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Can Molecular Biomarkers be Utilized to Determine Appropriate Adjuvant Therapy in Early-Stage Non-Small Cell Lung Cancer (NSCLC)?

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Keywords

LACE Bio; Adjuvant chemotherapy; Early-stage NSCLC; Immunotherapy

Commentary

Early-stage NSCLC, encompassing resectable stage I-III [1] are curable, and represents 25% of all lung cancers [2]. The management of non-metastatic NSCLC is a rapidly changing area of clinical oncology, where utilization of molecular biomarkers has become a cornerstone in informing appropriate management [3]. In current clinical practice, adjuvant chemotherapy is recommended after surgical resection for tumors ≥ 4 cms in size (AJCC 7th stage IB, AJCC 8th stage IIA, and higher stage groups thereafter) [4]. This was based on the meta-analysis done by the Lung Adjuvant Cisplatin Evaluation Biomarker (LACE Bio) using the data from 5 pivotal adjuvant trials that utilized modern platinum regimes, conducted after 1995. This involved 4,584 patients and showed that adjuvant chemotherapy use had an Overall Survival (OS) advantage of 5.4% [5]. Data from these 1990s studies have stood the test of time and is utilized in clinical practice even today [6]. For tumors >3 cms that have an EGFR exon 19 deletion or exon 21 L858R mutation, data from ADAURA has shown that using Osimertinib 80 mg Daily for 3 years improved overall survival by 10% [7]. Recently, Alectinib, an ALK inhibitor showed disease free survival (DFS) in this space. In the ALINA trial, ALK+ NSCLC patients who were stage IB-IIIA as per AJCC 7th edition, were randomized after surgery to alectinib alone or chemotherapy. ALK blockage was noted to have better DFS compared to chemotherapy, as well as a clinically meaningful Central Nervous System (CNS) DFS [8,9]. It was interesting that in this trial, chemotherapy was omitted in the experimental arm, in contrast to ADAURA where Osimertinib was given in addition to chemotherapy [8–10]. For patients, without an EGFR or ALK alteration, the immune checkpoint inhibitors (ICI) Pembrolizumab and Atezolizumab for

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Disclosures

None.

1 year, after chemotherapy significantly improves DFS. The benefit, however, is more pronounced when the PD-L1 expression is ≥ 1% [11,12]. The ongoing debate persists regarding the comparative benefits of administering systemic therapies neoadjuvantly versus adjuvantly. Equally relevant is the question of whether chemotherapy and immunotherapy are necessary for all eligible individuals undergoing perioperative systemic therapy [13,14]. KEYNOTE-671 used pembrolizumab with cisplatin-based chemotherapy neoadjuvantly for 4 cycles followed by the ICI alone adjuvantly and compared it to neoadjuvant chemotherapy alone. An improvement in EFS at 2 years of 21.8% was observed along with improved in pathologic complete response [13]. CheckMate-816 demonstrated similar results with Nivolumab but did not have a prescribed adjuvant component [15]. Very recently, neoadjuvant tislelizumab, a PD-1 ICI, when combined with chemotherapy for 3–4 cycles and then used adjuvantly for resectable NSCLC, showed a trend towards better event free survival (EFS) and OS, compared to neoadjuvant chemotherapy alone [16]. A summary of the adjuvant trials described in this paper is shown in Table 1.

From the above synopsis on the management of early-stage NSCLC, it is evident that there is a concerted effort to shift away from chemotherapy use in the era of better-tolerated ICIs and targeted oral agents [2,14]. This shift underscores an effort to select patients who stand to benefit most from specific drug classes while minimizing exposure to the potential toxicity of unnecessary systemic therapy [1]. With this context, the LACE Bio investigators recapitulated and re-reviewed the legacy LACE Bio data, to look at the molecular and biomarker correlation for adjuvant chemotherapy benefit [6]. The LACE bio group looked at the molecular profiles of the samples from the International Adjuvant Lung Trial, Cancer, and Leukemia Group B–9633, and National Cancer Institute of Canada Clinical Trials Group JBR.10. Samples from the Adjuvant Navelbine International Trialist Association (ANITA) trial was not available [6]. A cohort of 357 patients with adenocarcinoma were utilized to perform analysis of groups assigned based on molecular determinants. The first part subdivided the cohort into lung adenocarcinoma subtypes and compared the molecular characteristics between them. It was highlighted that the micropapillary/solid subtype had the highest frequency of biomarkers such as PD-L1. There was insufficient sample size to perform survival analysis between the histologic subtypes. The 2nd and the most significant part of the study, stratified patients based on PD-L1 (Positive ≥ 1%), (Tumor Mutational Burden (TMB) (High ≥ 10), and Tumor Infiltrating Lymphocytes (TILs) (Marked/other). Patients were subdivided based on these markers both individually and as combinations of PD-L1/TMB and TILs/TMB. The prognostic utility of these biomarker combinations and their predictive ability for adjuvant chemotherapy benefit was analyzed. While multiple outcomes were published, the most clinically relevant was that of the Hazard Ratio (HR) analysis pertaining to TMB and adjuvant chemotherapy benefit. When TMB was ≥ 10, OS with adjuvant chemotherapy use was 2.75 times worse than without it (2.75, 95% Confidence Interval (CI): 1.07–7.04, p=0.035). It has been hypothesized that this group could potentially be a cohort who may be able to forego chemotherapy and may benefit from ICI alone [6]. It was also noted that the marked TILs/low TMB group had a benefit for DFS (HR = 0.06, 95%CI: 0.01–0.53) with adjuvant chemotherapy use, that supported the theory, but the marked TILs cohort was relatively small in the study (26/357). Although these results do not change clinical practice at this time due to the obvious limitations of the

