Sociedad Andaluza de Oncología Medica

III REUNIÓN DE TRABAJO

EN CÁNCER DE CABEZA Y CUELLO

Lunes 22 de marzo de 2021

EXTREME versus QT + Pembro en CPS 1-20

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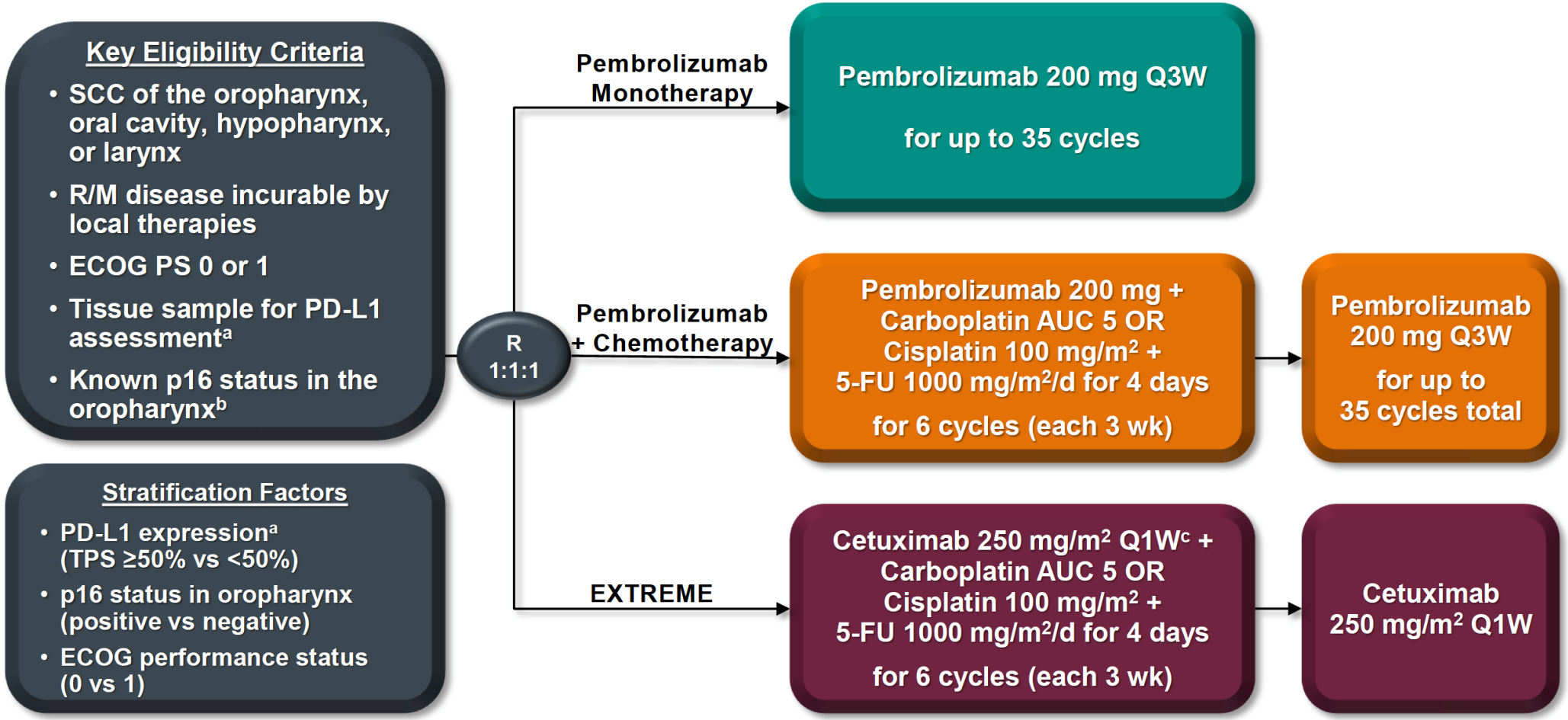
KEYNOTE 048: study design



Burtness B et al. Lancet 2019

KEYNOTE 048: TPS vs CPS

OS and PFS for the total population, **CPS ≥ 20, CPS ≥ 1**

TPS (Tumor Proportion Score)

$$\text{TPS} = \frac{\text{Number of PD-L1 stained } \textbf{tumor cells}}{\text{Total number of viable tumor cells}} \times 100$$

*Reported as a **percentage***

CPS (Combined Positive Score)

$$\text{CPS} = \frac{\text{Number of PD-L1 stained } \textbf{cells} \text{ (tumor cells, lymphocytes, macrophages)}}{\text{Total number of viable tumor cells}} \times 100$$

*Reported as a **number** (capped at 100)*

Burtness B et al. Lancet 2019

Study End Points: Pembrolizumab vs EXTREME and Pembrolizumab + Chemotherapy vs EXTREME

Primary

- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - OS
  - PFS[b]

Secondary

- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - PFS[b] rates at 6 and 12 mo
  - ORR[b]
  - Change from baseline and time to deterioration in quality of life (EORTC QLQ-C30 and H&N-35)[c]
- Total population
  - Safety and tolerability

Key Exploratory

- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - Duration of response[b]

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay. CPS = combined positive score = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
[b]Assessed per RECIST v1.1 by blinded, independent central review.
[c]To be presented at a later date.

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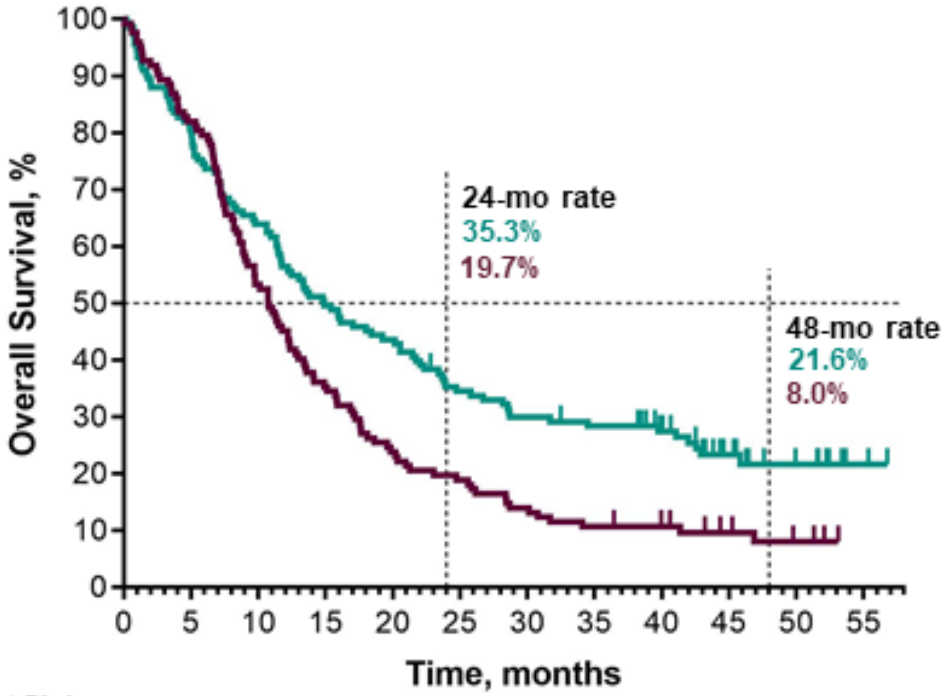
OS: Pembrolizumab vs EXTREME

