CheckMate 032.pdf.txt

# 研究患者

Methods The SCLC cohort of this phase 1/2 multicentre, multi-arm, open-label trial was conducted at 23 sites (academic centres and hospitals) in six countries. Eligible patients were 18 years of age or older, had limited-stage or extensive-stage SCLC, and had disease progression after at least one previous platinum-containing regimen.

# 样本量

Findings Between Nov 18, 2013, and July 28, 2015, 216 patients were enrolled and treated (98 with nivolumab 3 mg/kg, three with nivolumab 1 mg/kg plus ipilimumab 1 mg/kg, 61 with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and 54 with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg).

# 基线特征

Table 1: Baseline patient characteristics  
(248·0–288·0) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort (appendix p 24).

# 试验设计

PsiOxus, Nanobiotix Janssen, Abbvie, PharmaMar, PUMA, Sanofi, Lilly, Pfizer, Merck, Nektar, Amcure, Amgen, AstraZeneca, Principia, Bayer, CytomX, H3, Incyte, Kura, LOXO, Macrogenics, Menarini, Merck Serono, Merus, Millenium, Rigontec, Tahio, and BeuGene Tesaro; consultancy fees from Janssen-Cilag, Alkermes (and travel expenses), Seattle Genetics, Pierre Fabre, Cerulean Pharma, EUSA, Celgene, Novartis (speakers’ bureau), Nanobiotix, PsiOxus Therapeutics, Abbvie, AstraZeneca, Guidepoint Global, Roche/Genentech (and travel expenses), GLG, Pfizer, Servier, Amcure, and Boehringer-Ingelheim; ownership from START (leadership), Oncoarts Associated, and International Cancer Consultants; employment from START and HM Hospitals Group (honoraria); and president and founder of NPO Foundation Intheos (Investigational Therapeutics in Oncological Sciences), outside the submitted work. All other authors declare no competing interests. Acknowledgments We thank the patients and their families, as well as the participating study teams, for making this study possible; the staff of Dako North America for collaborative development of the automated immunohistochemical assay for PD-L1 assessment; Marina Tschaika for medical oversight of the study; and Michael Cunningham for serving as the protocol manager. Earlier versions of the manuscript were prepared with medical writing and editorial assistance from Britt Anderson, Vasupradha Vethantham, and Anne Cooper (StemScientific), with funding from Bristol-Myers Squibb. References 1 National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Small cell lung cancer. Version 1. http://www.nccn.org (accessed Dec 1, 2015). Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? Cancer 2015; 121: 664–72. 3 Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer.

# 研究背景

Background Treatments for small-cell lung cancer (SCLC) after failure of platinum-based chemotherapy are limited. We assessed safety and activity of nivolumab and nivolumab plus ipilimumab in patients with SCLC who progressed after one or more previous regimens.

# 研究结果

results from CheckMate 016: a phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). J Clin Oncol 2015; 33 (suppl): 4516 (abstr).

# 研究结论

Findings Between Nov 18, 2013, and July 28, 2015, 216 patients were enrolled and treated (98 with nivolumab 3 mg/kg, three with nivolumab 1 mg/kg plus ipilimumab 1 mg/kg, 61 with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and 54 with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg). At database lock on Nov 6, 2015, median follow-up for patients continuing in the study (including those who had died or discontinued treatment) was 198·5 days (IQR 163·0–464·0) for nivolumab 3 mg/kg, 302 days (IQR not calculable) for nivolumab 1 mg/kg plus ipilimumab 1 mg/kg, 361·0 days (273·0–470·0) for nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and 260·5 days (248·0–288·0) for nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. An objective response was achieved in ten (10%) of 98 patients receiving nivolumab 3 mg/kg, one (33%) of three patients receiving nivolumab 1 mg/kg plus ipilimumab 1 mg/kg, 14 (23%) of 61 receiving nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and ten (19%) of 54 receiving nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. Grade 3 or 4 treatment-related adverse events occurred in 13 (13%) patients in the nivolumab 3 mg/kg cohort, 18 (30%) in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort, and ten (19%) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort; the most commonly reported grade 3 or 4 treatment-related adverse events were increased lipase (none vs 5 [8%] vs none) and diarrhoea (none vs 3 [5%] vs 1 [2%]). No patients in the nivolumab 1 mg/kg plus ipilimumab 1 mg/kg cohort had a grade 3 or 4 treatment-related adverse event. Six (6%) patients in the nivolumab 3 mg/kg group, seven (11%) in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group, and four (7%) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg group discontinued treatment due to treatment-related adverse events. Two patients who received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg died from treatment-related adverse events (myasthenia gravis and worsening of renal failure), and one patient who received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg died from treatment-related pneumonitis.  
Interpretation Nivolumab monotherapy and nivolumab plus ipilimumab showed antitumour activity with durable responses and manageable safety profiles in previously treated patients with SCLC.

