September 20, 2021
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NCCN Guidelines® Panel: Head and Neck Cancers

On behalf of Bristol Myers Squibb, we respectfully request the Head and Neck Cancers Panel to review data recently presented at European Society for Medical Oncology (ESMO) Congress 2021 on the use of OPDIVO® (nivolumab) plus YERVOY® (ipilimumab) as first-line treatment for patients with previously untreated recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN).[1]

Specific Changes: Addition of nivolumab and ipilimumab as a Category 2A recommended first-line treatment option for R/M SCCHN with combined positive score (CPS) ≥ 1 and CPS ≥ 20 (page Syst-A 2 of 4).

FDA Clearance: OPDIVO® is indicated for the treatment of R/M SCCHN with disease progression on or after a platinum-based therapy.[2] The use of nivolumab and ipilimumab for patients with R/M SCCHN is considered investigational.[2,3]

Rationale: This data is being submitted in response to a standing request from the NCCN® for new data.

CheckMate 651 is a randomized, open-label phase 3 trial evaluating nivolumab + ipilimumab (NIVO 3mg/kg every 2 weeks + IPI 1mg/kg every 6 weeks) vs EXTREME regimen (cetuximab, cisplatin/carboplatin and fluorouracil every 3 weeks for 6 cycles followed by cetuximab monotherapy weekly) as first-line treatment of platinum-eligible R/M SCCHN. The study enrolled 947 patients with R/M SCCHN in the oral cavity, oropharynx, hypopharynx, or larynx who did not receive prior systemic treatment for R/M disease and had ECOG Performance Status of 0 or 1. Prior chemotherapy for locally advanced disease was permitted if patients were progression-free for at least 6 months after chemotherapy. Patients were stratified by p16 expression, tumor PD-L1 status, and prior chemotherapy. Eligible patients were randomized 1:1 to NIVO + IPI (n=472) or EXTREME (n=475) to continue until disease progression, unacceptable toxicity, or 2 years for NIVO + IPI.

There were two independently tested primary endpoints: overall survival (OS) in all randomized patients and OS in patients with PD-L1 CPS ≥ 20. The primary endpoints were tested with equal overall two-sided α=0.025 using stratified log-rank test in parallel. Key secondary endpoints included OS in PD-L1 CPS ≥1; progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) of all patients and those with PD-L1 CPS ≥ 20. Exploratory endpoints included PFS, ORR, and DOR for patients with PD-L1 CPS ≥ 1, patient-reported outcomes and safety. The minimum and median follow-up were 27.3 months and 39.1 months, respectively. PD-L1 staining was determined by PD-L1 IHC 28-8 pharmDx (Dako).

NIVO + IPI did not improve OS statistically compared to EXTREME for the primary endpoints, but the NIVO + IPI showed evidence of clinical activity in patients with CPS≥ 20 and CPS ≥1 with 2-year OS rates of 41% and 34%, respectively, and durable responses as shown in Table 1. In patients with CPS ≥1 and ≥20 who responded to NIVO + IPI, more than 50% of those patients were still in response at 18 months.

Compared to historical data, the median OS data observed for EXTREME in CheckMate 651 (13.2-14.6 months)[1] were higher than expected from previous studies of this treatment regimen (10.1-11 months).[4,5] In all randomized patients, 54% in the NIVO + IPI arm received subsequent therapy with 8% immunotherapy and 42% platinum-based chemotherapy. In the EXTREME arm, 63% received subsequent therapy with 46%

immunotherapy and 16% platinum-based chemotherapy. In the CPS ≥ 20 population, 46% (NIVO + IPI) and 60% (EXTREME) of patients with CPS ≥20 received subsequent systemic therapy; 11% (NIVO + IPI) and 43% (EXTREME) received subsequent immunotherapy.