PD-L1 CPS ≥20

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembrolizumab	75.9%	14.9 (11.5-20.6)	0.61 (0.46-0.81)	0.00034
EXTREME	91.0%	10.8 (8.8-12.8)		

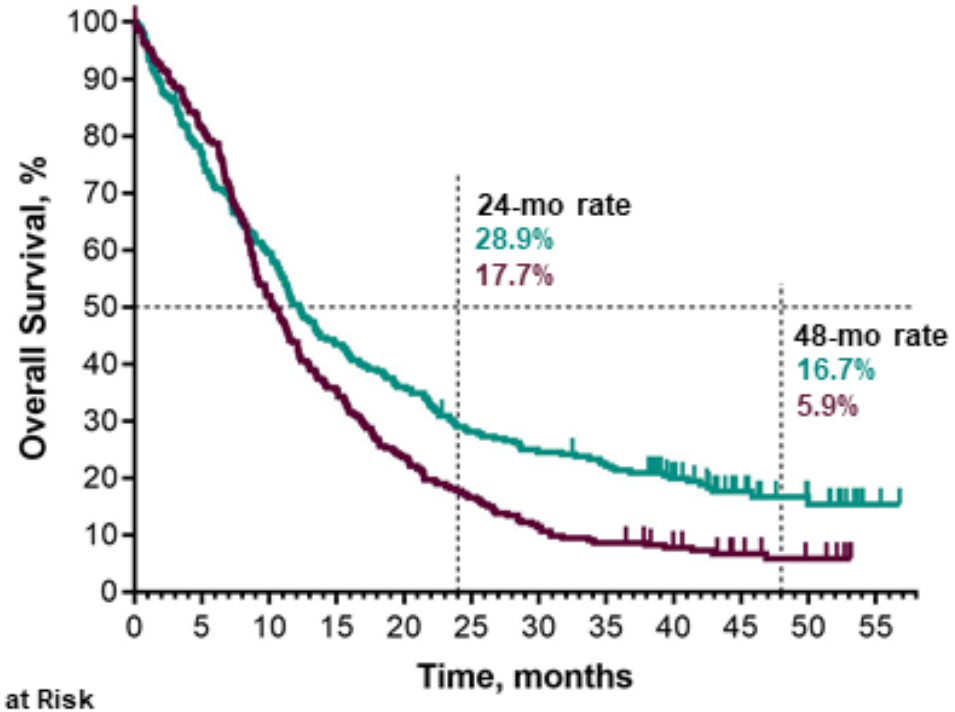


No. at Risk

Pembro	133	107	85	66	58	45	39	36	30	17	9	2
EXTREME	122	100	65	43	29	23	17	13	11	7	4	0

PD-L1 CPS ≥1

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembrolizumab	81.7%	12.3 (10.8-14.8)	0.71 (0.61-0.89)	0.00080
EXTREME	92.9%	10.4 (9.0-11.7)		



No. at Risk

Pembro	257	197	152	111	92	71	62	55	40	22	12	2
EXTREME	255	207	132	90	60	42	29	22	16	10	6	0

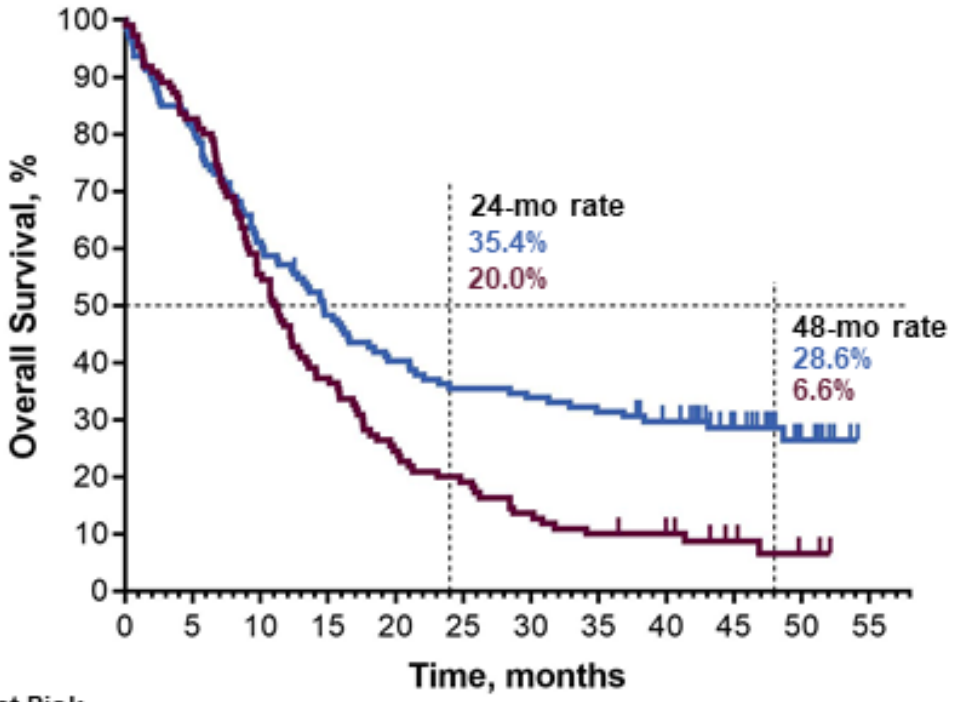
CI, confidence interval; HR, hazard ratio.

[a]Nominal, unadjusted one-sided *P* value based on log-rank test. Data cutoff: February 18, 2020.

