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REVIEW ARTICLE

The expanding importance of tissue sample analysis for biomarker testing in non-small cell lung cancer management and survival

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ABSTRACT

Non-small-cell lung cancer (NSCLC) is the most frequent type of lung cancer, currently a leading cause of cancer-related death worldwide. The development of molecular biomarkers has led to novel treatment strategies and subsequent improvement in survival outcomes in all stages of the disease.

To select the best therapeutic strategy, an adequate tissue sample by means of core needle biopsies or cytological blocks is required in order to carry out PD-L1 expression by immunohistochemistry and Next-Generation Sequencing (NGS) panels. Pneumologists specializing in NSCLC diagnosis and staging have a paramount role in selecting the best tumoral site for analysis, as primary tumour, regional lymph nodes, and metastatic sites can be selected.

With this review, we aim to highlight the most important biomarkers used to guide treatment selection in NSCLC and show the improvement in survival outcomes with the implementation of these treatment strategies, from the metastatic setting, unresectable stage III, and resectable disease.

Keywords: Biomarkers. Immunotherapy. Non-small-cell lung cancer. Targeted therapy.

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INTRODUCTION

Lung cancer is one of the most commonly diagnosed cancers and is currently a leading cause of cancer-related death worldwide[1,2]. Non-small cell lung cancer (NSCLC) is the most frequent type of lung cancer. Histologically, it can be divided into adenocarcinoma (LUAD), squamous cell carcinoma (LUSC), and large cell neuroendocrine carcinoma (LCNEC), among others[3]. Most patients are diagnosed at an advanced stage, where opportunities for cure are scarce and with five-year survival rates of less than 10%[4,5].

With novel surgical and radiotherapy approaches, administration of histology-specific chemotherapy regimens, and both targeted therapy and immunotherapy development, the survival rates of this disease have improved dramatically at all disease stages. It is through the application of molecular biomarkers that these improvements in the treatment landscape for NSCLC have been made possible[6-10].

Molecular biomarkers are tests that have the capacity to predict a clinically relevant endpoint, usually survival outcomes and response to therapy and therefore guide us to select treatment strategies[11]. Most of these biomarkers are evaluated in tissue samples, either from a metastatic site or from the primary tumour, and the amount of tissue obtained is of most importance, as approximately 20-30% of samples are inadequate for molecular testing[12].

In this sense, pneumologists specializing in NSCLC diagnosis and staging have a paramount role in the treatment of NSCLC, as without an adequate tissue sample most of the decisions regarding treatment selection could not be carried out[13,14].

In this review, we highlight the most important biomarkers used to guide treatment selection in NSCLC, from the metastatic setting going up to early stage, and review the survival outcomes of the different treatment strategies.

SETTING THE FOUNDATIONS OF BIOMARKER ANALYSIS IN NSCLC: FIRST-LINE TREATMENT OF METASTATIC PATIENTS

Immunotherapy alone or in combination with chemotherapy

Programmed cell death ligand-1 (PD-L1) and PD-1 are immune-checkpoint proteins expressed on the surface of tumour cells and tumour infiltrating immune cells that after binding together can negatively regulate the adaptive antitumour immune response[15,16].

The expression of PD-L1 detected by immunohistochemistry (IHC) on tissue samples is a predictive biomarker that can guide the use of anti-PD-1 or anti-PD-L1 antibodies as frontline therapy[17].

For patients with PD-L1 greater than or equal to 50%, three immune-checkpoint inhibitors (ICI) have demonstrated benefit in terms of progression-free survival (PFS) and overall survival (OS) compared to platinum doublet chemotherapy (PDCT) in patients

Table 1. Summary of treatment outcomes of first-line phase III clinical trials with ICI monotherapy

