ESMO
TOP TAKEAWAYS

beyond blue

Detailed findings

1 ADCs continue to shine and show no sign of stopping, with new combinations and next generation agents showing promising data.

- It wouldn't be an ESMO round up without discussing the landmark EV-302 trial. A historical moment in the treatment of bladder cancer with a doubling of overall survival for patients receiving enfortumab vedotin (EV) plus pembrolizumab vs. SOC platinum-based chemotherapy in 1L LA/mUC – an area that hasn't seen much in the way of advances. And there seems to be a theme emerging with ADCs. At two major oncology conferences, two different ADCs have received standing ovations. ADCs are continuing to deliver on their promise and show no signs of slowing down.
- EV + pembrolizumab is the first of the ADC + IO combinations to be successful (in a ph3 trial), but there are others in development. The BEGONIA trial investigating Dato-DXd + durvalumab as a 1L treatment for advanced TNBC, was also presented showing impressive response rates suggesting ADC + IO could be a winning combination.
- As for the future, we saw data for ADCs with novel targets (e.g. B7-H4), new payloads (TLR 7/8 agonist), and new linker designs (e.g. used by SKB264). In addition, there was data supporting the possibility of double ADC therapy (DAD) and the future possibility of triplet therapy (DAD-IO). It's certainly an exciting time for ADCs.

2 However, with the rise of ADCs comes a new wave of toxicities. There is a need for education (for HCPs and patients), close monitoring and better prediction.

It is to be expected – new MoAs bring new toxicities. But, in the case of ADCs, the toxicity profile – influenced by the choice of target, linker and payload – can be very different across individual agents, even those in the same 'class' (e.g. TROP-2 ADCs). The value of ADCs is clear, and guidance on the AE profiles will help support adoption in the clinic.

Key messages emerging across discussions included:

- Prescribers (and other HCPs e.g. nurses) need to be educated on relevant AEs and understand strategies for management (e.g. use of G-CSF to manage neutropenia).
- Setting expectations with the patient is an important step, a) to help avoid patient hesitation when AEs appear and b) because community care providers are unlikely to recognise the AE with this new class.
- Prediction of AEs is an important new focus. For example, identifying polymorphisms affecting genes encoding enzymes that are involved in payload metabolism, and increasing monitoring for these patients.

Increasing comfort with these new toxicity profiles is a crucial step as ADCs look to expand their use into early-stage disease.

3 Rivalling docetaxel in 2L advanced NSCLC (after chemo-IO) proves to be tricky – personalised/targeted approaches are likely to be required.

Despite huge trial efforts in this area – docetaxel is showing great staying power.

- Data from the SAPPHIRE trial showed no overall survival benefit for the combination of sitravatinib plus nivolumab. This is causing some to ask the question is it time to give up hope for oral anti-angiogenic agents in combination with ICIs to overcome resistance to IO?
- Another agent trying to conquer the same setting is Dato-DXd. While a statistically significant PFS benefit over docetaxel was shown in TROPION-Lung01 (primarily driven by patients with non-squamous histology), it wasn't a clear win.
- And these aren't the only regimens to have struggled in this area – think anti TIGIT, KRAS-G12C inhibitors...

So, what is the key to unlocking 2L NSCLC treatment? Discussions centred around the need for better personalisation of therapy (i.e. biomarker driven approaches, tailored therapy to the mechanisms of resistance), and in the case of 'IO plus' combinations - the need for a more consistent definition of acquired ICI resistance.

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4 Moving towards a more complex treatment algorithm for EGFR+ advanced NSCLC, with amivantamab combinations taking centre stage.

- Three presidential papers were dedicated to to amivantamab (ami) based combinations, tackling areas of significant unmet need (exon 20 insertion mutations, and TKI resistance) and challenging current frontline side of care, osimertinib.
- Results from PAPILLON supported ami + chemo as a new standard of care in the neglected space of EGFR exon 20 insertion mutations.
- For the MARIPOSA and MARIPOSA-2 trials (covering frontline and post-osimertinib settings in EGFR+ aNSCLC respectively), however, the future role of the ami-combinations was less clear cut. Meaningful PFS benefits over current standards of care were achieved (OS data still immature), but the toxicity profiles were considered challenging – raising the question of the risk vs. benefit of these regimens. In the frontline setting, the absence of OS benefit (at least as of yet!) added to this concern. Careful patient selection and shared decision making is expected.
- But the door isn't closed on these combinations – the subcutaneous administration, longer term follow-up (showing OS data and the impact of modified dosing regimen adopted in MARIPOSA-2), and advances in identifying patients who may benefit most from these intensified combinations, could carve a clearer role...

5 The murky realm of IO in resectable NSCLC remains murky – more positive trials with perioperative IO were reported, but the question that remains is 'who needs the adjuvant portion?'

- Two perioperative trials were reported, KEYNOTE-671 and CheckMate-77T. Both were positive – with KEYNOTE-671 being the first to show an OS benefit - and join the crowded market that is forming (NEOTORCH and AEGEAN, alongside other adjuvant/ neoadjuvant only trials).
- But are perioperative IO regimens superior to neoadjuvant IO? We still don't know but oncologists are keen to figure it out, as reflected by packed auditorium on Saturday morning for a controversy session dedicated to this very topic!
- One sentiment that was consistently raised is that the answer won't be 'one or the other'; decisions will need to be personalised depending on response to the neoadjuvant portion of therapy. Being able to select the patients who need the adjuvant portion of treatment is currently the missing piece of the puzzle. Today many are using pCR, but other measures are also being investigated (e.g ctDNA, depth of pathological response, PD-L1 expression, TIL by AI, MRD) which may help inform decision making.

Contact our oncology team below to discuss how we can best support you and share our insights with you.

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