OS: Pembrolizumab + Chemo vs EXTREME

PD-L1 CPS ≥20

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembro + Chemo	71.4%	14.7 (10.3-19.3)	0.62 (0.46-0.84)	0.00082
EXTREME	91.8%	11.1 (9.2-13.0)		

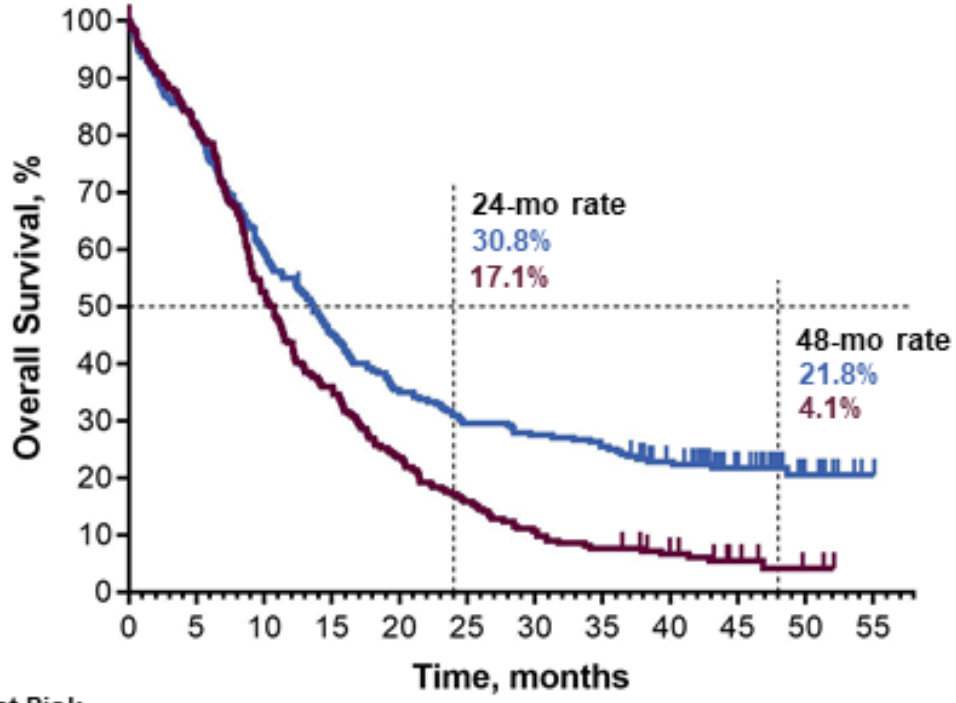


No. at Risk

Pembro + Chemo	126	102	77	60	50	44	42	39	33	22	7	0
EXTREME	110	91	61	41	27	21	15	11	9	5	2	0

PD-L1 CPS ≥1

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembro + Chemo	78.1%	13.6 (10.7-15.5)	0.64 (0.53-0.78)	0.00001
EXTREME	94.0%	10.6 (9.1-11.7)		



No. at Risk

Pembro + Chemo	242	197	144	109	84	71	66	61	48	29	9	1
EXTREME	235	191	123	84	55	37	25	18	12	6	2	0

[a]Nominal, unadjusted one-sided p-value based on log-rank test. Data cutoff: February 18, 2020.

Safety and Summary

Safety

TRAEs	Pembro (n = 300)	EXTREME (n = 287)
Any grade	58.3%	96.9%
Grades 3-5	17.0%	69.3%

TRAEs	Pembro + Chemo (n = 276)	EXTREME (n = 287)
Any grade	95.7%	96.9%
Grades 3-5	71.7%	69.3%

Summary

- Long-term follow-up confirmed statistically significant improvement in OS for
  - Pembrolizumab vs EXTREME in PD-L1 CPS ≥20 and CPS ≥1 populations; and
  - Pembrolizumab + chemotherapy vs EXTREME in PD-L1 CPS ≥20, CPS ≥1, and total populations
- DOR with pembrolizumab or pembrolizumab + chemotherapy remained longer than with EXTREME
- Safety was also favorable for pembrolizumab vs EXTREME and comparable for pembrolizumab + chemotherapy vs EXTREME

TRAE, treatment-related adverse event.
Data cutoff: February 18, 2020.

Incertidumbres

- Este ensayo cambia la práctica clínica
- No se analizan los resultados por subgrupos
  - CPS < 1
  - CPS 1-19
- No se tiene en cuenta la necesidad de una respuesta tumoral

9582

Efficacy of First-Line Pembrolizumab by PD-L1 Combined Positive Score <1, 1-19, and ≥20 in Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: KEYNOTE-048 Subgroup Analysis

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Background

- Immune exhaustion through activation of the PD-1 pathway contributes to head and neck cancer disease progression[1,2]
- PD-L1 is often overexpressed in head and neck squamous cell carcinoma (HNSCC), on both tumor and immune cells[2,3,4]
- Agents targeting PD-1, the receptor for PD-L1, such as pembrolizumab and nivolumab, provide antitumor activity and are tolerable in many cancers, including HNSCC[5,6]
- Combined positive score (CPS), an integrated measure of PD-L1 expression on tumor and immune cells, is a predictive biomarker for pembrolizumab activity[7]
- The phase 3 KEYNOTE-048 trial (NCT02358031) of pembrolizumab in patients with recurrent or metastatic (R/M) HNSCC included planned efficacy analyses in the total study population, as well as in PD-L1–enriched subpopulations[8]
  - First-line pembrolizumab monotherapy versus EXTREME (cetuximab + 5-fluorouracil + platinum-based agent) showed significant overall survival (OS) benefit in the PD-L1 CPS ≥20 and CPS ≥1 subpopulations, noninferior OS in the total study population, substantially longer duration of response (DOR) in all populations, and a favorable safety profile (Table 1)
  - First-line pembrolizumab combined with chemotherapy versus EXTREME had superior OS benefit in the PD-L1 CPS ≥20 and CPS ≥1 subpopulations and the total study population, as well as longer DOR with comparable safety

Table 1. Summary of Efficacy in the PD-L1 CPS ≥20, PD-L1 CPS ≥1, and Total Study Populations[8,9]

Population	Pembrolizumab vs EXTREME		Pembrolizumab + Chemotherapy vs EXTREME	
	Pembrolizumab	EXTREME	Pembrolizumab + Chemotherapy	EXTREME
PD-L1 CPS ≥20				
OS, median, months	14.9	10.7	14.7	11.0
HR (95% CI)	0.59 (0.44-0.78)		0.60 (0.45-0.82)	
DOR, median (95% CI), months	22.6 (11.0-NR)	4.2 (3.1-5.7)	7.1 (5.6-11.0)	4.2 (2.9-5.7)
PD-L1 CPS ≥1				
OS, median, months	12.3	10.3	13.6	10.4
HR (95% CI)	0.74 (0.61-0.90)		0.65 (0.53-0.80)	
DOR, median (95% CI), months	23.4 (14.9-NR)	4.5 (4.1-5.6)	6.7 (5.6-8.3)	4.3 (4.1-5.4)
Total study				
OS, median, months	11.5	10.7	13.0	10.7
HR (95% CI)	0.83 (0.70-0.98)		0.72 (0.60-0.87)	
DOR, median (95% CI), months	22.6 (14.9-NR)	4.5 (4.1-5.7)	6.7 (5.6-8.2)	4.3 (4.1-5.6)

HR, hazard ratio; NR, not reached.
[9]Data are from the final analysis data cutoff of February 25, 2019.

