Immunotherapy for non-oncogene driven resectable non-small cell lung cancer: A true gamechanger but for whom and when?

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Curative-intent surgery remains the definitive treatment for resectable non-small cell lung cancer (rNSCLC) in medically operable patients, offering a realistic cure, superior disease-free survival (DFS) and overall survival (OS). For several decades, adjuvant platinum-based chemotherapy (PBC) was the standard-of-care however despite R0 resections, recurrence rates remain unacceptably high with correspondingly poor survival and a modest 5.4% OS benefit over surgery alone.[1] Relapse is often due to occult micro metastasis present at initial therapy hence alternative agents and strategies are required to improve long-term prognosis. In recent years, the treatment paradigm for rNSCLC has evolved considerably. In non-oncogene driven rNSCLC, immune checkpoint pathway blockade with programmed cell death-1 (PD1) or programmed cell death ligand-1 (PDL-1) inhibitors have emerged true gamechangers for patients who achieve a major pathological response (MPR) or complete pathological response (pCR). Several phase 3 neoadjuvant/peri-operative chemo-immunotherapy trials (CM816, KN671, AEGEAN, Neotorch and CM77T) demonstrated impressive pCR rates that correlate with excellent event-free survival (EFS) and OS.[2-6] pCR is emerging as a good surrogate for EFS and OS. CM 816 (3 cycles of neoadjuvant nivolumab plus chemotherapy (CT) versus CT-only) reported excellent outcomes; median OS not reached (NR) (nivolumab arm) vs 73.7 months (CT-only) [HR 0.72 CI (0.523-0.998) (p=0.04)] and 5-year OS 65% vs 53% [HR 0.70 CI (0.47-1.05)] favouring nivolumab in patients with stage IIIA disease. Similarly, in KN671 (4 cycles of neoadjuvant pembrolizumab and CT followed by adjuvant pembrolizumab vs. CT-only) reported median OS was NR (pembrolizumab arm) vs 52.4 months (CT-only) and 4-year OS benefit: 67.1% vs 51.5% [HR 0.72 CI (0.56-0.93) p=0.005).

The relative benefit of any immunotherapy must be viewed in the context of an individual patient's baseline risk and weighed against financial cost, immune-related adverse events, and increased technical complexity and morbidity of surgery, compared to operating on a treatment-naive patient. Cancer physicians must be aware of potential delays in initiation of definitive treatment and crucially, missing the window for upfront curative surgery. Treatment failure, with resulting disease progression precluding resection contributes towards the reported surgical attrition rate (16.8-22%).[2-6]

Judicious patient selection for the optimal combination and sequence of therapies must be determined by tumour stage and biology, clinician experience, patient preference and affordability. A multi disciplinary approach with shared patient decision-making is required. Real-world care extends beyond clinical trials findings, and must be pragmatic and personalized. In Malaysia, approximately half of patients with rNSCLC will harbour an actionable sensitizing genomic mutation (EGFR, ALK), best treated with adjuvant TKI therapy after curative surgery. In patients without a driver mutation, up to 1 in 4 (17-25%) will achieve a pCR and 1 in 3 (30-37%) a MPR following neoadjuvant chemoimmunotherapy.

Several key clinical considerations merit discussion. First, which patients will accrue maximal benefit from immunotherapy needs evaluation. The magnitude of DFS, EFS and OS benefit appears greatest in EGFR and ALK- wild type patients with stage III disease and for tumours with higher PDL-1 expression, preferably > 1% and ideally > 50%.[2-6] However, PDL-1 expression is variable with considerable discordance even in matched samples due to intra-tumoural heterogeneity or temporal changes. Though useful for patient selection and treatment reimbursement, PDL-1 levels may not always predict therapy efficacy. Second, the optimal strategy for stage II non-oncogene driven rNSCLC remains contentious. No randomized trials compare a surgery-first approach (+/- adjuvant therapy) versus a neoadjuvant approach. Upfront surgery seems reasonable if an R0 curative resection is feasible, with adjuvant immunotherapy reserved for tumours which exhibit high-risk microscopic features or nodal disease. Most patients can commence therapy swiftly following contemporary minimally invasive surgery. Adjuvant pembrolizumab (KN091) and atezolizumab (IM010) provide good DFS benefit translating to meaningful OS benefit over best supportive care or adjuvant PBC-only, whilst interim results from the NADIM Adjuvant trial report promising cancer-specific DFS at 3 years with adjuvant nivolumab.[7-9] Conversely, a neoadjuvant approach may evoke a stronger immune response, is possibly better tolerated and less costly, and can address early on, occult microscopic disease, the culprit for relapse. Additionally, a potential downsizing effect may enhance resectability in borderline cases, although no trials were designed to convert patients with unresectable disease into surgical candidates.

