Možnosti imunoterapie v liečbe rekurentného a/alebo metastatického nádoru hlavy a krku

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Onkologický ústav sv. Alžbety

4. ESO TOUR

21. 10. 2021

Vyhlásenie o konflikte záujmov autora

□ Nemám potenciálny konflikt záujmov

x Deklarujem nasledujúci konflikt záujmov

Forma finančného prepojenia	Spoločnosť
Participácia na klinických štúdiách/firemnom grante	Bayer, Amgen
Nepeňažné plnenie (v zmysle zákona)	Eli Lilly, Pierre Fabre
Prednášajúci	Merck, AstraZeneca, MSD
Akcionár	
Konzultant/odborný poradca	Merck, Pierre Fabre
Ostatné príjmy (špecifikovať)	

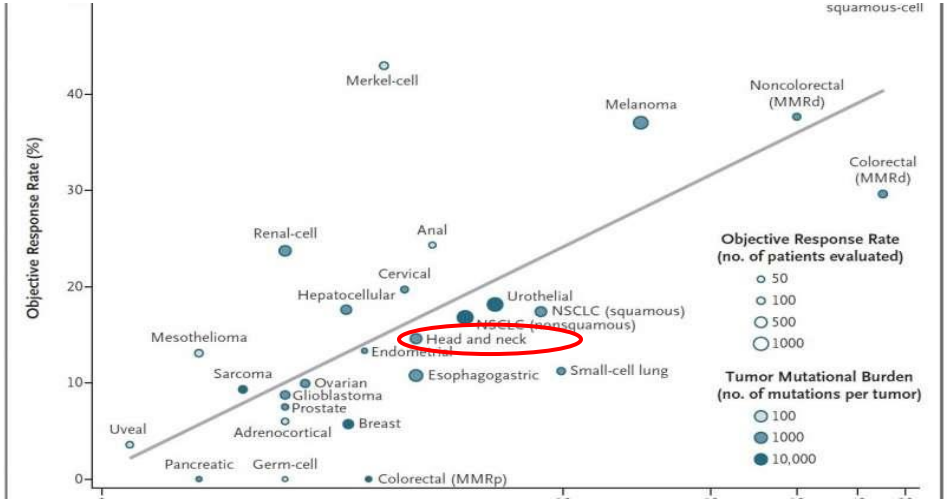
Podľa UEMS (upravené v zmysle slovenskej legislatívy)

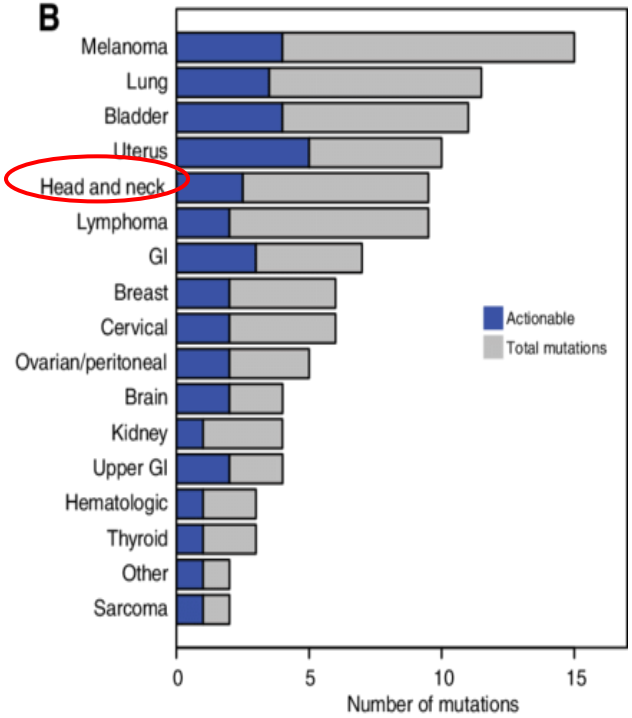
Prednášku podporila spoločnosť

MSD

Nádory hlavy a krku patria medzi tzv. „imunosenzitívne“ nádory

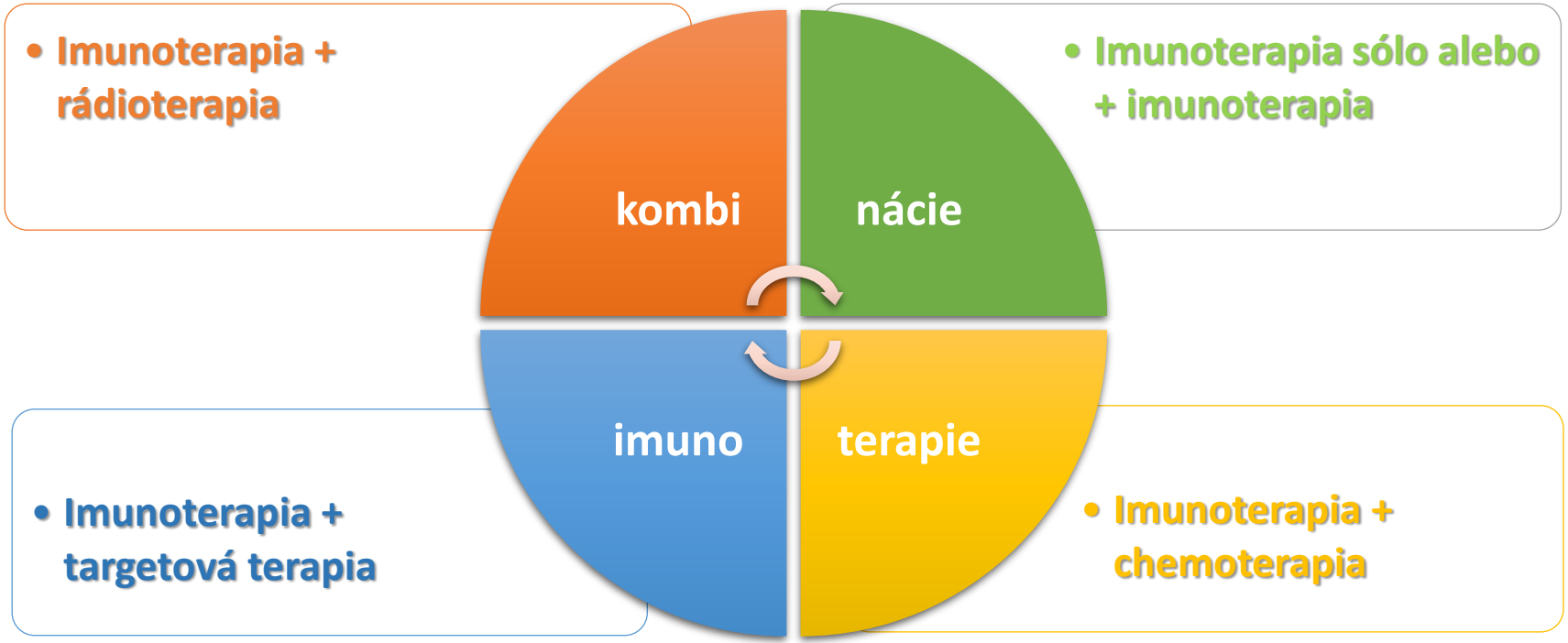
- **PD-L1 expresia**
- **Nádorová mutačná nálož (TMB, tumor mutation burden)**
- Infiltrácia imunitnými bunkami
- Genetický podpis hostiteľa
- Zloženie mikrobiómu





Oncology & Cancer, John Hopkins University School of Medicine, 2017
Yarchoan NEJM 2017;2500-1

Potenciálne kombinácie imunoterapie (IO)



IO v nádoroch hlavy a krku

Drug	Approved Indication	Target
Nivolumab[1]	Second line in R/M HNSCC with progression on/after platinum-based chemotherapy	PD-1
Pembrolizumab[2]	Second line in R/M HNSCC with progression on/after platinum-containing chemotherapy First line in R/M HNSCC as a single agent in patients with PD-L1–expressing tumors (CPS ≥ 1) and in combination with platinum + 5-FU for all patients	PD-1
Atezolizumab[3]	Not approved in HNSCC	PD-L1
Durvalumab[4]	Not approved in HNSCC	PD-L1
Avelumab[5]	Not approved in HNSCC	PD-L1

