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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

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Introduction

- Patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) have poor prognosis and notable morbidity, with deterioration of quality of life[1,2]
- The addition of cetuximab to chemotherapy improved overall survival (OS) vs chemotherapy alone in the first-line R/M setting[3]; however, the responses are not durable
- Immunotherapy alone or in combination increased OS benefit, particularly in patients with PD-L1 expression,[4-6] and standard of care has shifted to immunotherapy-based treatment[5]
- Nivolumab (NIVO) and ipilimumab (IPI) have distinct but complementary mechanisms of action, and have shown survival benefit and durable responses in several solid tumors[7-12]
- CheckMate 651 is a randomized, open-label phase 3 trial evaluating NIVO + IPI vs the EXTREME regimen as first-line treatment for platinum-eligible R/M SCCHN

1. Argiris A, et al. *Lancet* 2008;371:1695-1709; 2. Murphy B. *Curr Opin Oncol* 2009;21:242-247; 3. Vermorken JB, et al. *N Engl J Med* 2008;359:1116-1127; 4. Ferris RL, et al. *N Engl J Med* 2016;375:1856-1867; 5. Burtness B, et al. *Lancet* 2019;394:1915-1928; 6. Cohen EEW, et al. *Lancet* 2019;393:156-167; 7. Albiges L, et al. *ESMO Open* 2020;5:e001079; 8. Larkin J, et al. *N Engl J Med* 2019;381:1535-1546; 9. Pardoll DM. *Nat Rev Cancer* 2012;12:252–264; 10. Motzer RJ, et al. *Lancet Oncol* 2019;20:1370-1385; 11. Baas P, et al. *Lancet* 2021; 397:375-386; 12. Paz-Ares L, et al. *J Clin Oncol* 30, 2021 (suppl 15; abstr 9016).

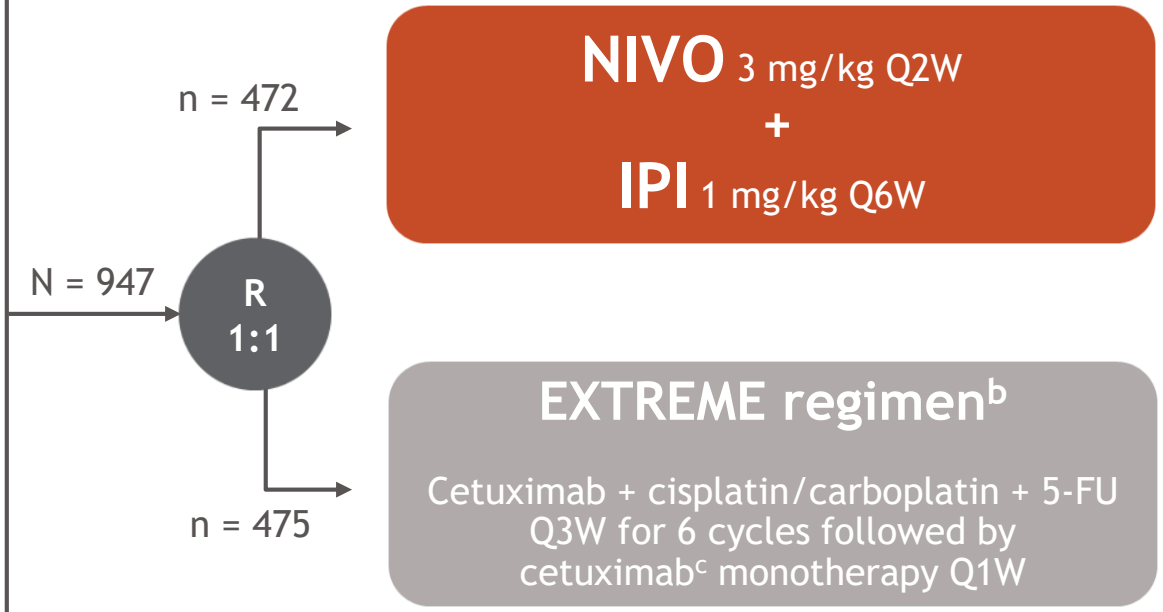
CheckMate 651 study design

Key eligibility criteria

- R/M SCCHN (oral cavity, oropharynx, hypopharynx, or larynx)
- No prior treatment for R/M disease
- Prior chemotherapy for LAD permitted if progression-free ≥6 months post-treatment
- ECOG PS 0–1

Stratified by:

p16 expression (OPC p16+ vs p16−/non-OPC)
Tumor PD-L1[a] status (<1% vs ≥1%)
Prior chemotherapy (yes vs no)



Until disease progression, unacceptable toxicity, *or* 2 years for NIVO + IPI

Primary endpoints (independently tested)

- OS in all randomized
- OS in PD-L1 CPS[a] ≥20

Secondary endpoints

- OS in PD-L1 CPS ≥1[d]
- PFS by BICR (all randomized, PD-L1 CPS ≥20)
- ORR/DOR by BICR (all randomized, PD-L1 CPS ≥20)

Exploratory endpoints

- PFS and ORR/DOR in PD-L1 CPS ≥1
- Patient-reported outcomes
- Safety

NCT02741570. Database lock: June 21, 2021; minimum / median follow-up: 27.3 months / 39.1 months.

[a]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [b]Initial cetuximab dose of 400 mg/m^2 once only, then cetuximab 250 mg/m^2 Q1W plus cisplatin 100 mg/m^2 or carboplatin AUC 5 on day 1, plus fluorouracil 1000 mg/m^2/d for 4 days for 6 cycles (Q3W); [c]Cetuximab 250 mg/m^2 Q1W; Q2W maintenance was allowed per local prescribing information; [d]Part of statistical testing hierarchy.
BICR, blinded independent central review; CPS, combined positive score; DOR, duration of response; LAD, locally advanced disease; OPC, oropharyngeal cancer; ORR, objective response rate.

Statistical testing hierarchy

- OS in all randomized and CPS ≥20 populations (primary endpoints) were tested in parallel,[a] with equal overall α = 0.025 (two-sided) using stratified log-rank test
  - OS in CPS ≥1 (secondary endpoint) was to be tested at the same α level as CPS ≥20, if and only if OS in CPS ≥20 were positive
  - If OS in all randomized was positive, OS in CPS ≥20 could be retested with overall α = 0.05
  - If OS in CPS ≥20 and CPS ≥1 were both positive, but OS in all randomized failed, OS in all randomized could be retested with overall α = 0.05

