Editorial

KEYNOTE-010: flash of a supernova (immune-checkpoint inhibitors) in second-line non-small cell lung cancer

Hidehito Horinouchi

Department of Thoracic Oncology, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan

Correspondence to: Hidehito Horinouchi, MD, PhD. Department of Thoracic Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 1040045, Japan. Email: hhorinou@ncc.go.jp.

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The KEYNOTE 021 trial was a randomized phase II/III trial comparing docetaxel and pembrolizumab as a second-line treatment for non-small cell lung cancer (NSCLC) in which 202 institutions from 24 countries participated (1). Eligible patients were as follows: progression after treatment with platinum combination therapy, EGFR-TKI or AKL-TKI; an age of 18 years or older; an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0/1; and programmed death-ligand 1 (PD-L1) with a tumor proportion score (TPS) of 1% or more. Subjects were assigned to equally numbered treatment groups in an unblinded manner and received 2 mg/kg of pembrolizumab, 10 mg/kg of pembrolizumab, or 75 mg/m^2 of docetaxel. Pembrolizumab was administered over 30 minutes every 3 weeks for as long as 24 months. The allocation was adjusted according to PS (0/1), region (East Asia/Non-East Asia), and PD-L1 TPS. The primary endpoint was overall survival (OS) for all eligible patients and for the subgroup with a PD-L1 TPS of 50% or more. The objective response rate (ORR) and treatment duration were set as secondary endpoints. Assuming a hazard ratio (HR) of 0.6, a total of 1,460 patients were required, taking the proportion of PD-L1-positive patients into account. In the subgroup with a PD-L1 TPS of 50% or more, the assumed OS HR was 0.55 with an 81% power (one-sided α =0.00825). In the entire population, the assumed OS HR was 0.70 with an 80% power (one-sided α =0.001).

This important trial revealed three key points: the efficacy of pembrolizumab in comparison with docetaxel, the prevalence of PD-L1 expression in a huge NSCLC population, and the dose setting for pembrolizumab.

First of all, in terms of efficacy, the superiority of pembrolizumab over docetaxel in terms of the OS time was shown for both the PD-L1 ≥50% and PD-L1 ≥1% populations. In the 2- and 10-mg/kg subgroups, the HRs were 0.71 (0.58–0.88, P=0.0008) and 0.61 (0.49–0.75, P<0.0001), respectively. The median OS time was 10.4 months in the 2-mg/kg group, 12.7 months in the 10-mg/kg group, and 8.5 months in the docetaxel group. The ORRs were 18%, 18% and 9%, respectively. Furthermore, in the group with a PD-L1 TPS of 50% or more, the OS HRs were 0.54 (0.38–0.77, P=0.0002) and 0.50 (0.36–0.70, P<0.0001) for the 2- and 10-mg/kg subgroups, respectively. The median OS was 14.9 months in the 2-mg/kg group, 17.3 months in the 10-mg/kg group, and 8.25 months in the docetaxel group. The ORRs were 30%, 29% and 8%, respectively.

To evaluate PD-L1 as a biomarker, clone 22C3 was used. Archived specimens were initially accepted; however, a new tissue sampled obtained during a biopsy performed immediately prior to trial registration became mandatory after the randomization of 456 patients. Also, after 441 patients had been randomized, the allocation was adjusted according to either a PD-L1 TPS of 1–49% or 50% or more. As a result, 2,699 patients were registered in this study, a PD-L1 expression analysis was performed for 2,222 patients, 1,475 (66%) were positive for PD-L1 TPS with an

Table 1 Efficacy results of major phase III trials (nivolumab, pembrolizumab, atezolizumab)

Trials	Drug	Dose	PD-L1	Histology	ORR (%)	mPFS (month)	PFS HR	MST (month)	OS HR
Borghaei *et al*., NEJM 2015	Nivolumab	3 mg/kg/2 weeks	Not applicable	NonSq	31	4.2	0.7	17.7	0.59
	Docetaxel	75 mg/m^2		NonSq	12	4.5		9	
Brahmer et al., NEJM 2015	Nivolumab	3 mg/kg/2 weeks	Not applicable	Sq	17	3.3	0.67	9.3	0.69
	Docetaxel	75 mg/m^2		Sq	11	2.8		7.2	
Herbst *et al*., Lancet 2016	Pembrolizumab	2 mg/kg/3 weeks	PD-L1 TPS ≥1%	NSCLC	18	3.9	0.88	10.4	0.71
	Docetaxel	75 mg/m^2		NSCLC	9.3	4		8.5	
Herbst *et al*., Lancet 2016	Pembrolizumab	10 mg/kg/3 weeks	PD-L1 TPS ≥1%	NSCLC	18.5	4	0.79	12.7	0.61
	Docetaxel	75 mg/m^2		NSCLC	9.3	4		8.5	
Rittmeyer *et al*., Lancet 2017	Atezolizumab	1,200 mg/3 weeks	All comer	NSCLC	14	2.8	0.95	13.8	0.73
	Docetaxel	75 mg/m^2		NSCLC	13	4		9.6	

PD-L1, programmed death-ligand 1; TPS, tumor proportion score; ORR, object response rate; PFS, progression-free survival; mPFS, median progression-free survival; HR, hazard ratio; MST, median survival time; OS, overall survival; NSCLC, non-small cell lung cancer.

expression of 1% or more, and 633 (28%) were positive for PD-L1 TPS with an expression of 50% or more. Finally, 1,034 people (70%) were registered after selecting 1,475 patients with a TPS of 1% or more according to the study's eligibility criteria.