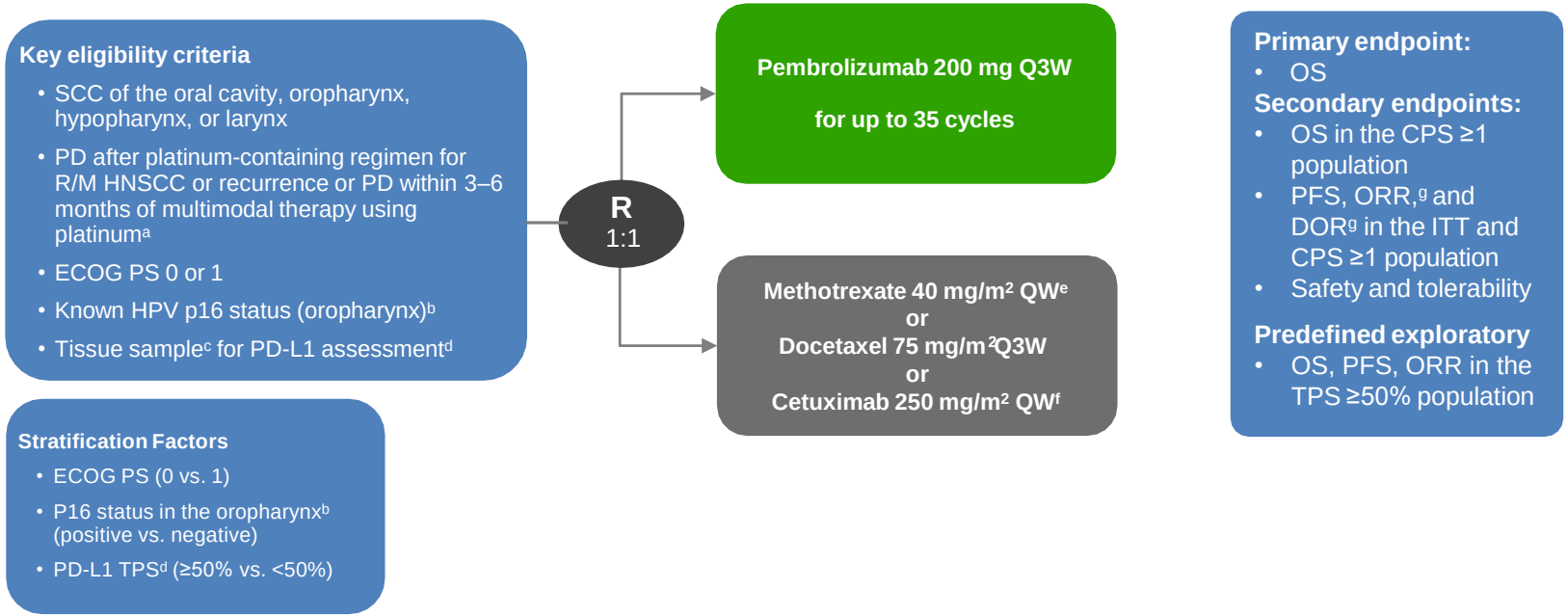
1.. Nivolumab PI. 2. Pembrolizumab PI. 3. Atezolizumab PI. 4. Durvalumab PI. 5. Avelumab PI.

Slide credit: clinicaloptions.com

Imunoterapia – platina refraktérny HNSCC

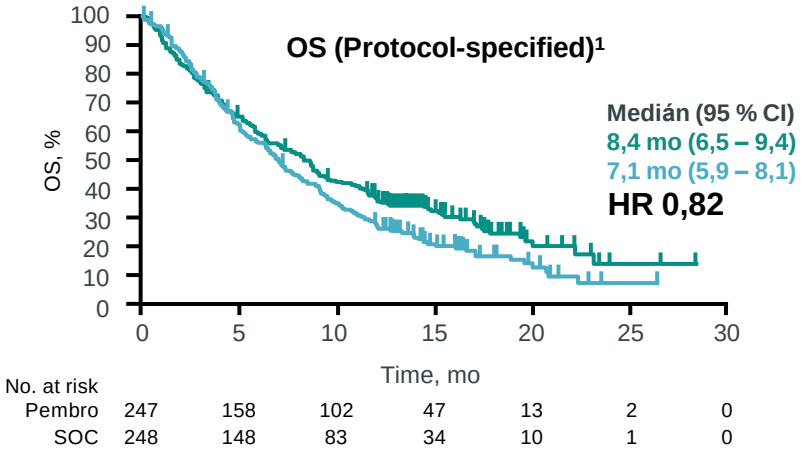
KEYNOTE-040 a CheckMate 141

KEYNOTE-040: dizajn štúdie

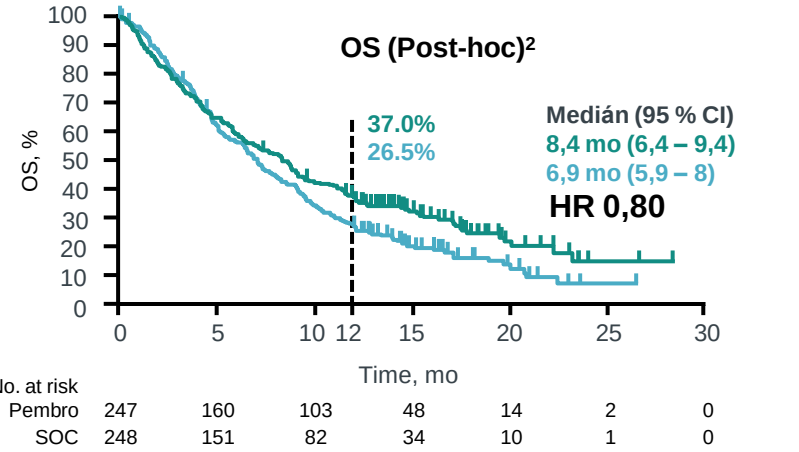


[a]Limit of 2 prior therapies for R/M HNSCC. [b]Assessed using the CINtec p16 Histology Assay (Ventana): cutpoint for positivity = 70%. [c]Newly collected preferred. dAssessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies).
[e]Could be increased to 60 mg/m2 QW in the absence of toxicity. [f]Following a loading dose of 400 mg/m2. [g]Assessed per RECIST v1.1 by blinded, independent central radiology review
Cohen EEW et al. *Lancet.* 2019;393(10167t):156–167.

KEYNOTE-040: OS v ITT populácii



Reprinted with permission from Elsevier Inc.: Cohen EEW et al. from Lancet. 2019;393(10167):156–167.



Reprinted with permission from Elsevier Inc.: Cohen EEW et al. from Lancet. 2019;393(10167):156–167.

Protocol-specified Final Analysis of OS (survival status of 12 patients unconfirmed; data cutoff 15 May 2017)			
	Events, n	HR (95% CI)	P
Pembro	179	0.82 (0.67–1.01)	one-sided P=0.0316 (non-significant)
SOC	198		

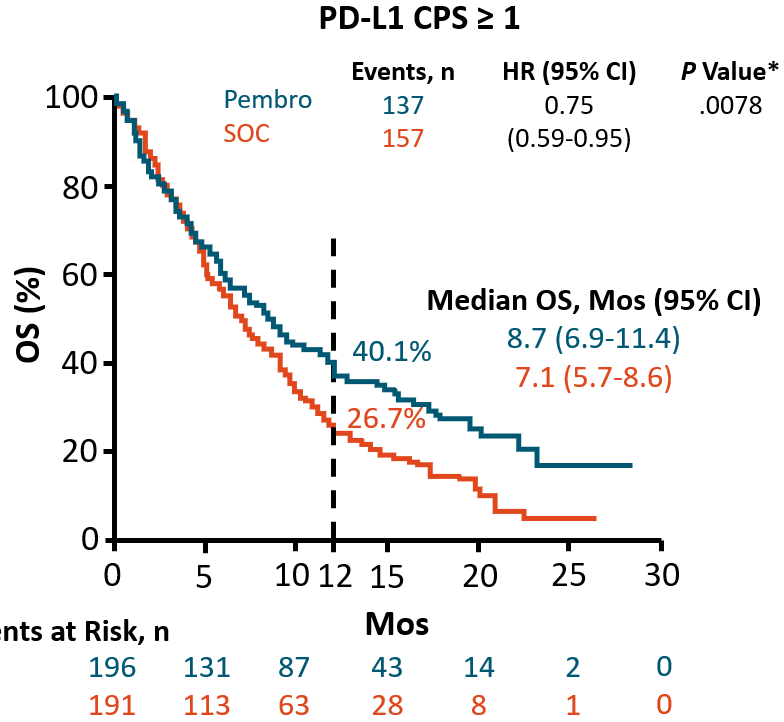
Pembro	181	0.80[a] (0.65–0.98)	0.0161[b] (nominal)
SOC	207		