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Third, in patients who are likely to benefit from neoadjuvant therapy, it is difficult to ascertain in whom a neoadjuvant-only protocol would suffice, rendering adjuvant treatment superfluous. Again, no head-to head randomized data exists comparing a neoadjuvant-only versus a peri-operative approach. It is difficult to tease out the relative additive EFS benefit of the adjuvant component from various peri-operative studies. An indirect propensity matched cross trial weighted analysis (CM816) (3 cycles of nivolumab) versus (CM77T) (4 cycles of neoadjuvant nivolumab and one or more adjuvant cycles) concluded adjuvant therapy enhanced EFS but only for non-pCR patients and low PDL-1 expressers (TPS < 1%).[10]

Circulating tumour deoxyribonucleic acid (ctDNA) holds promise as a predictive and prognostic biomarker for minimal residual disease (MRD). Patients who achieve ctDNA clearance pre-surgery are more likely to achieve a pCR and vastly superior EFS, DFS and OS.[2-4] Worse outcomes were observed in patients who remained ctDNA positive, pre and post surgery despite neoadjuvant therapy. In AEGEAN, all patients with pCR and > 93% who achieved MPR, had ctDNA clearance pre-surgery, illustrating the high negative predictive value (NPV) for pCR.[3] Patients with detectable ctDNA post surgery had significantly inferior DFS. In CM77T, ctDNA clearance was a strong predictor for EFS whilst CM816 reported excellent survival for patients with pCR and ctDNA clearance (5-year OS 95% vs 56% HR 0.11 CI [0.04-0.36]), tempting adjuvant therapy de-escalation, sparing financial and pharmacological toxicity.[2,4] However, presently, concerns persist regarding the NPV and sensitivity of ctDNA assays to facilitate a personalized MRD-based adaptive approach. Whilst pCR may indicate a molecular 'cure' at the primary tumour site, it cannot exclude possible occult micrometastases. Furthermore, it remains challenging for pathologists to accurately sample the entire tumour bed and concerns of inter-observer variability remain.

Finally, safety remains paramount. A recent meta-analysis of 8 contemporary neoadjuvant and peri-operative trials (CM816, TD-FOREKNOW, AEGEAN, CM77T, KN671, Neotorch, NADIM II and RATIONALE-315) concluded that EFS was similar for patients with a PDL-1 < 1% or 1-49%, with either a neoadjuvant-only or peri-operative approach however patients with PDL-1 > 50% derived a greater EFS benefit with neoadjuvant-only therapy and lower incidence of treatment related adverse events (TRAEs) [relative risk (RR 0.96) 95% CI (0.87—1.12)] over a peri-operative approach.[11]

The evolving treatment paradigm reflects recent advances in the diagnostic and treatment landscape for rNSCLC. Surgery, as part of a multi modality, still offers the best outcomes. Tumour biology plays a critical role alongside disease stage to select the optimal combination and sequence of therapy. For non-oncogene rNSCLC, immunotherapy beit neoadjuvant-only or peri-operative, offers excellent outcomes for patients who achieve pCR. A neoadjuvant-only approach may be sufficient for high PDL-1 expressers who achieve a pCR and ctDNA clearance suggesting no MRD and possibly a cure. Adjuvant therapy following upfront surgery remains a reasonable strategy particularly for stage II disease. Serial ctDNA monitoring facilitates a nuanced personalized adaptive MRD approach with appropriate therapy step-up or de-escalation. The challenge remains in selecting the right treatment, for the right patient, at the right time, taking into consideration real-world considerations of affordability, toxicity and patient preference and fitness.

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