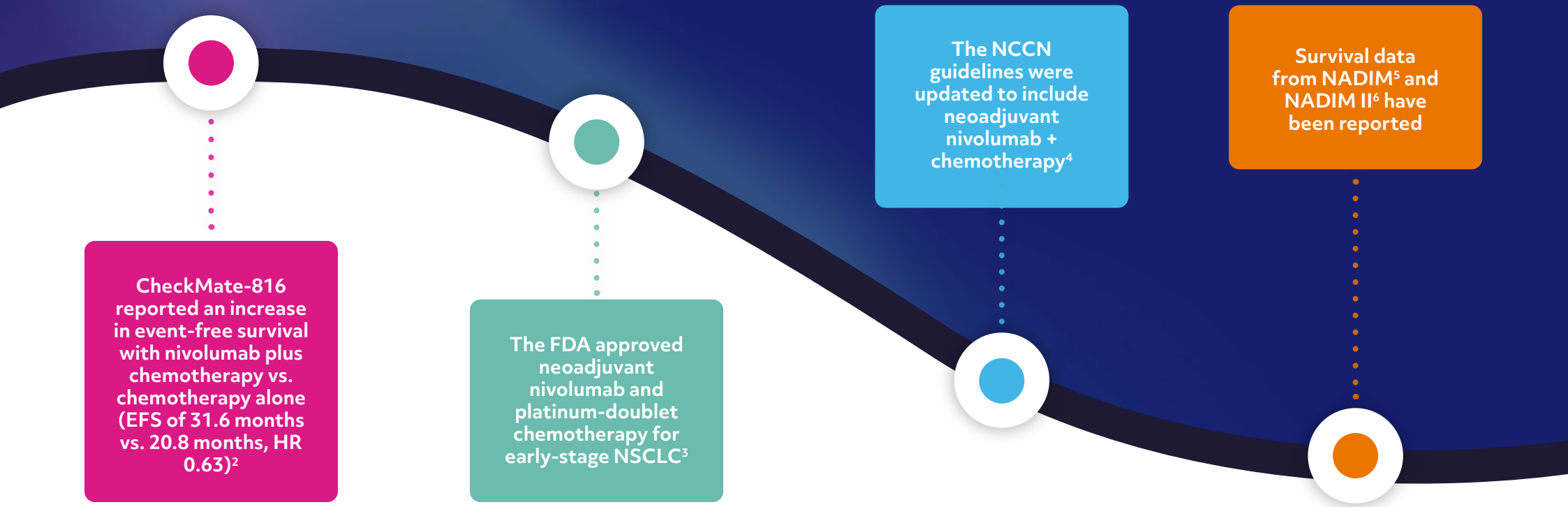
blueprint partnership

NEOADJUVANT CHEMO-IO, A NEW STANDARD FOR RESECTABLE NSCLC?

12 months ago, at ESMO 2021, the oncology community was asked "Are we ready to consider chemotherapy + checkpoint inhibitor as the preferred option in the neoadjuvant setting?"[1].

At that time, 71% felt the available efficacy data was not sufficient to implement neoadjuvant chemo-IO as standard of care for resectable NSCLC.

However, a lot has changed since then…



ONE YEAR ON, HAVE HCPS ACCEPTED NEOADJUVANT CHEMO-IO AS A NEW STANDARD FOR RESECTABLE NSCLC?

To find out, Blueprint Partnership spoke to n=6 global KOLs and conducted a short poll among US oncologists and thoracic surgeons (n=39 total).

- SERMO's RealTime platform was used to collect the survey data.
- US oncologists and thoracic surgeons recruited for the short poll worked outside NIH cancer centres to capture current practices and opinions outside of key academic institutions.
- The research took place during August 2022, following IASLC WCLC 2022, which means that survival data from NADIM II and IMpower010 were available for the KOLs to consider.

KEY FINDINGS

In brief

KOLs are not only ready to consider chemo-IO as the preferred option for resectable NSCLC in the neoadjuvant setting, they've adopted it...