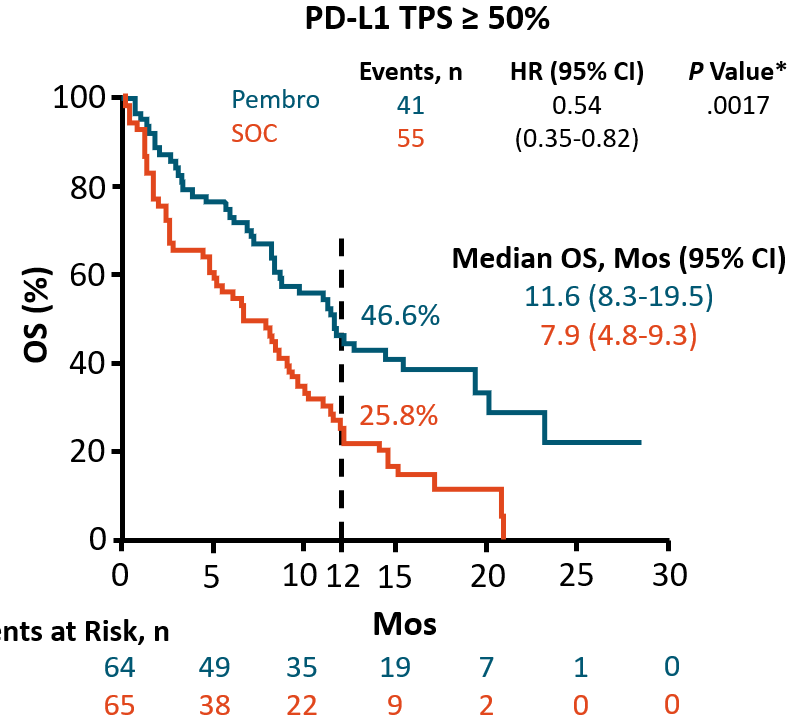
Data cutoff date: 15 May 2017.

[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. [b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors.

1. Cohen EEW et al. Supplement to: *Lancet*. 2019;393(10167):156–167. 2. Cohen EEW et al. *Lancet*. 2019;393(10167):156–167.

KEYNOTE-040: OS podľa expresie PD-L1





*Nominal 1-sided *P* value from log-rank test, stratified by randomization stratification factors.

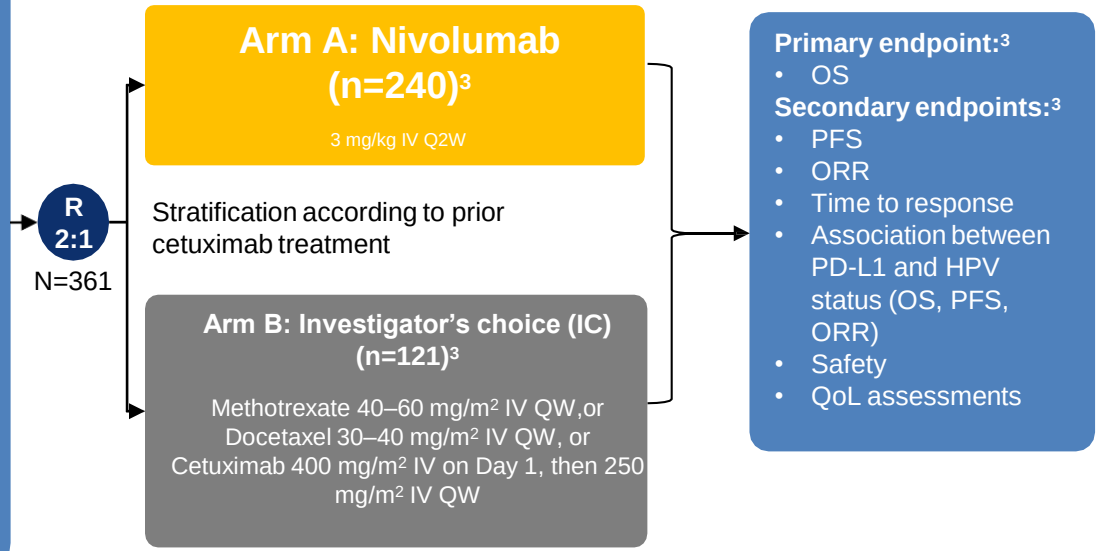
Cohen. Lancet. 2019;393:156.

Slide credit: clinicaloptions.com

CheckMate 141: dizajn štúdie

Inclusion criteria:[3]
- Aged ≥18 years
- Histologically confirmed R/M HNSCC (oral cavity, pharynx or larynx) not suitable for curative treatment
- Tumour progression or recurrence within 6 months after the last dose of platinum-containing chemotherapy administered as adjuvant therapy or in the context of primary or recurrent disease
- ECOG PS 0 or 1
- Adequate bone marrow, hepatic and renal function
- Measurable disease according to RECIST version 1.1

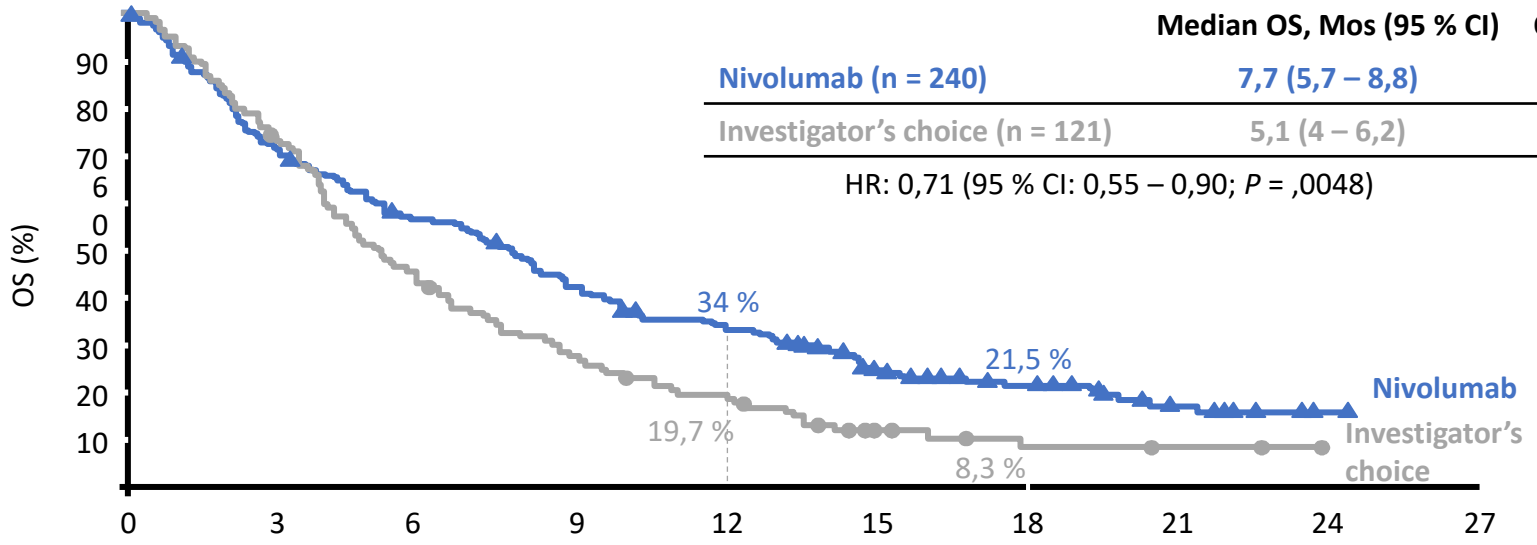
Key exclusion criteria:[3]
- Active brain metastases
- Autoimmune disease or systemic immunosuppression
- Known infection with HIV or hepatitis B or C virus
- Previous therapy targeting T-cell co-stimulating or immune-checkpoint pathways



ECOG PS, Eastern Cooperative Oncology Group performance status; HIV, human immunodeficiency virus; HPV, human papillomavirus; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; QoL, quality of life; Q2W, once every 2 weeks; QW, once weekly; RECIST, Response Evaluation Criteria in Solid Tumours.

1. Opdivo® (nivolumab) Summary of Product Characteristics. June 2019; 2. NCT02105636. 2018; ClinicalTrials.gov.; 3. Ferris RL et al. *N Engl J Med*. 2016;375:1856.