study (retrospective nature, small subset analysis, and older techniques to measure PD-L1), it does put forth a possibility of identifying a group of patients who may be able to forego systemic adjuvant chemotherapy [6].

There is evidence in the literature to suggest that the size of the tumor may not be the only factor impacting adjuvant chemotherapy benefit. In a study using the SEER database, adjuvant chemotherapy was associated with an improvement in survival in patients with 8th edition of stage IB, particularly in those with old age, poor differentiation, less than 15 lymph nodes examined, visceral pleural invasion, lobectomy and no radiotherapy use with a significant P value [17]. In a NCDB cohort, it was reported that in patients with tumors larger than 3 cm, adjuvant chemotherapy survival benefit was seen in patients who underwent sub lobar surgery. For those tumors larger than 4 cm, survival benefit was noted with at least 1 high risk pathological feature. It was concluded in the study that tumor size alone may not be sufficient to predict efficacy of adjuvant chemotherapy [18]. An open question persists regarding the actual extent of benefit derived by stage IB patients from adjuvant systemic therapy, especially when analyzed alongside stage I-III patients. One could argue that the magnitude of benefit for stage IB patients is likely substantially lower, particularly considering the significant toxicity involved [5,6]. One option would be to develop molecular assay-based risk stratification prognostic models, which has been attempted by Woodard *et al.*, but this hypothesis needs larger randomized control studies before it is incorporated into clinical practice [19]. Besides the ALINA trial, where adjuvant chemotherapy was omitted and substituted by an oral targeted therapy, a similar model was attempted in the CORIN (GASTO1003) trial in the EGFR mutated setting [8,9,20]. This phase 2 trial conducted in China randomized NSCLC patients (resectable Stage IB or higher per AJCC 7th edition, same as ADAURA) without any adjuvant chemotherapy use, to Icotinib, a first-generation EGFR agent like Gefitinb, or observation. The 3-year DFS was higher by 12.1% with Icotinib. Again, the omission of chemotherapy is something to note [20]. It is believed that surgical resection of a tumor leads to a cascade of inflammatory response and metabolic changes. There occurs an expansion of myeloid suppression cells, T regulatory cells and macrophages, resulting in post-operative immune suppressed milieu. ICIs potentiates the cytotoxic effect of T cells and enables anti-tumor activity [21]. In the KEYNOTE-091 study, 14% each in the pembrolizumab (84/590) and placebo arm (83/587), did not receive chemotherapy. In the subgroup analysis, DFS did not reveal a statistically significant difference with pembrolizumab in this cohort. But the number of events (35/84 and 29/83) were relatively small compared to entire study cohort [12].

While the LACE Bio analysis described above [6] infers a poor outcome for chemotherapy in high TMB patients, it is also understood that not all patients benefit from ICI. Hence there is a need to identify accurate biomarkers to aid patient selection for ICI use, which has been a challenge [17]. Utility of PD-L1 in the adjuvant space has been conflicting from IMpower010 and KEYNOTE-091 [11,12]. While KEYNOTE-091 showed that adjuvant pembrolizumab benefited all patients regardless of PD-L1 [12], only patients with PD-L1-positive (TC ≥ 1%) benefited from adjuvant atezolizumab in IMpower010 [11]. However, the benefit may have been skewed because of the higher PD-L1 cohorts [11,12,17]. Certain aspects remain perplexing such as the subgroup analysis in KEYNOTE-091, where PD-L1 1–49% had DFS benefit with adjuvant pembrolizumab, but the ≥ 50% did not. All

indications point towards the potential unreliability of PD-L1 in its current form. Moreover, it's plausible that there are other intricacies within the tumor microenvironment that may play significant roles in treatment response. It has become increasingly evident that even among patients with stage IV NSCLC and PD-L1 expression greater than 50%, the presence of KRAS mutations along with STK11 and KEAP1 mutations is associated with poor response to immune checkpoint inhibitor (ICI) therapy [22]. The utility of TMB has not expanded much beyond the tumor agnostic approval of pembrolizumab for TMB 110 in 2020 based on KEYNOTE-158 [23]. Current biomarker research seems to be more focused on circulating tumor (ct) DNA based Minimal Residual Disease (MRD) such as the MERMAID-1 and MERMAID-2 studies [21]. Despite this, based on our LACE Bio analysis results, we feel that TMB may still have a role in the adjuvant space, and warrants further research [6]. Innovative technologies like blood based TMB demonstrated in small studies to predict ICI response may aid this process [24]. There are multiple ongoing trials (BR31, ANVIL, ALCHEMIST Chemo-IO, MERMAID-1, MERMAID-2, NADIM-ADJUVANT and LungMate-008 [21]) looking at the utility of sequential and concurrent ICI and chemotherapy use in the adjuvant NSCLC setting. They aim to tailor therapy based on minimal residual disease (MRD) status. However, it is unfortunate that none of these studies specifically address the potential utility of omitting adjuvant chemotherapy and substituting it with ICI or targeted agents [21]. A prospective study analyzing this and the role of high TMB can be pursued by academia to help answer this important clinical aspect.