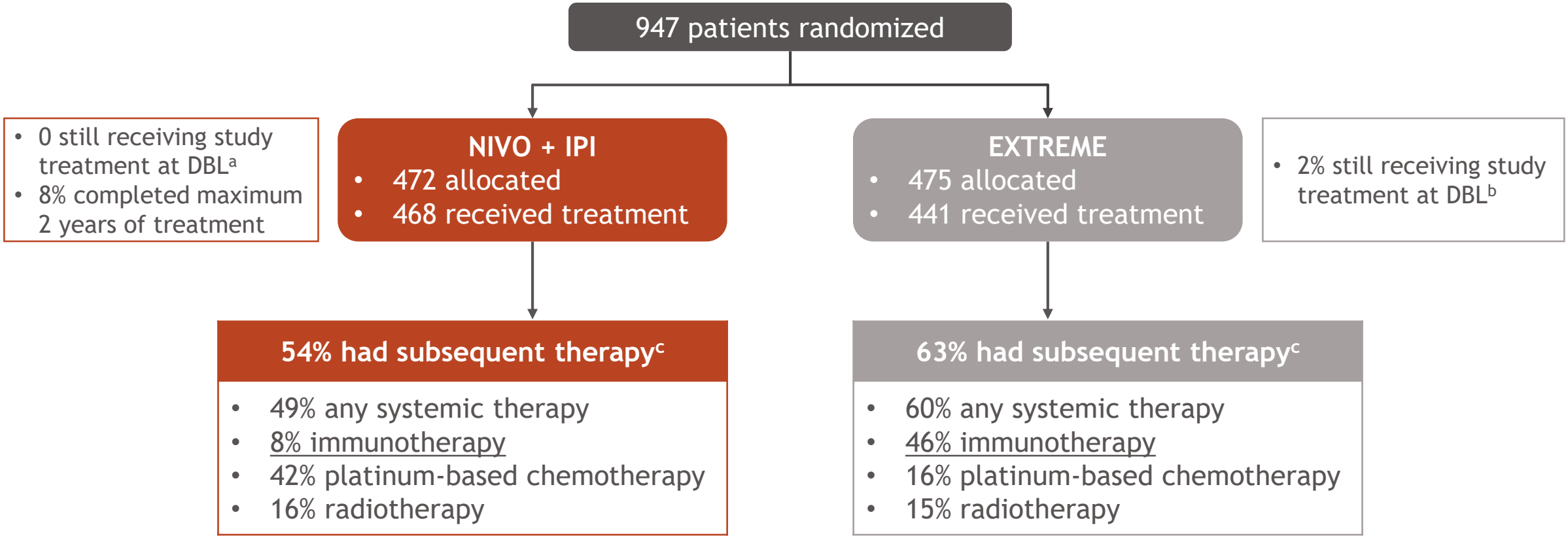
[a]For each endpoint, an O'Brien-Fleming α spending function was used. CPS, combined positive score.

Baseline characteristics

	All randomized patients		PD-L1 CPS ≥20	
	NIVO + IPI (n = 472)	EXTREME (n = 475)	NIVO + IPI (n = 185)	EXTREME (n = 178)
Age, median (range), years	61 (24–86)	62 (29–86)	61 (30–83)	61 (31–86)
Male, %	80	84	80	77
ECOG PS,[a] %				
0	32	36	35	37
1	67	63	64	62
Current or former smoker, %	76	78	72	78
Disease status, %				
Locally recurrent	28	36	32	35
Locally recurrent and metastatic	32	24	32	27
Metastatic	39	40	36	38
Primary site, %				
Oral cavity	27	28	38	33
Oropharynx	43	41	39	40
Hypopharynx	10	12	6	11
Larynx	21	19	17	16
OPC p16+,[b,c] %	20	20	17	22
Prior chemotherapy,[c,d] %	50	50	44	52
Tumor PD-L1 expression,[c] %				
<1% or non-evaluable	42	42	8	10
≥1%	58	58	92	90
PD-L1 CPS,[e] %				
<1	20	18	-	-
≥1	75	78	-	-
≥20	39	38	100	100

[a]ECOG PS 2 was reported in 2 and 1 patients in the NIVO + IPI and EXTREME arms respectively; ECOG PS was not reported in 1 patient in the EXTREME arm; [b]p16 status not reported in 1 patient each in both the NIVO + IPI and EXTREME arms; [c]Per interactive response technology; [d]Adjuvant, neoadjuvant, or multimodal therapy; [e]5% and 4% of patients in the NIVO + IPI arm and EXTREME arm, respectively, were non-evaluable for PD-L1 CPS. CPS, combined positive score; OPC, oropharyngeal cancer.

Treatment disposition and subsequent therapies



- The proportion of patients receiving subsequent systemic therapy was similar in the PD-L1 CPS ≥20 population[d]

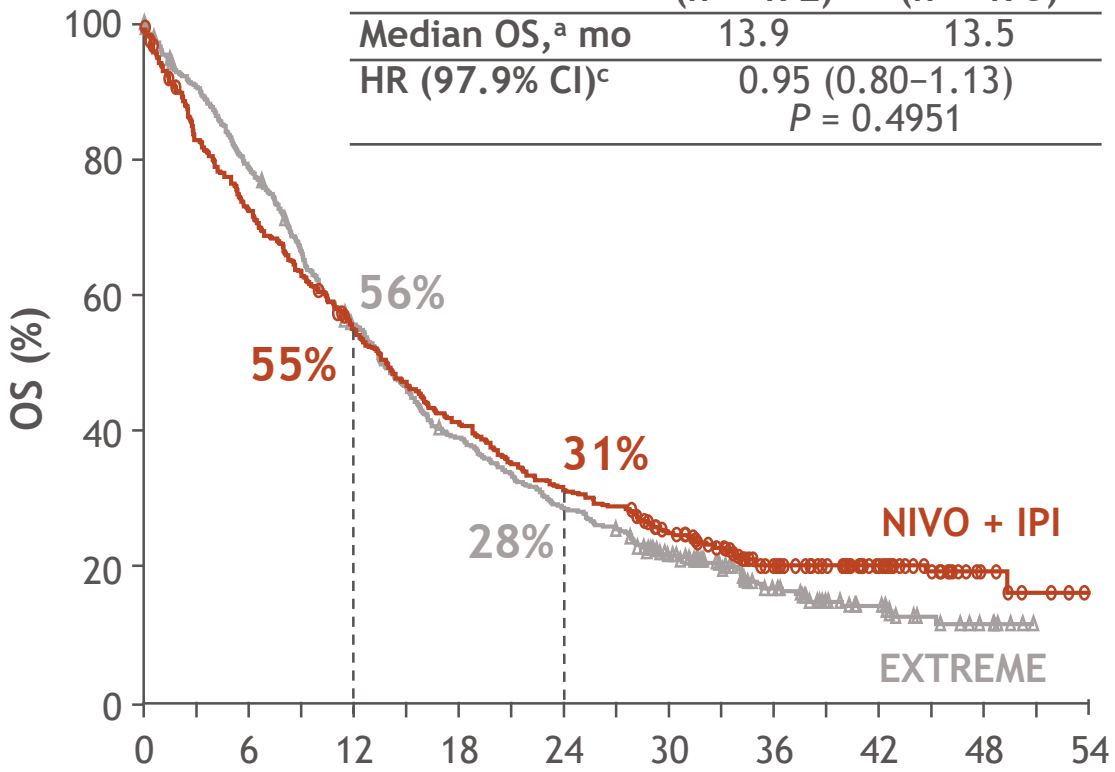
Minimum / median follow-up: 27.3 months / 39.1 months.

[a]Reasons for not continuing the treatment included disease progression (63%), study drug toxicity (12%), AE unrelated to study drug (9%), other (10%); [b]Reasons for not continuing the treatment included disease progression (69%), study drug toxicity (10%), AE unrelated to study drug (6%), other (2%); [c]Percentages based on randomized population; patients may have received more than 1 type of subsequent therapy; [d]46% (NIVO + IPI) and 60% (EXTREME) of patients with CPS ≥20 received subsequent systemic therapy; 11% and 43%, respectively, received subsequent immunotherapy.
CPS, combined positive score.

