Editorial

Induction treatment in operable non-small cell lung cancer: the immune oncology era unfolds

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Shinohara *et al*. provide a nice narrative overview of induction treatment approaches in operable non-small cell lung cancer (NSCLC) (1). We have been stuck too long with the small group benefits of adjuvant chemotherapy only improving the curability of resectable stage NSCLC, from 40.4% to 44.5% in the International Adjuvant Lung Trial (IALT) from two decades ago (2). The ADUARA trial in 2020 finally broke away from this group chemotherapy approach demonstrating markedly improved disease-free survival (DFS) in epidermal growth factor receptor (EGFR) mutated resectable NSCLC by targeting the tumor biology beyond chemotherapy alone (3).

Now we have entered the immune oncology (IO) era in resectable stage NSCLC. Published results within the past year have shown durable overall survival (OS) outcomes of phase I/II neoadjuvant trials with single agent immune checkpoint inhibitors (mono-IO) of 94% 3-year and 80% 5-year OS even in patient populations including 80% node-positive stages (4,5). We also now have results from phase III adjuvant sequential chemotherapy followed by immune checkpoint inhibitors (sequential chemo-IO) trials (6,7). Within the past year, phase III trials of neoadjuvant concurrent chemotherapy with an immune checkpoint inhibitor (concurrent chemo-IO) versus chemotherapy have been presented and published (8,9). Reassuringly, none of these IO studies have identified any unexpected surgical complications nor new safety issues of concern.

With this IO era arrival in operable NSCLC, new management decisions need to be addressed by multi-disciplinary thoracic oncology teams that were not issues before. Should the IO treatment be neoadjuvant or adjuvant? And should the IO treatment be mono-IO or chemo-IO?

With cisplatin-based doublet chemotherapy in resectable NSCLC, there was no difference whether given before or after surgery. With a pathogenic EGFR driver mutation (and hopefully with fusions, but still unknown), prolonged administration of the targeted agent is needed, thus only feasible in the adjuvant setting. However, IO therapies are different.

The phase III IMpower010 trial utilizing adjuvant sequential chemo-IO did show a DFS benefit of adding IO, but only when tissue programmed death-ligand 1 (PD-L1) protein was expressed (6). KEYNOTE-091/PEARLS had a similar design with adjuvant sequential chemo-IO versus chemotherapy, demonstrating a DFS benefit in the intent-to-treat population "regardless of PD-L1 expression" (7). Both trials demonstrated a near identical 36-month DFS improvement of less than 10% compared to chemotherapy. The interim analysis of the PEARLS trial is yet to show any difference in OS (HR 0.87, 95% CI: 0.67–1.15, P=0.17) and the first pre-planned OS of Impower010 only demonstrates

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an OS improvement in patients with tissue PD-L1 ≥50% (10).

Lack of OS notwithstanding in these adjuvant sequential chemo-IO trials, cross trial comparisons with neoadjuvant combined chemo-IO trials are not feasible, nor have neoadjuvant IO versus adjuvant IO therapies in NSCLC been studied. Yet individual treatment decisions need to be made today, with what we know today. Although all neoadjuvant IO approaches just utilize 2–3 cycles, neoadjuvant chemo-IO consistently achieves higher pathologic complete responses (pCR)/major pathologic responses (MPR) of <10% tumor viability than mono-IO alone (11).

There is also pre-clinical and clinical immune tumor biology supporting neoadjuvant IO approaches. In a pre-clinical murine model, the combination of anti-PD-L1 with chemotherapy was most effective in the neoadjuvant setting (12). The presence of the primary tumor can improve activation of T-cell clones that may be lost in the absence of the primary tumor (13). Anti-PD-(L)1 therapy can stimulate tumor-specific cytotoxic T-cells in the tumor microenvironment and prime tumor specific T-cells within the tumor draining lymph nodes (14). Neoadjuvant IO therapy also demonstrated greater efficacy in eradicating metastatic disease compared to adjuvant IO in murine models (15).

Clinically, SWOG S1801 has demonstrated this neoadjuvant pre-clinical support with superiority of neoadjuvant IO over adjuvant IO in resectable melanoma. Neoadjuvant-adjuvant IO demonstrated a superior 72% 2-year event-free survival (EFS) compared to 49% with adjuvant IO alone (16). Having an intact primary tumor and the tumor draining lymph nodes improves an IO therapeutic response. This may be melanoma and not proven in NSCLC, but the immune tumor biology principles are compelling to support neoadjuvant chemo-IO as a preferable approach compared to adjuvant IO treatment.

The treatment goal of neoadjuvant chemo-IO is not a surgical resectability question. It is an improved systemic treatment need aiming to eradicate metastatic disease to increase the OS of resected NSCLC. Are there prognostic or predictive biomarkers of individual outcome within the group treated with neoadjuvant chemo-IO that can correlate with that ultimate curability?