- For oncology KOLs, especially in the US where approval has been given, chemo-IO in the neoadjuvant setting has become part of their standard practice for resectable NSCLC. They also report acceptance of this approach among their surgical colleagues.
- The NADIM and NADIM II data has had limited impact on practice, given KOLs had already moved in the direction of neoadjuvant chemo-IO, before these data were available.

... but outside the key academic institutions there is still further work to be done to educate and empower HCPs to overcome barriers to a change in their practice. To support them, pharma will need to:

- Increase awareness of neoadjuvant data, and approval / guideline incorporation, as appropriate
- Reinforce surgical outcome data to relieve concerns on this topic
- Help HCPs articulate the benefit of neoadjuvant chemo-IO to their patients (to overcome issues with patient buy-in, which are seen as a barrier at present)
- Help ensure wider and more timely access to molecular testing to inform patient selection, especially in ex-USA markets

SO WHAT DID WE FIND?

In detail

KOLs are big believers and have been quick to adopt the neoadjuvant IO approach

The results from CheckMate-816 are considered impressive; KOLs are convinced of a benefit, based on the substantial EFS improvement and increase in pathological complete response reported, compared to chemo alone.

KOLs have been quick to adopt this approach. In the USA, where neoadjuvant chemo-IO has been approved for use, all the KOLs had already adopted neoadjuvant chemo-IO in the absence of OS data. The recent OS data from NADIM II data has strengthened their conviction about the benefits offered.

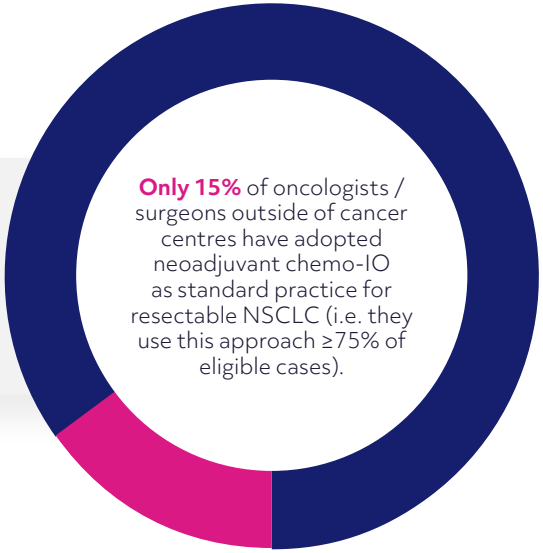
KOLs report acceptance from surgeons in their centres. Surgeons too are on board with the benefit of neoadjuvant chemo-IO, and the data on surgical outcomes has been reassuring.

In the EU, KOLs are also championing the neoadjuvant approach. They are keenly awaiting EMA and local approval, and anticipating high uptake.

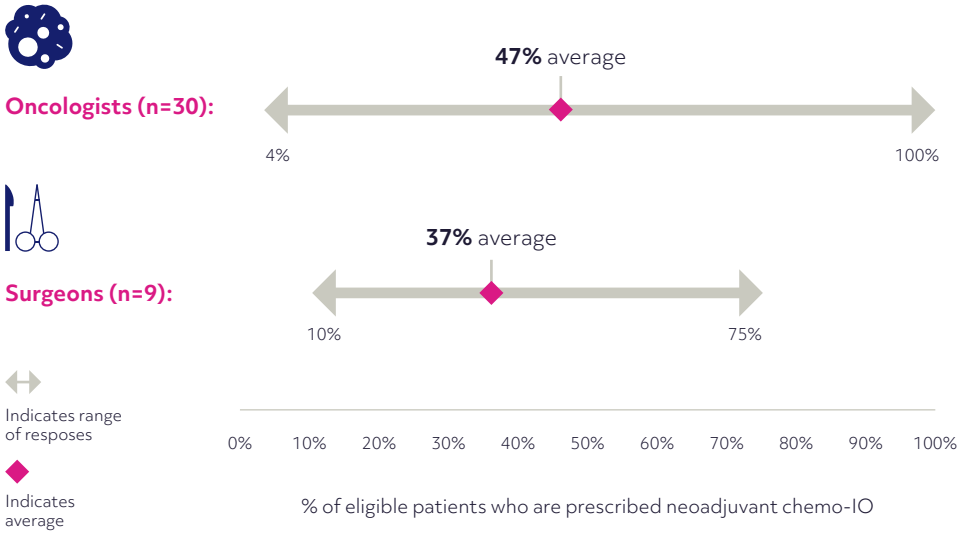
> *I was surprised how quickly neoadjuvant IO was adopted, it's now standard practice. It has helped expand the patient population undergoing surgery, with more R0 resections. Some stage IIIa patients were before defaulting to CRT + durvalumab (PACIFIC trial) – this is a chance to expand patients going into surgery.*
>
> US oncologist