Primary endpoints: OS with NIVO + IPI vs EXTREME

All randomized

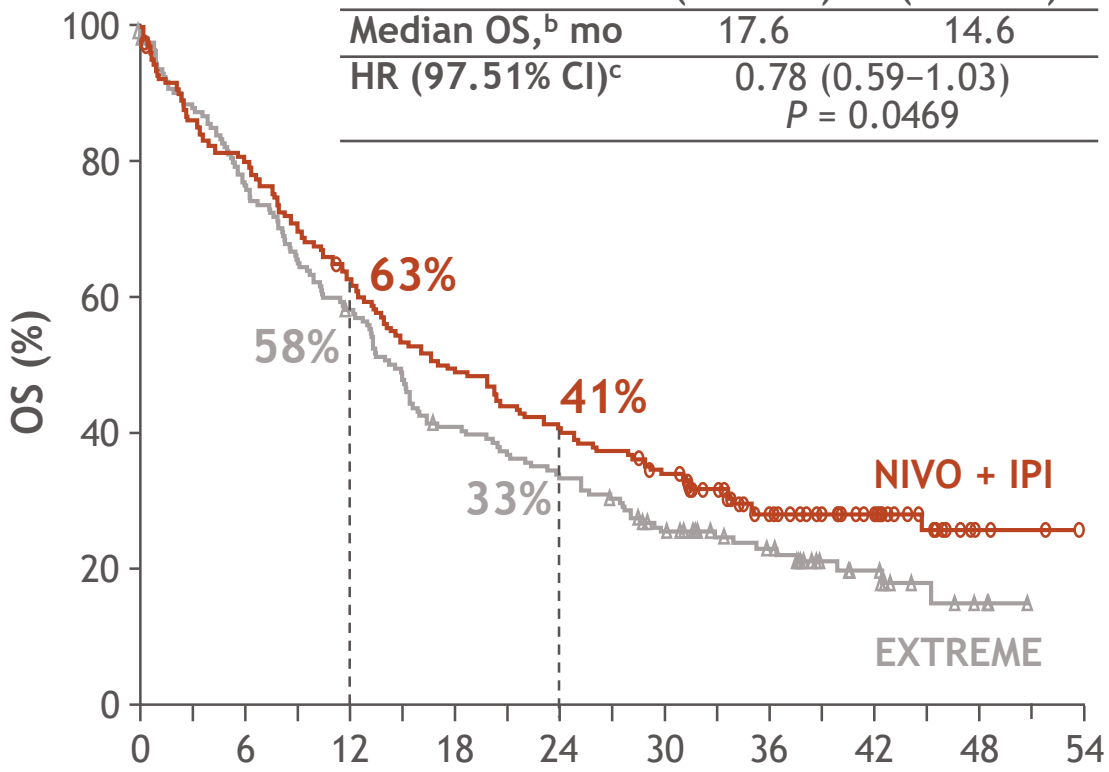
	NIVO + IPI (n = 472)	EXTREME (n = 475)
Median OS,[a] mo	13.9	13.5
HR (97.9% CI)[c]	0.95 (0.80–1.13) *P* = 0.4951	



No. at risk										
NIVO + IPI	472	340	254	190	144	108	58	32	8	0
EXTREME	475	366	255	177	129	88	47	21	6	0

PD-L1 CPS ≥20

	NIVO + IPI (n = 185)	EXTREME (n = 178)
Median OS,[b] mo	17.6	14.6
HR (97.51% CI)[c]	0.78 (0.59–1.03) *P* = 0.0469	



No. at risk										
NIVO + IPI	185	147	114	89	74	60	36	21	4	0
EXTREME	178	135	101	70	57	40	26	12	3	0

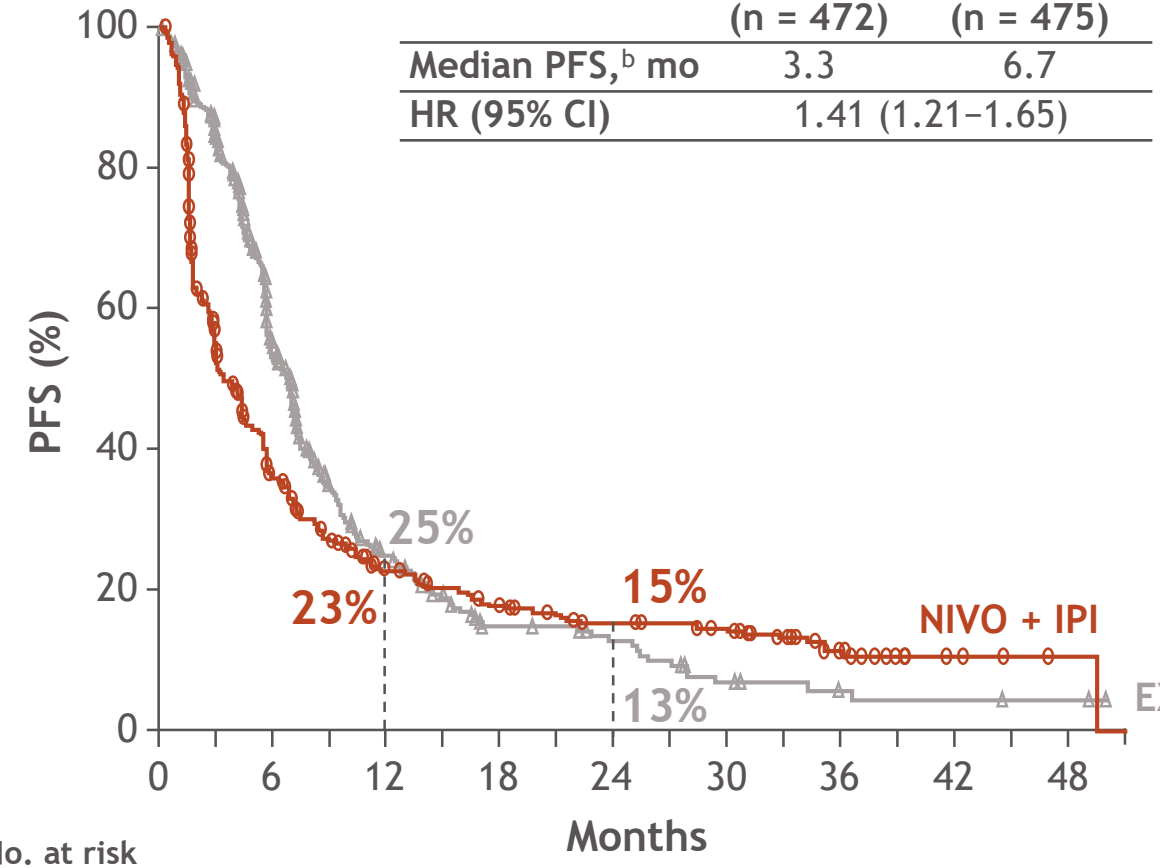
Minimum follow-up: 27.3 months.

