Five-Year Outcomes From the Randomised, Phase 3 Trials CheckMate 017/057: Nivolumab vs Docetaxel in Previously Treated Advanced NSCLC

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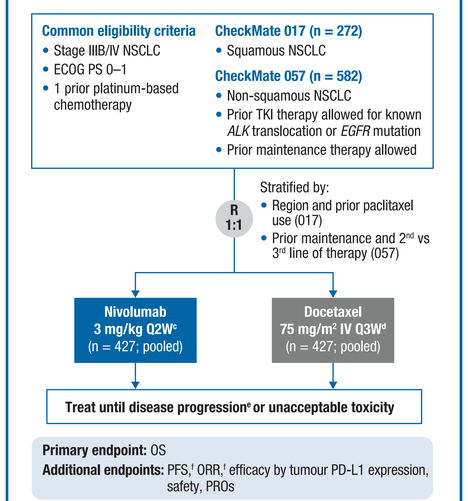
Background

- Nivolumab is a programmed death-1 (PD-1) inhibitor that is approved in Australia and globally for the treatment of patients with previously treated advanced non-small cell lung cancer (NSCLC)[1]
- This approval was based upon results of two randomised phase 3 trials, CheckMate 017 (squamous NSCLC) and CheckMate 057 (non-squamous NSCLC), in which nivolumab significantly improved overall survival (OS) and demonstrated a favourable safety profile compared with docetaxel[2–6]
- The longest follow-up for survival with nivolumab in previously treated advanced NSCLC is from CheckMate 003; in this single-arm, phase 1 study, the 6-year OS rate with nivolumab was 14.7%[6]
- Here we present the 5-year pooled results from CheckMate 017 and 057, including OS and duration of response (DOR) by tumour histology and baseline programmed death ligand-1 (PD-L1) status, representing the longest follow-up to date for randomised phase 3 trials of an immune checkpoint inhibitor in previously treated advanced NSCLC

Methods

- The study designs of CheckMate 017 and 057 are shown in **Figure 1**

Figure 1. CheckMate 017[a] and 057[b] study design



[a]Database lock: 8 May 2019; minimum follow-up for OS, 62.6 months; [b]Database lock: 16 May 2019; minimum follow-up for OS, 62.7 months; [c]Optional switch to nivolumab 480 mg Q4W allowed as per protocol amendment in September 2016; [d]After completion of the primary analysis, patients in the docetaxel arms who ended treatment at any time during the studies were allowed to cross over to nivolumab; [e]Defined by RECIST 1.1; patients receiving nivolumab may be treated beyond progression under protocol-defined circumstances; [f]As assessed by investigator.

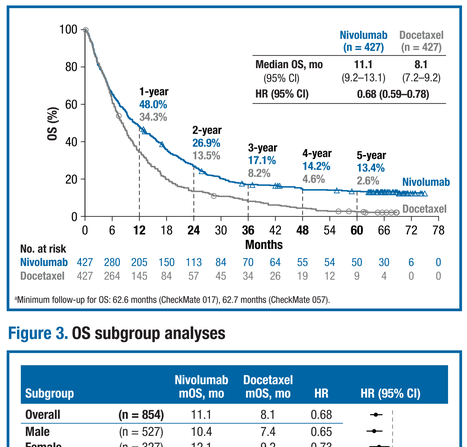
ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, objective response rate; PFS, progression-free survival; PRO, patient-reported outcome; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

Results

OS

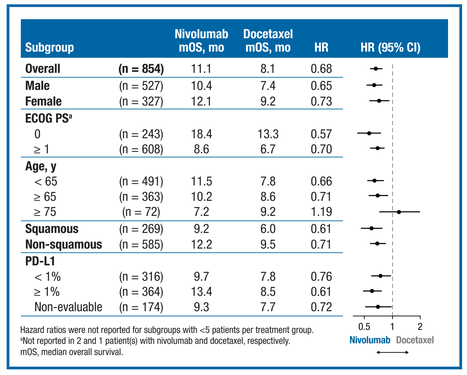
- At 5 years, OS remained longer with nivolumab vs docetaxel: hazard ratio (HR), 0.68; 95% confidence interval (CI), 0.59–0.78 (**Figure 2**). Estimated pooled 5-year OS rates were 13.4% with nivolumab vs 2.6% with docetaxel
- The OS benefit with nivolumab vs docetaxel was observed across subgroups including (but not limited to) patients with squamous or non-squamous tumour histology, and patients with PD-L1 ≥1% or <1% (**Figure 3**)
  - The 5-year OS rates for nivolumab vs docetaxel by histology were 12.3% vs 3.6% (CheckMate 017; squamous); 14.0% vs 2.1% (CheckMate 057; non-squamous) (**Figure 4**)
  - The pooled 5-year OS rates for nivolumab vs docetaxel by baseline PD-L1 status were 18.3% vs 3.4% (PD-L1 ≥1%); 8.0% vs 2.0% (PD-L1 <1%) (**Figure 5**)

Figure 2. 5-year pooled OS[a]



[a]Minimum follow-up for OS: 62.6 months (CheckMate 017), 62.7 months (CheckMate 057).