> *It's the potential of doubling someone's survival – it will be incorporated. When our one-year outcomes are monitored, they'll be even better, as the survival will be even more.*
>
> UK surgeon

However, outside the high-profile cancer centres in the US, uptake has been varied



When asked the proportion of eligible patients who are prescribed neoadjuvant chemo-IO, wide variations in practice were reported:



What is preventing more widespread adoption outside of key centres?

BARRIER 1

Patient reluctance to accept delay to surgery

However it is worth keeping in mind that within our sample, it was apparent that some HCPs were not familiar with the clinical data available and / or nivolumab's incorporation into NCCN guidelines – influencing their ability to inform and influence patients.

BARRIER 2

HCP's are not convinced of the benefit for all resectable patients, and may, for example, restrict use to IIIA vs. IB/II or PD-L1 positive tumors only

Uptake to date is likely to differ depending on the stage of NSCLC, as use in earlier stages will require a change in patient flow. Prior to this data, most stage IIIa patients would have received neoadjuvant chemotherapy, and therefore incorporation of IO is an easy adoption. However, use in stage II / Ib requires surgeons to send patients to a medical oncologist, and surgeons may be less keen to adopt in the Ib, node negative patients[7].

In addition, even among KOLs, there appears to be a greater conviction of benefit in PD-L1 positive and stage II/IIIa patients (despite widespread adoption at this time).

BARRIER 3

Concerns that surgery post-IO may be harder / technically more challenging

A lack of awareness of the available data may be driving concerns about surgical outcomes. For example, surgical-only data from CheckMate-816 was presented at ASCO 2021, showing no increase in risk of attrition or surgical delay and it appeared that the surgeries may be technically easier (by using blood loss, and open procedures and extent as proxies). KOLs report this was important in securing surgical acceptance[7], but it seems this is not so widely accepted – if it is known about – outside the specialist cancer centres.

Timely molecular testing; a challenge for all

The capacity to conduct molecular testing in a timely manner, to inform suitability for neoadjuvant chemo-IO*, is a challenge across all settings. US KOLs report using liquid biopsies or single gene tests for EGFR & ALK (with results in 24-72 hours), in attempt to support fast decision making. However, the requirement to have the EGFR and ALK testing completed can contribute to further delays to curative surgery, which some patients are not willing to accept.

Timely molecular testing is anticipated to represent an even greater challenge in the EU*. KOLs stated that only ~50% of cancer centres in Spain have access to NGS, and in the UK, hospitals are not equipped to get ALK and EGFR status before surgery, with only 4 genomic lab hubs serving the entire country. To support neoadjuvant chemo-IO uptake, there is a need for better and more timely access to molecular testing.

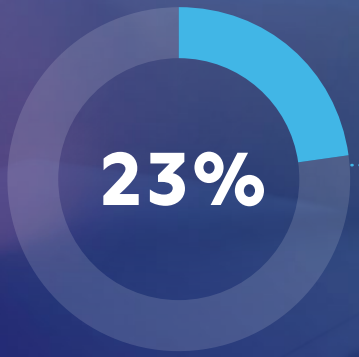
*Patients with known activating alterations in the EGFR or ALK genes were excluded from CheckMate-816 | Not all EU markets were represented in this research, only UK and Spain, however in both of these markets KOLs raised concerns

Is more robust survival data needed to drive further uptake?

