ESMO 21 a ASCO GI 2022 Update léčby karcinomu jícnu a žaludku

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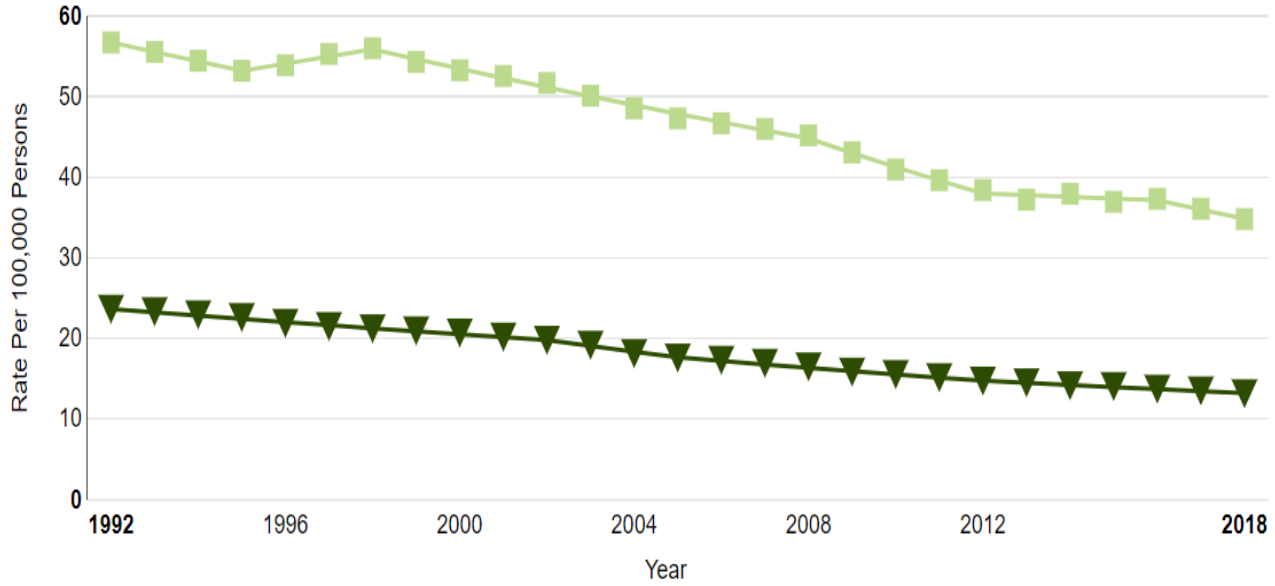
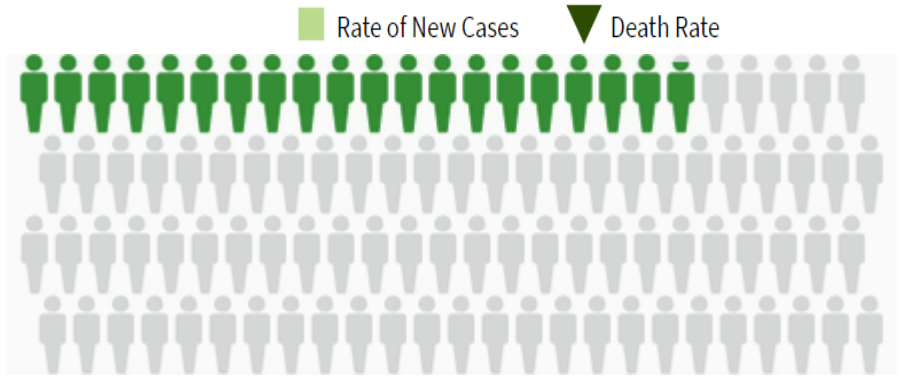
26.1.2022

Epidemiologická data

https://seer.cancer.gov/statfacts/more.html

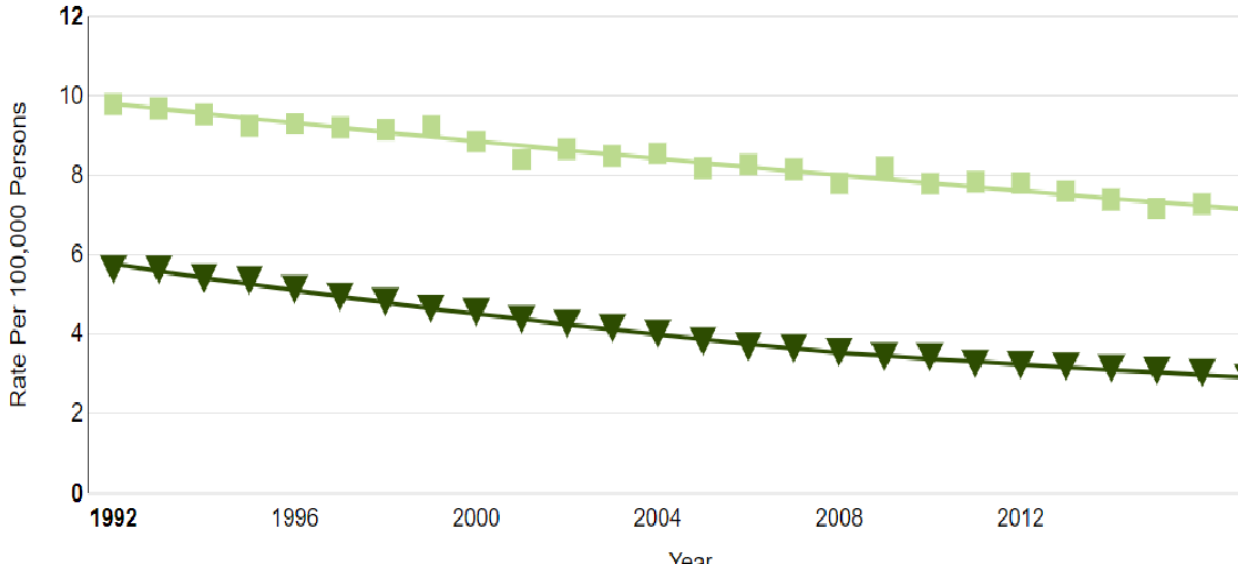
Nádory jícnu

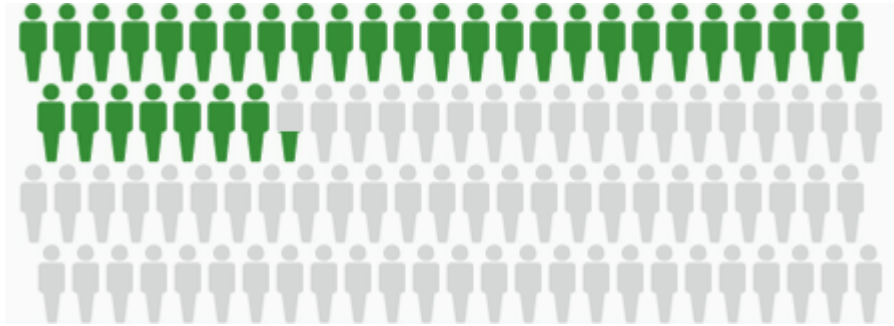




5-leté relativní přežití 19,9%

Nádory žaludku





5-leté relativní přežití 32,4%

2021 – REKAPITULACE

- Karcinom jícnu

✓Role předoperační radioterapie u nádorů GEJ (NEOAEGIS studie)

✓Adjuvantní imunoterapie po kurativní předoperační léčbě nádorů GEJ (CheckMate 577)

✓Role imunoterapie v léčbě metastatického onemocnění (KeyNote 590 a CheckMate 648)

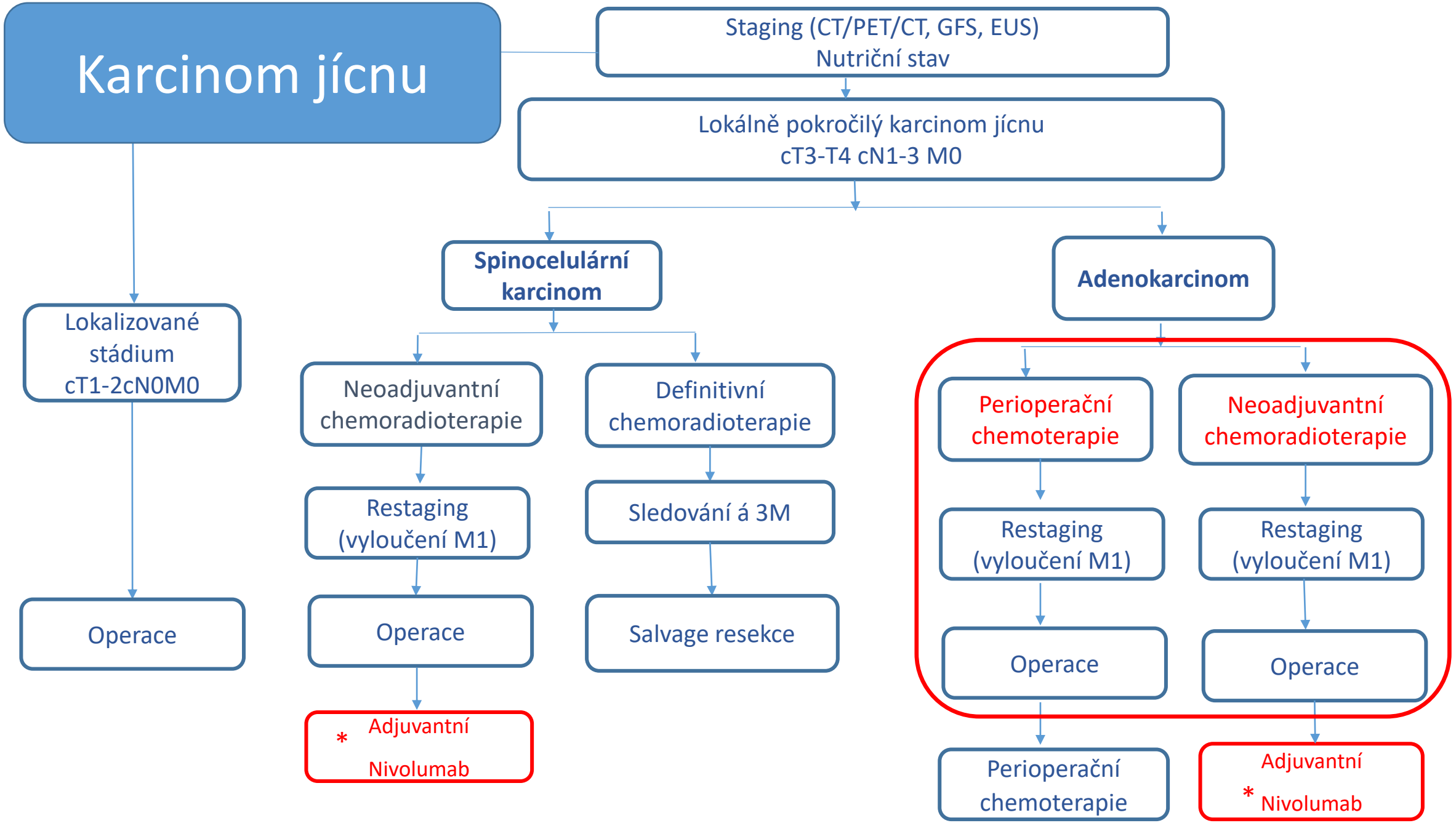
Metastatický karcinom GEJ a žaludku

✓Role imunoterapie v léčbě metastatického onemocnění

✓ (CheckMate 649)