[a]95% CI = 12.1–15.8 (NIVO + IPI) and 12.6–15.2 (EXTREME); [b]95% CI = 13.8–22.0 (NIVO + IPI) and 12.3–16.0 (EXTREME); [c]Confidence intervals are adjusted based on the final α levels for each primary endpoint. CPS, combined positive score.

Efficacy in all randomized patients

PFS[a]

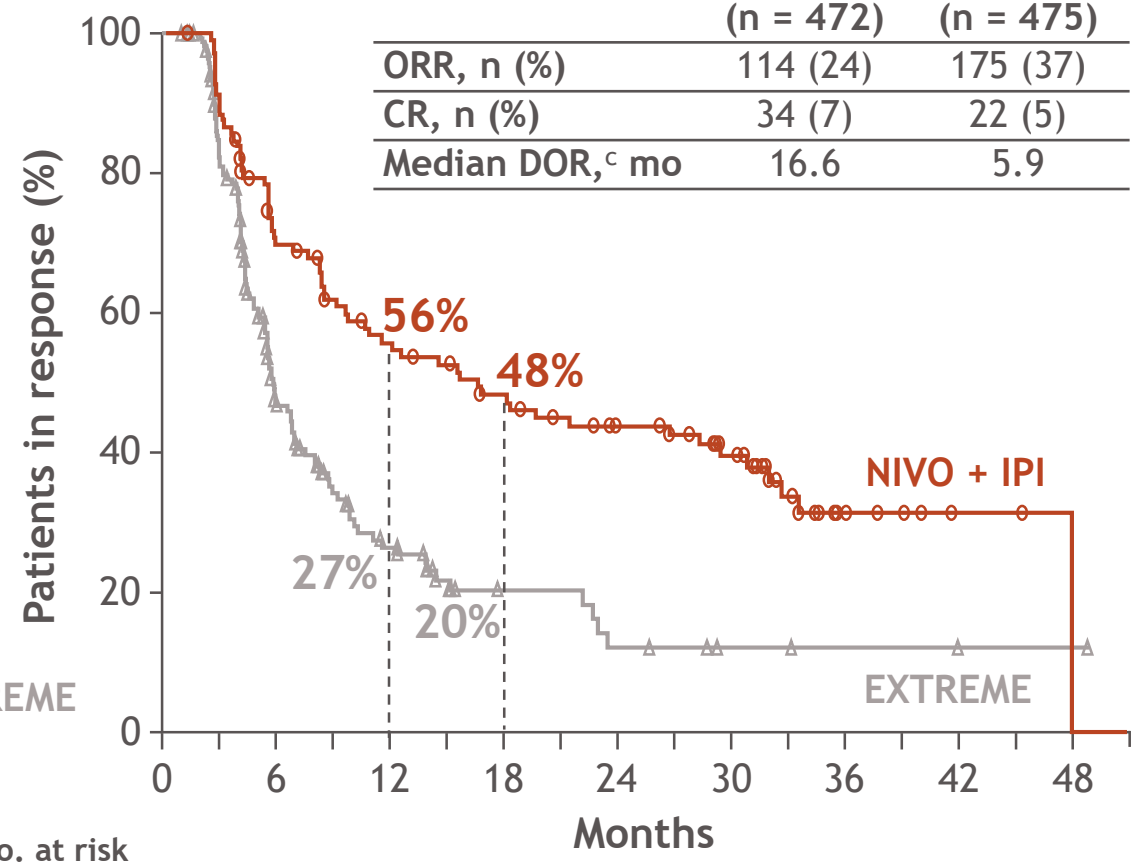
	NIVO + IPI (n = 472)	EXTREME (n = 475)
Median PFS,[b] mo	3.3	6.7
HR (95% CI)	1.41 (1.21–1.65)	



No. at risk										
NIVO + IPI	472	142	76	55	42	35	14	5	1	0
EXTREME	475	178	59	24	18	8	4	3	2	0

ORR[a] and DOR[a]

	NIVO + IPI (n = 472)	EXTREME (n = 475)
ORR, n (%)	114 (24)	175 (37)
CR, n (%)	34 (7)	22 (5)
Median DOR,[c] mo	16.6	5.9



No. at risk										
NIVO + IPI	114	73	54	44	35	26	8	3	0	0
EXTREME	175	62	26	10	6	3	2	1	1	0

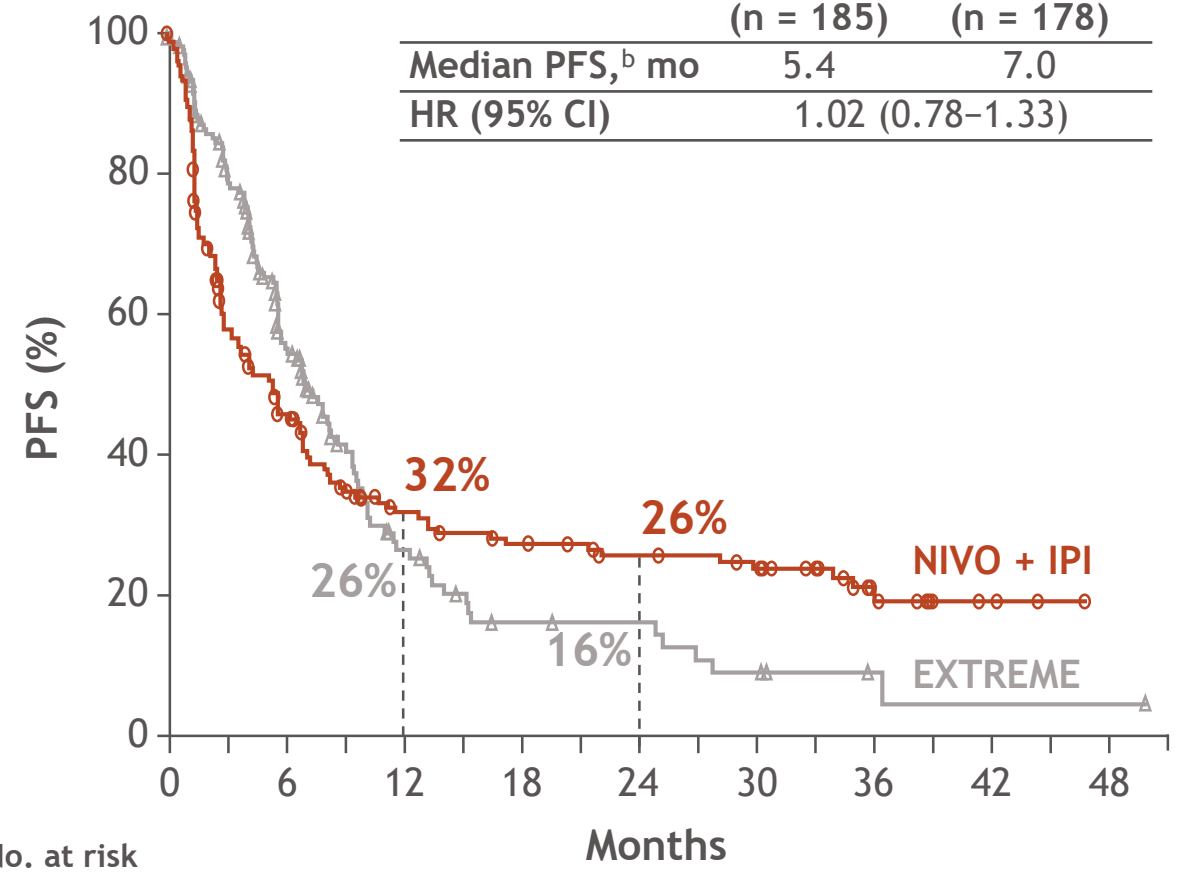
Minimum follow-up: 27.3 months.