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- Outcomes in KEYNOTE-048 PD-L1 CPS <1 and CPS 1-19 subgroups were not prospectively defined end points
  - Post hoc analyses of efficacy are presented

Objective

- To evaluate the efficacy of pembrolizumab monotherapy versus EXTREME and of pembrolizumab + chemotherapy versus EXTREME in patients with R/M HNSCC with PD-L1 CPS <1, CPS 1-19, and CPS ≥20

Methods

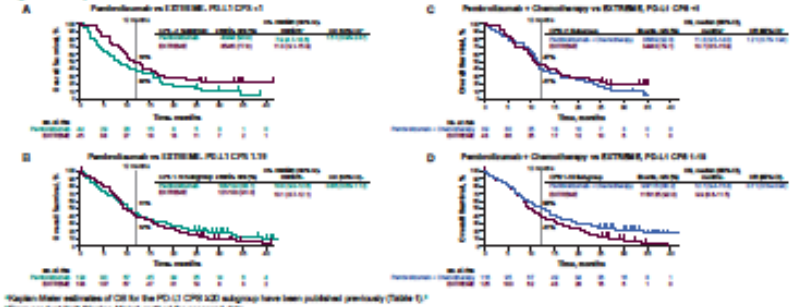
- KEYNOTE-048 was an open-label, phase 3 study in which patients with previously untreated R/M HNSCC were randomly assigned 1:1:1 to receive pembrolizumab, pembrolizumab + chemotherapy, or EXTREME
  - Randomization was stratified by the percentage of PD-L1–expressing tumor cells (≥50% vs <50%), p16 status for oropharyngeal cancers (positive vs negative; nonoropharyngeal tumors were considered p16 negative), and Eastern Cooperative Oncology Group performance score (0 vs 1)
- Primary end points were OS and progression-free survival (PFS) in the pembrolizumab versus EXTREME and pembrolizumab + chemotherapy versus EXTREME arms in the PD-L1 CPS ≥20, PD-L1 CPS ≥1, and total populations
- Secondary end points included safety and objective response rate (ORR)
- PFS, ORR, and DOR were assessed per RECIST v1.1 by blinded independent central review
- CPS was calculated as the number of PD-L1–positive cells (tumor, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100
  - A minimum of 100 viable tumor cells must have been present for the specimen to be considered evaluable
- HRs and 95% CIs for OS and PFS were estimated using a stratified Cox proportional hazards model with the Efron method of tie handling (stratified by the randomization stratification factors for the PD-L1 CPS ≥20 population, and unstratified for the PD-L1 CPS <1 and PD-L1 CPS 1-19 subgroups)
- Data cutoff was February 25, 2019

Results

- Median time from randomization to data cutoff was 33.3 months (range, 25.3-45.7 months) for pembrolizumab versus EXTREME and 32.7 months (range, 25.3-48.3 months) for pembrolizumab + chemotherapy versus EXTREME
- Baseline characteristics in the PD-L1 CPS<1, CPS 1-19, and CPS ≥20 subgroups were similar to those of the overall study population[8] and similar across treatment arms
- The most frequent reason for discontinuation across all subgroups was progressive disease

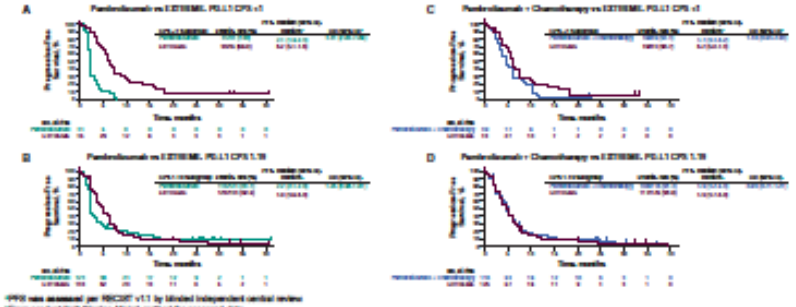
Efficacy

Figure 1. Kaplan-Meier Estimates of Overall Survival[a]



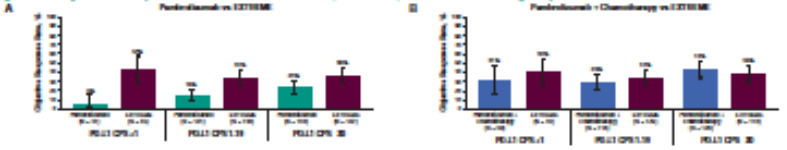
[a]Kaplan-Meier estimates of OS for the PD-L1 CPS ≥20 subgroup have been published previously (Table 1).[8]
[b]From product-limit (Kaplan-Meier) method for censored data.
[c]Based on a Cox proportional hazards model with the Efron method of tie handling with treatment as a covariate.

Figure 2. Kaplan-Meier Estimates of Progression-Free Survival[a]



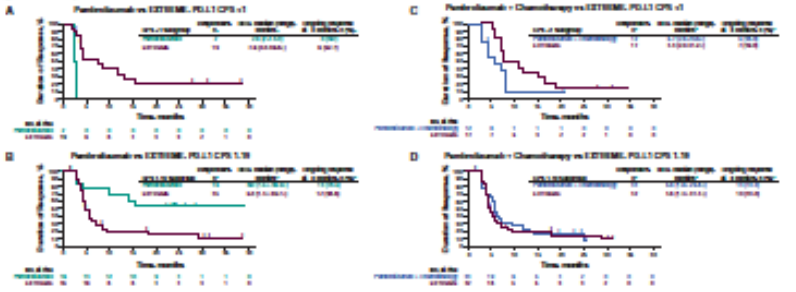
[a]PFS was assessed per RECIST v1.1 by blinded independent central review.
[b]From product-limit (Kaplan-Meier) method for censored data.
[c]Based on a Cox proportional hazards model with the Efron method of tie handling with treatment as a covariate.

Figure 3. Objective Response Rate[a] in PD-L1 CPS <1, CPS 1-19, and CPS ≥20 Subgroups



[a]Assessed per RECIST v1.1 by blinded independent central review.

Figure 4. Kaplan-Meier Estimates of DOR[a,b] in Patients With Confirmed Response



[a]Assessed per RECIST v1.1 by blinded independent central review.
[b]Kaplan-Meier estimates of DOR for the PD-L1 CPS ≥20 population have been published previously.[8]
[c]Includes patients with confirmed complete response or partial response.
[d]From product-limit (Kaplan-Meier) method for censored data.