Table 1. Efficacy outcomes from CheckMate-651

	All randomized		**PD-L1 CPS ≥ 20**		**PD-L1 CPS ≥ 1**	
	N+I n = 472	EXTREME n = 475	N+I n = 185	EXTREME n = 178	N+I n = 355	EXTREME n = 372
mOS, mo (95% CI)	13.9 (12.1-15.8)	13.5 (12.6-15.2)	17.6 (13.8-22.0)	14.6 (12.3-16)	15.7 (13.7-18.8)	13.2 (11.1-14.6)
HR	0.95 (97.9% CI: 0.80-1.13)[a] *p* = 0.04951		0.78 (97.51%: 0.59-1.03)[a] *p* = 0.0469		0.82 (95% CI: 0.69-0.97).	
mPFS[b], mo (95% CI)	3.3 (2.8–4.2)	6.7 (5.8–7.0)	5.4 (3.1–6.9)	7.0 (5.6–8.7)	4.2 (2.9–5.4)	6.1 (5.6–7.0)
HR (95% CI)	1.41 (1.21–1.65)		1.02 (0.78–1.33)		1.23 (1.03–1.47)	
ORR[b], n (%)	114 (24)	175 (37)	63 (34)	64 (36)	98 (28)	133 (36)
mDOR[b], mo (95% CI)	16.6 (9.7–29.4)	5.9 (5.4–7.0)	32.6 (12.1–NR)	7.0 (5.6–10.1)	18.3 (10.9–32.6)	6.0 (5.6–7.6)

Minimum follow-up: 27.3 months, adapted from Argiris A et al.[1]
[a]Confidence intervals are adjusted based on the final α levels for each primary endpoint; [b] Per blinded independent central review
CI, confidence interval; CPS, combined positive score; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; mo, months; N+I, nivolumab + ipilimumab; NR, not reached; ORR, objective response rate

Patient-reported outcomes in the PD-L1 CPS ≥ 20 population suggested that NIVO + IPI had a longer time to symptom deterioration from baseline in FHNSI-10 (Functional Assessment of Cancer Therapy Head & Neck Cancer Symptom 10-Item Index) score than EXTREME at 16.7 (7.4-31.6) months and 7.6 (4.3-10.9) months, respectively. Additionally, patients with CPS ≥ 20 on NIVO + IPI self-rated improved overall health status per the EQ-5D-3L VAS (EuroQol five dimension visual analog scale) while patients on EXTREME generally self-rated no change.

The median (range) of NIVO and IPI doses received by patients in CheckMate 651 were 8 (1-53) and 3 (1-18) doses, respectively. No new safety signals were observed. Any grade and grade 3/4 treatment-related adverse events (TRAEs) occurred in 72% and 28% in the NIVO + IPI arm and 98% and 71% in the EXTREME arm, respectively. Serious any grade and grade 3/4 TRAEs occurred in 16% and 12% in the NIVO + IPI arm and 28% and 24% in the EXTREME arm. In the NIVO + IPI arm, 12% and 10% of the patients discontinued any component of the regimen due to any grade and grade 3/4 TRAEs, respectively, with ipilimumab discontinued in 22 patients due to TRAEs. In the EXTREME arm, 13% and 9% of the patients discontinued any component of the regimen due to any grade and grade 3/4 TRAEs, respectively. Treatment-related deaths occurred in 1% of the patients in the NIVO + IPI arm due to pneumonitis (n=2), hepatitis (n=2), tumor lysis syndrome (1), and disseminated intravascular coagulation (1). In the EXTREME arm, treatment-related deaths occurred in 2% of the patients due to sepsis (n=5), pneumonia (n=2), and acute respiratory syndrome (n=1).

As part of the submission, the following resources are enclosed for your review.

Reference List:

1. Argiris A, Harrington K, Tahara M, et al. Nivolumab + ipilimumab vs EXTREME regimen as first-line treatment for recurrent/metastatic squamous cell carcinoma of the head and neck: final results of CheckMate 651. Oral presentation at: 2021 European Society for Medical Oncology Congress; September 16-20, 2021; Virtual Meeting.

2. Product Information, OPDIVO® (nivolumab) injection for intravenous infusion. Bristol Myers Squibb, Princeton, NJ. August 2021.
3. Product Information, YERVOY® (ipilimumab) injection for intravenous infusion. Bristol Myers Squibb, Princeton, NJ. May 2021.
4. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* 2019;394:1915–28.
5. Vermorken JB, Mesia R, Rivera F, et al. Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. *N Engl J Med* 2008;359:1116-27.

Thank you for your consideration of this request.

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