Back at ESMO 2021, when this very topic was being discussed in the controversy session, 70%+ indicated that OS is mandatory for a change in practice in the neoadjuvant setting.

However, fast forward to today, and only 23% consider the lack of OS data as one of the most significant challenges to adoption. For the rest, it would seem the combination of DFS data, FDA approval and incorporation into NCCN guidelines, has provided sufficient reassurance of the benefit, even in the absence of OS data.

However, for the subset who do perceive the lack of OS data to be a barrier, even for these the majority have been left unconvinced by the NADIM II data, are likely to be awaiting OS data from CheckMate-816.



consider the lack of survival data as one of the most significant barrier(s) to wider adoption...

OF THESE

3/9

find PFS and OS data reported from NADIM II to be suffciently motivating to implement as SOC

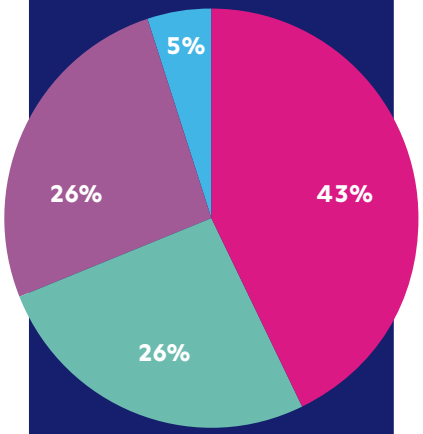
6/9

are unconviced / unsure

Note: awareness of the NADIM II survival analysis is moderate among the jobbing oncologists / surgeons with 50% claiming awareness 2 weeks following WCLC.

NEOADJUVANT VS. ADJUVANT IO: IS THERE A PREFERRED APPROACH?

For many jobbing oncologists / surgeons, adjuvant IO remains their preferred strategy...



... whereas KOLs have less enthusiasm for adjuvant IO, and cited a number of reasons why neoadjuvant IO was preferable:

Toxicity and financial toxicity: adjuvant treatment (up to 1 year) triggers significant drug and healthcare system costs. Patients often will not complete their intended duration of adjuvant therapy due to poor compliance or toxicity.

Convincing patients to "treat a risk": KOLs confirm patients are far more motivated to undergo neoadjuvant therapy vs. adjuvant therapy.

Scientific rationale: KOLs believe that using IO prior to resection is more effective than IO use post-surgical resection due to the presence of anti-tumour T-cells that reside in the bulk of the tumour, which in the case of adjuvant IO would have been removed via surgical resection
"you have more clonal T cells and more things to attack when you release the breaks with anti-PD-L1" - US, KOL.

Inconsistency across adjuvant trials: contradictory data across IMpower010 and PEARLS/KEYNOTE-091 makes it harder to determine which patients benefit most from adjuvant IO. Furthermore, KOLs were not enthused by the interim OS analysis from IMpower010, which raised the question of whether the benefit is limited to the PD-L1 high (>50%) cohort.

Giving a year of atezolizumab vs. 3 cycles of neoadjuvant nivolumab – that's a bad trade. There's way less conviction about patients receiving adjuvant. Patients are told by their surgeon "I got it all so" they're not that motivated to treat something they can't see and follow. Patients are more motivated to see their cancer shrinking vs. treating a risk.

US KOL

Also, KOLs largely reserve adjuvant IO for select situations where neoadjuvant chemo-IO is not used:

- **Stage I patients who are restaged and found to be node positive following surgery**
- **Patients who refuse chemotherapy.** While IMpower010, required standard adjuvant chemotherapy, PEARLS/KEYNOTE-091 allowed for the use of adjuvant IO with or without adjuvant chemotherapy. Therefore, for patients who do not wish to undergo chemotherapy, oncologists may consider adjuvant IO.

