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The not so small role of adjuvant chemotherapy in resected non-small cell lung cancer

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In this retrospective study of 231 patients, Harada and colleagues evaluated real-world data on adjuvant chemotherapy in patients with stage I-IIIA non-small cell lung cancer (NSCLC) who underwent lobectomy or pneumonectomy plus lymph node dissection. The primary end point was overall survival (OS), while the secondary end points were recurrence-free survival (RFS) and safety/feasibility of cisplatin and vinorelbine. Eighty patients received adjuvant chemotherapy, 62 of whom (68%) received a cisplatin-based regimen and 18 (22%), a carboplatin-based regimen. In patients with stage-II NSCLC, adjuvant chemotherapy improved RFS and OS; however, in stage-III patients, only RFS showed statistically significant improvement.

We congratulate the authors for this well-conducted and designed retrospective study from a single center in Brazil. It reinforces the significant survival benefit of adjuvant cisplatin-based chemotherapy in patients with resected stage IB-IIIA NSCLC. We are all aware of the extensive body of literature evaluating adjuvant chemotherapy in NSCLC; however, most of the data come from large prospective, randomized clinical trials, where most of the patients enrolled are not reflective of our daily practice.[1-8] Therefore, not infrequently, we extrapolate the results from a very limited and restricted population to a broader and heterogeneous group of patients. In this context, real-world data play an increasing role in health care decisions and help us fill some of the gaps in the literature. Although reports of adverse events in real-world data tend to be less accurate than the close monitoring of randomized trials, the former can still provide an idea of treatment tolerability and toxicity. In the study by Harada *et al*., 89% of the patients receiving cisplatin and vinorelbine had grade 3-4 toxicity, 49% were hospitalized due to toxicity, and 9% died. These numbers are alarming; nevertheless, the sample size was small (n = 62).[9] Multiple studies have evaluated cisplatin combined with vinorelbine versus other cisplatin doublets and found a strikingly lower incidence of febrile neutropenia and neutropenia, with no difference in RFS or OS.[7,8] In the United States, the standard adjuvant regimen is platinum-pemetrexed for non-squamous histology and platinum-docetaxel/gemcitabine for squamous cell histology.

After at least a decade of stagnation, the role of adjuvant treatment in resected NSCLC is finally taking important steps forward. The ADAURA trial recently reported an 80% reduction in the risk of recurrence or death with osimertinib compared to placebo in resected IB-IIIA NSCLC harboring *EGFR*-sensitive mutations.[10] This led to the approval of this third-generation tyrosine kinase inhibitor (TKI) by the Food and Drug Administration (FDA) in the adjuvant setting. The survival data is still immature; however, due to its impressive improvement in DFS and central nervous system DFS compared to placebo, osimertinib quickly became widely adopted in the United States. Continuing to build on biomarker-driven adjuvant therapy, the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) (NCT02194738) is a large National Cancer Institute (NCI) sponsored National Clinical Trials Network (NCTN) initiative to address the role of genomic testing and personalized therapies in the adjuvant treatment of NSCLC. The study is evaluating crizotinib in resected IB-IIIA NSCLC with an *ALK* rearrangement and erlotinib in resected patients with *EGFR*-sensitive mutations. In light of the ADAURA study results, the enrollment in the erlotinib arm was recently suspended. The LIBRETTOO-432 (NCT 04819100) is a phase III study, which will enroll resected patients with IB-IIIA *RET*-fusion positive NSCLC to selpercatinib or placebo. Many more studies are on the way, and hopefully, the treatment paradigm will continue to evolve in the adjuvant setting.

There is a strong rationale for incorporating immunotherapy in early-stage NSCLC, given the breakthrough results with checkpoint inhibitors as monotherapy or combined with cytotoxic therapy in patients with metastatic disease. Immunotherapy has produced durable responses and impressive survival rates in advanced NSCLC. The ANVIL arm of the ALCHEMIST study randomized patients in more than 600 sites in the United States to nivolumab or observation after surgical resection and standard of care adjuvant therapy (chemotherapy if indicated) in resected IB-IIIA NSCLC. Primary end points are DFS and OS.[11] The IMPOWER-010 is a phase III study, which randomized 1280 patients with resected IB-IIIA NSCLC to atezolizumab or best supportive care (BSC) after adjuvant chemotherapy. Atezolizumab showed a significant DFS benefit versus BSC in resected stage II-IIIA, with a more significant benefit in PD-L1 positive tumors.[12] KEYNOTE-091 is another phase III trial randomizing 1177 patients with resected IB-IIIA NSCLC to pembrolizumab or BSC after adjuvant chemotherapy. The primary end point is DFS as well. There are multiple adjuvant immunotherapy trials currently underway, and we are eagerly awaiting the results. Table 1 summarizes the current immunotherapy and targeted adjuvant trials.

We have been seeing an overwhelming number of FDA-approved tyrosine kinase inhibitors (TKIs),

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Table 1. Ongoing Phase III Adjuvant Trials in NSCLC

Therapy	Comparator arm	N	Biomarker	End Point	Trial Number
Durvalumab	Placebo	332	ctDNA	DFS	NCT04385368
Durvalumab	Placebo	1,360	PD- L1 positivity	DFS in patients with PD- L1 ≥25% in tumor cells, >1% and all randomized patients	NCT02273375
Atezolizumab	Observation	1,280	PD-L1 positivity	DFS in all patients (including PD-L1 subgroup)	NCT02486718
Pembrolizumab	Placebo	1,177	PD-L1 positivity	DFS	NCT02504372
Nivolumab	Observation	903	PD-L1 positivity	DFS and OS in all patients; DFS in patients with high PD- L1 (≥50% staining)	NCT02595944
Crizotinib	Observation	168	*ALK* fusion	OS	NCT02201992
Erlotinib	Observation	450	*EGFR* mutation	OS	NCT02193282
Osimertinib	Placebo	688	*EGFR* mutation	DFS	NCT02511106
Alectinib	Platinum Doublet	255	*ALK* fusion	DFS	NCT03456076
Icotinib	Placebo	124	*EGFR* mutation	DFS	NCT02125240
Selpercatinib	Placebo	170	*RET* fusion	EFS	NCT04819100
Almonertinib	Platinum Doublet	606	*EGFR* mutation	DFS	NCT04762459

OS: Overall Survival; DFS: Disease-Free Survival; EFS: Event-Free Survival; ctDNA: Circulating tumor DNA.

immunotherapies, and chemoimmunotherapy combinations in the late stage-setting of NSCLC. Unfortunately, and paradoxically, we haven't observed this progress in the early stages, where we are aiming for cure. With the approval of osimertinib and the possible role of adjuvant atezolizumab, we are finally starting to move the needle in this space. Besides the historic small benefit of adjuvant chemotherapy, reiterated by Harada and colleagues, cisplatin-based chemotherapy is still playing an important role as the backbone for most adjuvant TKI studies and for all the adjuvant immunotherapy trials. Therefore, selection of the least toxic adjuvant chemotherapy regimen will be even more important as we start to incorporate TKIs and checkpoint inhibitors in the adjuvant treatment of these patients. Based on the real-world data presented on adjuvant platinum-vinorelbine, this regimen should be discouraged in today's practice. First, do no harm, right?

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