Conclusions

- Overall, the results of this post hoc analysis showed increased efficacy of pembrolizumab and pembrolizumab + chemotherapy with increasing PD-L1 expression
- In the CPS 1-19 subgroup, OS results with pembrolizumab + chemotherapy versus EXTREME were consistent with treatment benefit
- Analysis of the CPS <1 subgroup was limited by small patient numbers
- Future exploratory analyses of tumor mutational burden and inflamed signatures could be used to further evaluate predictors of benefit in patients with low PD-L1–expressing HNSCC

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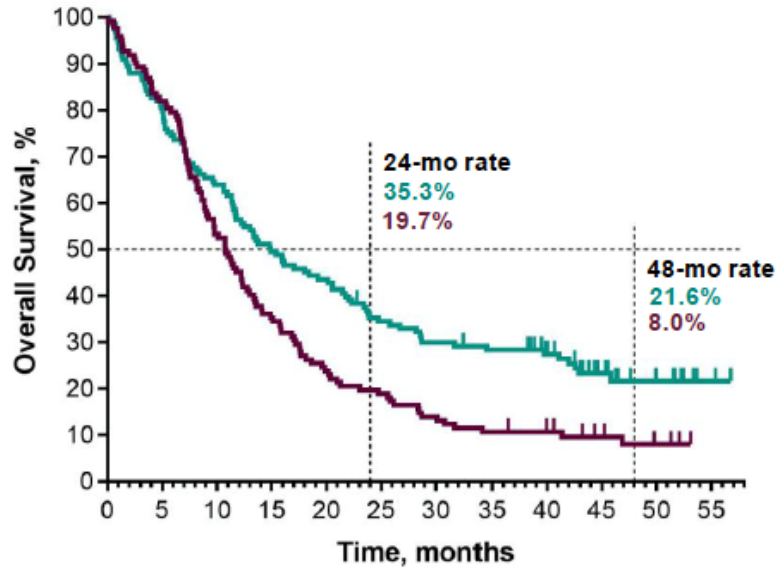
Análisis por subgrupos

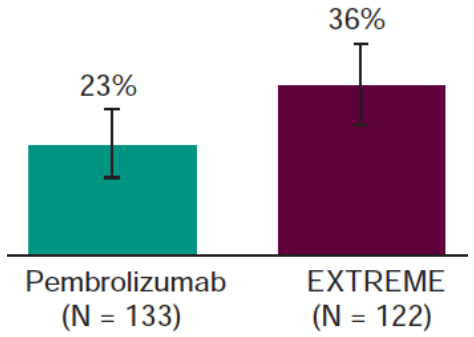
- CPS ≥ 20
- CPS 1-19
- CPS < 1

CPS ≥ 20

Pembrolizumab vs EXTREME

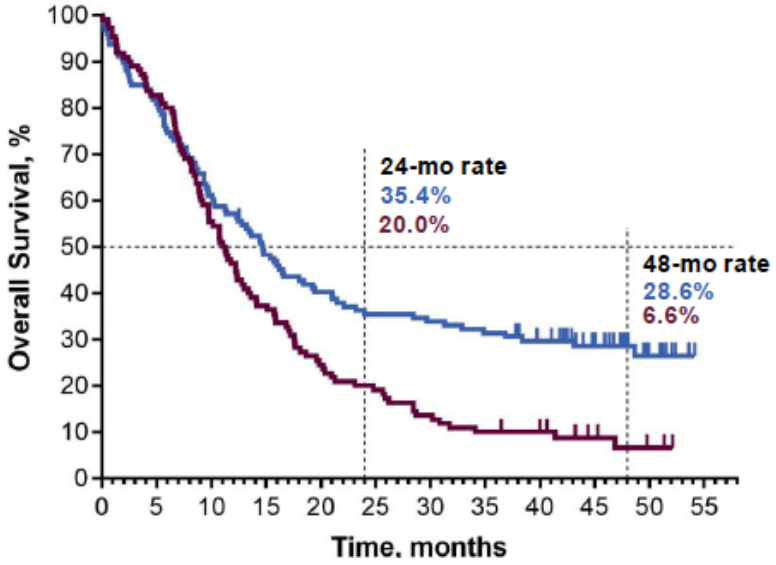
	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembrolizumab	75.9%	14.9 (11.5-20.6)	0.61 (0.46-0.81)	0.00034
EXTREME	91.0%	10.8 (8.8-12.8)		

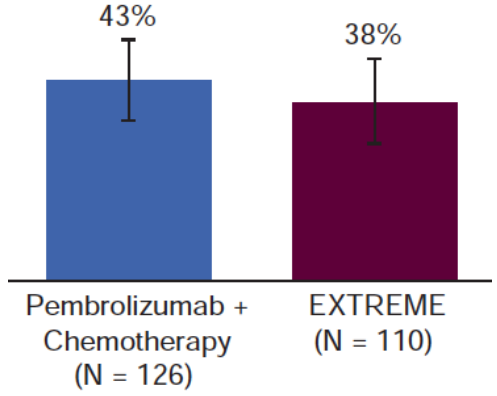




Pembrolizumab + Chemo vs EXTREME

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembro + Chemo	71.4%	14.7 (10.3-19.3)	0.62 (0.46-0.84)	0.00082
EXTREME	91.8%	11.1 (9.2-13.0)		





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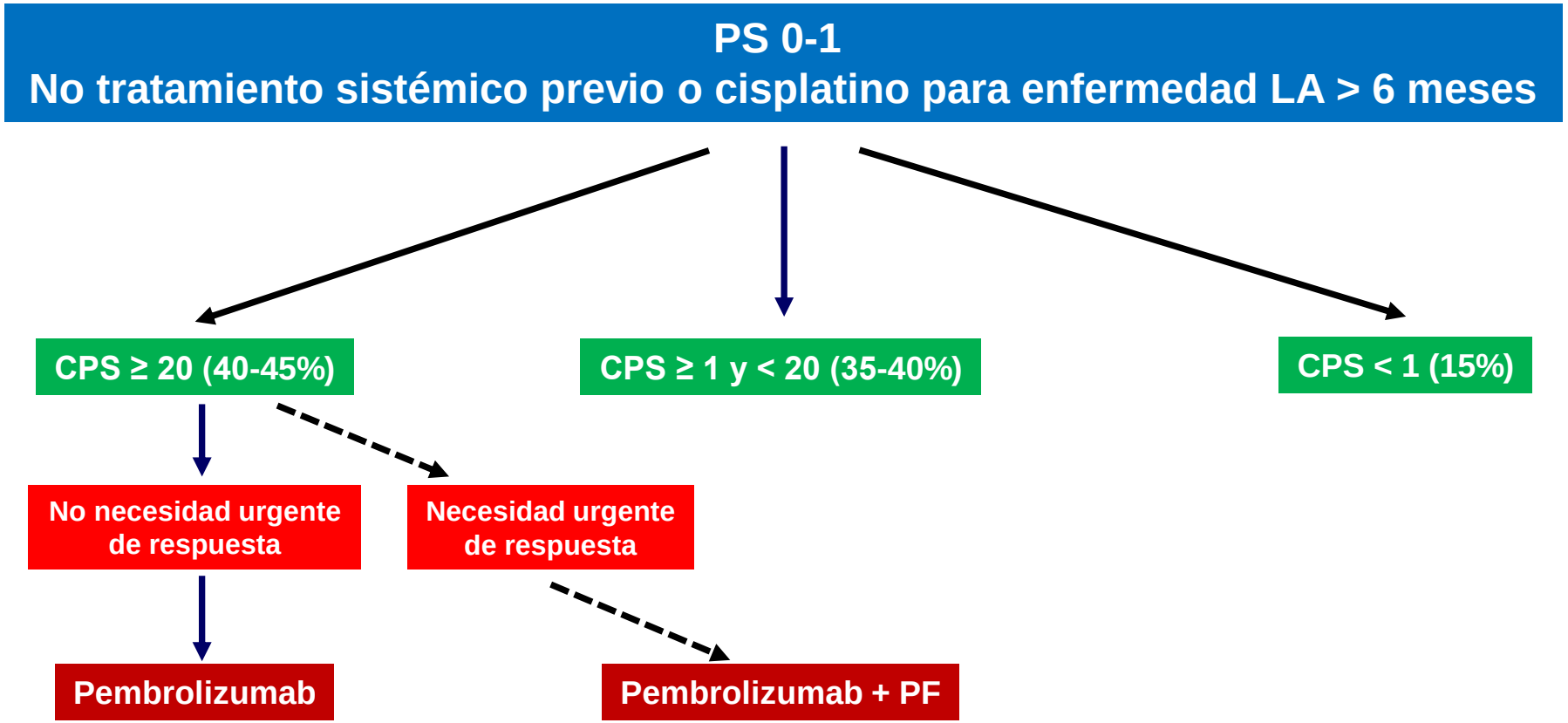