CheckMate 141: OS v ITT populácii



	Median OS, Mos (95 % CI)	ORR, %
Nivolumab (n = 240)	7,7 (5,7 – 8,8)	13,3
Investigator's choice (n = 121)	5,1 (4 – 6,2)	5,8

HR: 0,71 (95 % CI: 0,55 – 0,90; *P* = ,0048)

Patients at Risk, n

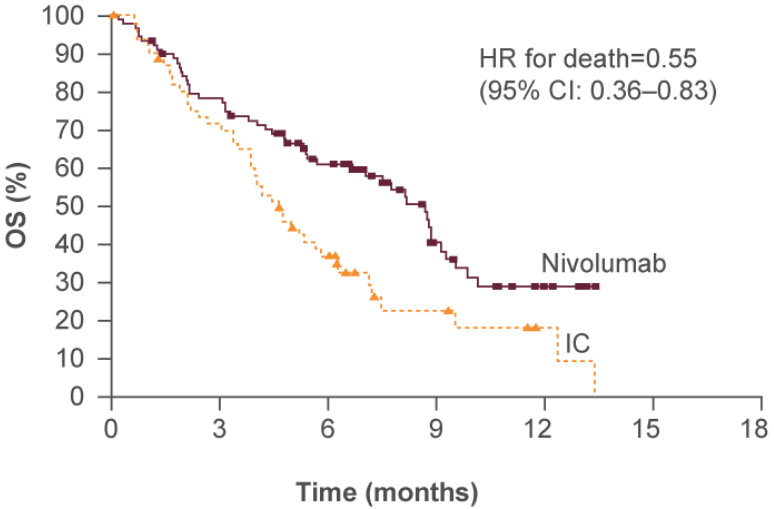
Nivo	240	169	132	98	76	45	27	12	3	0
IC	121	88	51	32	2	9	4	3	0	0

Median follow-up: 11.4 mos

Ferris. Oral Oncol. 2018;81:45.

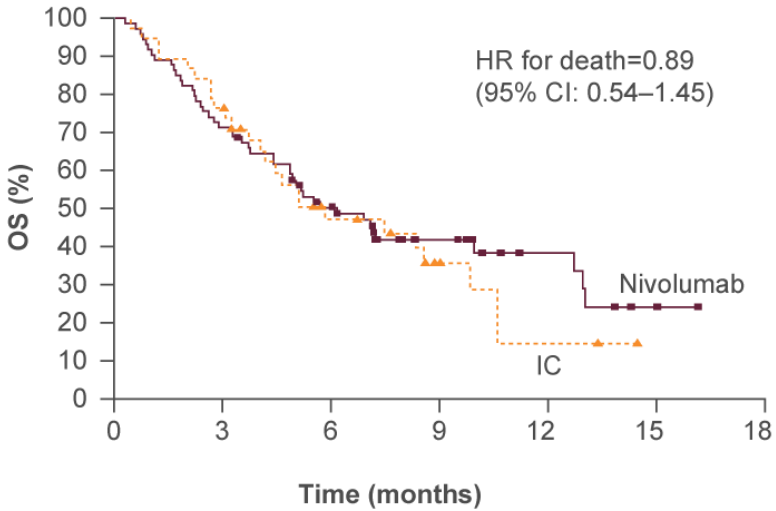
CheckMate 141: OS podľa PD-L1 expresie

PD-L1 expression ≥ 1 %



No. at risk						
Nivolumab	88	67	44	18	6	0
IC	61	42	20	6	2	0

PD-L1 expression < 1 %



No. at risk							
Nivolumab	73	52	33	17	8	3	0
IC	38	29	14	6	2	0	0

[a]Tumour PD-L1 expression status was evaluable in 260 of 361 patients (72.0%).
Ferris RL et al. *N Engl J Med*. 2016;375:1856.

Schválenie pembrolizumabu a nivolumabu

Indikovaný u pacientov s progresiou ochorenia počas alebo po liečbe chemoterapiou na báze platiny (podávanej či už ako paliatívna liečba, alebo multimodálna kuratívna liečba)

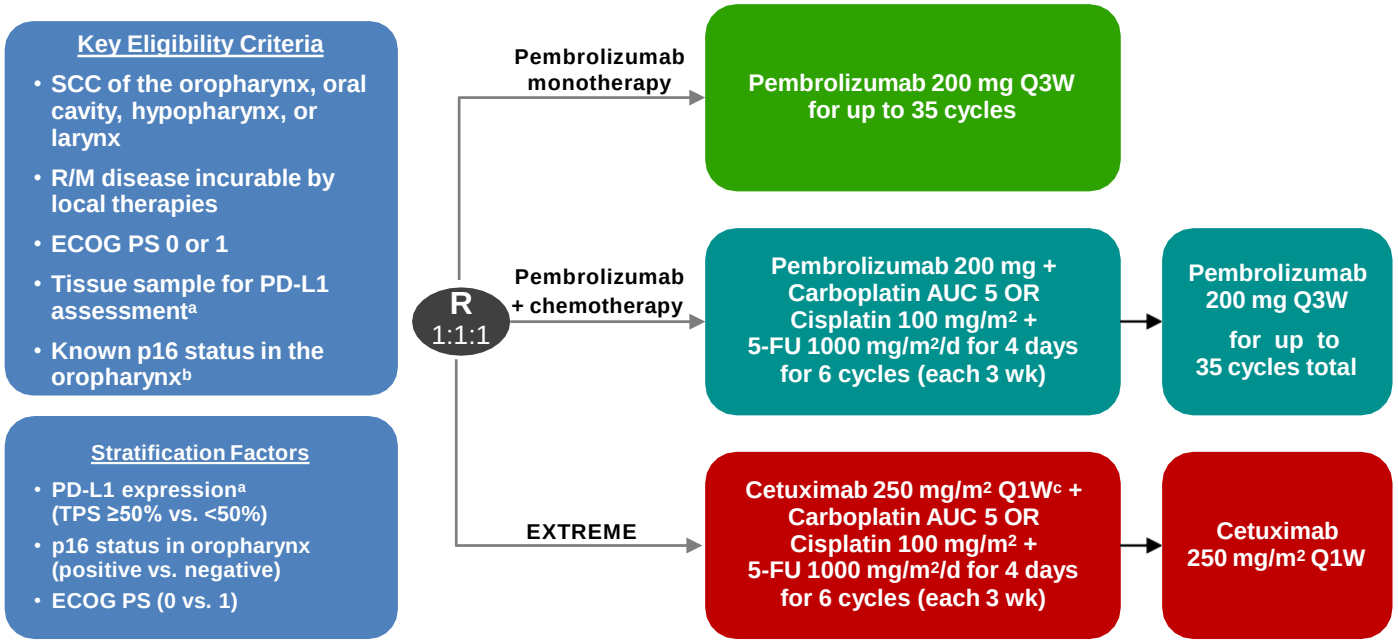
FDA
- schválený nivolumab aj pembrolizumab (2016)

EMA
- schválený nivolumab (I, A; ESMO-MCBS v1.1 score: 4)
- schválený pembrolizumab len pre pacientov s nádormi exprimujúcimi PD-L1 a TPS ≥ 50 % (I, A;) (2018)

Imunoterapia – 1. línia liečby R/M HNSCC

KEYNOTE-048

KEYNOTE-048: dizajn štúdie



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumour proportion score = % of tumour cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 histology assay (Ventana); cutpoint for positivity = 70%.
[c]Following a loading dose of 400 mg/m².
Rischen D et al. Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May–4 June, 2019.

KEYNOTE-048: ciele štúdie

Primárne

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

Sekundárne

- 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]

CPS= combined positive score = number of PD-L1–positive cells (tumour cells, lymphocytes, macrophages) divided by total number of tumour cells × 100

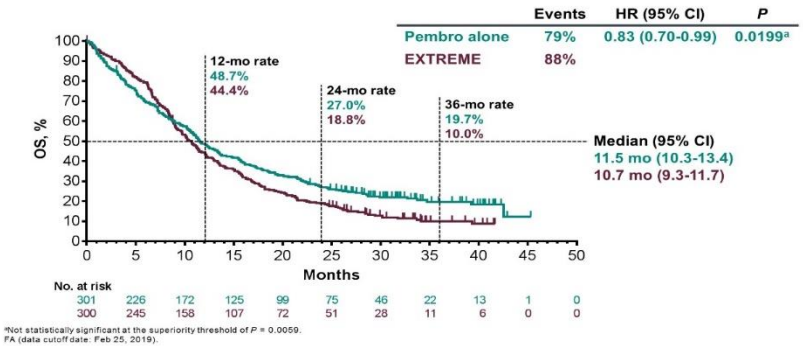
[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay. CPS = combined positive score = number of PD-L1–positive cells (tumour cells, lymphocytes, macrophages) divided by total number of tumour cells × 100.
[b]Assessed per RECIST v1.1 by blinded, independent central review. [c]To be presented at a later date.
Rischin D et al. Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May–4 June, 2019.