[a]Per BICR; [b]95% CI = 2.8–4.2 (NIVO + IPI) and 5.8–7.0 (EXTREME); [c]95% CI = 9.7–29.4 (NIVO + IPI) and 5.4–7.0 (EXTREME). BICR, blinded independent central review; CR, complete response; DOR, duration of response; ORR, objective response rate.

Efficacy in PD-L1 CPS ≥20 population

PFS[a]

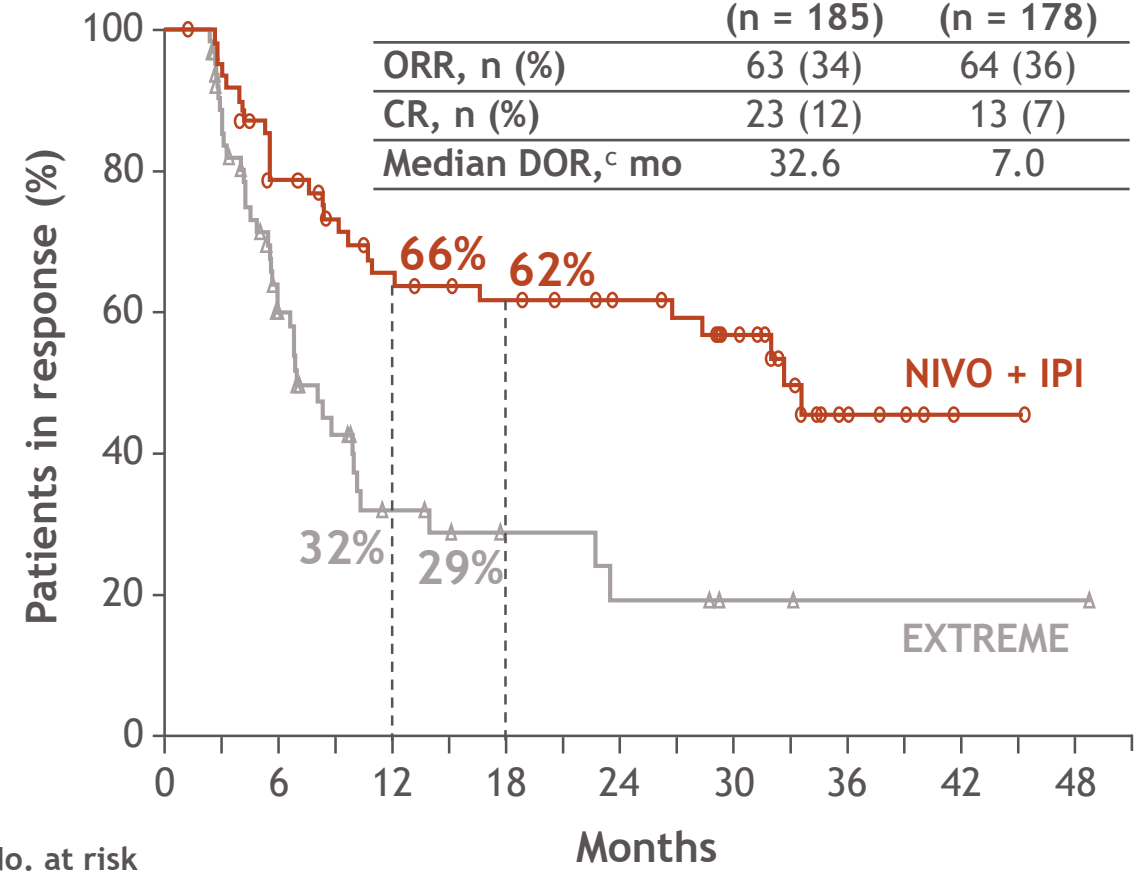
	NIVO + IPI (n = 185)	EXTREME (n = 178)
Median PFS,[b] mo	5.4	7.0
HR (95% CI)	1.02 (0.78–1.33)	



No. at risk										
NIVO + IPI	185	73	43	35	29	25	11	4	0	0
EXTREME	178	70	22	10	9	5	2	1	1	0

ORR[a] and DOR[a]

	NIVO + IPI (n = 185)	EXTREME (n = 178)
ORR, n (%)	63 (34)	64 (36)
CR, n (%)	23 (12)	13 (7)
Median DOR,[c] mo	32.6	7.0



No. at risk										
NIVO + IPI	63	46	34	30	26	20	7	2	0	0
EXTREME	64	30	11	6	4	2	1	1	1	0

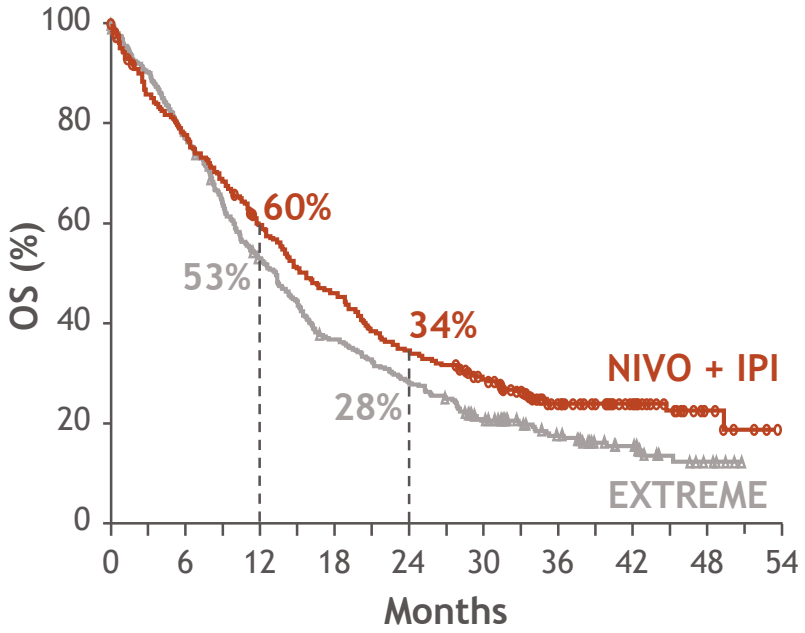
Minimum follow-up: 27.3 months.

[a]Per BICR; [b]95% CI = 3.1–6.9 (NIVO + IPI) and 5.6–8.7 (EXTREME); [c]95% CI = 12.1–NR (NIVO + IPI) and 5.6–10.1 (EXTREME). BICR, blinded independent central review; CR, complete response; DOR, duration of response; ORR, objective response rate.