✓MSI-High adenokarcinom žaludku(NEONIPIGA)

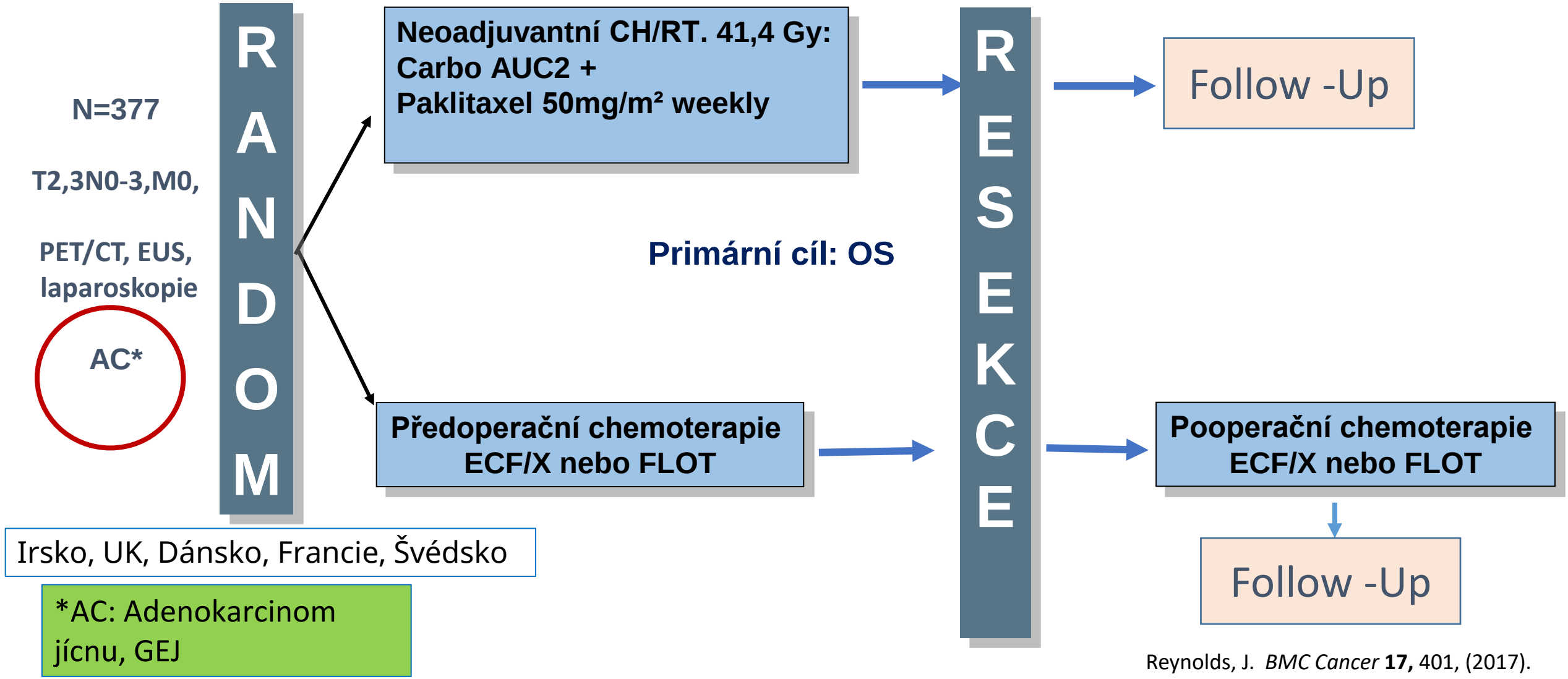
✓GO-2 studie



Obr.č.1. Algoritmus léčby lokálně pokročilého karcinomu jícnu. *CT počítačová tomografie; PET pozitronová emisní tomografie; GFS gastroduodenoskopie, EUS endoskopický ultrazvuk, M+ metastatické onemocnění*

Adaptováno dle ESMO guidelines 2016, 2022

Neoadjuvantní CH/RT Neo-AEGIS studie



Reynolds, J. *BMC Cancer* **17,** 401, (2017).

Neoadjuvantní CH/RT Neo-AEGIS studie

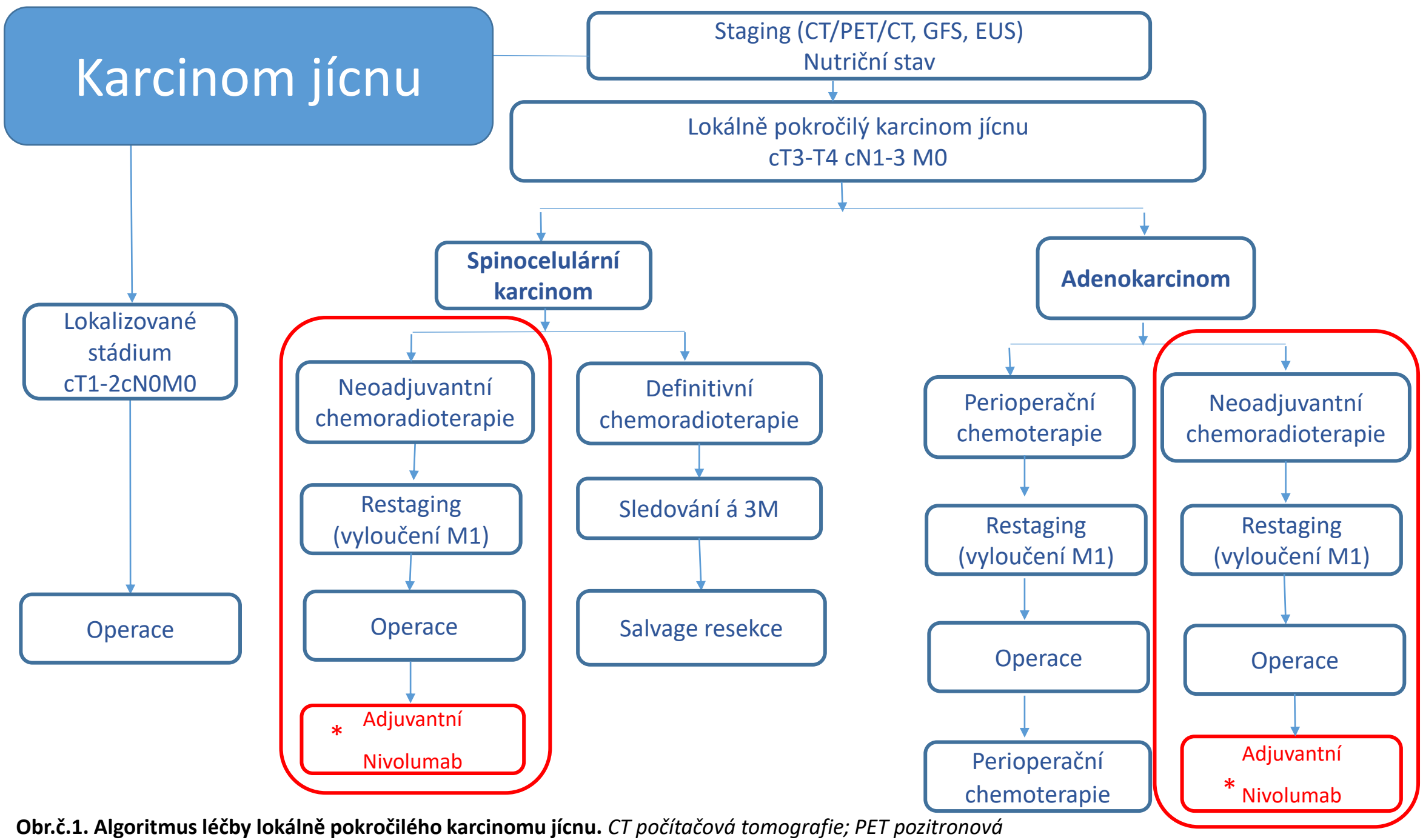
	Arm A (Magic/FLOT)	Arm B CROSS
R0 (negative margins)	82%	95%
ypN0	44.5%	60.1%
Tumor regression grade 1 & 2	12.1%	41.7%
Pathologic complete response	5%	16%
Neutropenia (Gr 3/4)	14.1%	2.8%
Neutropenic sepsis	2.7%	0.6%
Postoperative in-hospital deaths	3%	3%
Postoperative Pneumonia/ARDS	20%/0.6%	16%/4.3%
Anastomotic Leak	12%	11.7%
Clavien-Dindo > III<V	23.6%	22%

Medián sledování 24.5M

- pravděpodobnost 3-letého OS 56%(CROSS) a 57%(MAGIC/FLOT) [(HR 1.02 (95%CI. 0.74-1.42))]
- studie ukončena 12/2020
- po druhé futility analýze
- prokázana non-inferiorita

pouze kombinované chemoterapie

Reynolds, J JCO 39, no. 15_suppl (May 20, 2021) 4004-4004.