KEYNOTE-048:

Pembrolizumab vs. EXTREME

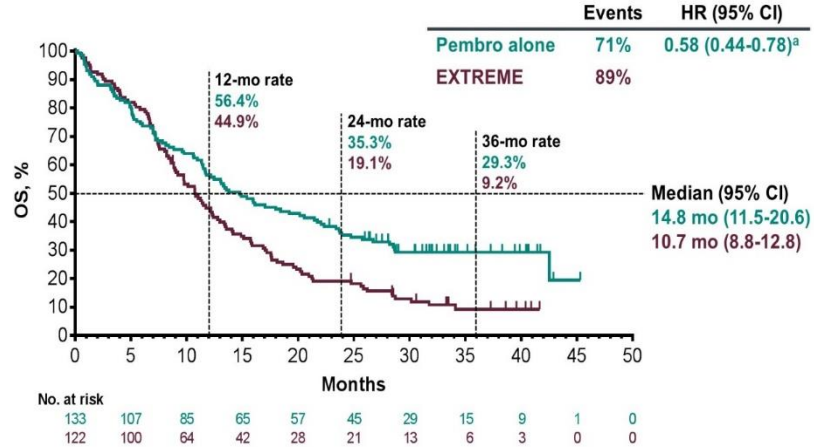
Celkové prežívanie (finálna analýza)

OS, P vs E, Total Population



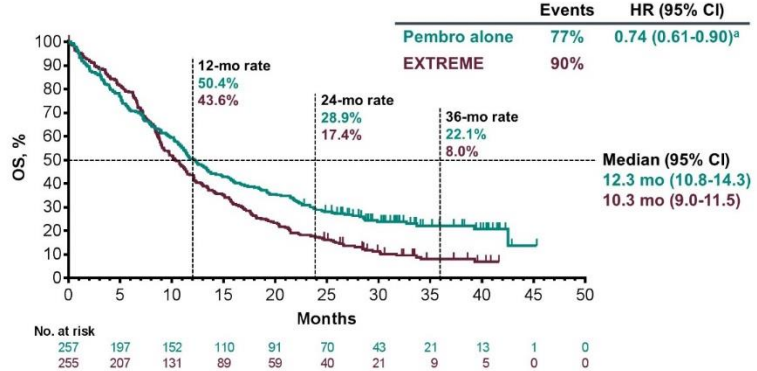
[a]Not statistically significant at the superiority threshold of $P = 0.0059$.
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, CPS ≥20 Population



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.61 (95% CI 0.45–0.83).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, CPS ≥1 Population



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.78 (95% CI 0.64–0.96).
FA (data cutoff date: Feb 25, 2019).

Rischin D et al. Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May–4 June, 2019.

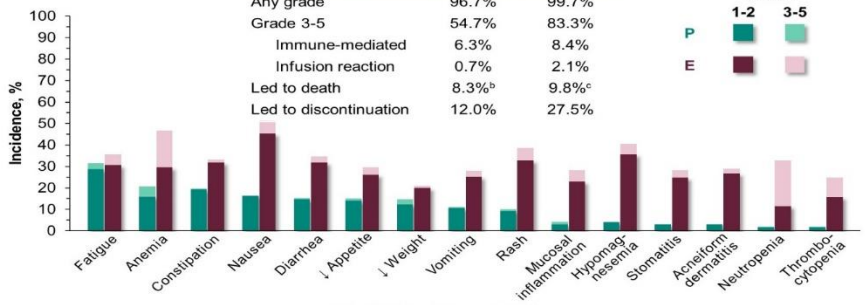
KEYNOTE-048:

Pembrolizumab vs. EXTREME

PFS, RR, AEs (finálna analýza)

All-Cause AEs,[a] P vs E, Total Population

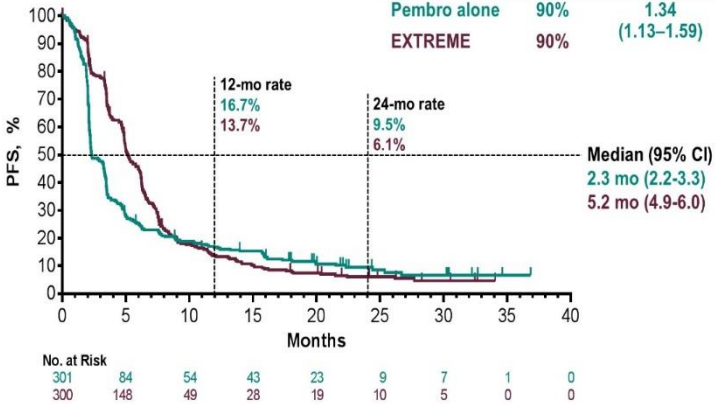
All AEs	P (n = 300)	E (n = 287)
Any grade	96.7%	99.7%
Grade 3-5	54.7%	83.3%
Immune-mediated	6.3%	8.4%
Infusion reaction	0.7%	2.1%
Led to death	8.3%[b]	9.8%[c]
Led to discontinuation	12.0%	27.5%



[a]Data for treatment-related AEs were presented at ESMO 2018. [b]Events were considered treatment related in 1.0%. [c]Events were considered treatment related in 2.8%. FA (data cutoff date: Feb 25, 2019).

PFS, P vs E, Total Population

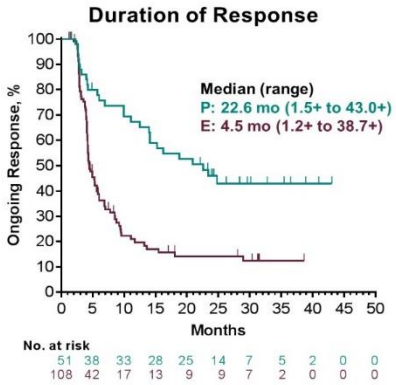
	Events	HR (95% CI)
Pembro alone	90%	1.34 (1.13–1.59)
EXTREME	90%	



IA2 (data cutoff date: Jun 13, 2018). PFS was assessed per RECIST v1.1 by blinded, independent central review.

Response Summary, P vs E, Total Population

Confirmed Response, n (%)	Pembro N = 301	EXTREME N = 300
ORR	**51 (16.9)**	**108 (36.0)**
CR	14 (4.7)	8 (2.7)
PR	37 (12.3)	100 (33.3)
SD	82 (27.2)	102 (34.0)
PD	122 (40.5)	37 (12.3)
Non-CR/non-PD[a]	14 (4.7)	11 (3.7)
Not evaluable or assessed[b]	32 (10.6)	42 (14.0)



[a]Patients without measurable disease per central review at baseline who did not have CR or PD. [b]Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. FA (data cutoff date: Feb 25, 2019).

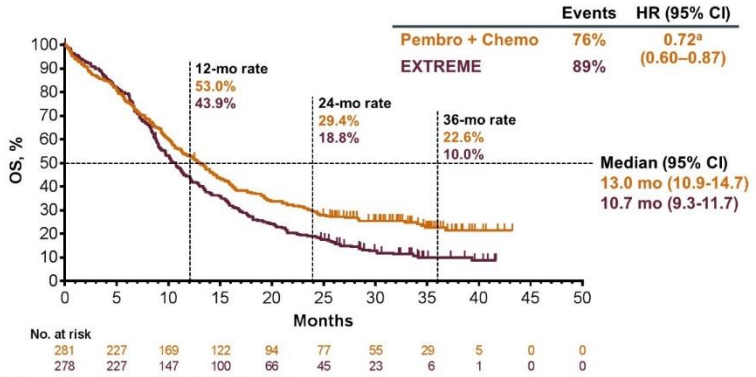
Rischin D et al. Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May–4 June, 2019.