# 表格相关

Methods The SCLC cohort of this phase 1/2 multicentre, multi-arm, open-label trial was conducted at 23 sites (academic centres and hospitals) in six countries. Eligible patients were 18 years of age or older, had limited-stage or extensive-stage SCLC, and had disease progression after at least one previous platinum-containing regimen. Patients received nivolumab (3 mg/kg bodyweight intravenously) every 2 weeks (given until disease progression or unacceptable toxicity)

>>>>>>>>>>>>>>>>>>

Using an interactive voice response system, patients with SCLC were enrolled in one of the following four cohorts in a sequential manner, or assigned if more than one cohort was open for enrolment: nivolumab alone 3 mg/kg bodyweight (nivolumab 3 mg/kg) intravenously every 2 weeks until disease progression or unacceptable toxicity, or combination treatment with nivolumab plus ipilimumab intravenously every 3 weeks for four cycles, at dose level 1 (nivolumab 1 mg/kg plus ipilimumab 1 mg/kg)

>>>>>>>>>>>>>>>>>>

Although the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg and nivolumab 3 mg/kg plus ipilimumab 1 mg/kg regimens were expected to be tolerable on the basis of previous evidence in other tumour types,15–17,19,20 an initial dose-escalating safety evaluation for the combination groups was done. The first dose cohort (nivolumab 1 mg/kg plus ipilimumab 1 mg/kg) was level 1; we used this dose to confirm the safety of the combination in this patient population. If this was deemed tolerable, we then initiated enrolment and allocation to level 2 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg). If dose level 2 was deemed not tolerable, enrolment and allocation to dose level 2b (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg) was investigated. Patients on active treatment needed to be followed up for at least 6 weeks after the start of study treatment before tolerability of a dose level was determined based on prespecified tolerability assessment criteria, which are detailed in the appendix pp 3, 20. However, tolerability beyond 6 weeks was also taken into consideration. After the highest dose level for further investigation was confirmed in the dose-escalating safety evaluation phase, the combination arms continued enrolling patients. Considerations for the dosing in the combination cohorts were as follows: the 1 mg/kg nivolumab plus 3 mg/kg ipilimumab regimen is the approved dose for the treatment of advanced melanoma;11,21 the 3 mg/kg nivolumab plus 1 mg/kg ipilimumab regimen was chosen to maximise the nivolumab dose based on nivolumab exposure response data (1 mg/kg vs 3 mg/kg).22 The safety of the 1 mg/kg nivolumab plus 3 mg/kg ipilimumab and the 3 mg/kg nivolumab plus 1 mg/kg ipilimumab regimens have been previously assessed in studies of other tumour types.15–17,19,20 For combination treatment, nivolumab was given first (60 min infusion), followed by ipilimumab (90 min infusion), as per previous studies evaluating nivolumab plus ipilimumab.19,20 Patients received open-label treatment until disease progression or occurrence of unacceptable toxicity. Treatment beyond RECIST (version 1.1)

>>>>>>>>>>>>>>>>>>

(248·0–288·0) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort (appendix p 24). Median follow-up for the overall survival data is shown in the appendix (p 24). Baseline characteristics are shown in table 1 and the appendix (p 21)

>>>>>>>>>>>>>>>>>>

; roughly half of patients had been treated with two or more previous regimens, and about a third had platinum-resistant disease. Patients received a median of 3·5 infusions of nivolumab (IQR 2·0–6·0) in the nivolumab 3 mg/kg cohort, 9·0 infusions of nivolumab (IQR not calculable) and 4·0 infusions of ipilimumab (IQR not calculable) in the nivolumab 1 mg/kg plus ipilimumab 1 mg/kg cohort, 3·0 infusions each of nivolumab (2·0–14·0) and ipilimumab (2·0–4·0) in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort, and 2·0 infusions each of nivolumab (2·0–6·0) and ipilimumab (2·0–4·0) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort. At the time of analysis, 77 (79%) patients had discontinued nivolumab 3 mg/kg, 42 (69%) had discontinued nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and 43 (80%) had discontinued nivolumab 3 mg/kg plus ipilimumab 1 mg/kg; the most common reason was disease progression (figure 1; appendix p 24). Two patients discontinued nivolumab 1 mg/kg plus ipilimumab 1 mg/kg (one due to disease progression, and one due to adverse event not related to study drug). By investigator-assessed RECIST, ten (10% [95% CI 5–18]) of 98 patients achieved a confirmed objective response with nivolumab 3 mg/kg, 14 (23% [13–36]) of 61 with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and ten (19% [9–31]) of 54 with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (table 2; figure 2)