In conclusion, it is uncertain if adjuvant chemotherapy benefits early-stage NSCLC with high TMB. The results of the LACE Bio analysis are preliminary, hypothesis generating, and should be analyzed in future adjuvant and neoadjuvant trials.

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Table 1.

Summary of the clinical studies pertaining to adjuvant systemic therapy described in this review.

S.No	Study	Experimental group	Control group	Results	Conclusions/Other findings
1	Adjuvant Navelbine International Trialist Association (ANITA) [25].	Stage IB-IIIA NSCLC - Cisplatin and Vinorelbine (367).	Stage IB-IIIA NSCLC - Observation (433).	OS at 5 years improved by 8.6% and at 7 years to 8.4% with chemotherapy. Risk of mortality decreased by 20%.	Adjuvant chemotherapy prolongs survival in resected NSCLC.
2	National Cancer Institute of Canada Clinical Trials Group, National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators [26].	Stage IB-II NSCLC - Cisplatin and Vinorelbine (242).	Stage IB-II NSCLC - Observation (242).	OS was 94 months with chemotherapy compared to 73 months in control.	Adjuvant chemotherapy prolongs DFS and OS in resected NSCLC.
3	International adjuvant lung cancer trial (IALT) [27].	Stage I-III NSCLC - Cisplatin and Etoposide/ Vinorelbine/ Vinblastine/ Vindesine (932).	Stage I-III NSCLC - Observation (935).	DFS at 5 years (39.4 vs 34.3%) and survival at 5 years (44.5 vs 40.4%) was better with chemotherapy.	Cisplatin based chemotherapy improves outcomes in resected NSCLC.
4	Cancer and Leukemia Group B (CALGB) 9633 [28].	Stage IB (T2N0) NSCLC - Paclitaxel and Carboplatin (173).	Stage IB (T2N0) NSCLC - Observation (171).	31% mortality benefit in patients with tumors ≥ 4 cms.	Adjuvant chemotherapy benefits NSCLC patients with tumor size ≥ 4 cms.
5	ADURA trial [7].	Stage IB-IIIA NSCLC EGFR mutated - Adjuvant Osimertinib for 3 years with or without adjuvant chemotherapy (339).	Stage IB-IIIA NSCLC EGFR Mutated -Placebo with or without adjuvant chemotherapy (343).	5-year OS was better with Osimertinib (88 vs 78%).	Adjuvant Osimertinib provided significant survival benefit in EGFR mutated resected NSCLC.
6	ALINA trial [9].	Stage IB-IIIA NSCLC ALK mutated - Adjuvant Alectinib for 2 years without adjuvant chemotherapy (130).	Stage IB-IIIA NSCLC ALK Mutated -platinum-based adjuvant chemotherapy (127).	Significant disease-free survival at 2 years (93.8 vs 63%) for the Alectinib group.	For ALK mutated and resected NSCLC, Alectinib demonstrated superior outcome compared to chemotherapy. Alectinib also demonstrated CNS activity.
7	CORIN (GASTO1003) trial [20].	Stage IB NSCLC EGFR mutated - Adjuvant Icotinib for 1 year without chemotherapy (63).	Stage IB NSCLC EGFR mutated - Observation (65).	3 year- DFS longer with Icotinib (96.1 vs 84%).	Adjuvant icotinib improved outcome in resected EGFR mutated Stage IB NSCLC.
8	PEARLS/KEYNOTE-091 [12].	Stage IB-IIIA NSCLC all PD-L1 - Pembrolizumab every 3 weeks for 18 cycles after chemotherapy (590).	Stage IB-IIIA NSCLC all PD-L1 -Placebo with chemotherapy (587).	Median DFS better with Pembrolizumab in the overall group (53.6 vs 42 months).	Adjuvant Pembrolizumab is a viable option after chemotherapy regardless of the PD-L1 status.
9	IMpower010 trial [29].	Stage IB-IIIA NSCLC - 16 cycles of atezolizumab every 3 weeks after chemotherapy (507).	Stage IB-IIIA NSCLC - chemotherapy alone (498).	Statistically significant mortality benefit observed with atezolizumab in PD-L1 ≥ 1% (29%) and ≥ 50% (57%) cohorts and not observed in the overall cohort.	Adjuvant atezolizumab is indicated for resected NSCLC with PD-L1 ≥ 1%.