the phase 1 cohort[2], but mark only the start of immunotherapy for breast cancer

Alpelisib [Novartis] on track to be the first PI3K inhibitor approved for breast cancer

Supported by the SOLAR-1 phase 3 trial of PI3Kα inhibitor alpelisib + fulvestrant vs placebo + fulvestrant for previously treated, HR+, HER2− advanced breast cancer (aBC):

- Adding alpelisib doubled the mPFS (11.0 vs 5.7 mo. by investigator review; 11.1 vs 3.7 mo. by independent review) in patients with *PIK3CA* mutation (30–40% of HR+ aBC)[3]
- ORR also doubled (26.6% vs 12.8%; 35.7% vs 16.2% in those with measurable disease)[3]
- Results compare very favorably with previous, now-discontinued PI3K programs, such as taselisib [Roche] + fulvestrant[4], or buparlisib [then Novartis, now Adlai Nortye] + fulvestrant[5]
- Alpelisib will thus be first-in-class, but with caveats: OS results are still pending, and mutation testing will be essential, as alpelisib does not benefit *PIK3CA* wild-type patients[3]

Other novel mechanisms for HR+ aBC on the horizon?

HDAC inhibitors **chidamide [Shenzhen Chipscreen]**[6] or **entinostat [Syndax]**[7] seem promising, while FGFRi lucitanib [Clovis] disappointed[8]. However, CDK4/6 inhibitors continue to become more entrenched, with new data on OS[9], PROs[10], men[11], and AE management[12]

1) ESMO 2018 #LBA1_PR; 2) SABCS 2015 # P2-11-06; 3) ESMO 2018 #LBA3_PR; 4) ASCO 2018 #LBA1006; 5) Lancet 2018; 19:87; 6) ESMO 2018 #2830_PR; 7) NPJ Breast Cancer 2018; 4:1; 8) ESMO 2018 #289PD; 9) ESMO 2018 #LBA2_PR; 10) ESMO 2018 #290P; 11) ESMO 2018 #293PD_PR; 12) ESMO 2018 #339P

New First-line Treatment Paradigms Emerge in Other Solid Tumors

Olaparib (Lynparza [AstraZeneca]) maintenance in 1L BRCA-mutant ovarian cancer

Supported by the SOLO-1 phase 3 trial of PARP inhibitor olaparib vs placebo:

- Olaparib had impressive benefit: mPFS not reached (41 mo. follow-up) vs 13.8 mo., HR 0.30[1]
- Olaparib is already approved in later-line treatment for ovarian cancer; the SOLO-1 results are likely to make olaparib standard of care in the first-line setting as well, for BRCA-mut patients

Avelumab (Bavencio [EMD Serono/Pfizer]) + axitinib (Inlyta [Pfizer]) in 1L RCC

Supported by the JAVELIN Renal 101 phase 3 trial of avelu + axi (anti-PD-L1 + TKI) vs sunitinib:

- Avelu + axi had superior efficacy vs sunitinib: mPFS 13.8 vs 8.4 mo., ORR 51% vs 21% by independent review, and the OS trend is favorable although data remain immature[2]
- Benefit was regardless of risk group or PD-L1 status unlike atezo + bevacizumab [Genentech][3]
- Avelu + axi will have a role in 1L RCC, but debate remains over its role vs nivolumab + ipilimumab (Opdivo + Yervoy [BMS])[4] and future competitors like pembrolizumab [Merck] + axi[5]

Pembrolizumab (Keytruda [Merck]) in 1L head and neck squamous cell carcinoma:

Supported by the Keynote-048 phase 3 trial of anti-PD1 pembro + chemo (platinum + 5-FU) vs anti-EGFR cetuximab (Erbitux [Eli Lilly]) + the same chemo regimen:

- Pembro alone was superior to the cetuximab regimen in PD-L1+ patients (CPS ≥1): mOS 12.3 vs 10.3 mo. Pembro + chemo was superior in all-comers: mOS 13.0 vs 10.7 mo.[6]
- Pembro is already approved in pretreated HNSCC, and is now likely to shift to 1L

1) ESMO 2018 #LBA7_PR; 2) ESMO 2018 #LBA6_PR; 3) ASCO 2018 #578; 4) NEJM 2018; 378:1277; 5) Press release 2018.10.18; 6) ESMO 2018 #LBA8_PR

Clarion | A LIFE SCIENCES CONSULTANCY

One Financial Center • Boston, MA 02111
617-757-7850 • dchang@clarionhealthcare.com

Clarion Perspectives from the

ESMO 2018 Congress

Oct. 19–23, 2018 • Munich, Germany

The Immuno-Oncology Field Continues to Wrestle with Key Questions

When should I-O be used?