Obr.č.1. Algoritmus léčby lokálně pokročilého karcinomu jícnu. *CT počítačová tomografie; PET pozitronová emisní tomografie; GFS gastroduodenoskopie, EUS endoskopický ultrazvuk, M+ metastatické onemocnění*

Adaptováno dle ESMO guidelines 2016, 2022

Imunoterapie- nový standard léčby lokálně pokročilého karcinomu GEJ

- Adjuvance po trimodální léčbě:

Trimodální léčba:

chemoterapie
radioterapie
operace

CheckMate 577- design studie ADJUVANCE po trimodální léčbě

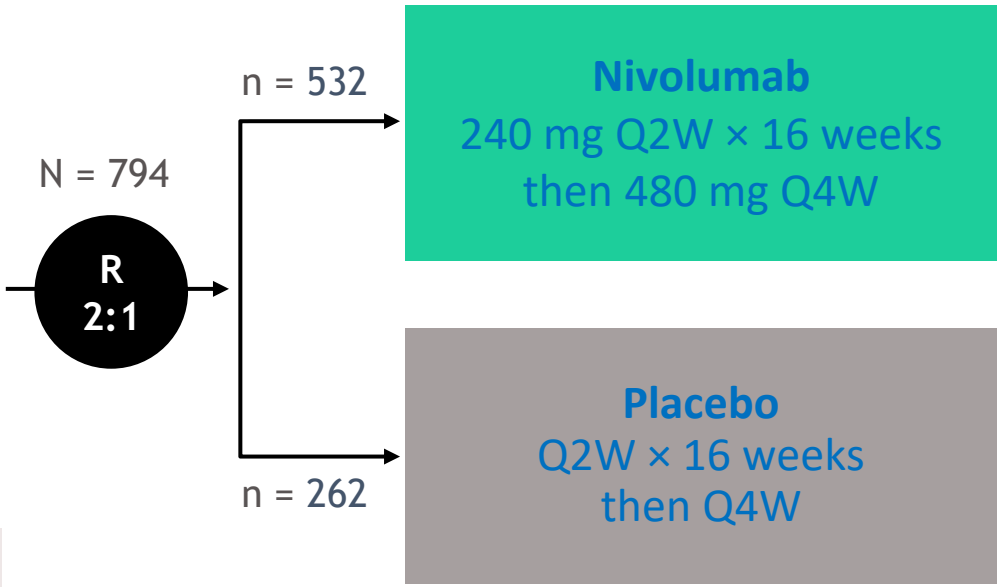
- **CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]**

Key eligibility criteria

- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0–1

Stratification factors

- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Primary endpoint:

- DFS[e]

Secondary endpoints:

- OS[f]
- OS rate at 1, 2, and 3 years

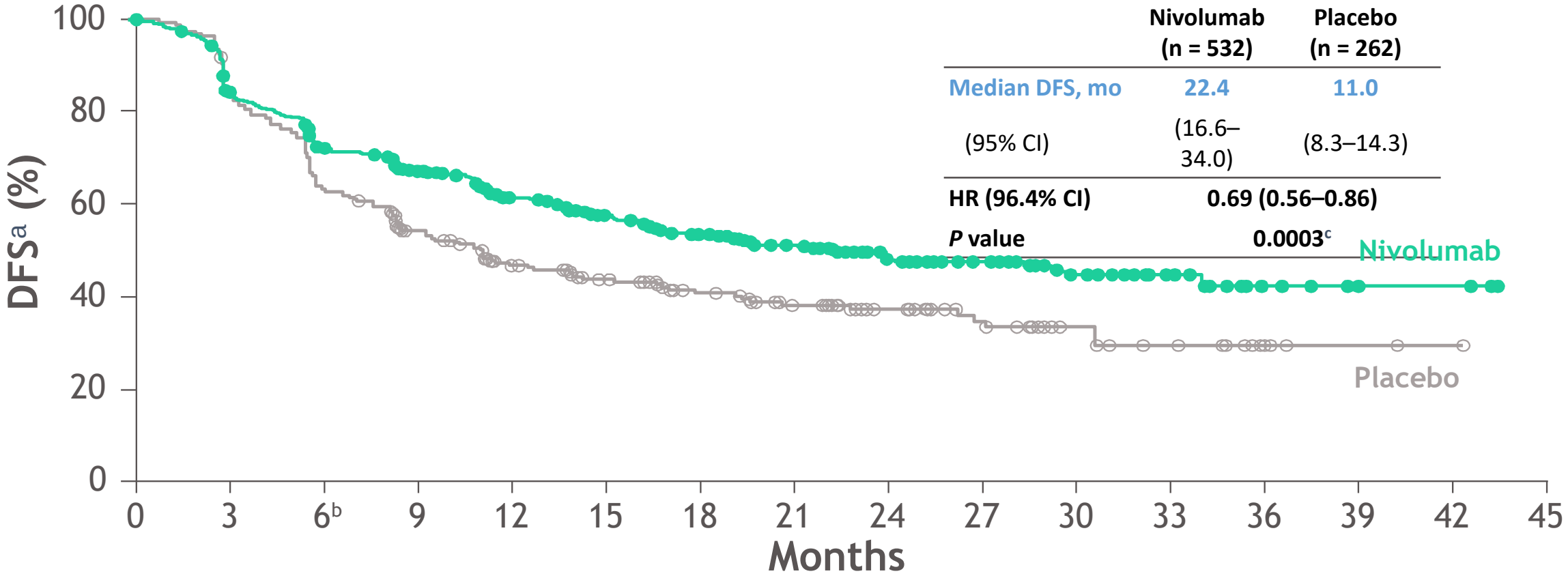
Total treatment duration of up to 1 year[d]

- Median follow-up was 24.4 months (range, 6.2–44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

Kelly et al. ESMO 2020 Presentation number LBA9

Disease-free survival



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6–34.0)	(8.3–14.3)
HR (96.4% CI)	**0.69 (0.56–0.86)**	
***P* value**	**0.0003[c]**	

No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the pre-specified interim analysis required the *P* value to be less than 0.036.

Kelly et al. ESMO 2020 Presentation number LBA9

Checkmate-577

Subgroup	No. of Patients	Median Disease-free Survival		Unstratified Hazard Ratio (95% CI)
		Nivolumab	Placebo	
		mo		
Overall	794	22.4	11.0	0.70 (0.58–0.86)
Histologic type				
Adenocarcinoma	563	19.4	11.1	0.75 (0.59–0.96)
Squamous-cell carcinoma	230	29.7	11.0	0.61 (0.42–0.88)
Tumor location at initial diagnosis				
Esophagus	462	24.0	8.3	0.61 (0.47–0.78)
Gastroesophageal junction	332	22.4	20.6	0.87 (0.63–1.21)

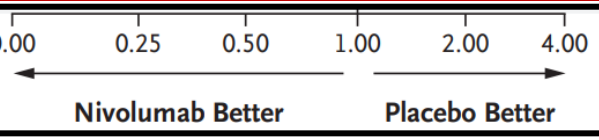
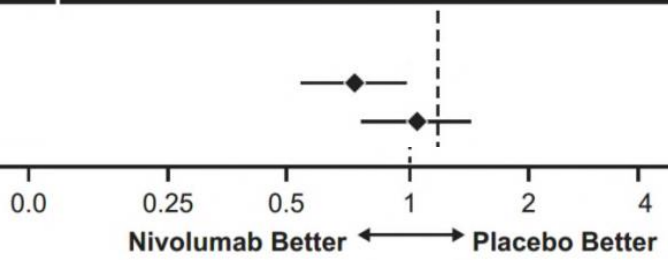


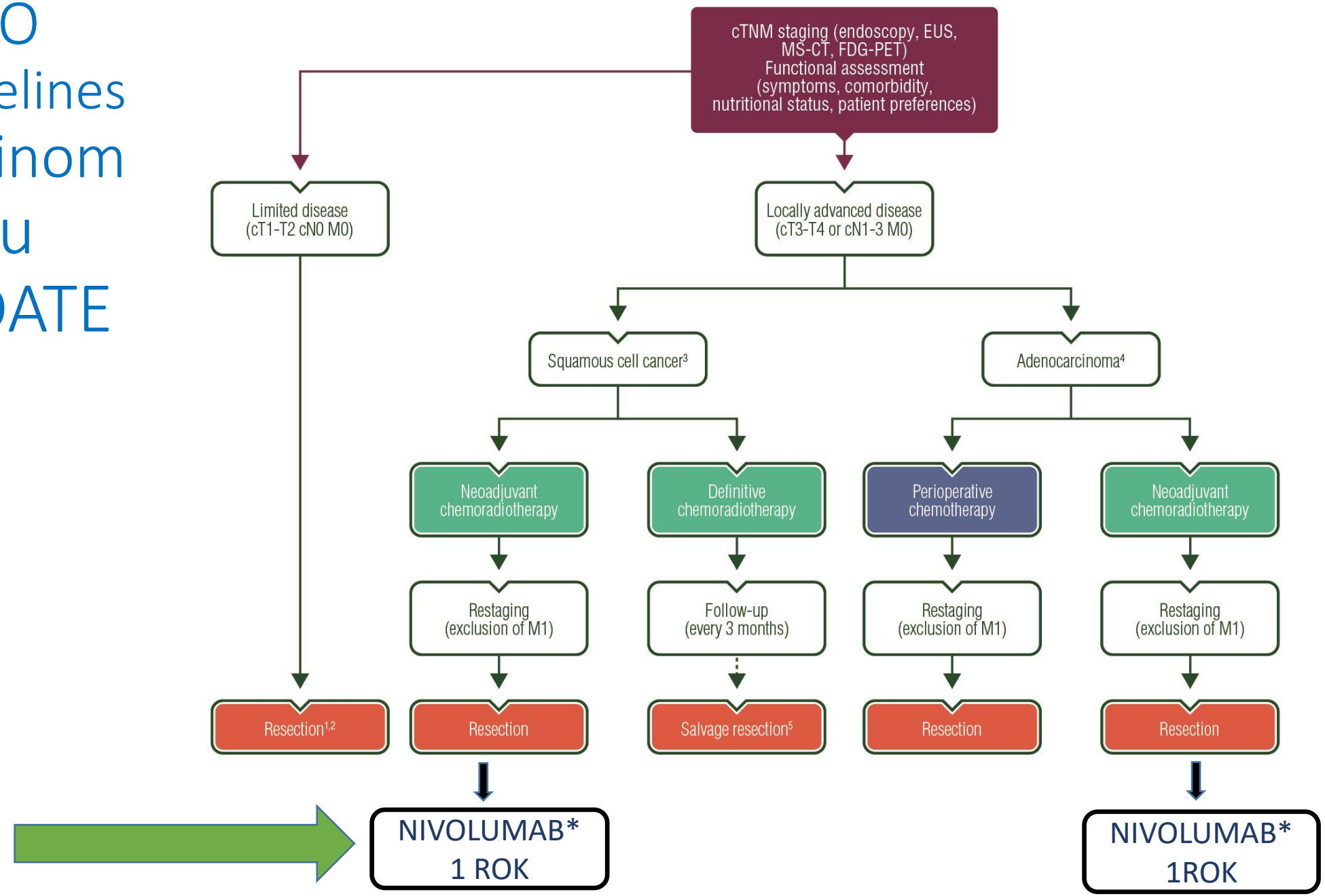
Figure S2. Post Hoc Assessment of Disease-free Survival by Subgroups.