Efficacy in PD-L1 CPS ≥1 population

OS (secondary endpoint)

	NIVO + IPI (n = 355)	EXTREME (n = 372)
Median OS,[b] mo	15.7	13.2
HR (95% CI)	0.82 (0.69–0.97)	

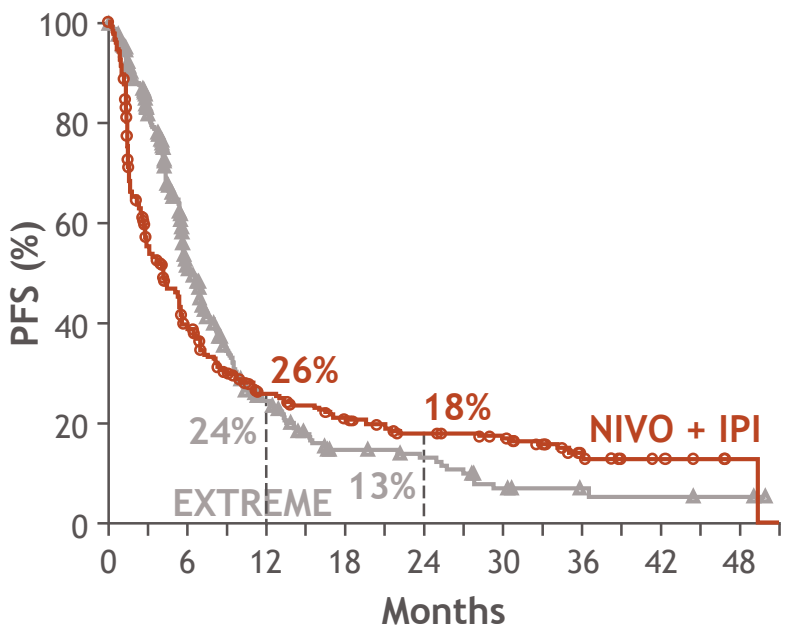


No. at risk

NIVO + IPI	355	271	206	158	118	92	49	27	8	0
EXTREME	372	280	189	130	99	66	39	20	6	0

PFS[a]

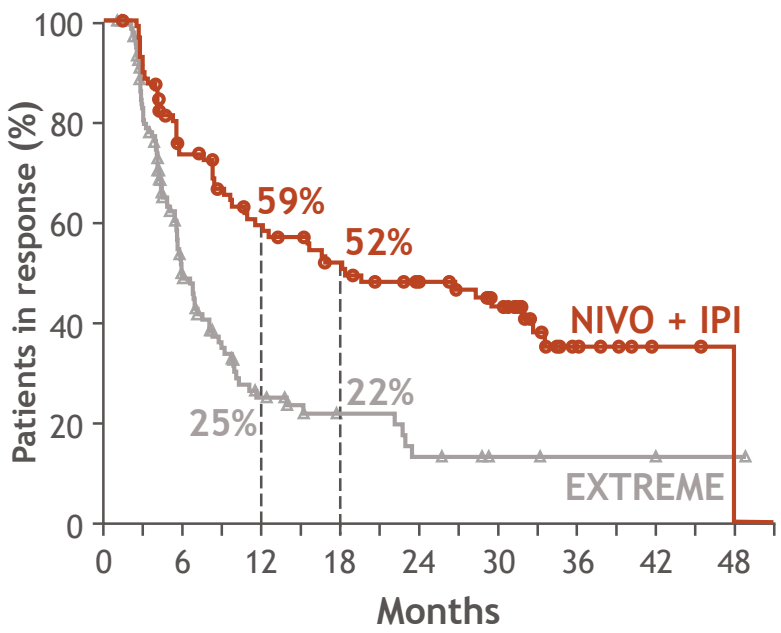
	NIVO + IPI (n = 355)	EXTREME (n = 372)
Median PFS,[c] mo	4.2	6.1
HR (95% CI)	1.23 (1.03–1.47)	



NIVO + IPI	355	120	67	51	38	32	12	5	1	0
EXTREME	372	131	46	20	16	7	4	3	2	0

ORR[a] and DOR[a]

	NIVO + IPI (n = 355)	EXTREME (n = 372)
ORR,[a] n (%)	98 (28)[d]	133 (36)[e]
Median DOR,[f] mo	18.3	6.0



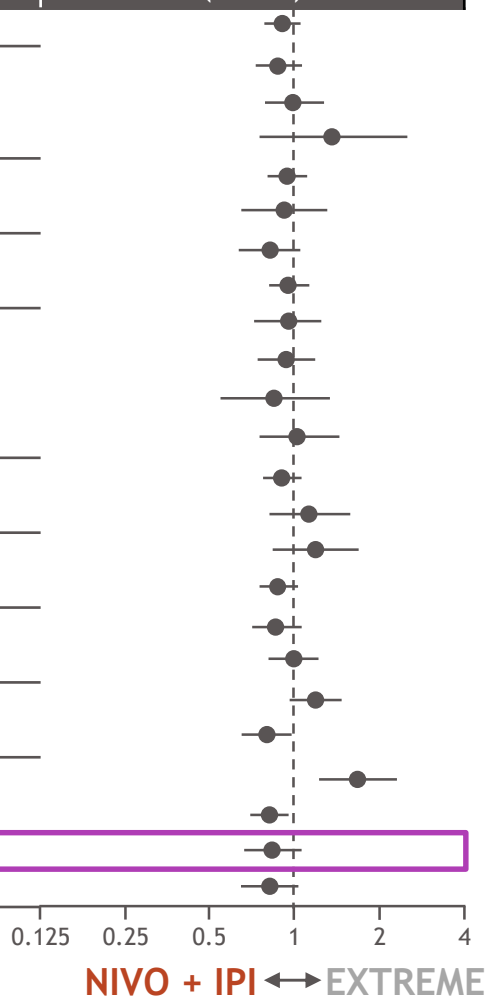
NIVO + IPI	98	66	49	40	32	24	8	3	0	0
EXTREME	133	50	19	10	6	3	2	1	1	0

Minimum follow-up: 27.3 months.

[a]Per BICR; [b]95% CI = 13.7–18.8 (NIVO + IPI) and 11.1–14.6 (EXTREME); [c]95% CI = 2.9–5.4 (NIVO + IPI) and 5.6–7.0 (EXTREME); [d]CR rate = 8%; [e]CR rate = 5%; [f]95% CI = 10.9–32.6 (NIVO + IPI) and 5.6–7.6 (EXTREME). BICR, blinded independent central review; CR, complete response; DOR, duration of response; ORR, objective response rate.

