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KEY THEMES

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KEY THEME ONE:

KEYNOTE-671 MUDDYING THE WATERS FURTHER IN EARLY-STAGE RESECTABLE NSCLC

A flurry of positive trials investigating IO as neoadjuvant treatment, adjuvant treatment and perioperative regimens in resectable NSCLC have been reported. Prior to this year, oncologists had been grappling with whether neoadjuvant or adjuvant IO should be the standard approach (see our research, here). But in the past few months positive perioperative trials are reading out, leaving the oncology community with the question of how they should apply IO; pre-op, post-op, or both?

Does perioperative IO bring a benefit above and beyond neoadjuvant IO?

Definitively, we don't know and you can feel the frustration growing as the ideal trial that would address this question, discussed by Dr Mark Awad, is not a reality. The data from KEYNOTE-671 was positive but, while cross-trial comparisons are challenging, at first glance it doesn't appear to have significantly outperformed CheckMate 816.

However, one data point from KEYNOTE-671 – the exploratory analysis of EFS by pathologic response – seems to have raised interest and has made a persuasive suggestion that there may be an added benefit of the adjuvant portion of treatment. "Even in patients who had no clear evidence of benefit from the neoadjuvant approach, we still see separation of the curves", said Dr. Heather Wakelee.

How will it influence brand choice in the early-stage setting?

Our pharma clients will be watching this situation unfold, evaluating the opportunity and risk for their respective assets. Opdivo® has established itself nicely in the neoadjuvant setting, but KEYNOTE-671 represents a meaningful threat. Already, there is a sense that the full perioperative regimen probably isn't for all, requiring an additional year of treatment and the inconvenience, potential toxicity and cost associated. Therefore, selecting who needs the adjuvant portion most (based on pathologic response or another measure) will be important. However, even if the perioperative regimen isn't for everyone, a key watch-out for BMS will be that oncologists favour a PD-(L)1 inhibitor with 'full' perioperative approval, providing the security that the agent is approved for continuation should it be deemed necessary, post-operatively.

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KEY THEME TWO:

PROGRESS FOR CAR-T IS CELEBRATED BUT BALANCED BY A SPOTLIGHT ON DISPARITIES AND CHALLENGES IN ACCESS

At this year's ASCO, there was much excitement for CAR-T cell therapy, and with very good reason. We saw data for Breyanzi® in CLL, an indication without any CAR-T approvals to date. In addition, data from the landmark ZUMA-7 and CARTITUDE-4 trials highlighted the benefit of moving CAR-T into earlier lines of therapy in LBCL and R/R multiple myeloma respectively.

The story doesn't end there, with sights now set firmly on moving CAR-T therapies into the frontline settling. The right indicators are in place – CAR-T cell therapy can challenge ASCT, better outcomes are achieved when CAR-T cell therapy is employed with fewer prior lines of therapy, alongside a lower incidence of toxicities, and there are more fit T-cells at these earlier lines. Also, it was clear from the questions and discussion that there is hope and excitement for this advance.

However, the conversation wouldn't have been complete without time being dedicated to the complex challenges associated with CAR-T therapies. The quote by Dr Lathan that the "CAR-T path is complicated, cumbersome, costly, choosy, but potentially a curable one…" reflects the current situation nicely – the tremendous potential for CAR-T is widely acknowledged but there are also multiple barriers to access. The limited number of CAR-T centres, limited slot availability, time to manufacture, affordability and equitable distribution were all discussed.

> "We have heard CAR-T earlier in the treatment paradigm, the demand is going to surge; we need partners to be ready for this demand, so we don't repeat mistakes with BCMA CAR-T" **– Leyla Shune, MD.**

And oncologists could all too easily recall stories where these challenges had a significant, and sometimes devastating, impact on their patients. One can only imagine that, as the role for CAR-T expands, these barriers will increase in significance.

WHAT FUTURE CHANGE IS REQUIRED TO FULLY DELIVER ON THE PROMISE OF CAR-T?

- Call for everyone to proactively build equitable delivery and access into oncology drug development, alongside patient and community engagement to increase trial enrolment among underrepresented groups.
- Enhanced accessibility beyond tertiary care centres. Whilst they are a long-term vision, and a significant shift from where we are today, CAR-T centres in the community would help to address referral challenges and logistics challenges relating to follow-up. Until then, expansion of patient assistance programmes to support with travel/ accommodation costs is beneficial.
- Decentralisation of CAR-T manufacturing in an effort to reduce production costs.
- Lowering healthcare out-of pocket costs by insurers.

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KEY THEME THREE:

ONGOING EXPLOSION OF PRECISION MEDICINE AND THE NEED TO OVERCOME LOGISTICAL COMPLEXITIES TO SUCCEED

This year's ASCO programme included several prominent presentations of targeted therapies, highlighting that precision medicine continues to represent a major cornerstone of oncology innovation.

- Data from THOR and MIRASOL confirmed the role of erdafitinib in mUC with FGFR3/2 alt and mirvetuximab soravtansine (MIRV) in FRα+ platinum-resistant ovarian cancer respectively.
- Two of the four plenary sessions illustrated the power of targeted therapy:
  - Delivering therapeutic progress in an area that has been stagnant for decades (Vorasidenib in IDH-mutant low-grade glioma).
  - Reinforcing the potential for targeted therapies to move from advanced disease to the early-stage setting (adjuvant osimertinib in resected EGFR mutated stage IB–IIIA NSCLC).
- T-DXd showed broad activity across a range of HER2 expressing tumors in DESTINY-PanTumor02, which has led to discussions regarding the possibility of a tumor agnostic indication.
- And the list continues….

However, within these presentations we were also reminded of the challenges that can be faced when launching a targeted therapy, including test availability (as seen initially following MIRV launch), encouraging widespread testing (with fewer than 50% of potentially eligible patients undergoing FGFR testing, despite accelerated approval of erdafitinib) and reliability/consistency of testing (e.g. discordance with HER2 status).

The challenges in current molecular testing behaviours were discussed more broadly in the health services research and quality improvement oral abstract session, where the focus was on NSCLC. Even for NSCLC, where ~50% of patients with non-squamous NSCLC present with actionable genomic alterations and there are nine immediately actionable biomarkers, only 50% receive NGS testing!

So, what is required to ensure the launch of your brand isn't impacted by inadequate testing, inadequate treatment match, or delayed initiation?

- Make it easy for physicians to do the right thing, e.g. behavioural economics-based electronic medical record nudges and real-time clinical decision support alerts to encourage action when a matched therapy exists.
- Empower pathologists to challenge biomarker testing, especially when they sit on the MDT.
- Consider the potential of liquid biopsies, equipping HCPs with the tools to overcome tissue availability challenges and potentially perform testing earlier to be ready and armed for more timely initiation.

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