Subgroup	Median Disease-free Survival, months		Unstratified Hazard Ratio (95% CI)
	Nivolumab	Placebo	
PD-L1 CPS expression			
≥5 (n = 371)	29.4	10.2	0.62 (0.46–0.83)
<5 (n = 295)	16.3	11.1	0.89 (0.65–1.22)



Kelly RJ et al., N Engl J Med. 2021 Apr 1; 384(13):1191-1203

ESMO Guidelines Karcinom jícnu UPDATE

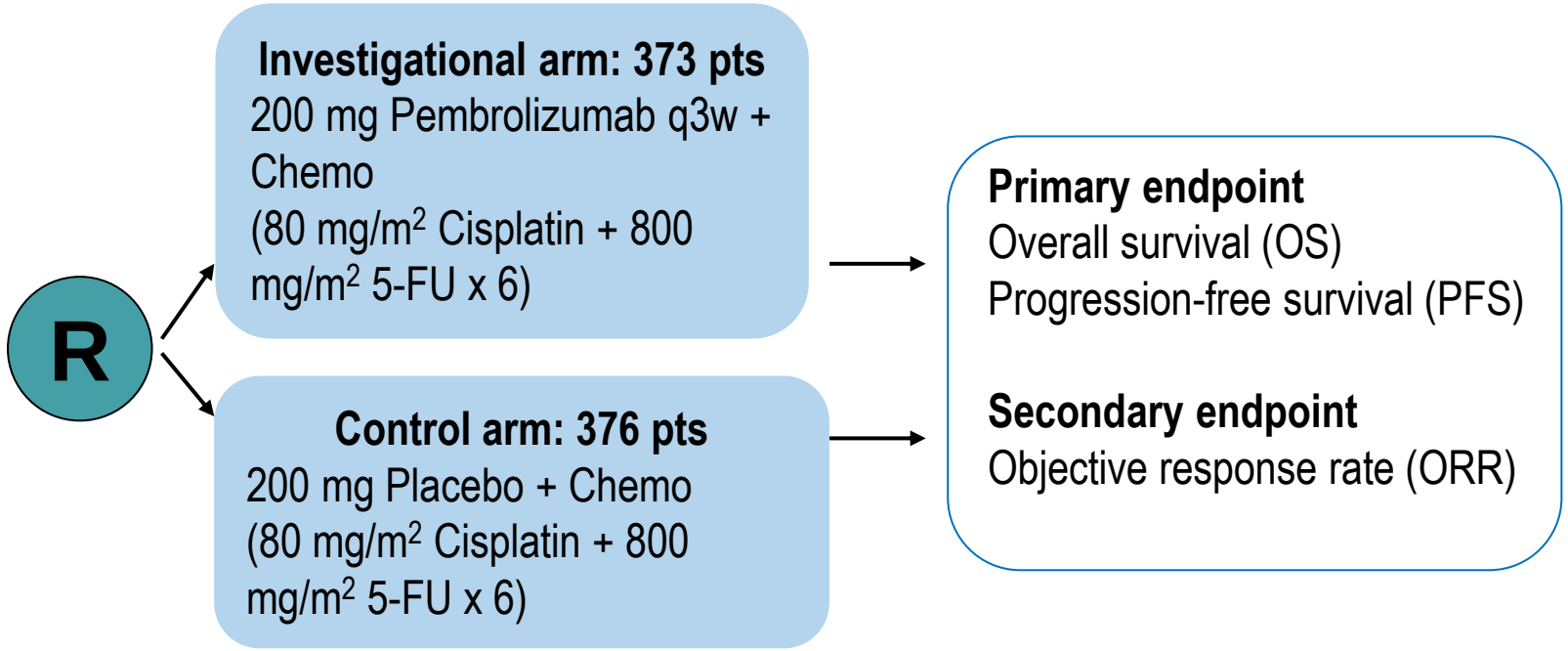


*v případě nádorových buněk v resekátu

Lordick et al. Ann Oncol 2016 a připravovaný ESMO guidelines update 2022

Keynote-590- 1.linie metastatického onemocnění

Fáze III: Pembro + Chemo vs Placebo + Chemo
Stádium IV karcinomu jícnu (ESCC a AC)

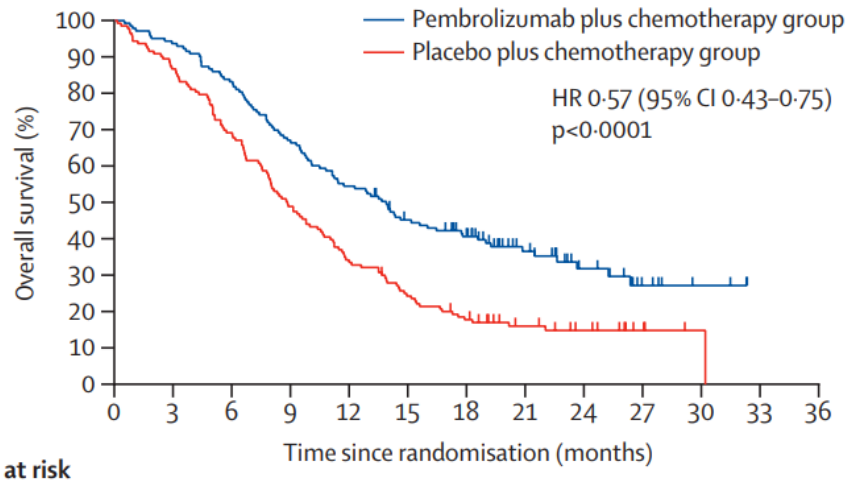


- Asia vs. Non-Asian countries
- Adenocarcinoma (AC) vs. Squamous Cell Carcinoma (ESCC)
- ECOG Performance-Index 0 vs. 1

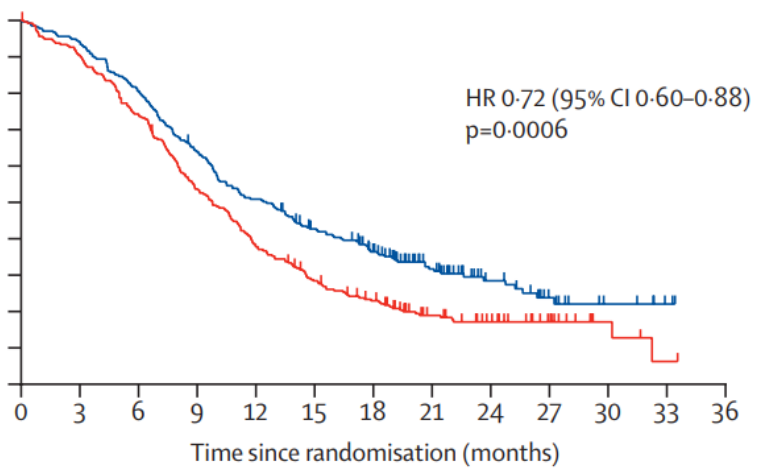
Sun JM et al., Lancet. 2021 Aug 28; 398(10302):759-771

Keynote-590- OS – skvamozní karcinom(ESCC)

ESCC PD-L1 CPS ≥10



ESCC



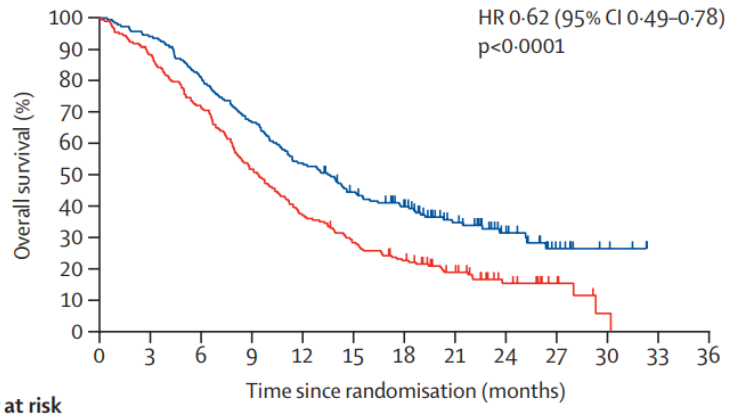
Number at risk (number censored)													
Pembrolizumab plus chemotherapy group	143 (0)	134 (0)	119 (0)	96 (0)	78 (0)	61 (4)	51 (8)	29 (25)	16 (35)	7 (42)	3 (46)	0 (49)	0 (49)
Placebo plus chemotherapy group	143 (0)	124 (0)	99 (0)	70 (0)	48 (0)	34 (1)	24 (2)	15 (9)	10 (13)	4 (19)	1 (22)	0 (22)	0 (22)

Pembrolizumab plus chemotherapy group	274 (0)	258 (0)	221 (0)	175 (1)	139 (1)	111 (7)	89 (13)	50 (43)	27 (62)	14 (71)	6 (78)	2 (82)	0 (82)
Placebo plus chemotherapy group	274 (0)	247 (1)	203 (1)	146 (2)	103 (2)	75 (5)	57 (9)	34 (23)	23 (31)	13 (42)	4 (50)	1 (51)	0 (51)