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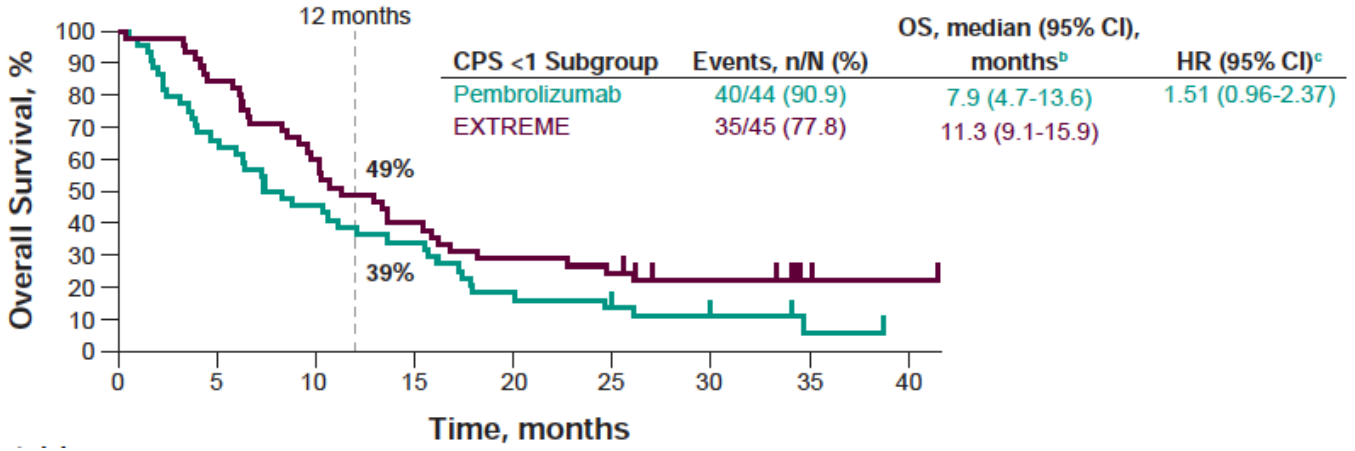
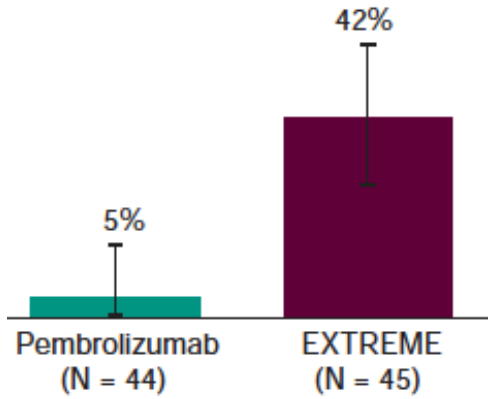
CPS < 1

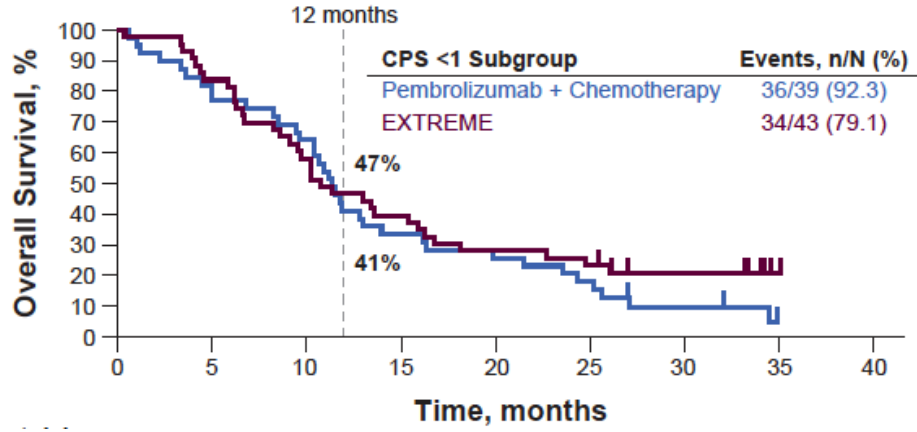
Pembrolizumab vs EXTREME



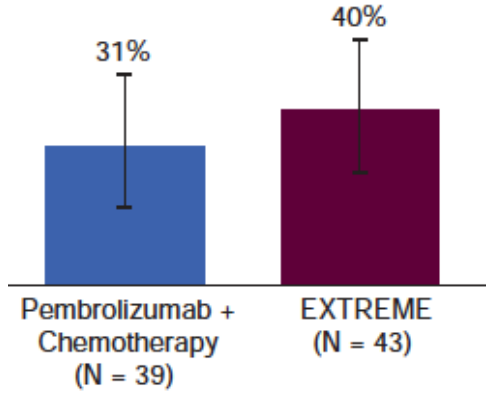
CPS <1 Subgroup	Events, n/N (%)	OS, median (95% CI), months[b]	HR (95% CI)[c]
Pembrolizumab	40/44 (90.9)	7.9 (4.7-13.6)	1.51 (0.96-2.37)
EXTREME	35/45 (77.8)	11.3 (9.1-15.9)	



Pembrolizumab + Chemo vs EXTREME



CPS <1 Subgroup	Events, n/N (%)	OS, median (95% CI), months[b]	HR (95% CI)[c]
Pembrolizumab + Chemotherapy	36/39 (92.3)	11.3 (9.5-14.0)	1.21 (0.76-1.94)
EXTREME	34/43 (79.1)	10.7 (8.5-15.9)	