>>>>>>>>>>>>>>>>>>

plus ipilimumab 1 mg/kg. 16 patients had a duration of response longer than 6 months: six patients in the nivolumab 3 mg/kg group, one patient in the nivolumab 1 mg/kg plus ipilimumab 1 mg/kg group, eight patients in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group, and one patient in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg group (median 9·6 months [IQR 7·1–14·3]). Median time to response is shown in table 2. Tumour response data in the nivolumab 1 mg/kg plus ipilimumab 1 mg/kg cohort are shown in the appendix (p 22)

>>>>>>>>>>>>>>>>>>

nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort (figure 3B). The nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort had not met the 1-year milestone for progression-free survival at the time of database lock. Two (67%) of three patients in the nivolumab 1 mg/kg plus ipilimumab 1 mg/kg cohort had died and one (33%) had a progression event. Nine patients crossed over from the nivolumab 3 mg/kg cohort to the combination cohorts after progression (one to nivolumab 1 mg/kg plus ipilimumab 3 mg/kg and eight to nivolumab 3 mg/kg plus ipilimumab 1 mg/kg); eight of these patients had further disease progression and one patient in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort withdrew consent and therefore response could not be determined. PD-L1 expression was assessable in 148 (69%) of 216 patient samples, of which 39 (27%) were provided as fresh biopsies and 109 (74%) were archived specimens. 25 (17%) had 1% or greater PD-L1 expression, and seven (5%) had 5% or greater PD-L1 expression (table 1; appendix p 21)

>>>>>>>>>>>>>>>>>>

. In a pre-planned exploratory analysis of the nivolumab 3 mg/kg, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohorts, tumour responses occurred in patients irrespective of PD-L1 expression (appendix pp 15–18). Grade 3 or 4 treatment-related adverse events occurred in 13 (13%) of 98 patients in the nivolumab 3 mg/kg cohort, 18 (30%) of 61 patients in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort, and ten (19%) of 54 patients in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort (table 3)

>>>>>>>>>>>>>>>>>>

Data presented as n (%).This table reports grade 1–2 treatment-related events in ≥10% of patients in any treatment cohort and all grade 3–4 events. Safety analyses included all patients who were enrolled at least 90 days prior to database lock; patients with adverse events after crossover from nivolumab 3 mg/kg to combination treatment are excluded. Some patients had more than one adverse event. Two patients in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group died from myasthenia gravis and worsening of renal failure, respectively; both events were regarded to be treatment related. One patient in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort died from pneumonitis, regarded as treatment related. All-causality adverse events and serious adverse events are shown in the appendix (pp 27–30)

>>>>>>>>>>>>>>>>>>

. Two patients who received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg died from treatment-related events of myasthenia gravis25 and worsening of renal failure, respectively, and one patient who received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg died from treatment-related pneumonitis (appendix p 4). Other than because of disease progression and study drug toxicity, the following deaths were reported: in the nivolumab 3 mg/kg group, three (3%) due to unknown causes, one (1%) due to sepsis and multiorgan failure, and one (1%) due to respiratory insufficiency not related to treatment; in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group, three (5%) due to unknown causes, one (2%) due to subdural haematoma unrelated to study drug, one (2%) due to sedation, one (2%) due to hypovolaemic septic shock and septic shock from candidaemia, and one (2%) due to abdominal sepsis and secondary intravascular disseminated coagulation; and in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg group, three (6%) due to unknown causes, and one (2%) due to adverse events not related to study drug. Two patients had grade 2 limbic encephalitis: one in the nivolumab 3 mg/kg cohort (reported as not treatment-related by investigator) and one in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort (reported as treatment-related by investigator); both events resolved with immunosuppressive treatment. One patient in the nivolumab 3 mg/kg cohort had grade 4 limbic encephalitis (reported as treatment- related by investigator) that did not resolve with intravenous immunoglobulin and corticosteroid treatment. Treatment-related pneumonitis occurred in eight patients and resolved in six of eight patients with treatment. The outcome was unknown for one patient, and one patient died. One patient who crossed over from nivolumab 3 mg/kg to nivolumab 1 mg/kg plus ipilimumab 3 mg/kg had treatment-related grade 3 elevations in alanine amino- transferase levels (appendix p 4). Five (8%) patients in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort had grade 3 or 4 asymptomatic lipase elevations without clinical signs of pancreatitis (table 3)

>>>>>>>>>>>>>>>>>>