Sun JM et al., Lancet. 2021 Aug 28; 398(10302):759-771

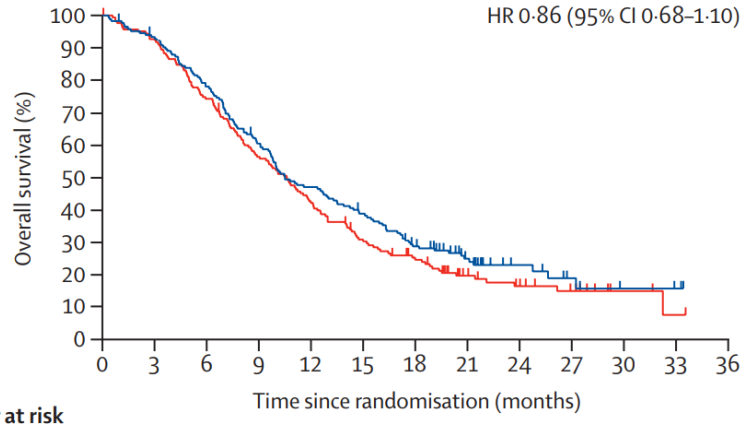
Keynote-590 – OS- skvamozní karcinom (ESCC) a adenokarcinom (AC)

ESCC a AC PD-L1 CPS ≥10



Number at risk (number censored)													
Pembrolizumab plus chemotherapy group	186 (0)	175 (0)	151 (0)	125 (0)	100 (0)	79 (4)	66 (9)	40 (28)	23 (42)	10 (52)	4 (58)	0 (58)	0 (58)
Placebo plus chemotherapy group	197 (0)	174 (0)	142 (0)	102 (0)	73 (0)	55 (1)	42 (3)	28 (11)	13 (22)	6 (29)	1 (32)	0 (32)	0 (32)

ESCC a AC PD-L1 CPS <10



Number at risk (number censored)													
Pembrolizumab plus chemotherapy group	175 (0)	162 (2)	135 (2)	104 (3)	81 (3)	66 (5)	47 (7)	26 (22)	12 (34)	6 (38)	3 (40)	2 (41)	0 (41)
Placebo plus chemotherapy group	172 (0)	159 (1)	127 (1)	96 (2)	72 (2)	51 (4)	38 (8)	21 (17)	14 (21)	9 (25)	3 (31)	1 (32)	0 (32)

Sun JM et al., Lancet. 2021 Aug 28; 398(10302):759-771

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Oesophageal carcinoma

Keytruda, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10 (see section 5.1).

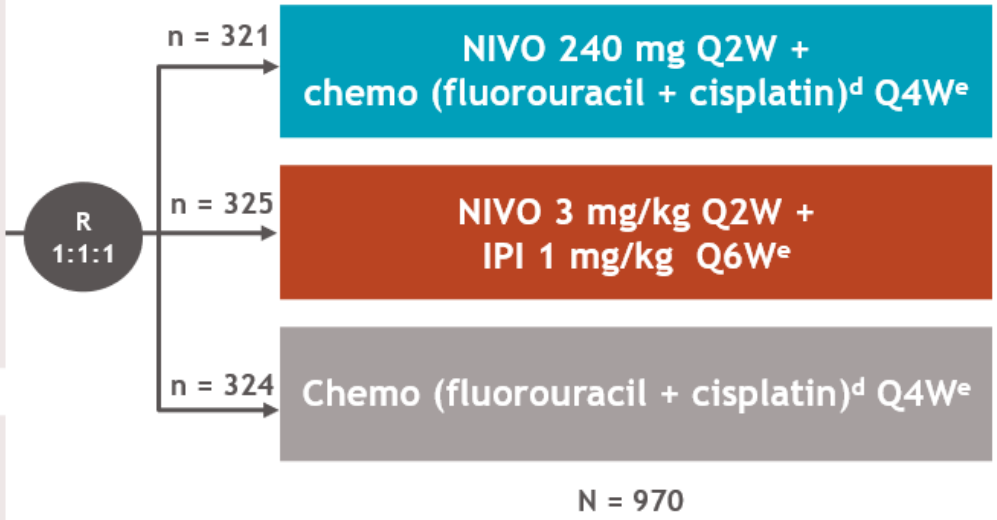
Není úhrada v ČR

ESOPHAGEAL CANCER – CHECKMATE-648

Checkmate-648: Randomized global Phase III – First-line esophageal squamous cell cancer

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[g]

[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [f]Per blinded independent central review (BICR); [g]Time from last patient randomized to clinical data cutoff.

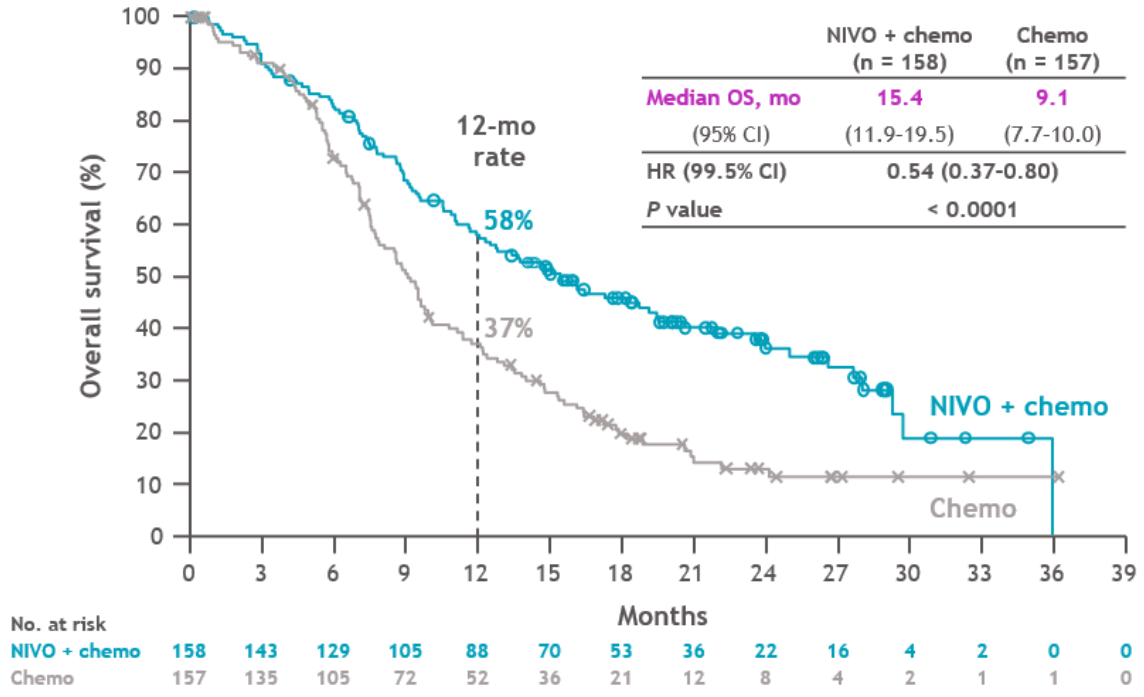
Chau I et al *ASCO* 2021; LBA 4001

ESOPHAGEAL CANCER – CHECKMATE-648

Checkmate-648: Randomized global Phase III – First-line esophageal squamous cell cancer

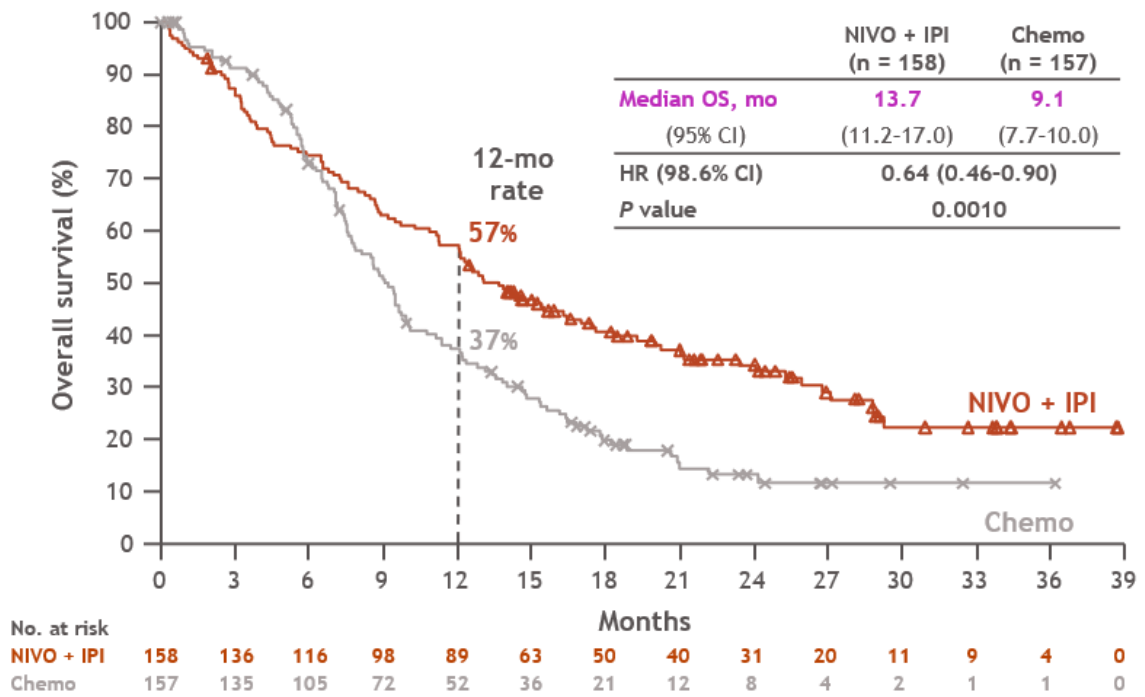
Nivolumab + Chemo versus Chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