OS subgroup analysis: all randomized patients

Subgroup	Median OS, mo		Unstratified hazard ratio
	NIVO + IPI (n = 472)	EXTREME (n = 475)	
All randomized (N = 947)	13.9	13.5	0.94[a]
<65 years (n = 605)	14.8	13.8	0.88
≥65 and <75 years (n = 285)	12.1	12.3	0.99
≥75 years (n = 57)	16.0	23.1	1.37
Male (n = 777)	14.2	14.0	0.95
Female (n = 170)	11.6	11.6	0.91
ECOG PS 0 (n = 325)	20.1	18.1	0.83
ECOG PS ≥1 (n = 621)	10.7	11.1	0.97
Oral cavity (n = 259)	10.9	12.9	0.94
Oropharynx (n = 396)	16.0	15.0	0.93
Hypopharynx (n = 101)	13.4	12.5	0.84
Larynx (n = 190)	15.0	13.3	1.02
Current or former smoker (n = 729)	14.2	13.4	0.91
Never smoker (n = 186)	11.4	14.3	1.13
OPC p16+ (n = 186)[b]	**19.8**	**23.8**	**1.19**
OPC p16− or non-OPC (n = 761)[b]	**13.1**	**12.6**	**0.89**
Prior chemotherapy (n = 474)[b]	**14.2**	**14.2**	**0.87**
No prior chemotherapy (n = 473)[b]	**13.5**	**13.5**	**1.00**
Tumor PD-L1 <1% or non-evaluable (n = 401)[b]	**11.7**	**15.5**	**1.18**
Tumor PD-L1 ≥1% (n = 546)[b]	**15.8**	**12.8**	**0.80**
PD-L1 CPS <1 (n = 178)	7.9	17.7	1.66
PD-L1 CPS ≥1 (n = 727)	15.7	13.2	0.81[c]
PD-L1 CPS 1–19 (n = 364)	14.5	11.2	0.83
PD-L1 CPS ≥20 (n = 363)	17.6	14.6	0.81[d]

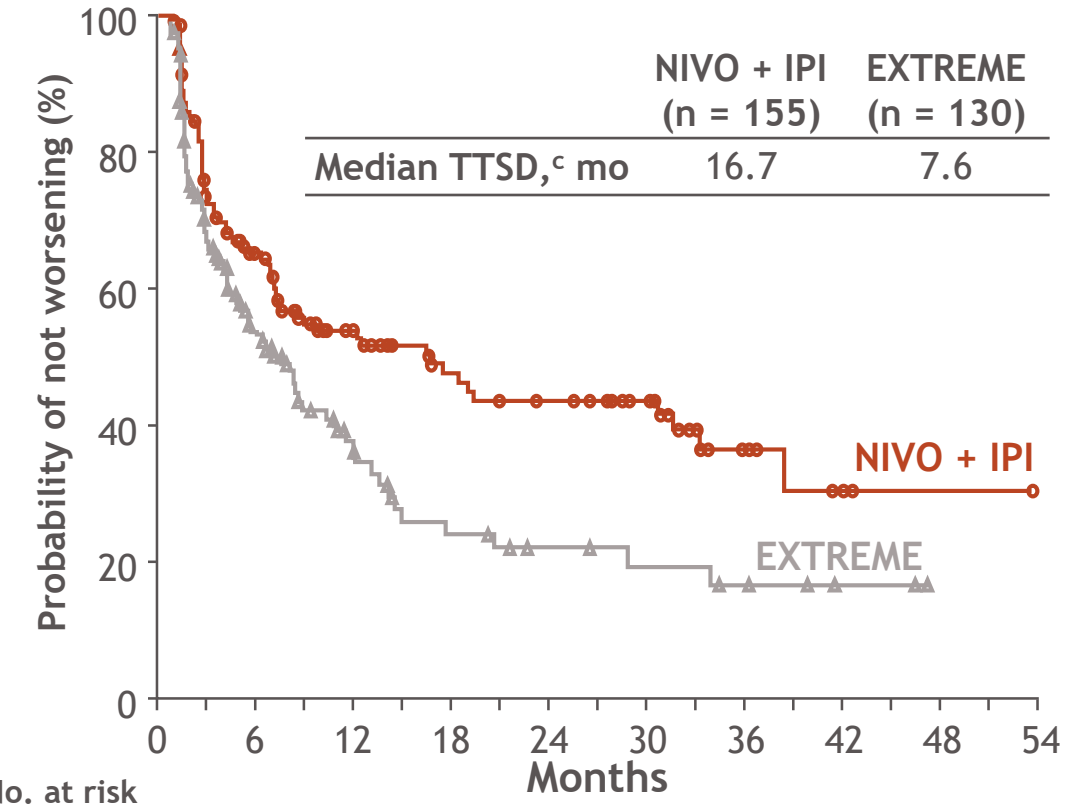


Minimum follow-up: 27.3 months.

Bold text indicates study stratification factors. [a]Stratified HR, 0.95; [b]Per interactive response technology; [c]Stratified HR, 0.82; [d]Stratified HR, 0.78. CPS, combined positive score; OPC, oropharyngeal cancer.

Patient-reported outcomes: PD-L1 CPS ≥20 population

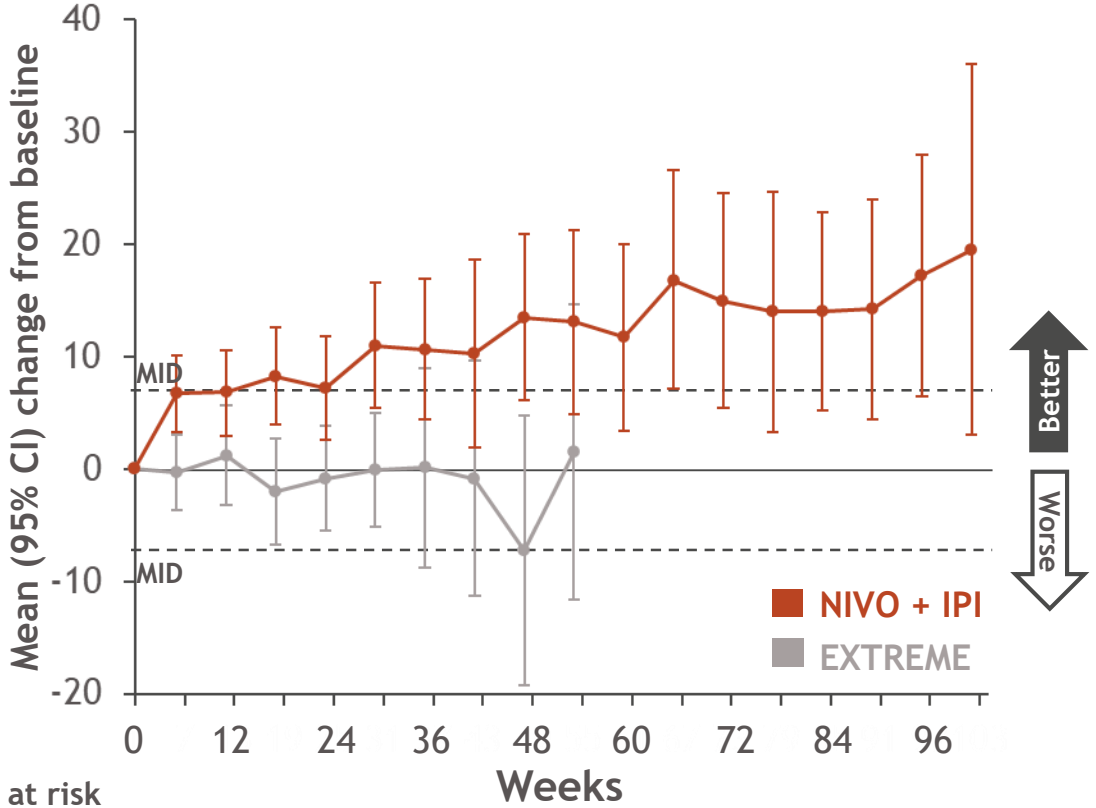
Time to symptom deterioration[a] (FHNSI-10)[b,1]



	NIVO + IPI (n = 155)	EXTREME (n = 130)
Median TTSD,[c] mo	16.7	7.6

No. at risk										
NIVO + IPI	155	81	49	35	30	24	9	4	1	0
EXTREME	130	48	22	13	9	7	5	2	0	0

