Clarion Healthcare's Highlights from the

ESMO 2017 Annual Congress

Clarion attended this year's ESMO and with almost 24,000 attendees convening for presentations and discussions of over 1,700 abstracts, we thought we would highlight some of the themes that emerged:

Combination therapy: a common theme

Throughout the history of cancer therapy, combination approaches have repeatedly proven more powerful than single-agent therapies[1]—though finding the optimal combination is nontrivial. At this year's ESMO, advances were reported across different tumor types in finding combinations that enhance efficacy significantly. Progress included:

Nivolumab + Ipilimumab in RCC: The "**nivo + ipi**" combination led the pack of IO-based combinations with its approval in 2015 for metastatic melanoma, and is the leader again in renal cell carcinoma. The hotly anticipated CheckMate 214 trial presentation reported significant efficacy benefit of nivo + ipi versus sunitinib in the frontline setting in the intermediate/poor risk group of RCC patients across all metrics—including an unprecedented CR rate (9% vs 1%) and superior overall survival[2]. Importantly, the unprecedented efficacy does *not* come at the cost of severe toxicity; it helped that the dose of ipi here was 1/3 the dose used in the CheckMate 067 trial in melanoma. Broad frontline use is expected for nivo + ipi, although sunitinib and other TKIs still have a role to play in the favorable risk group and in later lines of therapy. Combinations of anti-PD1/PD-L1 agents with TKIs or bevacizumab are also in development—but their durability remains unproven, and nivo + ipi has just set a high bar.

Targeted therapies enhancing standard of care: **Abemaciclib + anastrozole or letrozole**, a combination of a CDK4/6 inhibitor with non-steroidal aromatase inhibitors, has confirmed PFS and OS benefit as initial treatment of HR+, HER2− advanced breast cancer, based on interim analysis of the MONARCH 3 trial[3]. This was hardly a surprise given prior FDA and EMA approvals of similar regimens with other CDK4/6 inhibitors palbociclib and ribociclib, but the approval of a third competitor could affect pricing and reimbursement strategies across the field. **Ramucirumab + docetaxel**, a combination of a VEGFR2 antagonist antibody with taxane chemotherapy, improved PFS (4 months vs 2.4 months) and ORR (24.5% vs 14%) over chemo alone in platinum-refractory advanced urothelial carcinoma in the Ph 3 RANGE trial [4] and could support the first targeted therapy approval for urothelial cancer—though multiple immunotherapy approvals will limit its uptake.

Novel IO combinations showing promise: Among the hundreds of novel IO mechanisms in exploratory trials, a few highlights from this year's ESMO showed interesting efficacy with minimal toxicity:

- **Durvalumab + AZD9150**, anti-PD-L1 + STAT3 inhibitor, was active in both anti-PD(L)1-naïve and pretreated recurrent/metastatic HNSCC patients (ORR 29% and 11% respectively, including 3 CRs in the naïve population)[5]
- **CA-170**, a first-in-class oral small molecule dual inhibitor of immune checkpoints PD-L1 and VISTA, showed a pharmacodynamic signal in a Ph 1 study[6].
- **PF-04518600 + Utomilumab**, OX40 + 4-1BB agonists, combining two immunostimulatory agonist antibodies was active in a Ph 1 study including 2 ongoing PRs in melanoma patients[7].

Sources: (1) Scarlett 2016 Cancer Discov 6:956; (2) LBA5; (3) 236O; (4) LBA4 (5) 1135O; (6) 1141PD; (7) 1142PD; (8) Press Releases

Adjuvant therapy practice-changers

Most people diagnosed with cancer in developed countries do not die of cancer[9], largely because early-stage solid tumors may be curable through surgery and/or radiation therapy. However, there remains room for improvement in the cure rates for certain cancers; better adjuvant therapies are vital. This year's ESMO showcases several adjuvant options that will change medical practice in the near future.

Multiple breakthroughs in melanoma: The most excitement was around locally advanced melanoma, where four distinct regimens showed impressive survival benefits in the adjuvant setting. For BRAF-mutant melanoma, both the **dabrafenib + trametinib** combination and (in stage IIC–IIIB melanoma) single-agent **vemurafenib** showed significant improvement in relapse-free survival/disease-free survival versus placebo with ~3 years of follow-up[10,11]. The immunotherapies **nivolumab** and **ipilimumab** both showed recurrence-free survival of >50% at 2 years, though nivo was clearly superior to ipi[12].

Durvalumab in stage III NSCLC: The anti-PD-L1 immunotherapy **durvalumab** applied as consolidation therapy after platinum-based chemoradiation nearly tripled the median PFS versus placebo (16.8 vs 5.6 months) in the phase 3 PACIFIC trial[13]. Anti-PD1/PD-L1 agents are already standard of care in the second-line setting of metastatic NSCLC, but this study may herald the application of immunotherapy in earlier stages of lung cancer.