KEYNOTE-048:

Pembrolizumab + CT vs. EXTREME

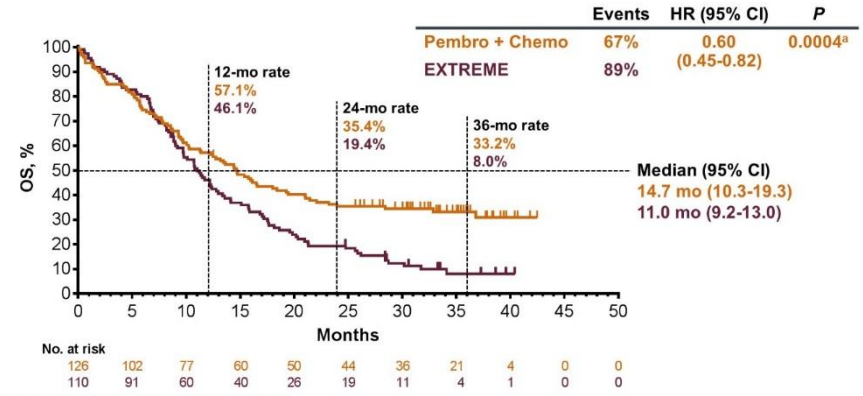
Celkové prežívanie (finálna analýza)

OS, P+C vs E, Total Population



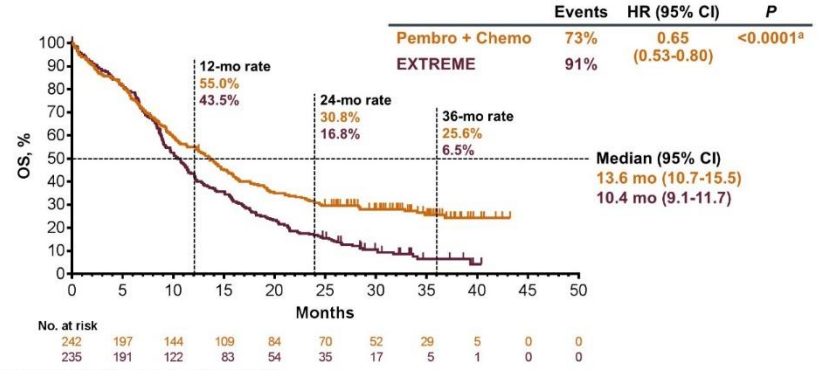
[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).

OS, P+C vs E, CPS ≥20 Population



[a]Statistically significant at the superiority threshold of $P = 0.0023$.
FA (data cutoff date: Feb 25, 2019).

OS, P+C vs E, CPS ≥1 Population



[a]Statistically significant at the superiority threshold of $P = 0.0026$.
FA (data cutoff date: Feb 25, 2019).

Rischin D et al. Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May–4 June, 2019.

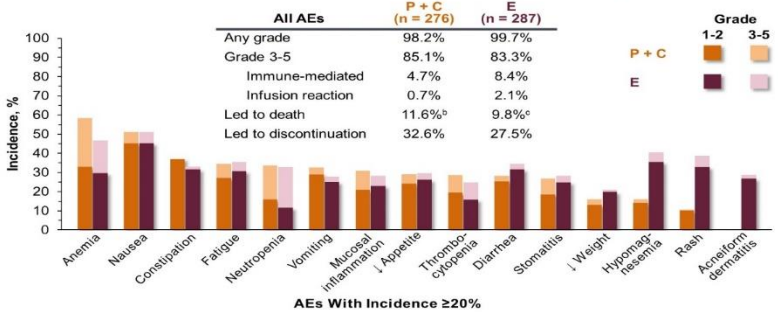
KEYNOTE-048:

Pembrolizumab + CT vs. EXTREME

PFS, RR, AEs (finálna analýza)

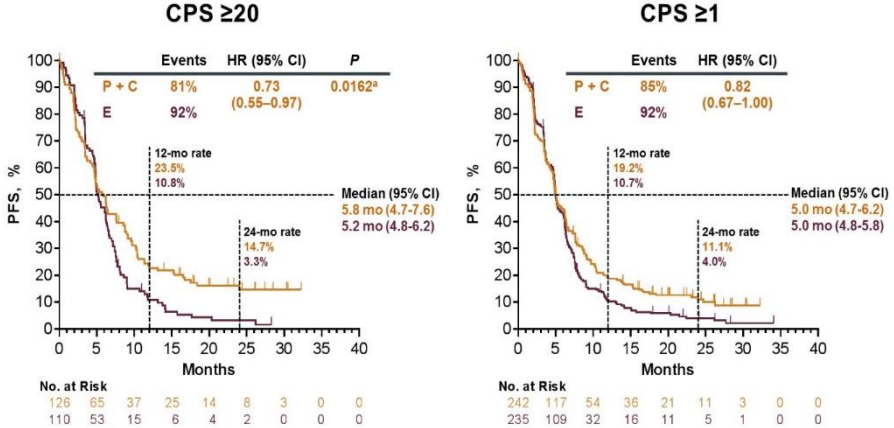
All-Cause AEs,[a] P + C vs E, Total Population

All AEs	P + C (n = 276)	E (n = 287)
Any grade	98.2%	99.7%
Grade 3-5	85.1%	83.3%
Immune-mediated	4.7%	8.4%
Infusion reaction	0.7%	2.1%
Led to death	11.6%[b]	9.8%[c]
Led to discontinuation	32.6%	27.5%



[a]Data for treatment-related AEs were presented at ESMO 2018. [b]Events were considered treatment related in 4.0%. [c]Events were considered treatment related in 2.8%. FA (data cutoff date: Feb 25, 2019).

PFS, P+C vs E, CPS ≥20 and ≥1

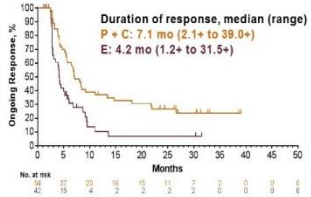


[a]Not statistically significant at the superiority threshold of 0.0017.
IA2 (data cutoff date: Jun 13, 2018). PFS assessed per RECIST v1.1 by blinded, independent central review.

Response Summary, P+C vs E

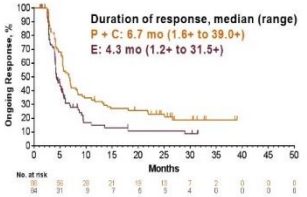
CPS ≥20

Confirmed Response, n (%)	P + C N = 126	E N = 110
ORR	54 (42.9)	42 (38.2)
CR	12 (9.5)	4 (3.6)
PR	42 (33.3)	38 (34.5)
SD	29 (23.0)	38 (34.5)
PD	19 (15.1)	9 (8.2)
Non-CR/non-PD[a]	4 (3.2)	5 (4.5)
Not evaluable or assessed[b]	20 (15.9)	16 (14.5)



CPS ≥1

Confirmed Response, n (%)	P + C N = 242	E N = 235
ORR	88 (36.4)	84 (35.7)
CR	16 (6.6)	7 (3.0)
PR	72 (29.8)	77 (32.8)
SD	64 (26.4)	77 (32.8)
PD	42 (17.4)	29 (12.3)
Non-CR/non-PD[a]	11 (4.5)	9 (3.8)
Not evaluable or assessed[b]	37 (15.3)	36 (15.3)



[a]Patients without measurable disease per central review at baseline who did not have CR or PD. [b]Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. FA (data cutoff date: Feb 25, 2019).

Rischin D et al. Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May–4 June, 2019.

KEYNOTE-048: závery a odporúčania

Pembrolizumab monoterapia vs. EXTREME

- Lepšie OS pre PEMBRO v populácii pacientov s CPS ≥ 20 a CPS ≥ 1
- Noninferiórne OS pre PEMBRO v ITT populácii
- Dlhšie trvanie odpovede pre PEMBRO
- Priaznivejší bezpečnostný profil pre PEMBRO