Achieving a pCR has been predictive of OS in the neoadjuvant chemo-IO trials. In three phase III neoadjuvant chemo-IO trials, pCR was significantly higher in the chemo-IO arm than in chemotherapy arms, 24% to 2.2% in CheckMate-816 (stage IB–III), 36.8% to 3.9% in NADIM II (stage IIIA), and 17.2% to 4.3% in AEGEAN (stage II/III) trials respectively (8,9,17). Published and presented data demonstrated survivals were doubled if a pCR was achieved. In CheckMate-816, 3-year EFS was 75% compared to 40% without a pCR (8). In NADIM II, 3-year OS was 100% and ongoing with a pCR, compared to 50% with a lack of pCR (9). OS still lacks maturity, but clearly a dramatically better OS occurs with a pCR. Without a pCR, group outcomes are right back to where they were two decades ago with group adjuvant chemotherapy.

Group median outcomes do not always fully reflect the potential individual benefit of neoadjuvant chemo-IO. In CheckMate-816, the median EFS with neoadjuvant chemo-IO in stage IB/II patients had a HR of only 0.87 (95% CI: 0.48–1.56) compared to chemotherapy indicating a lack of group benefit. However, looking at the individual benefit of a pCR (translating into high curability), the pCR rate was significantly improved in these patients, 26.2% with chemo-IO compared to only 4.8% with chemotherapy (8). For the individuals within that 26.2%, it was a 100% benefit, whereas for the other 73.8%, it was little benefit.

Waiting for the surgical pathologic response assessment presents ongoing management questions of potential interrupted systemic treatment benefit for those without an achieved pCR. Is there a biomarker that can predict a pCR and OS benefit…or can identify those who will not achieve a pCR?

Liquid biopsy with plasma next generation sequencing (NGS) can identify targetable driver mutations/fusions and IO sensitive/resistant alterations. Pre-operative plasma NGS testing has also evolved into a powerful staging and prognostic indicator in NSCLC. Circulating tumor DNA (ctDNA) shedding will occur more frequently the higher the metabolic tumor burden and anatomical stage. In anatomical stage I NSCLC, shedding of ctDNA will occur in half of patients. With N1/N2 lymph node involvement, the frequency of identifying ctDNA shed into the plasma increases to the 75% range. That is on par to even stage IV NSCLC with 80% shedding (18).

Shedding of ctDNA also identifies a far more aggressive underlying tumor biology with poorer outcomes than no shedding of ctDNA in NSCLC (19). ctDNA shedding is powerfully associated with lung cancer recurrence even in anatomical stage I disease (20). Stage IIIA patients treated in the phase 2 NADIM study with 3 cycles neoadjuvant concurrent chemo-IO, a lack of baseline ctDNA shedding was associated with a 4-year OS over 80% compared to just

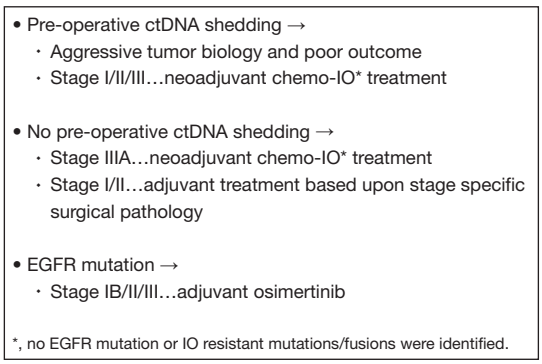

Figure 1 A potential paradigm of utilizing pre-surgical ctDNA to guide neoadjuvant or adjuvant treatment decisions in operable NSCLC. ctDNA, circulating tumor DNA; IO, immune oncology; chemo-IO, chemotherapy-immune oncology; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

45% if there is baseline plasma NGS ctDNA shedding (21). Notably, the NADIM study used a cut-off of ctDNA mutant allele fraction of 1% making this data ready for use in the clinic today with commercial plasma NGS assays.

The NADIM and Checkmate-816 trials also went one step further with plasma NGS testing at diagnosis before any neoadjuvant treatment, and then repeating a plasma NGS after completion of the neoadjuvant treatment. Two striking results were seen. First, even if ctDNA shedding was present at baseline, if it cleared with the neoadjuvant chemo-IO, OS outcomes were astoundingly high in the 90% range at the 3-year mark (in stage IIIA disease) and greatly improved compared to detectable ctDNA persisting (HR 0.04, 95% CI: 0.00–0.55, P=0.004). This clearance of shedding ctDNA as a predictor of OS was clearly better than radiologic response assessment and even better than pCR (21). A bad group changed to an exceptionally good group. Second, conversely if shedding of ctDNA did not clear there were no associated pCR responses with the neoadjuvant chemo-IO in CheckMate-816 (8).

Thinking and extending clinical utility in the IO era of treating earlier-stage NSCLC needs to evolve as our understanding of neoadjuvant chemo-IO and the tumor biology impact of ctDNA shedding evolves. Recently reported seven-year follow up of the lobar or sub-lobar resection study for peripheral stage IA NSCLC was a stark reminder that stage IA NSCLC is still a potential lethal disease and could benefit from effective systemic therapy. One-third of patients had cancer recurrence by 5 years post-surgery and only 80% of patients are alive 5 years out that falls to one-third dead by 8 years (22). Why did these patients recur and die? What looked like anatomical stage I disease was not tumor biology stage I disease.

