Evaluate Vantage

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Esmo 2017 – Practice-changing studies abound

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Esmo heard detailed data from seven studies considered by formal discussants to be practice-changing – some were well signalled and planned with simultaneous journal publications, while others came as a surprise.

In a ranking by *EP Vantage* in terms of impact the collaborative group-run Stampede trial emerges as this year's unlikely winner, following its strong showing at the last two Ascos. *EP Vantage* ranked Astrazeneca's Flaura study of Tagrisso next, while a battle between Bristol-Myers Squibb and Exelixis signals practice-changing potential in renal cancer (see table below).

Stampede looks likely to propel Johnson & Johnson's Zytiga from castration-resistant to hormone-sensitive prostate cancer, in the way it has already advanced docetaxel (*Esmo 2017 – Academic boffins Stampede over the pharma industry, September 9, 2017*). Moreover, the head-to-head comparison of Zytiga with docetaxel reported at Esmo favoured the androgen blocker by a slim margin.

J&J might seek to obtain approval to support such a change – perhaps depending on the outcome of patent challenges – but according to Stampede's Professor Nicholas James, guideline and recommendation changes for docetaxel occurred despite the lack of a corporate sponsor.

Moreover, adoption of the new use of docetaxel was rapid partly because the agent is generic and thus cheap, something to consider if J&J's patents do not hold. Zytiga's move up the treatment cascade looks unstoppable and, in addition to a significant positive impact on patients, will send a shockwave though most of the competing registration studies in prostate cancer.

Flaura blooms

Astra's Flaura study seems likely to catalyse a rapid adoption of Tagrisso as the first-line standard of care for EGFR-mutated NSCLC, despite its OS data remaining largely immature, and probably ahead of its formal approval (*Esmo 2017 – A chance for Astra to save face in lung cancer, September 9, 2017*).

Next comes the high-profile Checkmate-214 result for Opdivo plus Yervoy in first-line metastatic renal cell carcinoma, which despite some questionable data redactions by the principal investigator ahead of its presentation has set a new bar with combination immunotherapy in this condition (*Esmo 2017 – Renal cancer battlefront moves to the front line, September 11, 2017*).

However, Checkmate-214 is unlikely to hand Bristol the renal cancer market on a plate. Detailed results showed surprising trends that could favour its smaller competitor Exelixis and its partner Ipsen, which together announced an update of their own first-line study, Cabosun, at Esmo. Cabosun's practice-changing potential has been boosted by the Checkmate-214 findings.

Indeed, Checkmate-214 has shown that the Opdivo/Yervoy combo either offers no advantage over Sutent in some patient subgroups, handing these to Cabometryx, and in others might even be an even poorer choice. Its practice-changing potential might well be limited to PD-L1-positive, poor/intermediate-risk patients, while Cabometyx captures the PD-L1-negatives.

Checkmate-214 has confirmed that selection based on PD-L1 status will become a feature of this indication, throwing into considerable doubt all but one of the six competing phase III renal cancer trials involving anti-PD-(L)1 agents. For that reason alone its impact on competitors could be considerable.

Meanwhile, two highly positive phase III studies, Checkmate-238 of Opdivo and Combi-AD of Tafinlar/Mekinist, will establish new therapies in adjuvant melanoma; in both cases the drugs are already used as standard treatment for metastatic disease. New studies will have to establish whether the patients who have received these agents in the adjuvant settings respond in the same way if re-treated later.

Finally, the Range study of Eli Lilly's Cyramza was identified as practice changing, providing a modest though significant benefit on top of docetaxel in refractory urothelial cancer.

Esmo 2017 – the practice changers	
Study	**Likely outcome**
Stampede	Zytiga moves to front-line therapy in patients starting androgen-deprivation therapy for hormone-sensitive prostate cancer. Zytiga marginally favoured vs docetaxel in robust head-to-head comparison.
Flaura	Tagrisso advances to first line for EGFR-mutated NSCLC. Currently approved for EGFR T790M mutation-positive NSCLC, after progression on an EGFR TKI therapy.
Checkmate-214	Opdivo/Yervoy potentially preferred choice in first-line PD-L1+ poor/intermediate RCC, replacing Sutent.
Cabosun	Cabometyx potentially preferred choice in PD-L1-, and an option in PD-L1+, poor/intermediate RCC, replacing Sutent. Changes likely to be mediated by reference to Checkmate-214.
Checkmate-238	Opdivo replaces Yervoy (in US) as adjuvant therapy in completely resected stage III/IV melanoma.
Combi-AD	Tafinlar/Mekinist established as adjuvant therapy for resected BRAFV600E/K mutant melanoma.
Range	Cyramza plus docetaxel becomes option in platinum-refractory advanced urothelial cancer.

The list has several potentially controversial exclusions. Astrazeneca's Pacific study was featured prominently at the conference, but *EP Vantage* considers it premature to call it practice-changing in the absence of OS data, based on commentary by lung cancer KOLs – although the study might eventually establish a new setting.

This might raise questions about the effect of adding a PD-(L)1 therapy before first-line metastatic use, since this might alter the effectiveness of subsequent anti PD-(L)1 agents.

Two studies that featured prominently at Esmo have been excluded for a different reason: the Monarch-3 trial of Lilly's abemaciclib and the Ariel-3 study of Clovis' rucaparib. Both were highly positive, but also established that these agents have efficacy equal to the two other agents in their respective classes of CDK 4/6 inhibitors and Parp inhibitors.

What is evident is that 2017 has seen more of these landmark data than ever before, and the Esmo conference has become one that cannot be missed.