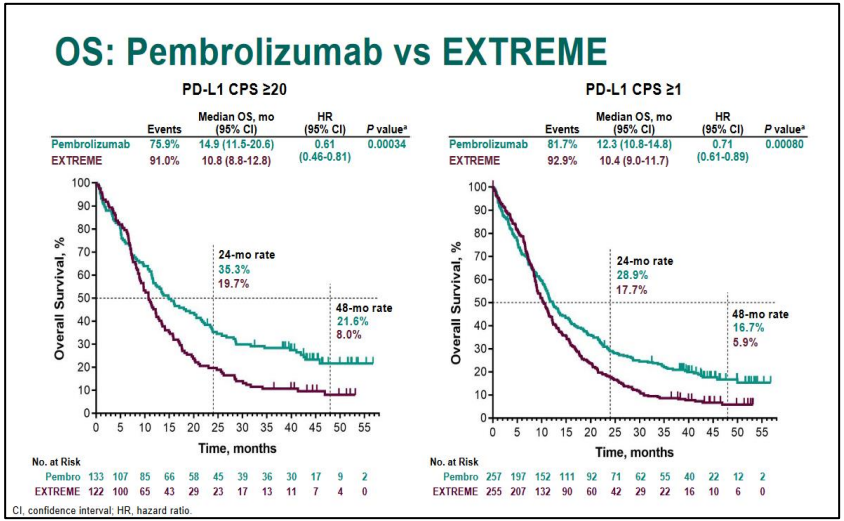
Pembrolizumab + CHT vs. EXTREME

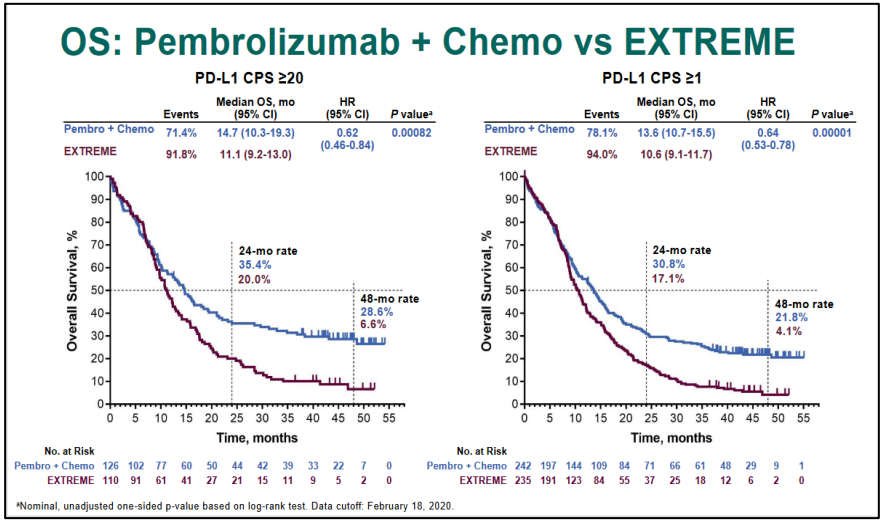
- Lepšie OS pre PEMBRO + CHT v populácii pacientov s CPS ≥ 20, CPS ≥ 1 aj v ITT
- Dlhšie trvanie odpovede pre PEMBRO + CHT
- Porovnateľný bezpečnostný profil pre PEMBRO + CHT aj EXTREME

Dáta podporujú použitie pembrolizumabu v monoterapii alebo v kombinácii s CHT ako nový štandard 1. línie liečby R/M SCCHN

Rischin D et al. Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting, 31 May–4 June, 2019.

KEYNOTE-048: 4-ročný follow-up



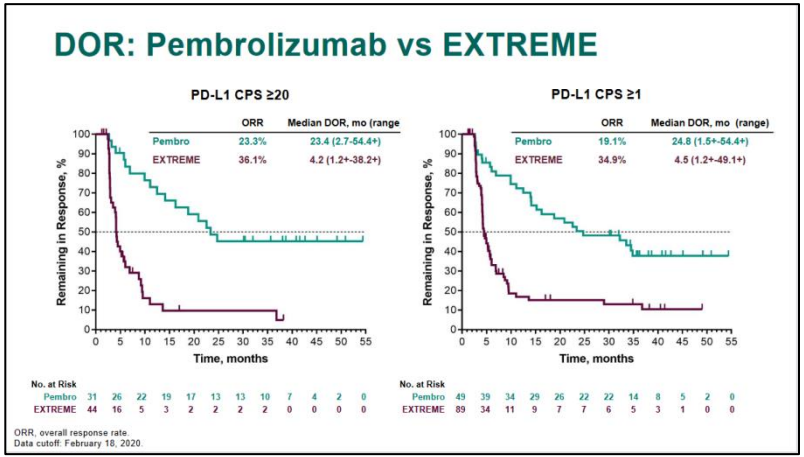


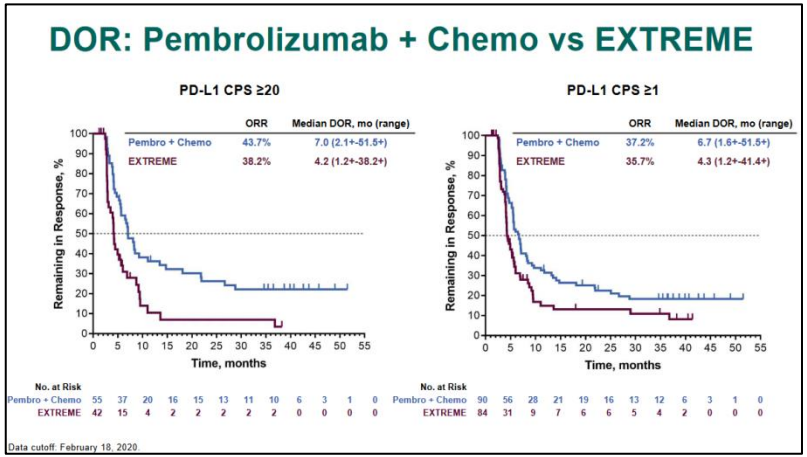
Long-term follow-up potvrdil štatisticky signifikantné zlepšenie OS pre pembrolizumab vs. EXTREME v populácii s PD-L1 CPS ≥ 20 a CPS ≥ 1; a pre pembrolizumab + chemoterapia vs. EXTREME vo všetkých podskupinách pacientov (PD-L1 CPS ≥ 20, CPS ≥ 1 a ITT)

dáta 4-ročného follow-up (data cutoff: February 18, 2020)
čas od randomizácie po cutoff: 45 mesiacov pre pembrolizumab vs. EXTREME; 44,5 mesiaca pre pembrolizumab + chemo vs. EXTREME

Greil R et al. Presented at the 2020 ESMO Meeting, abstract 915MO

KEYNOTE-048: 4-ročný follow-up





Trvanie odpovede (DOR) pre pembrolizumab alebo pembrolizumab + chemoterapia zostáva dlhšie ako pre EXTREME

Bezpečnosť bola v prospech pembrolizumabu vs. EXTREME a porovnateľná pre pembrolizumab + chemoterapia vs. EXTREME

dáta 4-ročného follow-up (data cutoff: February 18, 2020)
čas od randomizácie po cutoff: 45 mesiacov pre pembrolizumab vs. EXTREME; 44,5 mesiaca pre pembrolizumab + chemo vs. EXTREME