	KEYNOTE-024	IMpower110	EMPOWER-Lung1
Patients (N)	305	572 (205 PD-L1 high)	563
Experimental arm	Pembrolizumab	Atezolizumab	Cemiplimab
Control arm	PDCT	PDCT	PDCT
Primary endpoint	PFS	OS	OS & PFS
ORR (%)	46.1 versus 31.1	40.2 versus 28.6	39 versus 20
Median PFS (months)	7.7 versus 5.5	8.2 versus 5.0	8.1 versus 5.3
HR (95% CI)	0.5 (0.39-0.65)	0.59 (0.43-0.81)	0.51 (0.42-0.62)
Median OS (months)	26.3 versus 13.4	20.2 versus 13.0	26.1 versus 13.3
HR (95% CI)	0.62 (0.48-0.81)	0.69 (0.48-0.99)	0.57 (0.46-0.71)
36 months OS (%)	43.7 versus 24.7	40 versus 28	not reported

CI: confidence interval; HR: hazard ratio; ORR: objective response rate; OS: overall survival; PDCT: platinum-doublet chemotherapy; PFS: progression-free survival.

with metastatic NSCLC not previously treated with systemic therapy: pembrolizumab (Anti-PD-1 antibody), cemiplimab (Anti-PD-1) and atezolizumab (Anti-PD-L1). The median OS of patients receiving either of these drugs approaches 24 months and nearly 40% of patients are alive after three years of starting therapy. The main results of the phase III clinical trials of these ICI can be seen in table 1[18-23].

In patients with PD-L1 less than 50%, combination with chemotherapy and ICI is the preferred treatment strategy as several combination regimens have demonstrated improved OS and PFS when compared to PDCT alone. In this sense, the election of the combination will depend on many factors including histology (non-squamous versus squamous), chemotherapy duration (two, four or four to six cycles), choice of platinum agent, possibility of maintenance with pemetrexed, among others. The possibility of avoiding chemotherapy with nivolumab and ipilimumab (Anti-CTLA4 agent) is approved by the FDA but not by the European Commission. After three years of therapy, approximately 30% of patients will be alive after receiving any of the multiple treatment schemes[24-35].

Targeted therapy

Targetable molecular alterations (TMA) are genomic modifications (mostly oncogenes) that activate kinase signalling that would normally be regulated by ligand-dependent activation, producing cell proliferation, and leading to oncogene addiction. This was the basis for the development of tyrosine kinase inhibitors (TKI) and the development of precision medicine[36,37].

Most TMA are found in LUAD, and the European Society For Medical Oncology (ESMO) guidelines recommend genomic biomarker testing in non-squamous histology. However, testing should also be carried out in LUSC if the following criteria apply: younger than

