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NCCN Guideline® Panel: Small Cell Lung Cancer (SCLC)

Dear Panel Members,

On behalf of Bristol-Myers Squibb Company, I respectfully submit the enclosed Opdivo clinical data that has been published in the Lancet Oncology and presented at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting, for the Panel's consideration. The phase 1/2 study evaluated the use of nivolumab monotherapy or in combination with ipilimumab for the treatment of patients with unresectable locally advanced or metastatic small cell lung cancer (SCLC).[1,2]

These data are being submitted in response to a standing request from NCCN for new clinical data.

FDA Clearance (Non-Small Cell Lung Cancer [NSCLC] indication)[3]: Currently, nivolumab is approved for the treatment of patients with metastatic NSCLC who have progressed on or after platinum-based chemotherapy. Patients with EGFR or ALK aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.

Rationale: We are herein providing recently published data from a cohort in a phase 1/2 trial (CA209-032), that evaluated the safety and efficacy of nivolumab monotherapy or in combination with ipilimumab for the treatment of patients with recurrent SCLC, who had received at least one prior platinum-containing regimen.

Study CA209-032, SCLC cohort[1]: This open-label, phase 1/2 study, included patients with histologically or cytologically confirmed recurrent SCLC. Patients evaluated in the study had progressive disease after receiving ≥ 1 prior platinum-containing regimen, and were eligible to receive nivolumab 3 mg/kg every 2 weeks (n=98) or nivolumab 1 mg/kg and ipilimumab 1 mg/kg (n=3) or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n=61) or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n=54), every 3 weeks for 4 cycles, followed by nivolumab 3 mg/kg every 2 weeks.

The primary endpoint was objective response rate. Secondary endpoints included overall survival, progression free survival, duration or response, and treatment-related adverse events leading to discontinuation. Correlation between PD-L1 expression and anti-tumor activity was a pre-specified exploratory endpoint.[1]

Data on the 3 patients in the nivolumab 1 mg/kg + ipilimumab 1mg/kg cohort are provided in the journal supplement.[1]

Baseline characteristics, highlights:

Table 1. Selected Baseline Characteristics[1]

	Nivolumab 3 mg/kg (n = 98)	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n = 61)	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n = 54)
Prior treatment regimens, %			
▪ 1	41	52	43
▪ 2-3	56	38	52
▪ >3	3	10	6
PD-L1 expression level, %			
▪ ≥ 1%	14	24	13
▪ < 1%	86	76	88
▪ ≥ 5%	6	5	3
▪ < 5%	94	95	98
▪ Not evaluable/missing	30	39	26
First line platinum-treated patients*,%			
▪ Platinum-sensitive	56	41	39
▪ Platinum-resistant†	31	38	39
▪ Unknown	10	18	15

*3 patients in the nivolumab 3 mg/kg group, 2 patients in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group, and 4 patients in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg group did not receive first-line platinum therapy and did not meet eligibility criteria, although they were treated and included in the analysis. †Defined as a patient who relapsed <90 days after chemotherapy.

Efficacy findings, highlights:

Table 2. Efficacy Data[1]

	Nivolumab 3 mg/kg (n = 98)	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n = 61)	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n = 54)
Objective response rate, % (95% CI)	10 (5-18)	23 (13-36)	19 (9-31)
Median duration of response, months (95% CI)	NR (4.4–NR)	7.7 (4.0–NR)	4.4 (3·7–NR)
Best overall response, %			
▪ Complete response	0	2	0
▪ Partial response	10	21	19
▪ Stable disease	22	21	17
▪ Progressive disease	53	38	54
Median PFS, months (95% CI)	1.4 (1.4, 1.9)	2.6 (1.4, 4.1)	1.4 (1.3,2.2)

Abbreviations: NR, not reached; PFS, progression-free survival.

- Overall, PD-L1 expression was evaluable in 148 of 216 patient samples (69%), of which 25 (17%) and 7 (5%) had PD-L1 expression ≥1% and ≥5%, respectively. Tumor responses occurred in patients irrespective of PD-L1 expression.[1]

Safety findings, highlights:

A summary of safety findings is presented in Table 3. A total of 3 treatment related deaths were reported, 1 death in the nivolumab 1mg/kg + ipilimumab 3 mg/kg cohort from treatment-related myasthenia gravis,1 death in the nivolumab 1mg/kg +ipilimumab 3mg/kg cohort from treatment related worsening of renal failure, and 1 death in the nivolumab 3mg/kg + ipilimumab 1 mg/kg cohort from treatment-related pneumonitis.[1]

Table 3. Safety Data[1]

	Nivolumab 3 mg/kg (n = 98)	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n = 61)	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n = 54)
Treatment-related AEs			
• Grade 1-2 events, reported in ≥10% of patients in any cohort	40	49	56
▪ All Grade 3-4 events, %	13	30	19
Treatment-related AEs leading to discontinuation, %	6	11	7

Abbreviations: AE, adverse event.

The following resources are included for your reference. We would like to acknowledge the contributions of NCCN Panel members who are also co-authors or co-contributors of the publication.

1. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (Checkmate 032): a multicentre, open-label phase 1/2 trial. *Lancet.* 2016 and Supplement. Published Online: June 4 2016 (http://dx.doi.org/10.1016/S1470-2045(16)30098-5).
2. Antonia SJ, Lopex-Martin JA, Bendell J et al. Checkmate 032: Nivolumab alone or in combination with ipilimumab for the treatment of recurrent small cell lung cancer. Oral presentation presented at: The 52nd American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2016; Chicago, Illinois, USA.
3. OPDIVO Prescribing Information.

Sincerely,

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