



Nivolumab for NSCLC in Japanese patients: similar benefits, but beware of pneumonitis

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In this issue, Nishio *et al* report the results of the multicentre phase II trial with nivolumab checkpoint inhibitor (CPI) immunotherapy in Japanese patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC), who progressed after platinum-containing chemotherapy.¹

Over the last 5 years, CPI therapy has revolutionised the treatment of advanced NSCLC. Several international phase III randomised trials compared CPI therapy with docetaxel chemotherapy in patients with relapsed NSCLC. Based on the results of these trials, nivolumab was approved in this setting by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA),^{2,3} pembrolizumab was approved in programmed cell death 1 ligand (PD-L1) expressing tumours by EMA and FDA⁴ and atezolizumab was recently approved by FDA, while EMA approval is pending.⁵ In that respect, the data of Nishio *et al* are not groundbreaking. They are of interest, however, as several globally established treatments for NSCLC have proved to have a different implementation in Japanese population. There are several examples underpinning this finding.

The first example is the comparator regimen in the phase III studies on CPI therapy in relapsed NSCLC, docetaxel chemotherapy. Based on several phase II and phase III studies, a significantly higher risk for grade 3/4 neutropenia (OR 19, 95% CI 3.6 to 99) was noted in South-East Asian patients who were on docetaxel once every 3 weeks.⁶ Based on this finding, the standard dose for docetaxel in Japanese patients is 60 mg/m², compared with 75 mg/m² in Caucasian patients. Another example is the transpacific analysis of carboplatin–paclitaxel, a commonly used regimen in patients with NSCLC.⁷ A prospective pharmacogenetic comparison of the biopsy samples of carboplatin–paclitaxel treated patients was made in one US phase III trial⁸ and two Japanese phase III trials.^{9,10} Clinical results were similar

in the two Japanese trials, but significantly different in the US trial, both for survival and haematological toxicity. Several genotypic differences in paclitaxel disposition or DNA repair between the two ethnic groups were documented as a probable explanation for clinical outcome differences. Similar data have been reported with irinotecan-based regimens when comparing the phase III data from the US SWOG 0124 study¹¹ with those from the Japanese JCOG 9511 study.¹² In a common-arm cross-trial analysis, significant differences in objective response rate (ORR), overall survival (OS) and toxicity were noted between the two trials.¹³

In the setting of tyrosine kinase inhibitor (TKI) therapy, remarkable differences were noted in efficacy and safety. In a comparison between US and South-Korean patients with NSCLC, the South-East Asian ethnicity was a favourable prognostic factor overall, and a clearly greater survival benefit was noted in the epidermal growth factor receptor (EGFR)-TKI era for Korean patients.¹⁴ In a global review of interstitial lung disease (ILD) caused by gefitinib or erlotinib in advanced NSCLC, the overall incidence of ILD events was 1.2%.¹⁵ In contrast, ILD was quite common in a prospective Japanese cohort study.¹⁶ The incidence of an ILD event in Japanese patients on gefitinib therapy was 4.5 per 1000 person-weeks. Likewise, in a retrospective study, the incidence of ILD was 5.4%.¹⁷

The study of Nishio *et al* is an opportunity to judge nivolumab in an exclusively Japanese cohort,¹ and to compare the findings with more global datasets. As Nishio *et al* included only patients with non-squamous NSCLC, by far the most common histology in Japan, the most appropriate comparison is the one with the Checkmate 057 study.³ In the latter, only 3% of the patients were of Asian ethnicity. With the caveat of the smaller number of patients in the Japanese study, the efficacy data seem to be rather comparable (table 1).

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Table 1 Comparison of efficacy and toxicity between the global phase III study with nivolumab in relapsed non-squamous NSCLC (Checkmate 057)³ and the corresponding Japanese data

	Checkmate	
	057 n=292	JapicCTI-132073 n=76
Objective response rate		
Proportion (%)	19 *	22 †
Median duration (months)	17.2	Not reached
Time to response (months)	2.1	1.4
Progression-free survival		
Median (months)	2.3	2.8
1 year (%)	19	24
Overall survival		
Median (months)	12.2	17.1
1 year (%)	51	68
Safety		
All TRAEs (%)	69	84
Grade 3–4 TRAEs (%)	10	22
Discontinued for AEs (%)	5	16
All pneumonitis (%)	3	8
Grade 3–4 pneumonitis (%)	1	3

*Investigator assessed.

†Independent review committee assessed.

AEs, adverse events; NSCLC, non-small cell lung cancer; TRAEs, treatment-related adverse events

In the Japanese study, there were 27.6% never-smokers and 26.3% of patients with *EGFR*-mutated tumours. In that respect, the ORR of 22% is at least as good as in Western population, as never-smokers and patients with *EGFR*-mutated tumours are in general—and in this Japanese study as well—less optimal candidates for CPI therapy. The most remarkable difference is the better OS outcome in the Japanese patients, but that probably also is the result of the important proportion of patients with *EGFR*-mutated tumours, who survive longer when appropriately treated with TKIs.¹⁸ As for toxicity, however, the data suggest that Japanese patients may be more vulnerable to side effects of CPI, especially as 16% of the patients were discontinued from CPI therapy, a figure clearly higher than in most western studies. Again, there is the caveat of low numbers, and the possibility that a learning curve on how to deal with these toxicities may explain the results. Remarkable, and of potential concern, is the higher incidence of all grade and grade 3–4 immune-related pneumonitis in the JapicCTI-132073 study.

PD-L1 expression is a biomarker for CPI immunotherapy. In Checkmate 057, there was no benefit in OS for nivolumab compared with docetaxel in patients with a tumour with PD-L1 expression of <10% (HR for

Table 2 Comparison of PD-L1 expression in relation to response rate between the global phase III study with nivolumab in relapsed non-squamous NSCLC (Checkmate 057)³ and the corresponding Japanese data

	Checkmate 057 Response rate (%)	JapicCTI-132073 Response rate (%)
PD-L1 ≥1%	31	33
PD-L1 <1%	9	23
PD-L1 ≥5%	36	47
PD-L1 <5%	10	14
PD-L1 ≥10%	37	50
PD-L1 <10%	11	14

PD-L1, programmed cell death 1 ligand; NSCLC, non-small cell lung cancer.

OS was 1.00).³ Moreover, in the OS curve, patients on nivolumab initially did worse, then there was a cross-over, and in the long run patients on nivolumab did better. The test method in the Japanese data was the same as in the Checkmate 057 study (automated immunohistochemical assay on Dako platform with the rabbit anti-human PD-L1 antibody clone 28–8). We should, however, be very careful in the interpretation of the PD-L1 expression data in the Japanese phase II trial with only 76 patients, as the different PD-L1 expression groups become very small there, but overall the same trend of PD-L1 acting as a positive predictive biomarker seems to be in place (table 2).

As a whole, the results of Nishio *et al* are reassuring that CPI therapy with nivolumab is just as worthwhile in Japanese patients with relapsed non-squamous NSCLC. Factors of particular interest in their population are the relationship between CPI therapy effects in *EGFR*-mutated and wild-type tumours, and the potential differences in toxicity patterns, especially in immune-related pneumonitis. Based on this series, these factors deserve special attention in future larger Japanese clinical trials.

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