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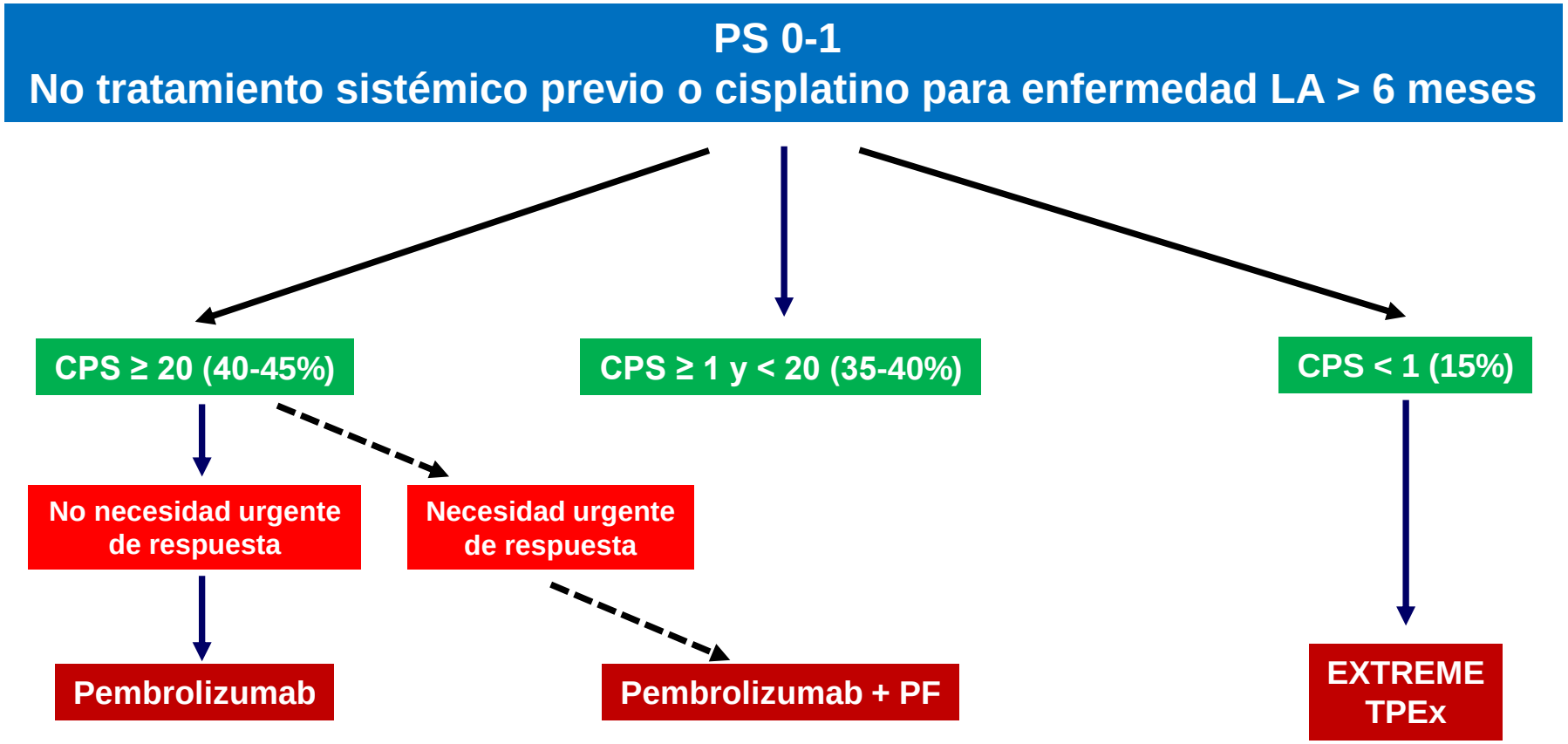

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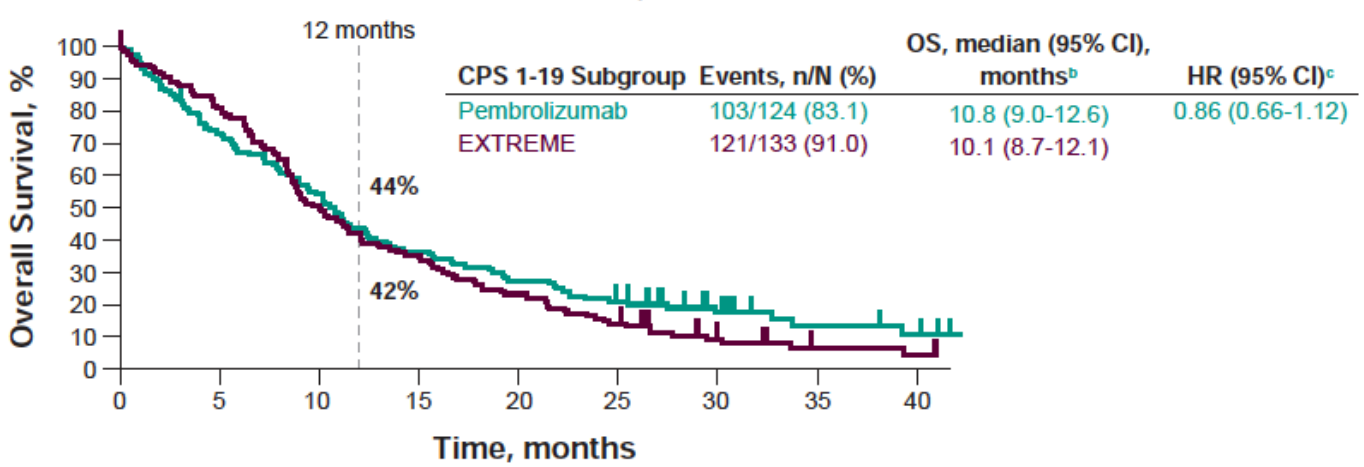
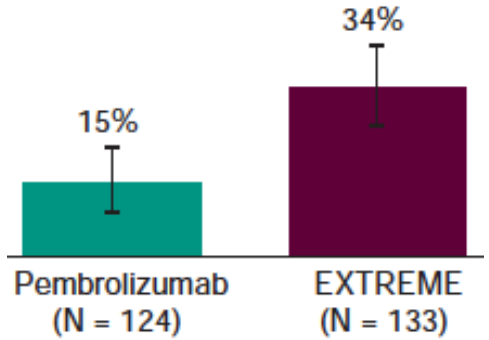
CPS 1-19

