Supplementary Material

Journal: Clinical Drug Investigation

Nivolumab Versus Docetaxel for Previously Treated Advanced Non-Small Cell Lung Cancerin China :A Cost-effectiveness Analysis

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Appendix 1 The selection of survival models for the docetaxel arm

The pseudo-individual patient data were fitting using R software (version 3.3.1, http://www.r-project.org) based on four commonly used parametric survival models, including weibull, exponential, log-logistic and log-normal distributions.

OS Fit

As for the pseudo-individual patient OS data of docetaxel, the visual fits and statistical fits of four parametric survival models are displayed in Figure1-1and Table1-1. The visual fits of the OS curves showed that the extrapolation of exponential, log-logistic and log-normal distributions produced extended tails, which would likely overestimate OS in the long term. Based on the statistic goodness-of-fit tests including Akaike information criteria (AIC) and Bayesian information criteria (BIC),the Weibull distribution provide the lowest AIC and BIC. Therefore, the Weibull distribution was the optimal fit for OS of docetaxel.

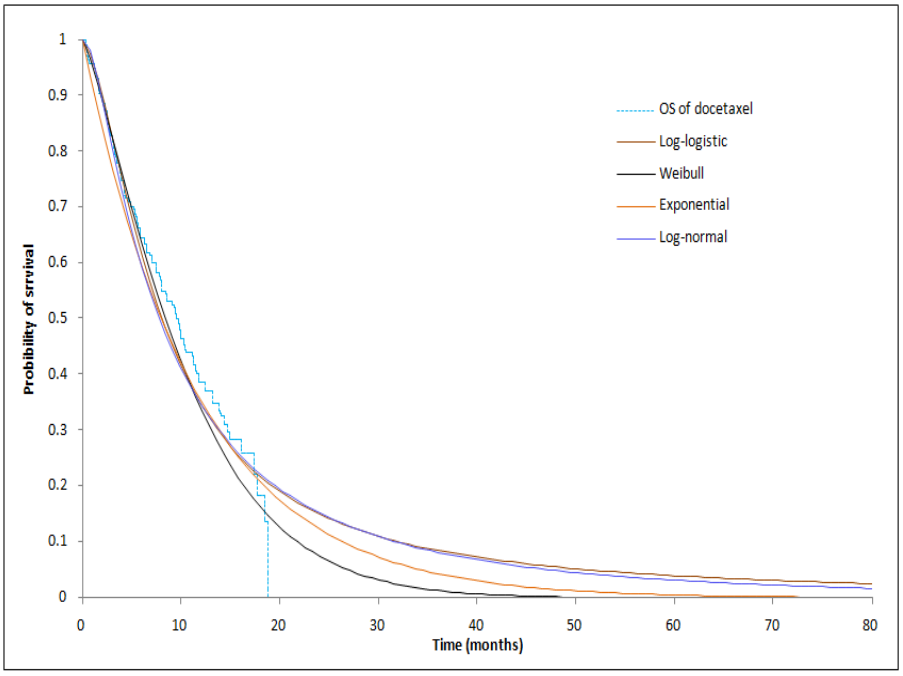

Figure1-1 Docetaxel OS data fitting and extrapolation

Table 1-1. The summary of docetaxel OS fitting

Distribution	AIC	BIC
Exponential	799.5163	802.6283
Weibull	795.1152	801.3392
Log-logistic	800.8650	810.5235
Log-normal	804.2995	807.0889

PFS Fit

As for the pseudo-individual patient PFS data of docetaxel, the visual fits and statistical fits of four parametric survival models are displayed in Figure A1-2and Table A1-2. The visual fits of the PFS curves showed that all four distributions provided a similar fit. Based on the statistical goodness-of-fit alone, log- logistic distribution had the lowest AIC and BIC, however the log- logistic distribution produced the longest extended tail, which meant PFS would be overestimated in long term. Meanwhile, the AIC and BIC of Weibull distribution was slightly higher than that of log- logistic distribution. Considering that the fitting for OS and PFS in the same group were as consistent as possible, Weibull distribution was chosen for PFS of docetaxel.