Sources: (9) Globocan; (10) LBA6; (11) LBA7; (12) LBA8; (13) LBA1

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Precision oncology: ongoing challenges

Customizing oncology care to the individual patient remains a vision that the field is actively pursuing; several sessions at ESMO were dedicated to the latest progress with predictive biomarkers, but also highlighted major ongoing challenges that hinder faster, broader advances:

No single biomarker is sufficient for immunotherapy: The optimal approach to predict response to anti-PD(L)1 therapies is still not settled. **PD-L1 expression** is not enough: for example, in the OAK trial in NSCLC, even patients without PD-L1 expression, as defined by both SP142 and 22C3 IHC assays, show improved survival with atezolizumab compared with docetaxel[14]. **Tumor mutational burden in blood (bTMB)** is also not enough: while it was associated with improved atezolizumab efficacy in retrospective analyses of the POPLAR and OAK studies in NSCLC, there was little overlap seen between bTMB and PD-L1 expression[15]. Thus at minimum, both PD-L1 and TMB may be required for NSCLC, but neither of those markers seem to be highly predictive for RCC[16]. **Stromal TILs (sTIL)** are not enough: in the KEYNOTE-086 trial in metastatic triple-negative breast cancer, pembrolizumab monotherapy produces more responses in sTIL high vs sTIL low patients, but the effect is more pronounced if the tumor samples were also PD-L1 high[17].

Designing biomarker studies demands trade-offs: Prospective and retrospective clinical studies to identify predictive biomarkers have distinct advantages and disadvantages[18]. Prospective studies allow for optimal sample collection and processing, and appropriate ethical approvals. Retrospective studies are faster and easier if samples are already available; on the other hand, it is still critical that they have adequate sample size, follow-up, hypotheses, and funding.

New platforms raise new questions: Liquid biopsy approaches and other emerging technologies garner much enthusiasm over their potential, but are still mired in questions regarding validation: for example, whether the information captured in peripheral blood truly reflects the changes in tumor biology before and after treatment for different cancers, and whether learnings from one cancer will be applicable to another[19].

A collaborative effort will be essential: Thus considerable research may be required to identify and validate a novel biomarker strategy. Furthermore, this research is challenged by tumor-intrinsic factors such as heterogeneity, dynamic changes, and evolution, as well as extrinsic factors related to the techniques and specimens. Currently, commercial interests tend to drive many competing studies for the same small number of markers or targets[20]. Collaboration across different industry, academic, non-profit, and government stakeholders may be required to overcome these challenges and make faster, broader progress towards the precision oncology future.

Sources: (14) 1296O; (15) 1295O;(16) ASCO 2017 #3016; (17) LBA13; (18) ESMO-SEOM Joint Symposium: Integrating Biomarkers into Oncology; (19) ESMO-CSCO: Liquid Biopsy in the Clinic: From Myth to Reality; (20) ESMO-SEOM Joint Symposium: Biomarkers in Lung Cancer

Reining in cost while improving quality of care

The emergence of new treatment regimens, their impact on the health-related quality of life of patients as well as the cost implications were part of the discussion throughout ESMO:

The rising cost of cancer care: As in the US, the cost of cancer care in Europe is rising unsustainably. Total direct healthcare cost of oncology in the EU has risen from €51B in 2009 to €83B in 2014, accounts for ~6% of total health expenditure, and is expected to rise even further with more expensive regimens, particularly combinations. Complicating the issue are inequities in price, demand, and access surrounding cancer medicines among the EU member states[21].

Can a focus on value turn the tide? The ESMO Congress ended with an appeal to embrace value-based pricing of cancer medicines: to distinguish between inexpensive and essential cancer medicines and expensive and innovative medicines; to apply the ESMO Magnitude of Clinical Benefit Scale, which considers outcomes of survival, quality of life, or surrogates as well as treatment toxicity in determining price; to exclude non-beneficial treatments; to enforce price transparency; and to use organized purchasing power to negotiate greater price rebates[7]. These measures strive to control costs while continuing to reward the developers of the most beneficial medicines, but they are likely insufficient—drug costs are only a small fraction of total healthcare costs[22].

Sources: (21) ESMO Congress Highlights 2 – The Best of ESMO 2017: Public Health and Health Economics, ESMO Congress Highlights 1 & 2 – The Best of ESMO 2017; FDA.gov; clinicaltrials.gov; OncLive; ESMO 2017: Press Releases;(22)Wilking et al. ASCO 2016 #6618

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