In this study, two levels (2 and 10 mg/kg) of pembrolizumab were studied. This interesting dose setting (actually 5 times wider in range) was based on previously reported results for the PK/PD analysis of pembrolizumab. According to the previous study, the minimum dose for which the antitumor activity of pembrolizumab could be anticipated was 2 mg/kg (2). The KEYNOTE 010 trial was conducted to verify the clinical significance of these two dose settings. As a result, the response rates were 18% *vs.* 18% in the population with a TPS of 1% or more and 30% *vs.* 29% in the population with a TPS of 50% or more. Furthermore, no clear survival difference was seen regardless of the TPS. Based on this result, 2 mg/kg was subsequently used as the standard dose.

The breakthrough of immune checkpoint inhibitors in NSCLC is remarkable. In both the CheckMate 017 and the CheckMate 057, nivolumab was superior to docetaxel regardless of the expression of PD-L1 (*Table 1*) (3,4). In the OAK trial, atezolizumab surpassed docetaxel regardless of the expression of PD-L1 (5). Pembrolizumab was superior to docetaxel in the KEYNOTE 010. At the same time, the results of the REVEL trial, in which docetaxel + ramucirumab outperformed docetaxel monotherapy, have been reported (6). The 15-year era of using docetaxel as a second-line treatment for NSCLC has recently come to an end. Regarding the effectiveness of immune checkpoint inhibitors, the expression of PD-L1 is considered to be the most influential biomarker at present. The KEYNOTE 010 trial contained a patient population with a PD-L1 TPS of more than 1%; however, the CheckMate 017, CheckMate 057, and OAK trials included patients regardless of PD-L1 expression. Among the PD-L1 antibody clones that have been adopted, 22C3 for pembrolizumab has been used as a companion diagnostic, and 28-8 for nivolumab and SP-142 for atezolizumab have been developed as complementary diagnostics. As a result, the superiority of immunity checkpoint inhibitors over docetaxel has been confirmed regardless of PD-L1 expression. In contrast, in the population with a PD-L1 TPS of 50% or more, pembrolizumab outperformed platinum combination therapy in the KEYNOTE 024 trial. Thus, researchers have been confused by a lack of consistency in terms of the value of PD-L1 expression as a biomarker for immune-checkpoint inhibitors.

Regarding safety, the CheckMate 017, CheckMate 057, KEYNOTE 010, and OAK trials have consistently shown a good trend for immune checkpoint inhibitors, compared with docetaxel (*Table 2*). The incidences of grade 3 and higher adverse events are reported to be 7–10% for nivolumab, 13–16% for pembrolizumab, and 15% for atezolizumab, making these agents safer than docetaxel. Regarding the difference in safety among immune checkpoint inhibitors, nivolumab tends to be

Table 2 Safety results of major phase III trials (nivolumab, pembrolizumab, atezolizumab)

Trials	Drug	Dose	Grade	Any AE	Fatigue	Nausea	Decreased appetite	Asthenia	Rash	Diarrhea	Hypothyroidism	Adrenal	Pneumonitis
Borghaei *et al.*, NEJM 2015	Nivolumab	3 mg/kg/2 weeks	Any	69	16	12	10	10	9	8	7	–	3
			Grade 3–5	10	1	1	0	0.3	0.3	1	0	–	1
Brahmer *et al.*, NEJM 2015	Nivolumab	3 mg/kg/2 weeks	Any	58	16	9	11	10	4	8	4	–	5
			Grade 3–5	7	1	0	1	0	0	0	0	–	0
Herbst *et al.*, Lancet 2016	Pembrolizumab	2 mg/kg/3 weeks	Any	63	14	11	14	6	9	7	8	1	5
			Grade 3–5	13	1	0.3	1	0.3	0.3	1	0	0	2
		10 mg/kg/3 weeks	Any	66	14	9	10	6	13	6	8	1	4
			Grade 3–5	16	2	1	0.3	1	1	0	0	0.3	2
Rittmeyer *et al.*, Lancet 2017	Atezolizumab	1,200 mg/3 weeks	Any	64	26.8	17.7	23.5	19	–	15.4	–	–	1
			Grade 3–5	15	2.8	0.7	0.3	1.3	–	0.7	–	–	<1

associated with a slightly lower frequency of grade 3 or higher adverse events. In addition, attention should be paid to the frequency of immune-related adverse events, such as thyroid dysfunction, adrenal insufficiency, and pneumonitis, which are characteristic of immune checkpoint inhibitors.

For the second-line treatment of NSCLC, several phase III trials, including the KEYNOTE 010 trial, have resulted in the triumph of immune checkpoint inhibitors over docetaxel. This is a remarkable achievement in medical history; however, as already mentioned, pembrolizumab has become the standard therapy for the primary treatment of patients with a PD-L1 TPS of 50% or more. Although the KEYNOTE 021 was a phase II trial, it revealed that pembrolizumab in combination with a platinum-doublet provided superior results than the platinum-doublet alone (7). As a result, the FDA approved pembrolizumab for the first-line treatment of patients with a PD-L1 TPS of 50% or greater and pembrolizumab plus platinum combination therapy in patients regardless of PD-L1 expression. The position of immune checkpoint inhibitors is quickly shifting from a second-line setting to a first-line treatment. The time to savor the brilliant achievements in the battlefield of second-line treatments may be unexpectedly short.

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