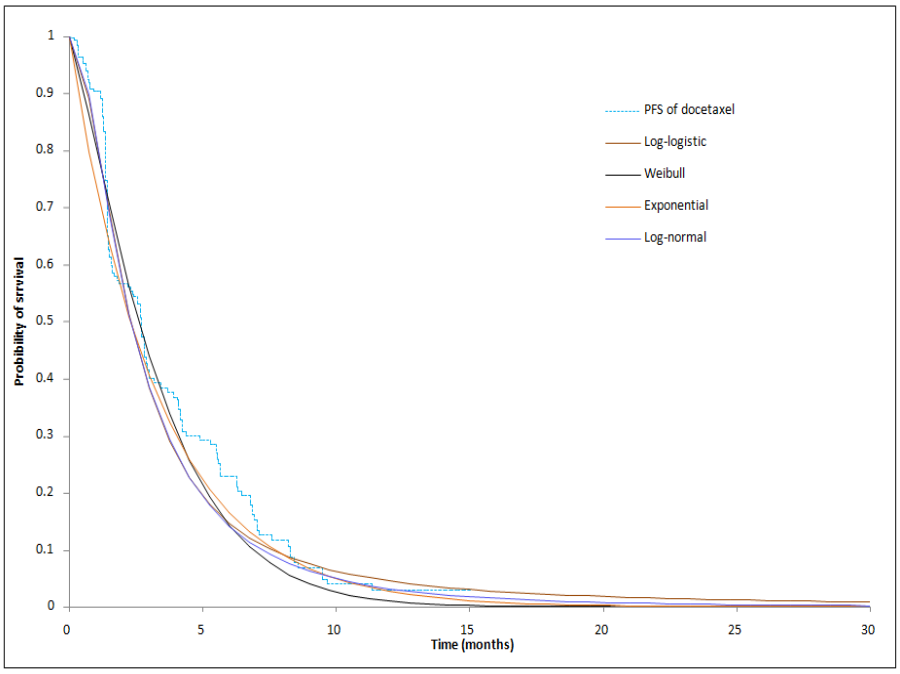

Figure 1-2. Docetaxel PFS data fitting and extrapolation

Table 1-2. The summary of docetaxel PFS fitting

Distribution	AIC	BIC
Exponential	695.3264	698.4384
Weibull	688.2550	694.4790
Log-logistic	693.8375	692.5693
Log-normal	686.3453	700.0615

Appendix 2 The results of the subgroup analyses.

Based on model hypothesis and clinical rationality, we choose Weibull distribution to fit the OS and PFS data for all subgroups in CheckMate 078 trial, therefore, the Weibull parameters were adjusted using the same method as previously described in our manuscript, that is, the shape (γ) parameters of all nivolumab subgroups were the same as those of the docetaxel arm ($\gamma_{Nivolumab} = \gamma_{Docetaxel}$), and the scale ($\lambda$) parameters were multiplied by those of the docetaxel arm and the HR ($\lambda_{Nivolumab} = HR \times \lambda_{Docetaxel}$).

As for gender subgroup, considering that the weight differences, a base case patient with an average weight of 65 kg and 58kg were used in male subgroup and female subgroup respectively. The other model parameters were assumed to be same. For male subgroup and female subgroup, the nivolumab strategy added costs of $22,739 and$15,587, respectively, relative to docetaxel strategy, resulting in ICERs of $95,302 and $85,273 per QALY, respectively. Therefore, nivolumab was likely to be more cost-effective for female patients with advanced NSCLC.