Most I-O approvals are for metastatic disease, but I-O has a strong rationale for use earlier, as seen with nivo or ipi as adjuvant therapy for melanoma[1], and anti-PD-L1 durvalumab (Imfinzi [Astra-Zeneca]) as consolidation therapy after chemoradiation in stage III NSCLC[2]. New evidence presented:

- Stage I–IIIA NSCLC: Neoadjuvant **Nivo ± ipi** induced major pathologic response in 31% of 26 resected patients[3]
- Stage I–III colon cancer: With neoadjuvant **nivo + ipi**, 7/7 MMR-deficient tumors responded[4]
- High-risk, non-muscle invasive bladder cancer unresponsive to BCG therapy: **Pembro**, as an alternative to cystectomy, had a CR rate of 38.8% (n=103), and most responses were durable[5]

What treatment duration is sufficient for I-O?

Jeffrey Weber (NYU Langone) reviewed current data and made a compelling case that 2 years of anti-PD1 treatment is likely sufficient for those who respond, perhaps 1 year in melanoma. PET scan and/or biopsy may inform the timing of discontinuation[6]

How should we treat patients after anti-PD1/PD-L1 treatment failure?

As immune checkpoint inhibitor (ICI) use grows, the need for treatments after immunotherapy failure also grows. Although most treatments have ORR <20% in this setting, some are showing greater promise:

- Multi-TKI **sitravatinib [Mirati]** + nivo had ~29% ORR (n=56) in nonsquamous NSCLC post-ICI[7]
- FAP-targeted IL-2v agent **RO6874281 [Roche]** monotherapy had ~20% ORR (n=10) in melanoma post-ICI[8]
- Intratumoral TLR9 agonist **IMO-2125 [Idera]** + ipi had ~39% ORR (n=21) in melanoma post-ICI[9]

How can we turn "cold" tumors "hot"?

Most patients do not respond to ICI therapy, because of T cell suppression, T cell exclusion, and/or lack of T cell activation. Novel mechanisms/combinations continue to be tested, with mixed results:

- Cytokine IL-10 agonist **pegilodecakin [Armo/Lilly]** had ORR 67% (n=9) in platinum refractory ovarian cancer[10]. Pegilodecakin + FOLFOX had mOS 10.2 mo. in previously treated pancreatic cancer[11], which compares favorably with 2L nal-irinotecan (Onivyde [Ipsen]) + 5-FU/LV (mOS 6.1 mo)[12]. Combinations with anti-PD1 therapy remain inconclusive[13]
- Chemokine CXCR4 inhibitor **balixafortide [Polyphor]** + eribulin has early data in HER2-negative breast cancer that seems markedly better than historical data for eribulin alone[14]
- Bispecific inhibitor of TGFβ and PD-L1, **M7824 [EMD Serono]** reported ORR of ~13–30% in esophageal[15,16], gastric[17], and biliary[18] cancers. Efficacy is higher in PD-L1+ NSCLC (not previously treated with ICI)[19]
- STING agonist **MK-1454 [Merck]** had 0% ORR as monotherapy and 24% ORR in combination with pembro—but only in tumor types where pembro monotherapy is known to have activity[20]. RIG-1 agonist **MK-4621 [Merck]** has not yet reported clinical efficacy data[21]

Which patients should receive I-O and which should not?

Diverse I-O biomarkers are being actively explored. The following are just two distinct examples:

- **Blood tumor mutation burden (bTMB):** In the B-F1RST phase 2 trial in NSCLC (n=119), atezo had ORR of 28.6% in bTMB ≥16 patients, but only 4.4% in bTMB <16 patients[22]. A confirmatory phase 3 trial is ongoing
- **Immune-related adverse events (irAEs):** Patients who had irAEs were reported to have better responses to nivo than those who did not, in both RCC[23] and NSCLC[24,25]. However, a different study of anti-PD1 in melanoma and NSCLC patients found no correlation of irAEs with survival[26]

1) NEJM 2017; 377:1824; 2) NEJM 2017; 377:1919; 3) ESMO 2018 #LBA49; 4) ESMO 2018 #LBA37_PR; 5) ESMO 2018 #8649; 6) ESMO 2018 CYE session "The right time for discontinuing immunotherapy"; 7) ESMO 2018 #11290; 8) ESMO 2018 #412PD; 9) ESMO 2018 #1245PD; 10) ESMO 2018 #1146P; 11) ESMO 2018 #1143P; 12) Onivyde product label; 13) ESMO 2018 #1144P; 14) ESMO 2018 #285PD; 15) ESMO 2018 #642P; 16) ESMO 2018 #643P; 17) ESMO 2018 #661P; 18) ESMO 2018 #757P; 19) ESMO 2018 #1463P; 20) ESMO 2018 #LBA15; 21) ESMO 2018 #LBA16; 22) ESMO 2018 #LBA55; 23) ESMO 2018 #3169P; 24) ESMO 2018 #1227P; 25) ESMO 2018 #1391P; 26) ESMO 2018 #1141PD

Clarion | A LIFE SCIENCES CONSULTANCY

For more information on Clarion's oncology offerings, please contact:

Dennis Chang, PhD *Principal*
dchang@clarionhealthcare.com
One Financial Center • Boston, MA 02111
617-757-7850