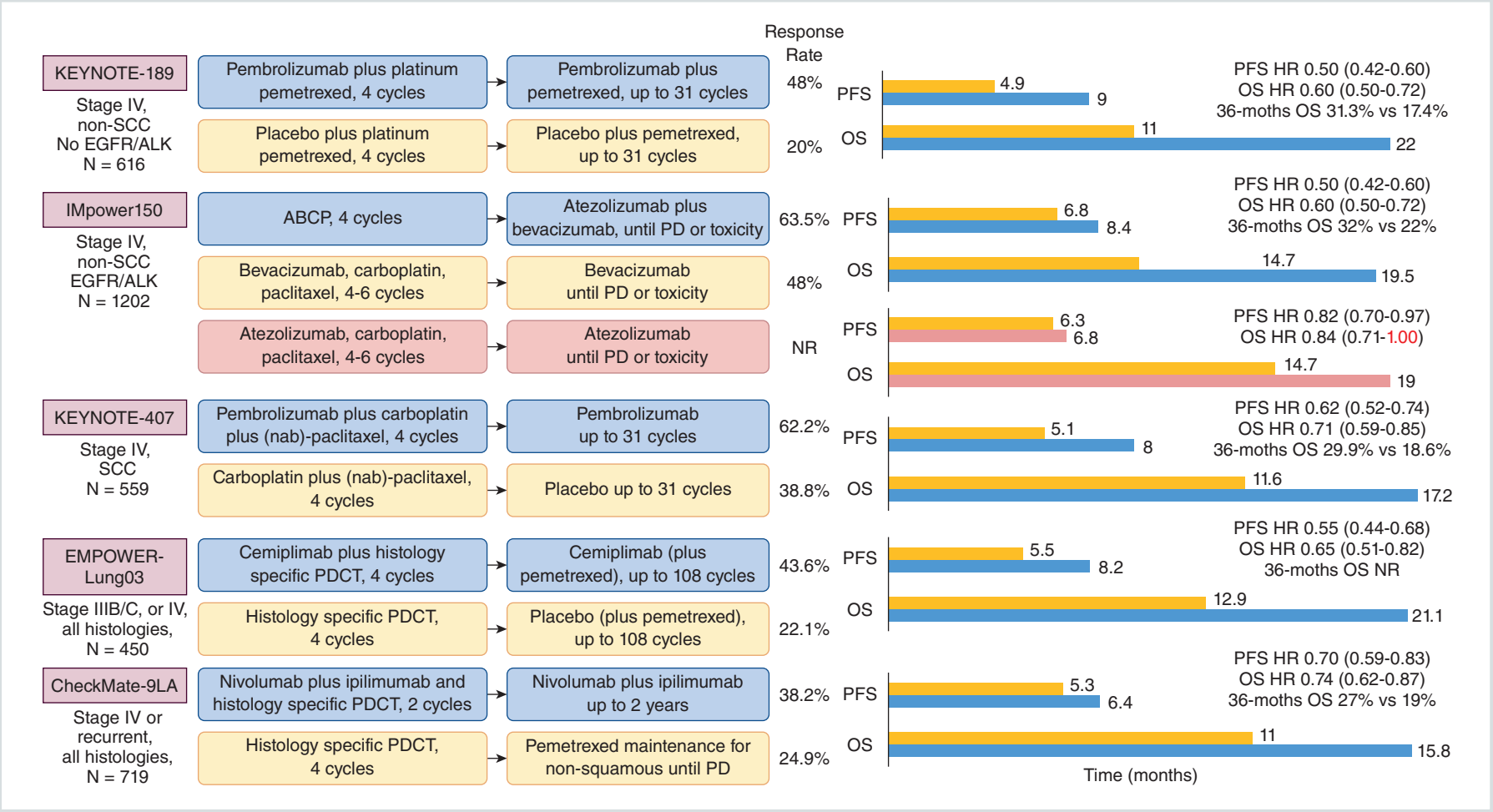

Figure 1. Overview of first-line phase III clinical trials with ICI in combination with chemotherapy for patients with metastatic NSCLC, any percentage of PD-L1 and approved by the European Commission and available in Spain.

ABCP: atezolizumab-bevacizumab-carboplatin-paclitaxel; NR: not reported; non-SCC: non-squamous histology; OS: overall survival; PDCT: platinum-doublet chemotherapy; PFS: progression-free survival; SCC: squamous histology.