The stage IB 4.0 cm (one withholds adjuvant treatment if T is 3.9 cm?) size threshold for adjuvant treatment remains a very arbitrary exploratory analysis of CALGB 9633 that was otherwise a negative adjuvant trial. A prognostic gene expression array from JBR.10 in stage IB patients was able to discern a marked 5-year disease-specific survival difference in low-risk tumor biology of 90% compared to a high-risk tumor biology of only 25%. When the high-risk patients received adjuvant chemotherapy there was an absolute 50% improvement in OS, whereas in low-risk patients receiving adjuvant chemotherapy was associated with a higher mortality HR of 3.67, P=0.013 (23). The anatomical stage or size of node-negative NSCLC is a poor discriminator of recurrence risk or potential systemic treatment benefit. It is the underlying tumor biology aggressiveness that matters.

This sparks a potential changing paradigm on the horizon guiding individual treatment decision making in operable NSCLC (*Figure 1*). Integrating pre-operative ctDNA shedding could help identify those patients with potential lymph node involvement and those who have a far more aggressive underlying tumor biology beyond the anatomical stage. When pre-operative ctDNA shedding is identified, there is a strong tumor biology rationale supported by clinical phase 3 trial data for a neoadjuvant chemo-IO treatment approach (provided there are no IO resistant mutations/fusions). Given the tumor biology impact of pre-operative ctDNA shedding even in stage I NSCLC, it is oncologically very compelling to step forward with neoadjuvant chemo-immune therapy irrespective of the anatomical stage.

There is an important clinical caveat in positron emission tomography (PET) and/or endobronchial ultrasound (EBUS) confirmed stage IIIA NSCLC patients. To achieve the best OS possible, these patients benefit from neoadjuvant chemo-IO in stage IIIA disease irrespective of ctDNA shedding or not.

Conversely, in stage I/II pre-operative ctDNA non-shedders, given the more favorable underlying tumor biology and outcomes data, could be managed with an adjuvant treatment approach guided by stage specific surgical pathology findings.

Beyond a simple changing paradigm, other issues need to be understood to extend these potential remarkable OS outcomes for all groups of patients. How to best manage

patients who do not clear ctDNA with neoadjuvant chemo-IO? Strong consideration of a more aggressive multi-modality approach or extended systemic therapy is warranted. Different or additional (as these trials only used 3 cycles) chemo-IO, (chemo-) dual IO, and/or prolonged IO, just as stage IV disease would be managed, a radiation therapy immune boosting synergy, or PORT (if ypN2 persists and no radiation therapy resistant mutation is identified), and other approaches need to be evaluated. There is not data (yet) in this scenario. Yet so many times, in cancer care, individual management decisions need to be made today, yet we do not have specific group data today. That is when individual patients trust us to think through what data is available and give them our best recommendation for their best treatment plan.

IO resistant mutations present another issue and need to be known before embarking on neoadjuvant chemo-IO to avoid closing the surgical window with potentially ineffective treatment. There have been insightful steps forward in mitigating the detrimental impact of some of the IO resistant mutations. In the POSEIDON trial, patients with STK11 or KEAP1 mutations benefitted from a chemo-dual IO approach of anti-PD-1/PD-L1 in combination with anti-CTLA-4 monoclonal antibodies, compared to chemo-IO outcomes (24).

Lack of PD-L1 expression is also a considered issue of impact on neoadjuvant chemo-IO outcomes. In a multivariate analysis of the phase 2 NADIM trial, only baseline ctDNA was predictive of OS. Baseline tumor mutation burden (TMB) or PD-L1 expressions were not (21). A pCR still occurred in 16.7% of the PD-L1 negative chemo-IO treated patients supporting a high OS in those patients. Additionally in the phase II NEOSTAR trial, tissue PD-L1 negative patients doubled a MPR from 22% with chemo-IO up to 40% with the use of chemo-dual IO therapy, providing support of that approach when PD-L1 negative (25). Just as in advanced NSCLC, chemo-IO can overcome a lack of PD-L1 expression.

All surgical outcomes are limited by systemic recurrences. Any improvement in curing resected NSCLC can only be achieved by better systemic treatment approaches. Neoadjuvant chemo-IO can achieve remarkable curative outcomes in operable NSCLC, far exceeding the group adjuvant chemotherapy days. This new IO era in resectable NSCLC warrants new thinking and new clinical utility paradigms. Better individual IO biomarkers are an important part of the immune era unfolding story in resectable NSCLC, but so is understanding and utilizing what plasma NGS ctDNA shedding is telling us about the underlying tumor biology aggressiveness and guiding treatment decisions. We can no longer just keep making group management decisions when ctDNA can tell us what an individual needs. Our treatment goal in operable NSCLC is clear…curing a curable NSCLC 100% of the time.

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Footnote

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