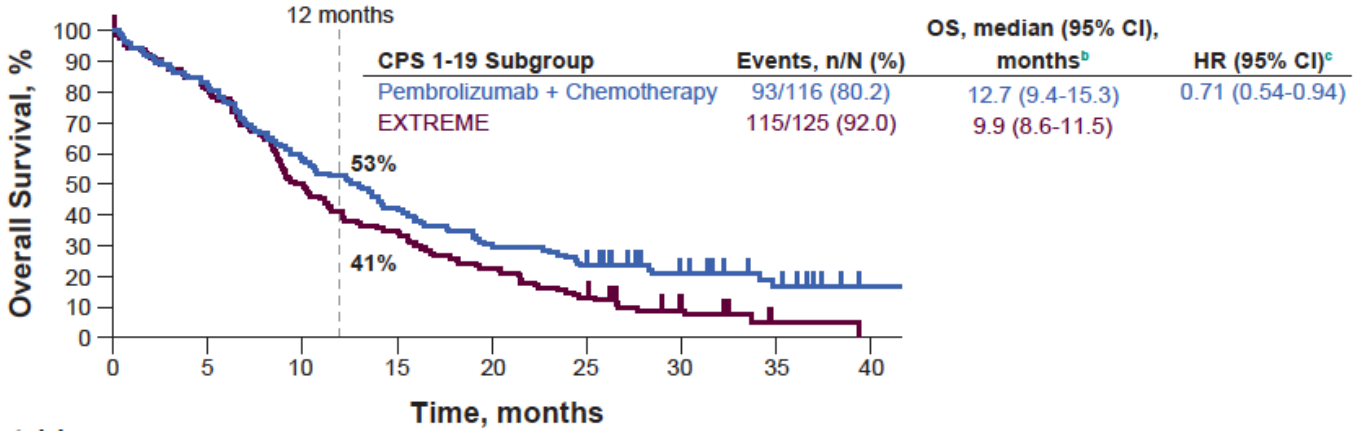
Pembrolizumab vs EXTREME



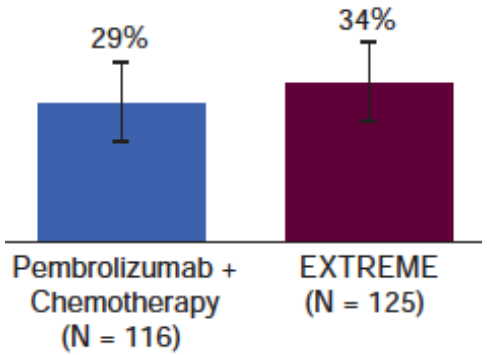
CPS 1-19 Subgroup	Events, n/N (%)	OS, median (95% CI), months[b]	HR (95% CI)[c]
Pembrolizumab	103/124 (83.1)	10.8 (9.0-12.6)	0.86 (0.66-1.12)
EXTREME	121/133 (91.0)	10.1 (8.7-12.1)	



Pembrolizumab + Chemo vs EXTREME



CPS 1-19 Subgroup	Events, n/N (%)	OS, median (95% CI), months[b]	HR (95% CI)[c]
Pembrolizumab + Chemotherapy	93/116 (80.2)	12.7 (9.4-15.3)	0.71 (0.54-0.94)
EXTREME	115/125 (92.0)	9.9 (8.6-11.5)	



EMA/CHMP/591139/2019
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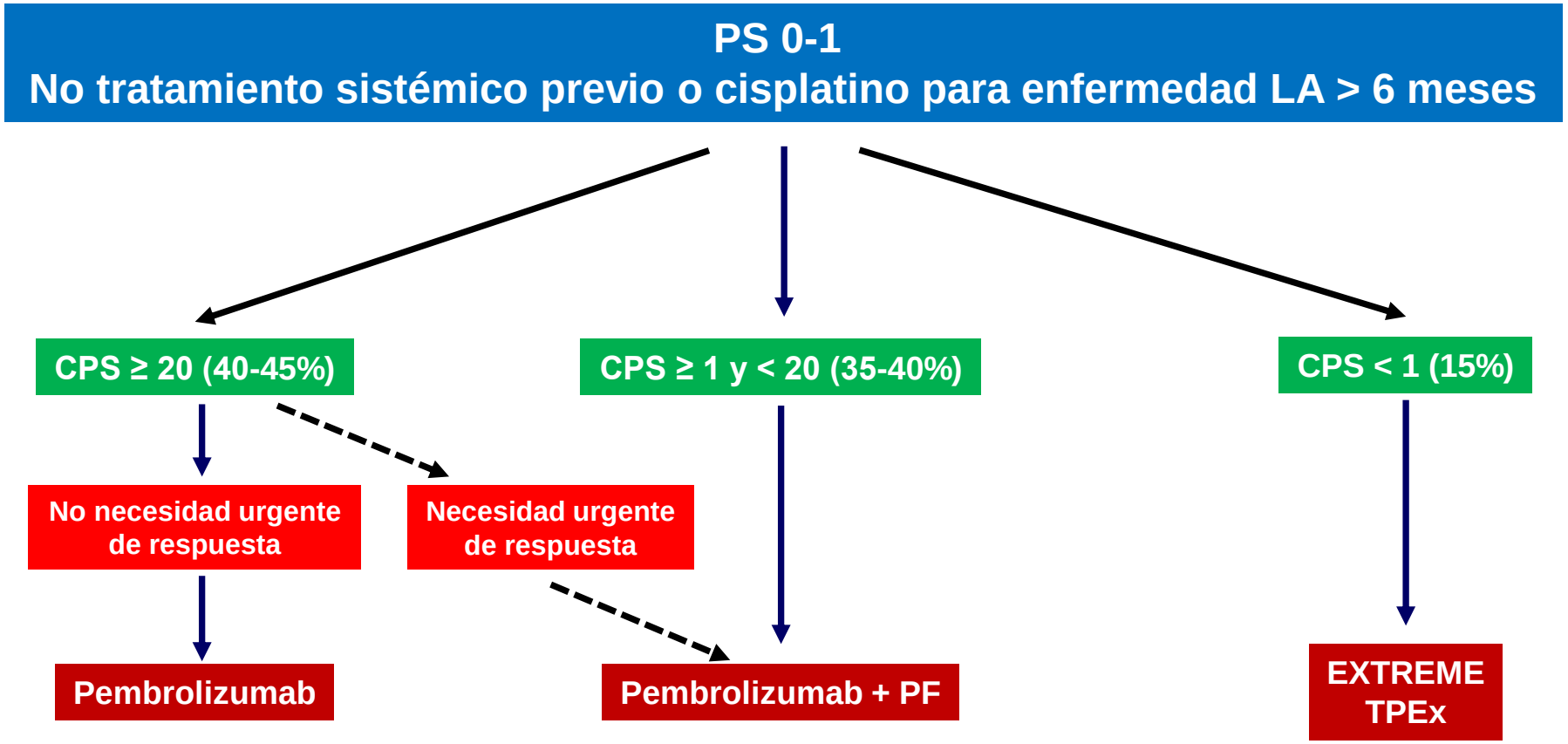

Mesía R et al. SEOM Guidelines, Clin Transl Oncol 2021

Conclusiones CPS 1-19

- Pembrolizumab vs EXTREME
  - Supervivencia global similar: 10.8 vs 10.1 meses
  - Menor tasa de respuesta: 15% vs 34%
- Pembro + quimioterapia vs EXTREME
  - Mayor supervivencia global: 12.7 vs 9.9 meses
  - Similar tasa de respuesta: 29% vs 34%

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Muchas gracias!!!!!!