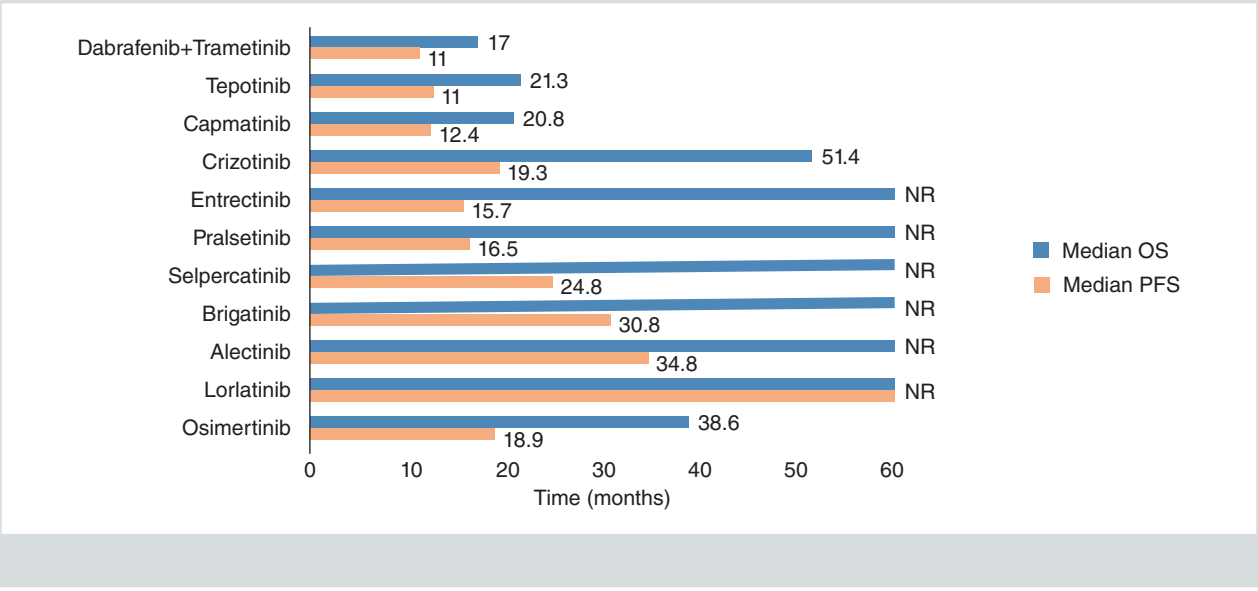

Figure 2. Survival outcomes of patients harbouring oncogene-addicted NSCLC after receiving targeted agents as first-line therapy according to the respective targetable alteration[39-61].
NR: not reached.

50 years of age, never-smokers (less than 100 cigarettes in a lifetime), former light smokers (less than 15 pack-years) or patients that quit smoking more than 15 years before diagnosis. Currently, broad genomic testing with next-generation sequencing (NGS) panels are preferred and must include at minimum: *EGFR* and *HER2* mutations, *BRAF V600E* mutation, *MET* exon 14 skipping mutations, and fusions of *ALK*, *ROS1* and *RET*. Biomarker testing of circulating-tumour DNA (ctDNA, liquid biopsy) can obtain molecular information if tissue sample is not available, or the quantity is scarce. However, the gold standard for most genomic biomarker testing continues to be tissue sample analysis[38].

As we can see, patients with targetable alterations benefit from exceedingly prolonged survival rates when they receive targeted agents. Hence, the search for targetable alterations in adequate tumour samples is mandatory.

IMPROVING SURVIVAL IN UNRESECTABLE STAGE III NSCLC PATIENTS

Immunotherapy consolidation after concurrent chemoradiotherapy

Standard of care for patients with unresectable stage III NSCLC was a combination of chemotherapy and radiotherapy. This combination was given either concurrently or sequentially, with a 5% survival benefit if patients were able to receive concurrent chemoradiotherapy. Unfortunately, survival was poor, and improvement was an important unmet need in this setting[62,62].

The PACIFIC phase III clinical trial was the first trial that showed an improvement in overall survival with a consolidation strategy by administering a durvalumab (Anti-PD-L1 agent) after concurrent chemoradiotherapy[64].

Table 2. Ongoing consolidation clinical trials containing targeted therapies for patients with unresectable stage III NSCLC

ClinicalTrial.gov Identifier	Trial Name	Molecular biomarker	Phase	Treatment regimen
NCT03521154	LAURA	EGFR	III	Osimertinib
NCT05338619	PLATINUM	EGFR	III	Lazertinib
NCT05170204	HORIZON-01	Platform study: *ALK, RET, ROS1* fusions.	I-III	Alectinib, entrectinib, pralsetinib
NCT05718297	BOUNCE	ALK	II	Alectinib

After a follow-up of five years, consolidation durvalumab continued to demonstrate important benefits with a median OS of 47.5 months in the durvalumab arm versus 29.1 months in the control arm (HR 0.72, 95% CI 0.59-0.89) and five-year survival rates of 42.9% versus 33.4%, respectively. Importantly, benefit in OS was seen in patients with PD-L1 scores ≥ 1%, and currently, the European Commission's approval of consolidation durvalumab is in this population of patients[65-67].