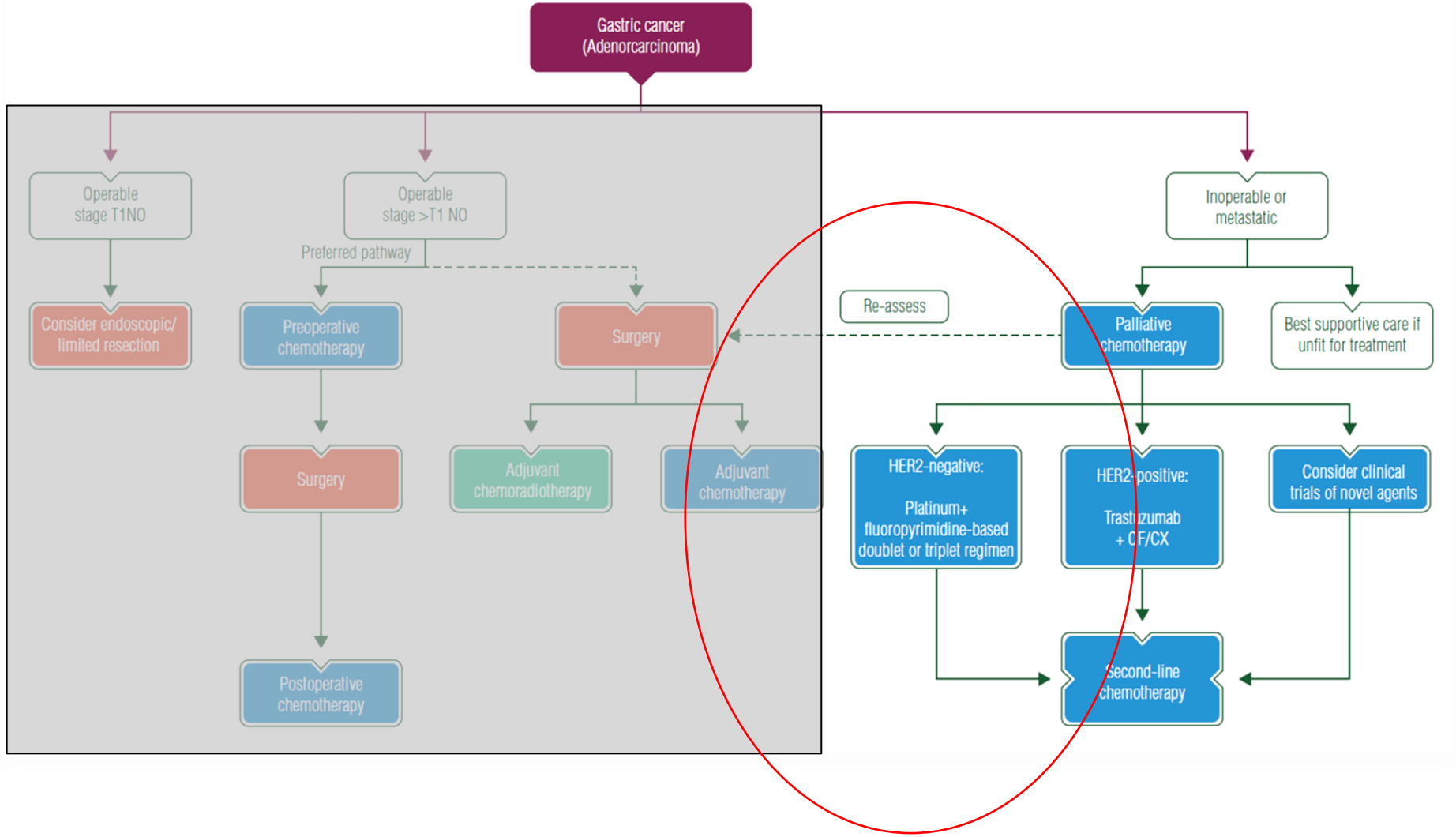
Nivolumab + Ipilimumab versus Chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



Chau I et al ASCO 2021; LBA 4001

Karcinom žaludku- ESMO Guidelines



Smyth EC et al. Ann Oncol 2016 Sep;27(suppl 5):v38-49

IMUNOTERAPIE
CheckMate 649 -1.linie adenokarcinom žaludku

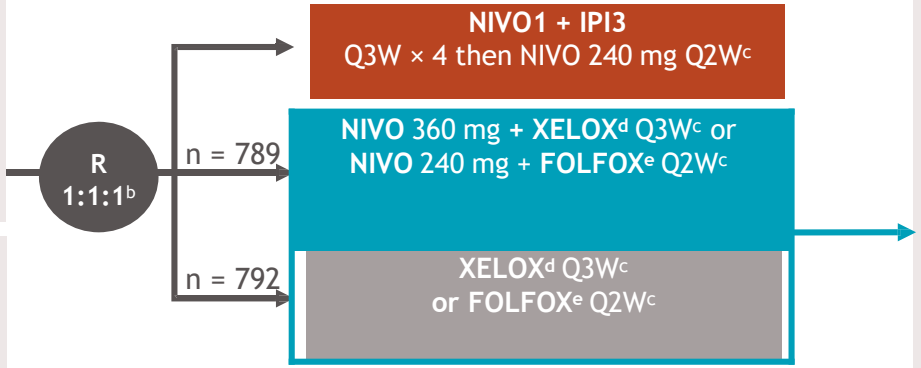
ESMO 2021: F-U 24měsíců, publikace výsledků z ramene ipilimumab/nivolumab, MSI-high/dMMR podskupina

CheckMate 649: study design[1-4]

Randomized, open-label, phase 3 study of nivolumab plus ipilimumab, or nivolumab plus chemotherapy, versus chemotherapy in gastric/gastroesophageal junction cancer and esophageal adenocarcinoma[1-3]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0–1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[a])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



- **Global: N = 1581, including 955 patients (60%) with PD-L1 CPS ≥ 5[1,2]**
- **Chinese subgroup[f]: n = 208, including 156 patients (75%) with PD-L1 CPS ≥ 5[3]**

Dual primary endpoints:
- OS and PFS[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- OS (PD-L1 CPS ≥ 1 or all randomized)
- OS (PD-L1 CPS ≥ 10)
- PFS[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- ORR[g]

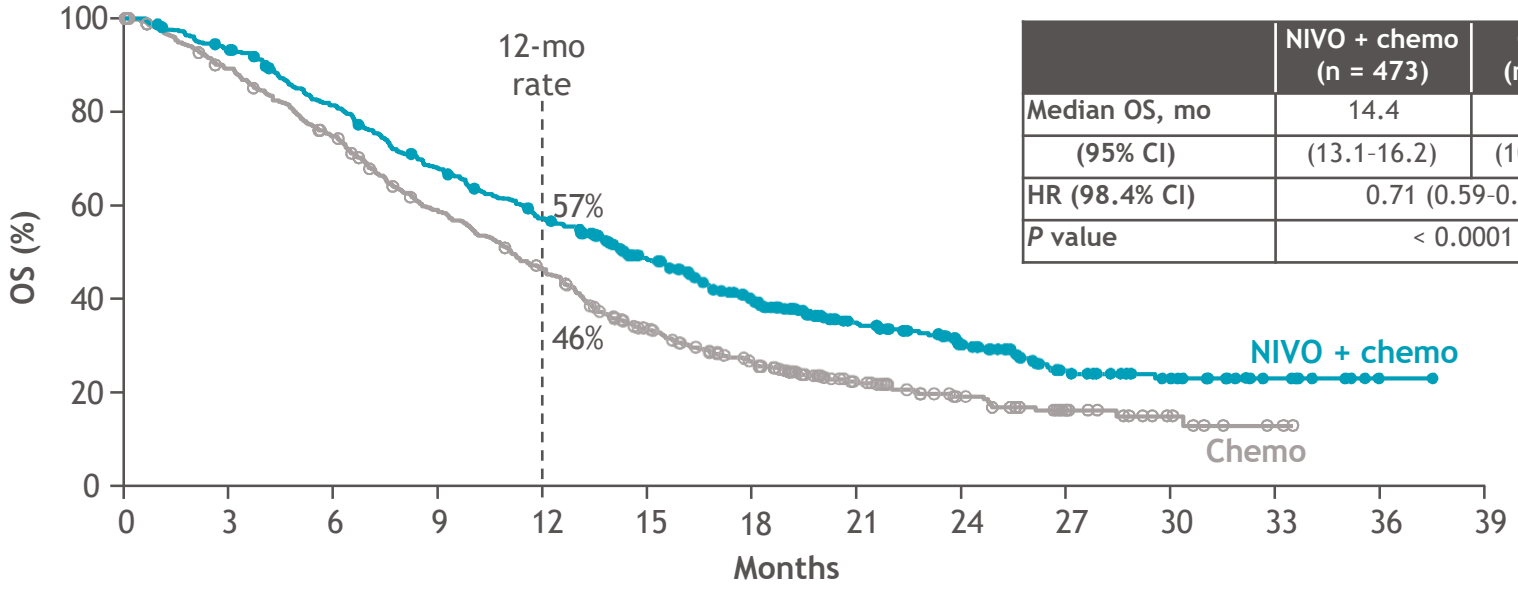
Exploratory endpoints:
- Safety
- QoL (TTSD, FACT-Ga GP5)

- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]
- Per protocol, the results of the NIVO + IPI arm will be evaluated at the final analysis

[a]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako). [b]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed. [c]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years. [d]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14). [e]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1–2). [f]Chinese by race and enrolled from mainland China. [g]BICR assessed. [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff. Abbreviations and references in speaker notes.