Overall self-rated health status (EQ-5D-3L VAS)[d,2]



No. at risk										
NIVO + IPI	152	99	65	51	38	30	26	26	18	
EXTREME	129	82	54	27	15	8	7	4	4	

Completion rates at baseline were 92% vs 81% in the NIVO + IPI and EXTREME arms, respectively; [a]Time to symptom deterioration is defined as time from randomization to first clinically meaningful decline (reduction of ≥3 points) from baseline in FHNSI-10 score; [b]FHNSI-10 assesses the effects of disease symptoms on functioning and well-being using a 10-item index (pain, lack of energy, swallowing, pain in mouth/throat/neck, trouble breathing, ability to communicate, nausea, eating solid foods, worry about condition worsening, contentedness with quality of life); [c]95% CI = 7.4–31.6 (NIVO + IPI) and 4.3–10.9 (EXTREME); [d]EQ-5D-3L VAS records self-reported health status on a 100-point VAS; 7-point change is a MID; only on-treatment time points with data for ≥10 patients in either treatment group are shown; not adjusted for multiplicity. 1. Yount S, et al. *Qual Life Res* 2007;16:1615-1626; 2. Pickard AS, et al. *Health Qual Life* 2007;5:70. CPS, combined positive score; EQ-5D-3L VAS, EuroQol five dimension visual analog scale; FHNSI-10, Functional Assessment of Cancer Therapy Head & Neck Cancer Symptom 10-Item Index; MID, minimally important difference; TTSD, time to symptom deterioration.

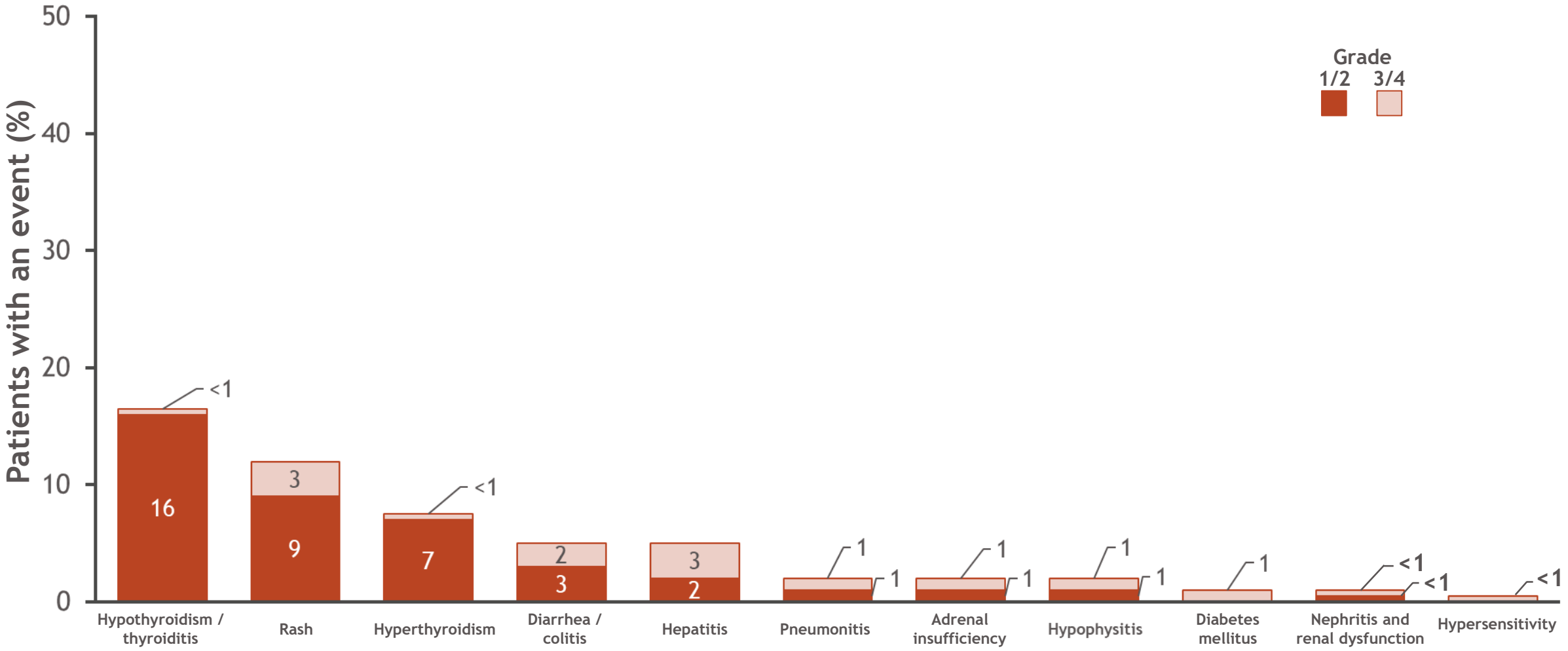
Safety and exposure summary in all treated patients

TRAE, %	NIVO + IPI (n = 468)		EXTREME (n = 441)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAEs	72	28	98	71
TRAEs leading to discontinuation of any component of the regimen	12[a]	10	13	9
Serious TRAEs	16	12	28	24
Treatment-related deaths	1[b]		2[c]	

- Median (range) duration of therapy was 3.8 (<0.1–24.0) months in the NIVO + IPI arm vs 5.0 (<0.1–50.7) months in the EXTREME arm
- Patients in the NIVO + IPI arm received a median (range) of 8 (1–53) doses of NIVO and 3 (1–18) doses of IPI

[a]Treatment-related AEs led to discontinuation of IPI treatment only in 22 patients; [b]2 due to pneumonitis, 2 due to hepatitis, 1 due to tumor lysis syndrome, and 1 due to disseminated intravascular coagulation; [c]5 due to sepsis, 2 due to pneumonia, and 1 due to acute respiratory syndrome. TRAE, treatment-related adverse event.

Immune-mediated AEs[a] with NIVO + IPI



[a]Events in all treated patients; immune-mediated AEs are specific events, regardless of causality and occurring within 100 days of last dose of study drug, for which patients received immunosuppressive medication for treatment of the event, with the exception of endocrine events, which are included regardless of treatment since these events are often managed without immunosuppression.

Summary: NIVO + IPI vs EXTREME

- In CheckMate 651, there was no statistical improvement in OS with NIVO + IPI vs EXTREME in all randomized (HR: 0.95; *P* = 0.4951) as 1L treatment of R/M SCCHN
  - OS in the EXTREME control arm was better than expected based on historical data
- In patients with PD-L1 CPS ≥20 or CPS ≥1, NIVO + IPI showed evidence of clinical benefit vs EXTREME as seen with prolonged OS and durable responses
  - Median OS: 17.6 vs 14.6 months (CPS ≥20) and 15.7 vs 13.2 months (CPS ≥1), respectively
  - With NIVO + IPI, more than half of responders were still in response at 18 months in both populations
- NIVO + IPI tended to delay symptom deterioration and clinically improved overall health status vs EXTREME in the CPS ≥20 population
- NIVO + IPI had a favorable safety profile vs EXTREME; no new safety signals were observed


ANY
QUESTIONS

Thank You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