FINALLY – WHAT IMPACT WILL THE ONGOING 'PERI-OPERATIVE' TRIALS (E.G. AEGEAN, KEYNOTE-671, CHECKMATE 77T) HAVE?

KOLs are waiting to see if "more is better" and will be drawing comparisons to CheckMate-816, as the preferred strategy currently, to understand the additive benefit of incorporating adjuvant IO.

There is a fear of "over-treating", and the clinical and financial toxicity that comes with continuing IO in the adjuvant setting.

Therefore, KOLs will be looking for both a high magnitude of benefit, as well as consistency across trials, to convert practice away from the neoadjuvant-only approach and justify the additional adjuvant treatment.

> *We are definitely over-treating. Patients may be cured after 3 cycles and surgery – we're then exposing them to toxicity and a very expensive [adjuvant] treatment and we don't know if that's necessary*
>
> ES KOL

- Assuming positive outcomes from the trials, KOLs seem to be considering who will benefit most from IO regimens that span both the neoadjuvant and adjuvant setting vs. using IO in the neoadjuvant setting only.
- Personalized adjuvant therapy dependent upon response to neoadjuvant immunotherapy is felt to be likely. KOLs comment on the "remarkable" results shown in CheckMate-816 for patients who achieve pCR, and are looking forward to seeing how this data matures. The continuation of IO into the adjuvant setting may only be relevant for patients who do not achieve pCR.
- KOLs are also eagerly watching how trials incorporating ctDNA perform (e.g. MERMAID, which uses ctDNA to detect minimal residual disease ahead of adjuvant treatment), and recognise this may shape how they select candidates for adjuvant treatment in the future. They would like to see a situation in which ctDNA is able to inform the need for, and length of, adjuvant treatment.

Contact Siobhan Davies or Lindsay Widger for more information:
s.davies@blueprintpartnership.com l.widger@blueprintpartnership.com

REFERENCES

1. European Society of Medical Oncology congress 2021. Are we ready to consider chemotherapy + checkpoint inhibitor as the preferred option in the neoadjuvant setting? [Congress session]. Virtual.

2. Forde PM, Spicer J, Lu S, et al. (2022). Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022; 386:1973-1985. DOI: 10.1056/NEJMoa2202170

3. Food and Drug Administration (03 Mar 2022). FDA approves neoadjuvant nivolumab and platinum-doublet chemotherapy for early-stage non-small cell lung cancer/ [Press release]. [Accessed 08 Sept 2022]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neoadjuvant-nivolumab-and-platinum-doublet-chemotherapy-early-stage-non-small-cell-lung

4. NCCN. Clinical Practice Guidelines in Oncology. Non-small cell lung cancer, version 3.2022. [Accessed 08 Sept 2022]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450

5. Provencio M, Serna-Blasco R, Nadal E, et al. (2022). Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non–Small-Cell Lung Cancer (NADIM phase II trial). Journal of Clinical Oncology 40, no. 25:2924-2933. DOI: 10.1200/JCO.21.02660

6. Provencio M, Serna-Blasco R, Nadal E, et al. (2022). Progression Free Survival and Overall Survival in NADIM II Study [meeting abstract]. In IASLC 2022 World Conference on Lung Cancer; August 6 - 9, 2022; Vienna

7. OncLive (26 July 2022). Neoadjuvant Strategies in Resectable Non–Small Cell Lung Cancer. [Panel discussion]. [Accessed 08 Sept 2022]. Available from: https://www.onclive.com/view/neoadjuvant-strategies-in-resectable-non-small-cell-lung-cancer

8. Benjamin Besse (@BenjaminBesseMD). Want to know what will happen with immunology in early NSCLC in the next years? Just look at the melanoma track. Neoadjuvant pembro outperformed adjuvant pembro: HR=0.38 / EFS. Would not be surprised by similar outcomes with chemo IO in resected stage III NSCLC. #ESMO22. 17:53, 11 Sept 2022 [Twitter].