Overall survival

Primary endpoint (PD-L1 CPS ≥ 5)



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P value	< 0.0001	

No. at risk														
NIVO + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

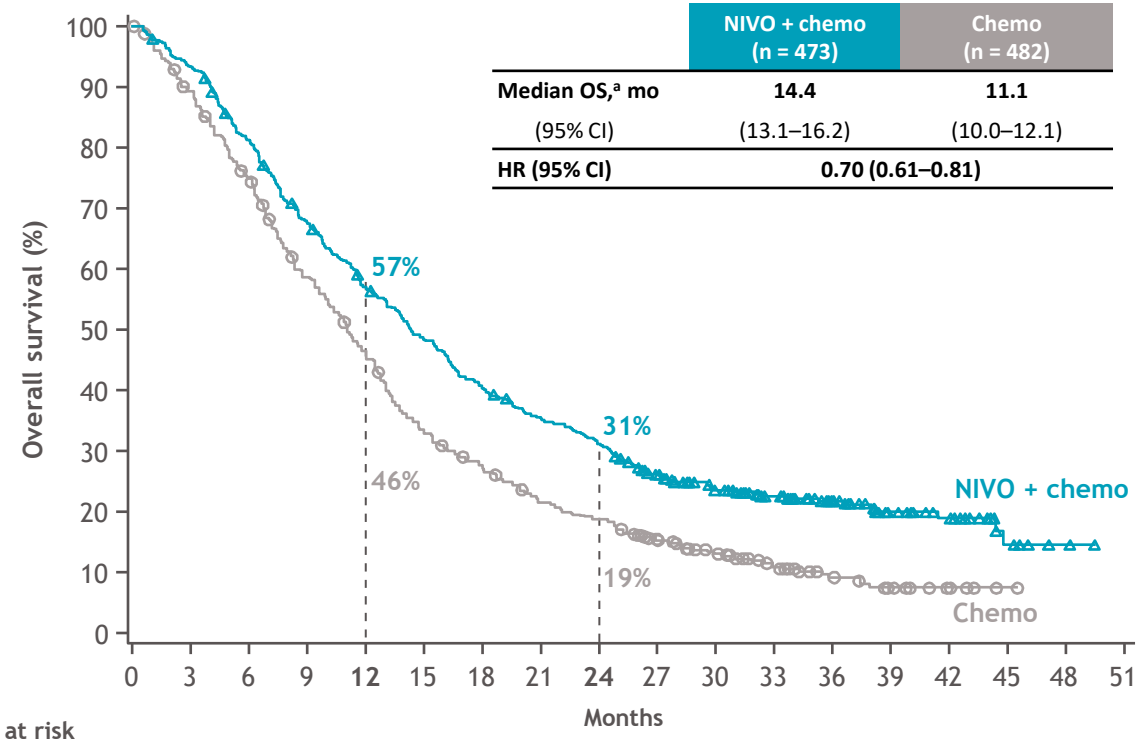
- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

Moehler M et al. Oral presentation at ESMO; September 19-21, 2020; Virtual. Abstract 3047.

Celkové přežití: NIVO + chemo vs chemo- F-U 24 měsíců

PD-L1 CPS ≥ 5

	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS,[a] mo	**14.4**	**11.1**
(95% CI)	(13.1–16.2)	(10.0–12.1)
HR (95% CI)	**0.70 (0.61–0.81)**	

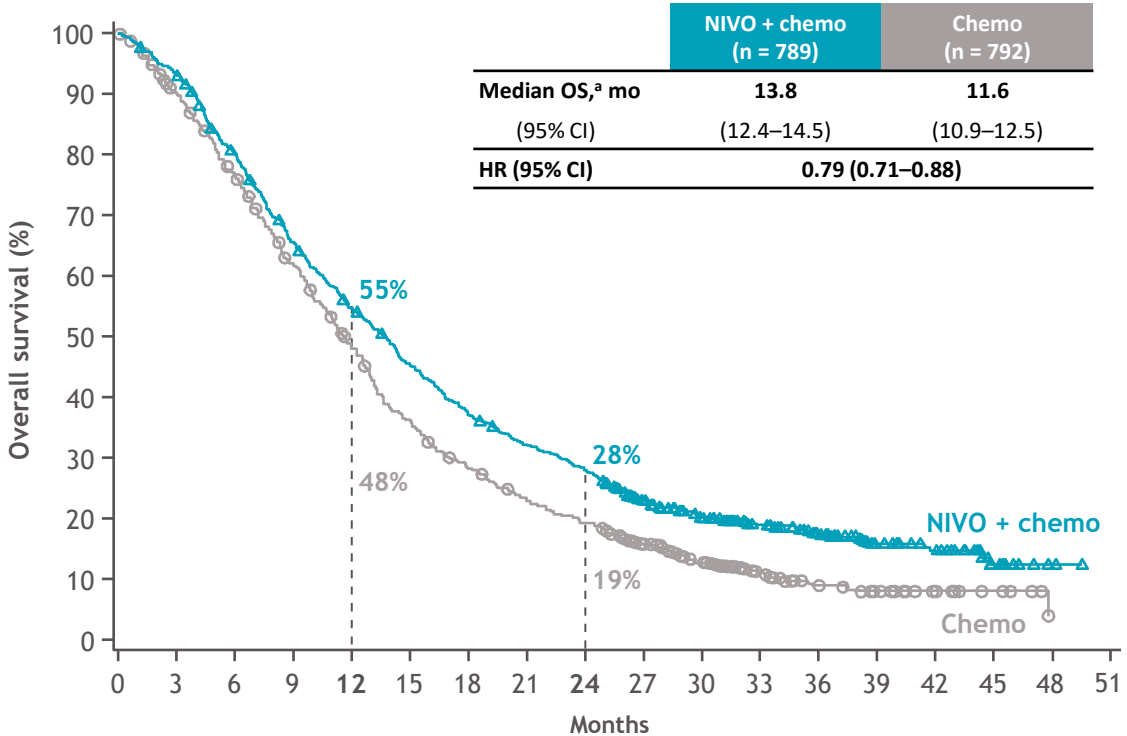


No. at risk

NIVO + chemo	473	440	380	315	263	223	187	161	141	107	81	61	43	26	19	6	2	0
Chemo	482	424	353	275	215	154	125	97	83	62	46	31	18	11	6	1	0	0

All randomized

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS,[a] mo	**13.8**	**11.6**
(95% CI)	(12.4–14.5)	(10.9–12.5)
HR (95% CI)	**0.79 (0.71–0.88)**	



	789	733	624	508	422	349	287	246	212	156	115	84	57	33	25	9	2	0
	792	701	591	475	364	273	215	170	144	103	72	46	28	20	12	6	0	0

- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up
  - PD-L1 CPS ≥ 5: 30% reduction in the risk of death and 12% improvement in 24-month OS rate
  - All randomized: 21% reduction in the risk of death and 9% improvement in 24-month OS rate
  - Directionally improved HRs relative to the 12-month follow-up (PD-L1 CPS ≥ 5, 0.71 [98.4% CI, 0.59-0.86]; all randomized, 0.80 [99.3% CI, 0.68-0.94])[1]

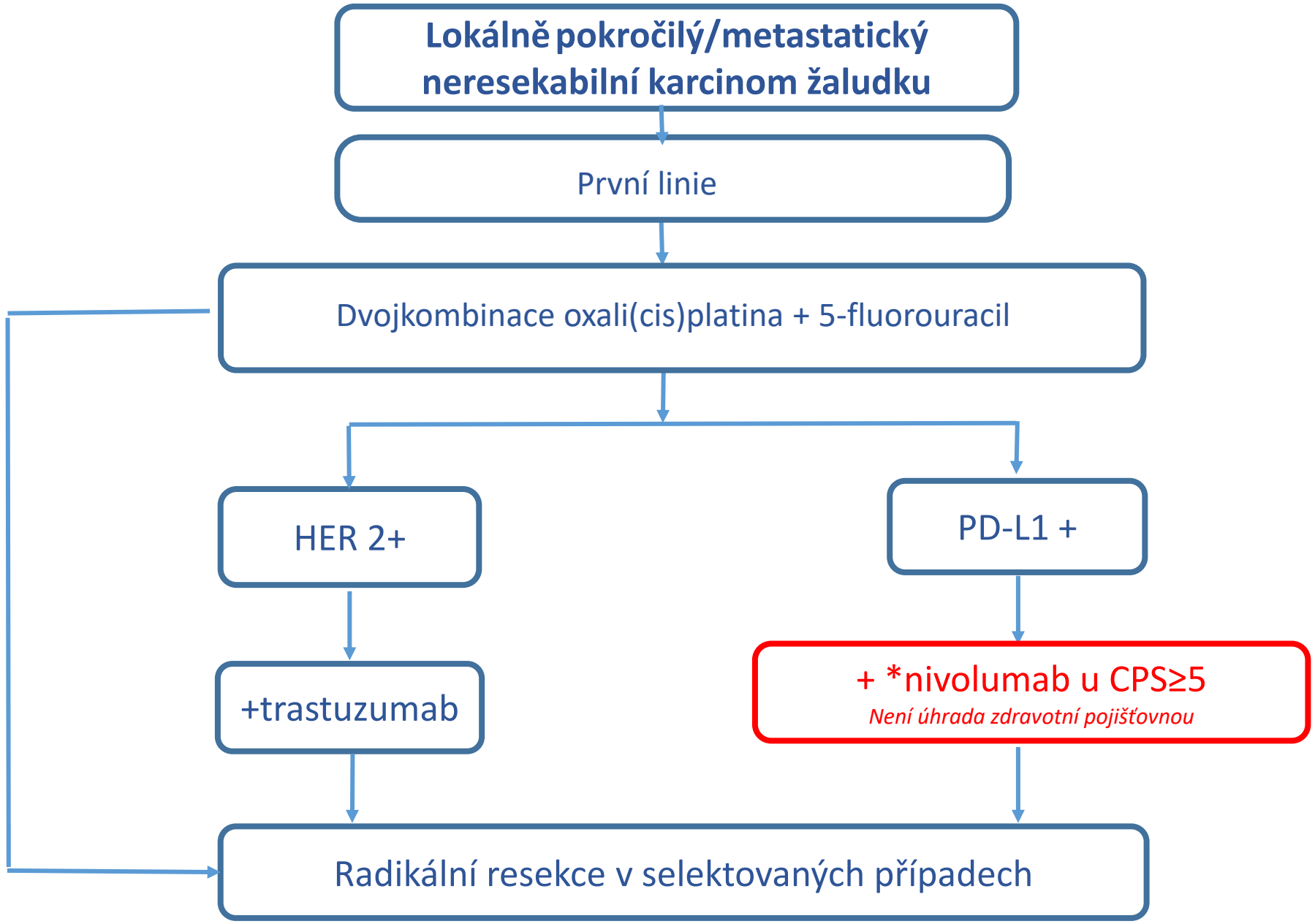
Janjigian YY, et al. Lancet 2021;398:27-40

CheckMate 649 – analýza podskupin

A Overall survival

Population*	Median overall survival, months		Unstratified hazard ratio for death (95% CI)	Interaction test p value
	Nivolumab plus chemotherapy	Chemotherapy alone		
Overall (N=1581)	13·8	11·6	0·79 (0·70–0·89)	
PD-L1 CPS <1 (n=265)	13·1	12·5	0·92 (0·70–1·23)	
PD-L1 CPS ≥1 (n=1296)	14·0	11·3	0·76 (0·67–0·87)	0·2041
PD-L1 CPS <5 (n=606)	12·4	12·3	0·94 (0·78–1·13)	
PD-L1 CPS ≥5 (n=955)	14·4	11·1	0·70 (0·60–0·81)	0·0107†

Janjigian YY et al., Lancet. 2021 Jul 3; 398(10294):27-40 (suppl.)