Figure 3. OS subgroup analyses



Hazard ratios were not reported for subgroups with <5 patients per treatment group. [a]Not reported in 2 and 1 patient(s) with nivolumab and docetaxel, respectively. mOS, median overall survival.

Figure 4. 5-year OS by tumour histology

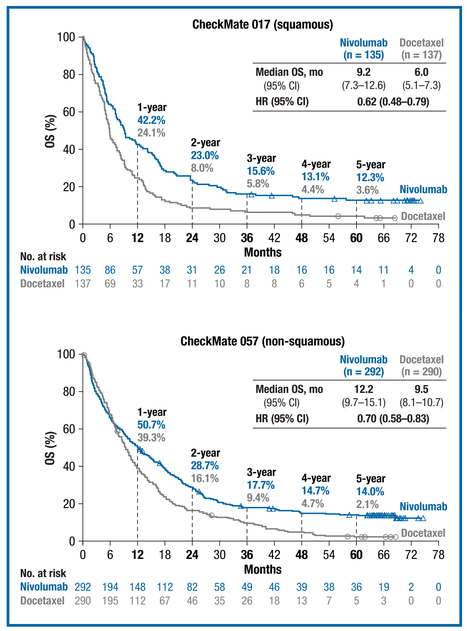
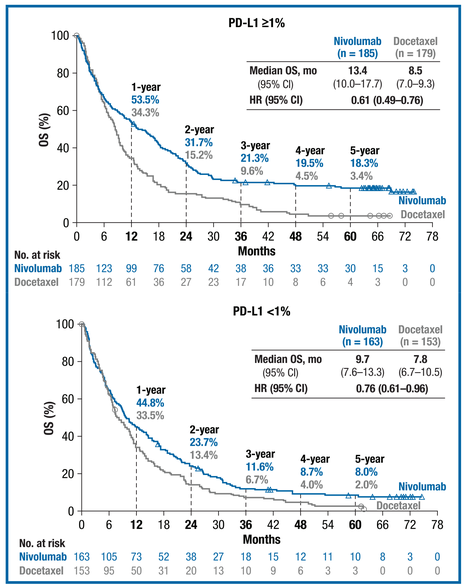


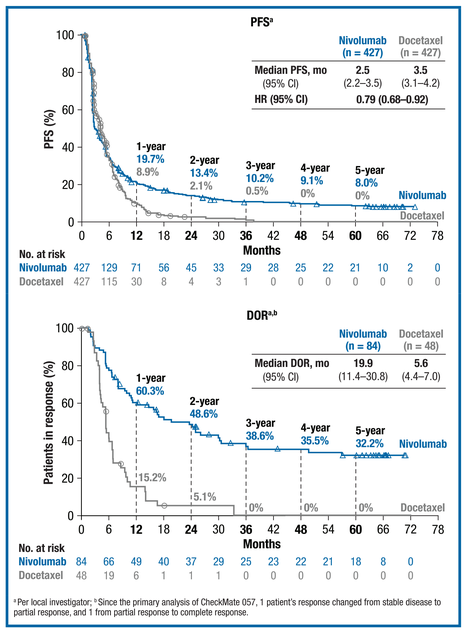
Figure 5. 5-year pooled OS by baseline PD-L1 status



PFS, ORR and DOR

- PFS rates consistently favoured nivolumab over docetaxel; 5-year pooled rates were 8.0% vs 0% (**Figure 6**)
- ORR was 19.7% (84/427) for nivolumab and 11.2% (48/427) for docetaxel
- Median DOR was longer with nivolumab vs docetaxel (**Figure 6**)
  - Of confirmed responders in the nivolumab arm, the 5-year pooled DOR rate was 32.2%; no patients in the docetaxel arm had ongoing responses

Figure 6. 5-year pooled analyses of PFS and DOR

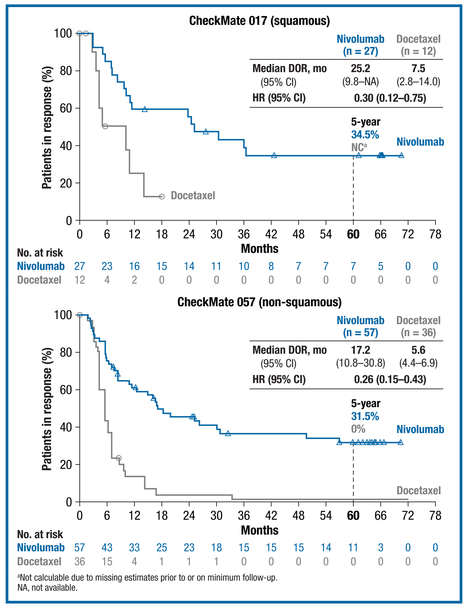


[a]Per local investigator; [b]Since the primary analysis of CheckMate 057, 1 patient's response changed from stable disease to partial response, and 1 from partial response to complete response.