Although PD-L1 analysis by IHC was initially validated on tissue blocks from core needle biopsies or surgical resection samples, this biomarker can be carried out during regional lymph node evaluation by means of fibreoptic bronchoscopy with endobronchial ultrasound as cytological evaluation of PD-L1 has been validated[68].

Targeted therapy in unresectable stage III NSCLC

In contrast to patients with non-oncogene addicted NSCLC, patients with targetable alterations derive less therapeutic benefit from ICI in the metastatic setting[69]. Extrapolating this to earlier stages, a post-hoc exploratory analysis from the PACIFIC clinical trial reported the efficacy of patients harbouring *EGFR* mutations. In this subset of patients, PFS and OS were not improved with durvalumab consolidation. The ESMO consensus statement does not recommend durvalumab consolidation in these patients. Further research is mandated for patients with unresectable stage III NSCLC harbouring *EGFR* mutations and other driver alterations[70,71].

Clinical trials evaluating targeted therapy as a consolidation strategy in patients with unresectable stage III NSCLC harbouring TMA are currently underway. Some examples are seen in table 2.

BIOMARKER IMPORTANCE FOR PATIENTS IN EARLIER STAGES: NOVEL TREATMENT STRATEGIES IN RESECTABLE NSCLC.

Adjuvant, neoadjuvant and perioperative immunotherapy

Neoadjuvant or adjuvant therapy with PDCT has been standard of care for patients with early-stage NSCLC with a five-year survival rate improvement of 5.4%[72]. The addition of ICI to PDCT has led to dramatic improvement in treatment outcomes for patients with resectable early-stage NSCLC. Adjuvant atezolizumab has demonstrated an improvement in