As for CNS metastases and No CNS metastases subgroups, we assumed all the model parameters were the same, except for the CNS metastases management costs and health utility values of the PFS and PS states with CNS metastases. The cost of CNS metastases management included radiotherapy [whole brain radiotherapy (WBRT) and stereotactic radiotherapy (SRT)], symptomatic treatment and auxiliary examination. Symptomatic treatment, including mannitol, glucocorticoids and diuretics therapy), was used to relieve intracranial hypertension and alleviate cerebral edema, however, due to the low-priced of these drugs, the cost of symptomatic treatment wasn't added into the total cost. The costs associated CNS metastases management were listed in table2-1. Health utility values of the PFS states with CNS metastases were 0.52, which was captured from one quality of life study. As a result of the absence of a utility value for the PS state with CNS progression, this value was assumed to 0.21. Compared to docetaxel arm, the ICERs in nivolumab arm were $143,663 per QALY gained for CNS metastases subgroup and $94,292per QALY gained for no CNS metastases subgroup, respectively, therefore, nivolumab was likely to be more cost-effective for advanced NSCLC without CNS metastases. Subgroup-specific model parameters were listed in Table2-1.

As for other subgroups, we assumed the same data in all subgroups except for the OS HRs and PFS HRs in the model. The results of the subgroup analyses were present in Table 2-2.

Table 2-1Subgroup-specific model parameters of CNS metastases and No CNS metastases subgroups

Parameter	Base-case	Range	Distribution	Soure
Cost				
Radiotherapy [a]				
WBRT per person	3926	3141-4712	Lognormal	Published study
SRT per person	6282	5026-7539	Lognormal	Published study
Supplementary examination [b]				
MRI per cycle	31	24.8-37.2	Lognormal	Local charge
CT per cycle	15	12-18	Lognormal	Local charge
Utilities				
PFS state without CNS progression	0.804	0.643-0.965	Beta	Our manuscript
PFS state with CNS progression	0.52	0.42-0.62	Beta	Published study
PS state without CNS progression	0.321	0.257-0.385	Beta	Our manuscript
PS state with CNS progression [c]	0.21	0.17-0.25	Beta	Published study

WBRT: whole brain radiotherapy; SRT: stereotactic radiotherapy; MRI: magnetic resonance imaging; CT: computed tomography; PFS: progression-free survival; PS: progression survival; CNS: central nervous system.

[a] If patients developed CNS metastases, they would receiveWBRT (60%), SRT (30%) or WBRT combined with SRT (10%), and the associated costs per person were based on the clinical expert opinions and a recent study.

[b]The common used auxiliary examination were MRI (90%) and CT (10%), both of which were performed every 3 months according to Chinese guidelineson the diagnosis and treatment of brain metastases of lung cancer.

[c]This value was assumed to 0.21, which meant that the reductionproportion between two utilities of PFS state without and with CNS metastases was consistent with that of two utilities of the PS state

Table 2-2 The results of the subgroup analyses.

Subgroup	HR		ICER	
	OS	PFS	Per LY	Per QALY
Age<65 years	0.76	0.79	97,810	97,732
Age≥65 years	0.50	0.68	49,424	85,171
Male	0.71	0.70	86,734	95,302
Female	0.74	1.03	74,552	85,273
ECOG PS 0	1.01	1.22	-1685,338	121,267
ECOG PS 1	0.69	0.70	80,920	94,246
Current/former smoker	0.73	0.72	91,812	96,286
Never smoker	0.67	0.87	67,146	92,199
Squamous	0.61	0.61	68,528	90,934
Non-squamous	0.76	0.87	92,196	97,492
CNS metastases	0.82	0.62	154,271	143,663
No CNS metastases	0.70	0.79	78,014	94,292
PD-L1<1	0.75	0.74	97,703	97,320
PD-L1≥1	0.62	0.75	63,006	90,309

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; CNS, central nervous system; PD-L1, programmed death ligand 1. ICER, incremental cost-effectiveness ratio; QALY: quality-adjusted life-year.