Greil R et al. Presented at the 2020 ESMO Meeting, abstract 915MO

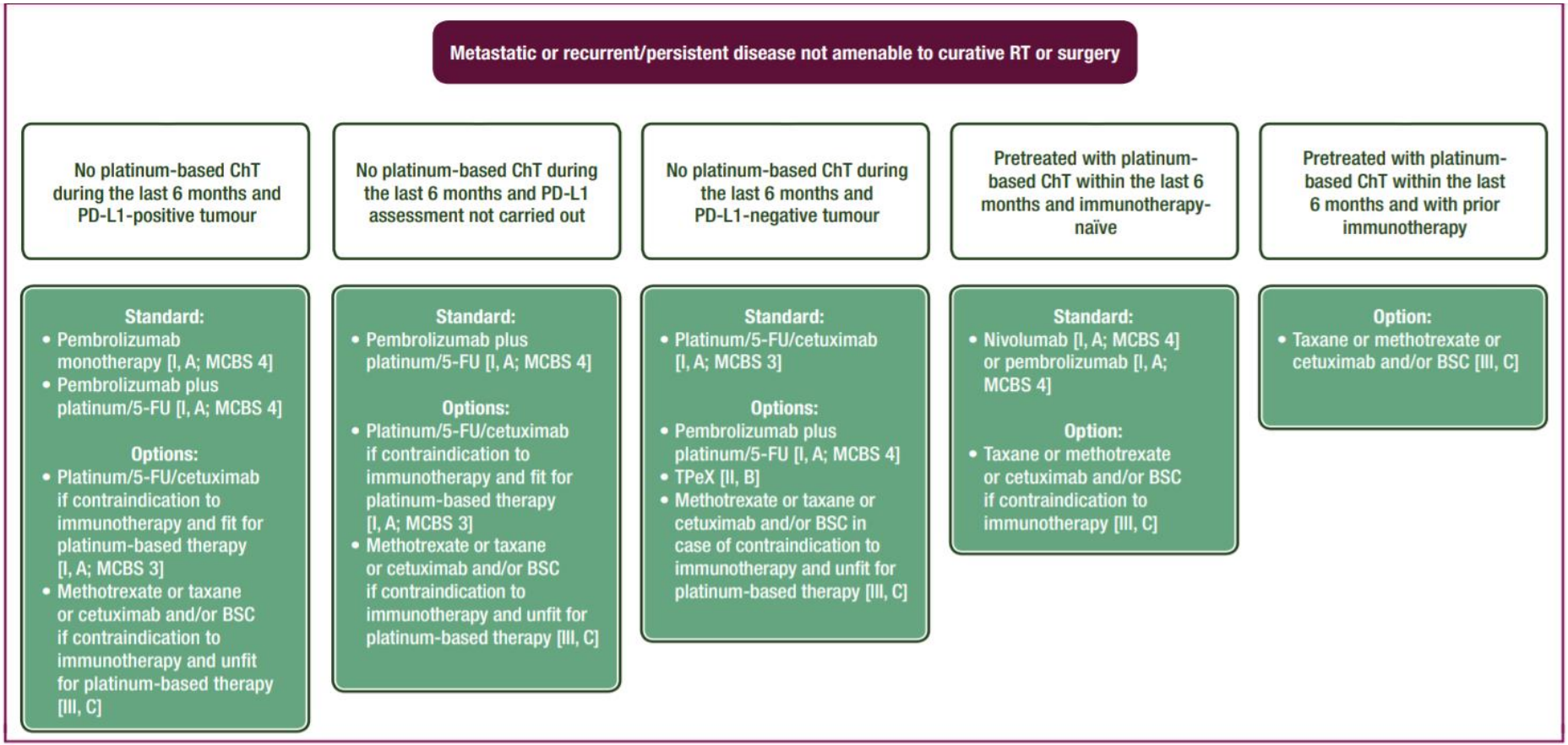
Nové indikácie pembrolizumabu R/M SCCHN

1. línia liečby rekurentného alebo metastatického skvamocelulárneho karcinómu hlavy a krku (pembrolizumab sólo alebo v kombinácii s chemoterapiou)

FDA schválenie (2019) - pre pembrolizumab v kombinácii s CHT nezávisle od expresie PD-L1
- pre sólo pembrolizumab u pacientov s CPS ≥ 1

EMA schválenie (2020) - pembrolizumab sólo alebo s chemoterapiou len pre pacientov s CPS ≥ 1
(I, A; ESMO-MCBS v1.1 score: 4)

ESMO guidelines pre R/M SCCHN



NCCN guidelines pre R/M SCCHN

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Head and Neck Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR NON-NASOPHARYNGEAL CANCERS
(Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary)

- **The choice of systemic therapy should be individualized based on patient characteristics (eg, PS, goals of therapy).**

Recurrent, Unresectable, or Metastatic (with no surgery or RT option)

Preferred Regimens	Other Recommended Regimens (First- and Subsequent-Line)	Useful in Certain Circumstances (First- and Subsequent-Line)
First-line[c] • Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU (category 1)[c,29] • Pembrolizumab (for tumors that express PD-L1 with CPS ≥1) (category 1 if CPS ≥ 20)[c,29] **Subsequent-Line (if not previously used)** • Nivolumab[30] (if disease progression on or after platinum therapy) (category 1) • Pembrolizumab[31-33] (if disease progression on or after platinum therapy) (category 1)	**Combination regimens** • Cetuximab/platinum (cisplatin or carboplatin)/5-FU[34] (category 1) • Cisplatin/cetuximab[35] • Cisplatin or carboplatin/docetaxel[36] or paclitaxel[37] • Cisplatin/5-FU[37,38] • Cisplatin or carboplatin/docetaxel/cetuximab[39] • Cisplatin or carboplatin/paclitaxel/cetuximab[40] • Pembrolizumab/platinum (cisplatin or carboplatin)/paclitaxel (category 2B)[29,37] • Pembrolizumab/platinum (cisplatin or carboplatin)/docetaxel (category 2B)[29,36] **Single Agents** • Cisplatin[35,41] • Carboplatin[42] • Paclitaxel[43] • Docetaxel[44,45] • 5-FU[41] • Methotrexate[38,46] • Cetuximab[47] • Capecitabine[48] • Afatinib[49] (subsequent-line only, if disease progression on or after platinum therapy) (category 2B)	• For select ethmoid/maxillary sinus cancers (small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features): ▸ Cisplatin/etoposide or carboplatin/etoposide[14] ▸ Cyclophosphamide/doxorubicin/vincristine (category 2B) • Pembrolizumab (for MSI-H tumors)[50]

Možnosti imunoterapie R/M SCCHN v Česku

Od marca 2020 je schválený *nivolumab* u pacientov s progresiou ochorenia počas alebo po liečbe chemoterapiou na báze platiny

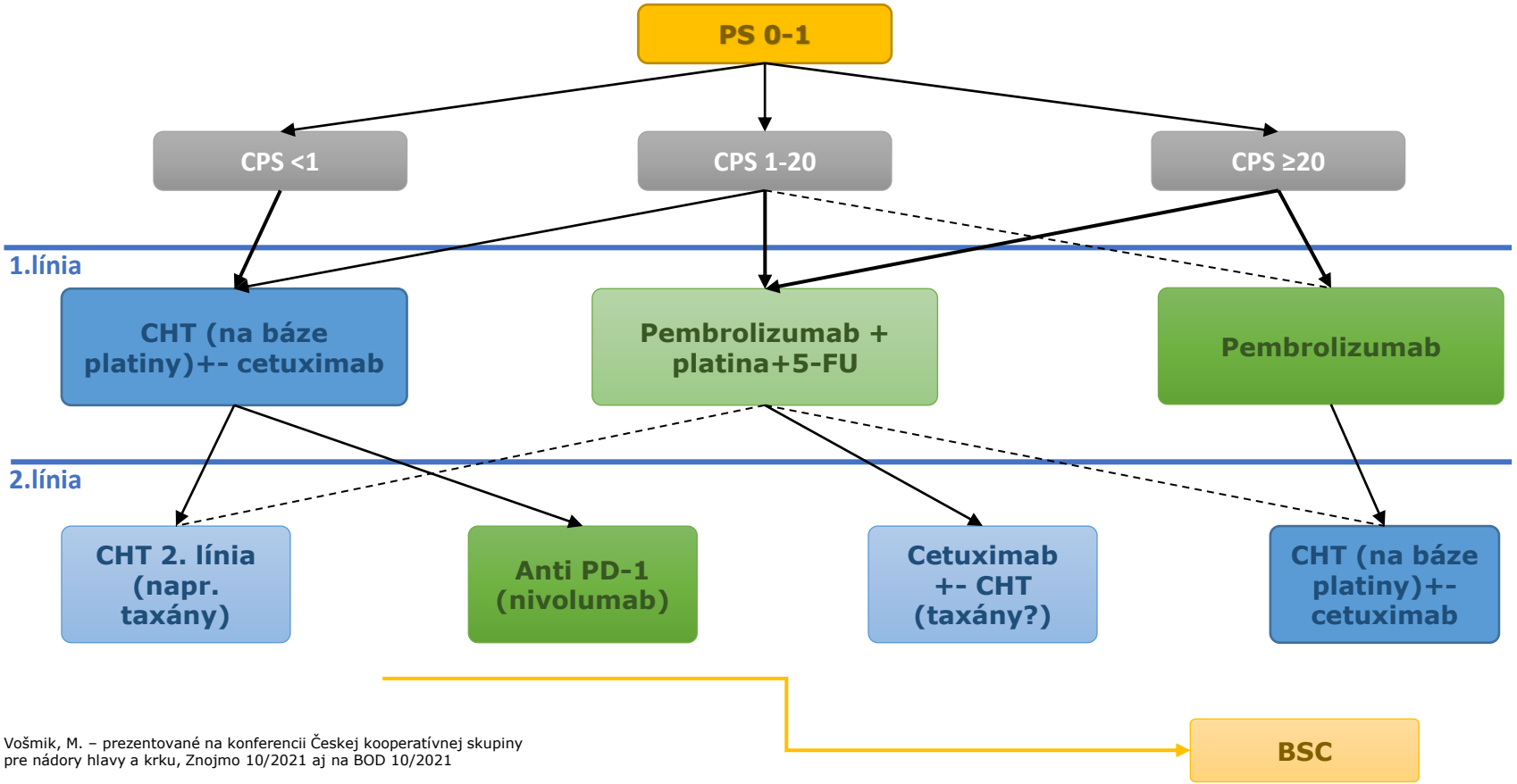
Od augusta 2021 je schválený *pembrolizumab* sólo alebo s chemoterapiou (platina/5FU) v 1. línii R/M SCCHN

Možnosti imunoterapie R/M SCCHN na Slovensku

Obidva lieky sú v SR registrované, ale nie kategorizované na liečbu SCCHN

Zdravotná poisťovňa liek môže, ale nemusí schváliť...

R/M SCCHN: evidence-based indikácie systémovej terapie



Vošmik, M. – prezentované na konferencii Českej kooperatívnej skupiny pre nádory hlavy a krku, Znojmo 10/2021 aj na BOD 10/2021

Imunoterapia je vo svete realitou aj v skupine pacientov s nádormi hlavy a krku

Sme pripravení?

Ďakujem za pozornosť