DOR subgroup analyses

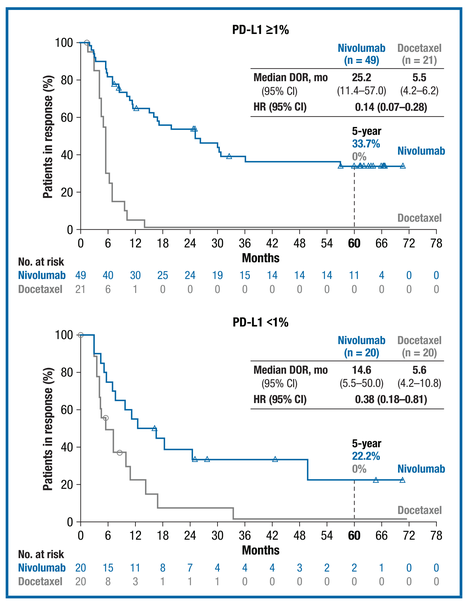
- Improvements in DOR with nivolumab vs docetaxel were observed regardless of histology or tumour PD-L1 expression
  - The 5-year DOR rate for nivolumab vs docetaxel by histology was 34.5% vs not calculable (CheckMate 017; squamous); 31.5% vs 0% (CheckMate 057; non-squamous) (**Figure 7**)
  - The pooled 5-year DOR rate for nivolumab vs docetaxel by baseline PD-L1 status was 33.7% vs 0% (PD-L1 ≥1%); 22.2% vs 0% (PD-L1 <1%) (**Figure 8**)

Figure 7. 5-year DOR by tumour histology



[a]Not calculable due to missing estimates prior to or on minimum follow-up. NA, not available.

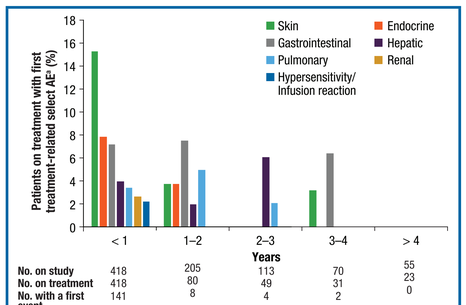
Figure 8. 5-year pooled DOR by baseline PD-L1 status



Safety

- Overall, 284 of 418 patients (68%) treated with nivolumab had treatment-related adverse events (TRAEs); 45 patients (11%) had grade 3–4 events
- Between 3–5 years' follow-up,[5] 8 of 31 (26%) nivolumab-treated patients had a TRAE of any grade; 1 (3.2%) was grade 3 (increased lipase). No grade 4 events occurred
  - One patient experienced a TRAE leading to discontinuation (recurrent grade 2 eczema nummular); no new treatment-related deaths occurred
- The majority of treatment-related select AEs occurred within the first year of treatment (**Figure 9**)

Figure 9. Nivolumab-treated patients with first treatment-related select AE[a,b]



Median (range) nivolumab treatment duration: 2.8 (0–76.2+) months. [a]Includes events of any grade reported between first dose and 30 days after last dose of study therapy; [b]Select AEs were events with a potential immunological cause.

Conclusions

- CheckMate 017 and 057 are the first randomised phase 3 trials to report 5-year outcomes for a programmed death-1 inhibitor in patients with previously treated advanced NSCLC
  - The 5-year pooled OS rate: 13.4% with nivolumab vs 2.6% with docetaxel (5-fold increase)
  - The 5-year pooled PFS rate: 8.0% with nivolumab vs 0% with docetaxel
- Patients without disease progression at 2 and 3 years after treatment with nivolumab had a 60% and 78% chance of remaining progression free at 5 years
- No baseline clinical or tumour characteristics clearly distinguished long-term survivors receiving nivolumab
- At 5 years, 10% of nivolumab survivors were off study drug (after 8.8–43.5 months of treatment), had not progressed, and had not received subsequent therapy
- With 5 years of minimum follow-up, no new safety signals were identified for nivolumab; there was no evidence of late-onset grade 3–4 select TRAEs

References

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6. Antonia SJ, *et al. Lancet Oncol* 2019;20:1395–1408 (including supplementary appendix).

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