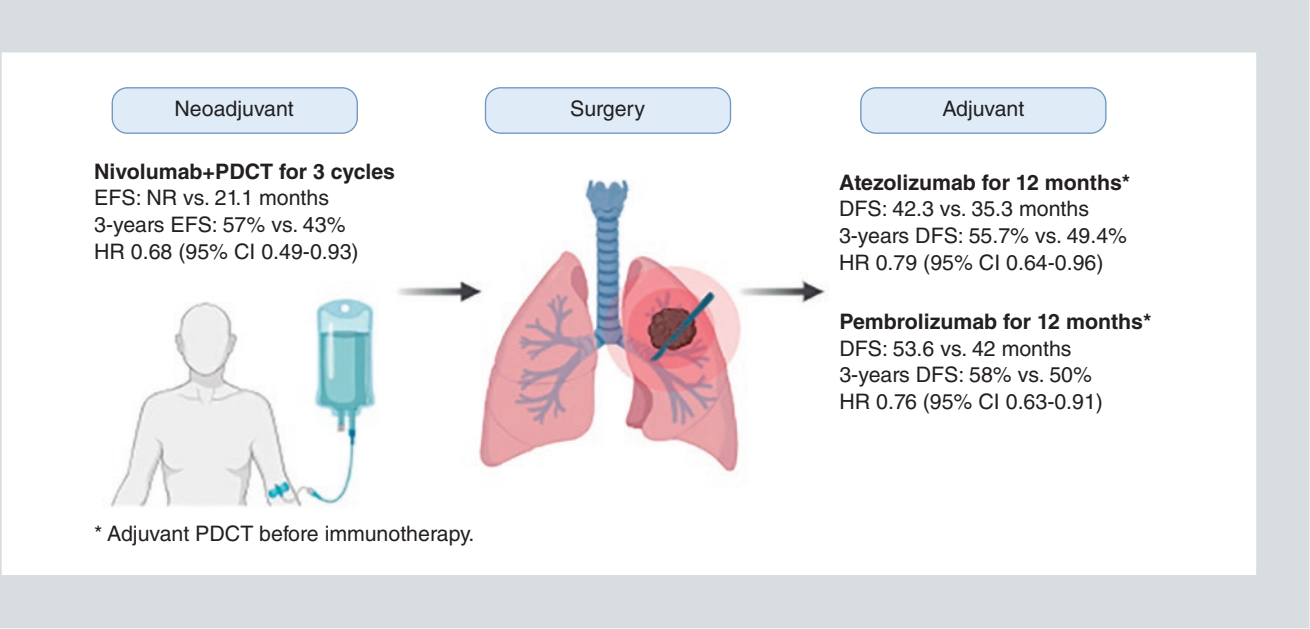

Figure 3. Currently approved ICI based strategies in early-stage resectable NSCLC.
DFS: disease-free survival; EFS: event-free survival; NR: not reached; PDCT: platinum doublet chemotherapy.

disease-free survival (DFS) when compared to observation after PDCT. The greatest benefit was seen in the PD-L1 ≥ 50% subgroup of patients, where a positive trend in OS benefit has been seen. Similarly, pembrolizumab, when given after PDCT, has also demonstrated benefit in DFS compared to observation alone. In this case, benefit was seen regardless of PD-L1 expression[73-75].

The European Commission has approved adjuvant atezolizumab for patients with PD-L1 ≥ 50% and pembrolizumab irrespective of PD-L1 expression, both after PDCT[76,77].

In the neoadjuvant setting, nivolumab in combination with chemotherapy for three cycles resulted in a significant improvement in event-free survival (EFS), pathological complete response (pCR) and major pathological response (MPR). A trend in OS improvement has also been seen. EMA recommends neoadjuvant nivolumab in combination with PDCT for patients with PD-L1 ≥ 1%, where greater benefits were observed[78-80].

Figure 3 depicts currently approved immunotherapy-based adjuvant and neoadjuvant strategies for patients with resectable early-stage NSCLC in Europe.

Finally, multiple combinations of perioperative (neoadjuvant and adjuvant) ICI with chemotherapy have also demonstrated improvement in efficacy outcomes when compared to PDCT alone and are pending imminent approval by European agencies[81-85].

Adjuvant targeted therapy

Targeted therapy has also demonstrated improvement in survival for patients with resected NSCLC. Osimertinib became the first targeted agent approved as adjuvant treatment for patients with resected NSCLC and *EGFR*

mutations as the ADAURA trial demonstrated improvement in both DFS and OS when compared to observation alone. DFS was 65.8 months for Osimertinib and 21.9 months for placebo, while five-year survival rates were 85% versus 73%, respectively (HR 0.49, 95% CI 0.33-0.73)[86,87].

In a recent congress, alectinib demonstrated improvement in DFS when compared to placebo in patients with resected NSCLC harbouring *ALK* fusions. A significant benefit in DFS was observed with alectinib versus chemotherapy, not reached versus 44.4 months (HR 0.24, 95% CI 0.13-0.45). 36-month DFS rates were also improved by adjuvant alectinib, 88.3% versus 53.3% months. Data on OS is pending[88].

The adoption of adjuvant targeted therapies demands identification of TMA through molecular testing. Even though there is currently approval of a targeted agent for only one alteration (*EGFR*), broad NGS testing is still recommended. Future trials will probably demonstrate improvement in survival for patients with other alterations. Furthermore, patients with oncogene-addicted early-stage NSCLC will most likely benefit less from adjuvant immunotherapy[89].

CONCLUSION

With the development of targeted therapy and immunotherapy, the treatment landscape of NSCLC has revolutionized dramatically. Starting from the metastatic setting, we can see how nowadays these approaches have caught up to earlier stages. To select the most precise therapeutic strategy, PD-L1 expression and NGS panels will be needed in most patients. In this sense, pneumologists specializing in lung cancer diagnosis and staging have a tremendous role in finding the most suitable site for tissue sample analysis, as they will probably be the first specialists who will receive the consultation of lung cancer patients.

DISCLOSURES

The authors have nothing to disclose.

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