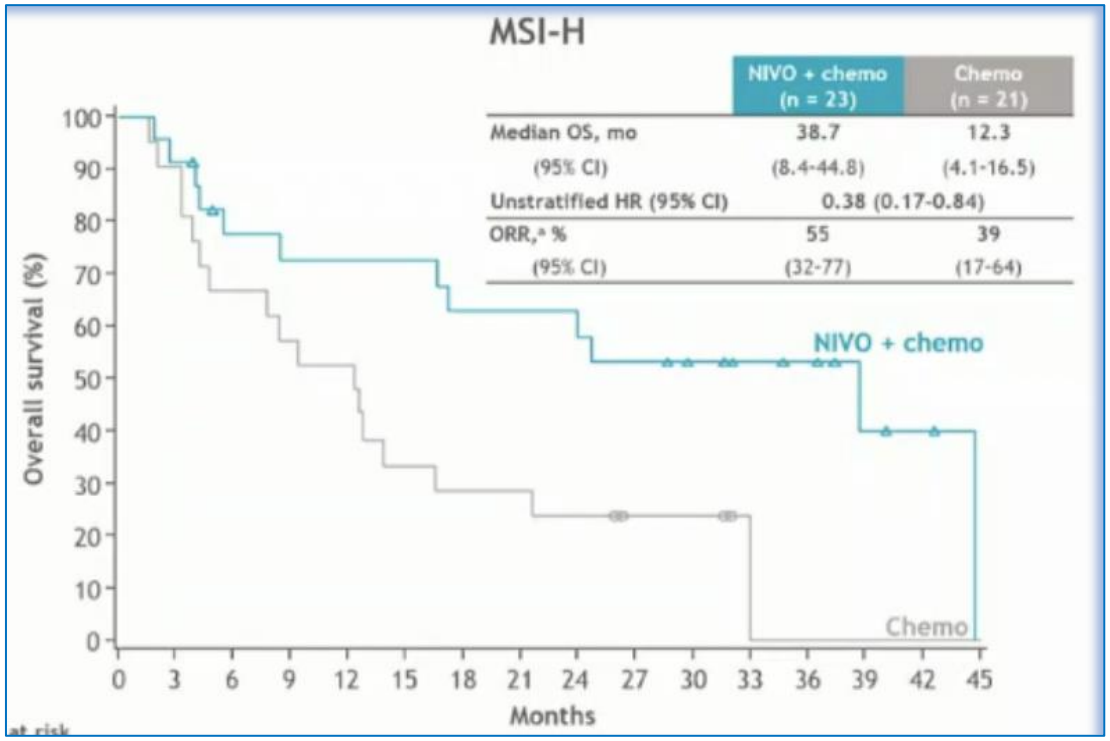


Obr. č 2. Algoritmus první linie léčby lokálně pokročilého neresekabilního či metastatického karcinomu žaludku: *HER2 receptor pro lidský epidermální růstový faktor 2; ligand membránového proteinu programované buněčné smrti 1 (PD-L1), CPS kombinovaná pozitivní skóre*

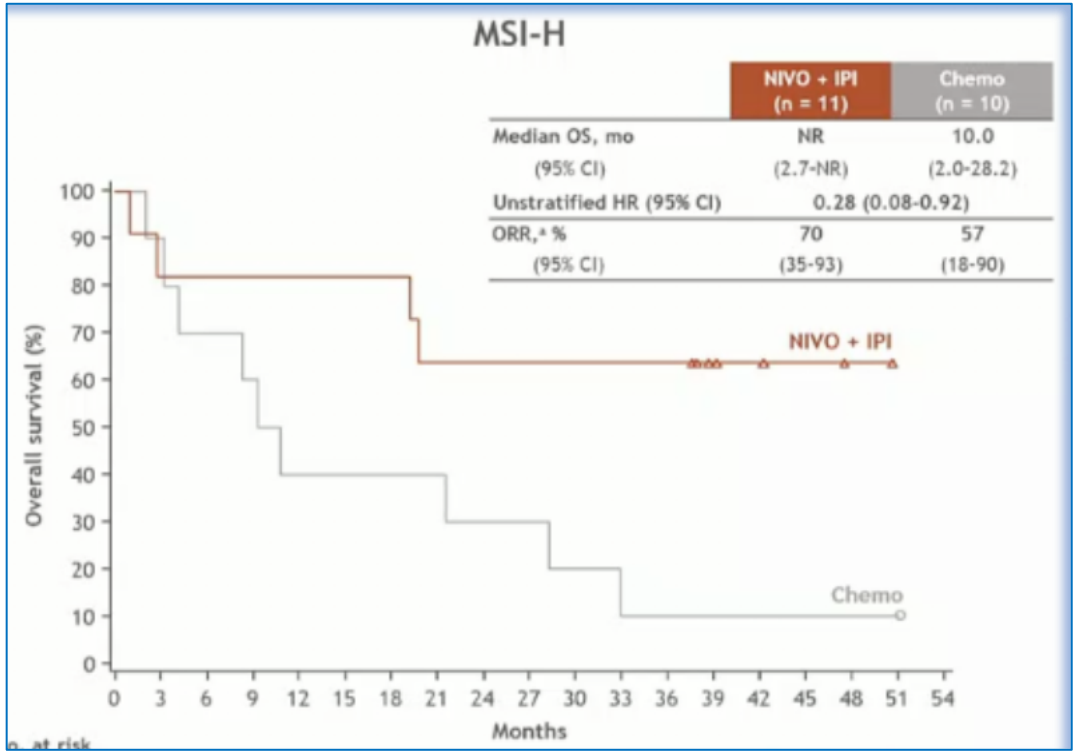
Adaptováno dle ESMO guidelines 2022

CheckMate 649 analýza dle MSI-high/dMMR

Nivo + Chemo



Nivo + Ipi



Janjigian Y ESMO2021

MSI-High adenokarcinom žaludku(NEONIPIGA)

Perioperační imunoterapie

ASCO Gastrointestinal Cancers Symposium

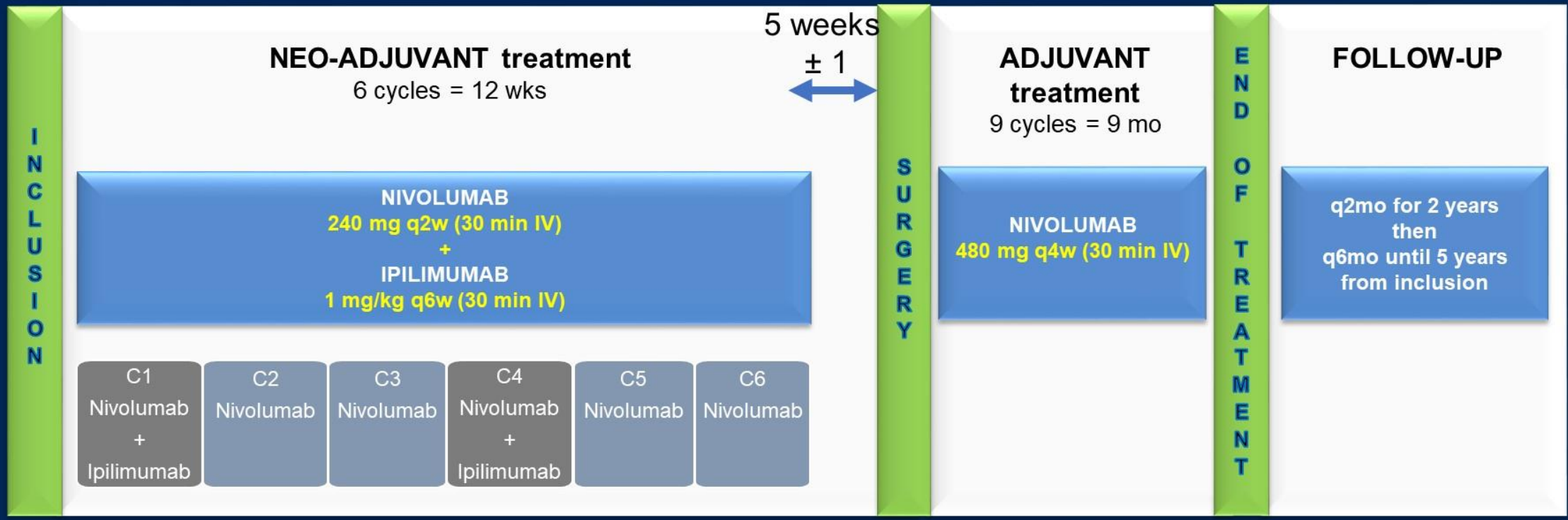
Neo-adjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients (pts) with localized MSI/dMMR gastric or oeso-gastric junction (G-OGJ) adenocarcinoma NEONIPIGA phase II GERCOR study

T André,[1] D Tougeron, G Piessen, C de la Fouchardière, C Louvet, A Adenis, M Jary, C Tournigand, T Aparicio, J Desrame, A Lièvre, ML Garcia-Larnicol, T Pudlarz, J Henriques, R Cohen, J Lefèvre, M Svrcek

[1]Sorbonne University, Saint-Antoine Hospital, Department of Medical Oncology, Paris, France

NEONIPIGA: Study design/metods

- Phase II study evaluating efficacy of neo-adjuvant nivolumab and ipilimumab followed by adjuvant nivolumab in pts with resectable OGA MSI/dMMR, T2-T4 NxM0
- The primary objective was pathological complete response rate (pCRR).



ClinicalTrials.gov: NCT04006262

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Results (1): Surgery and TNM and Tumor Regression Grading (TRG)

Type of surgery (N=29)	N	%
R0	29	100
Total oesogastrectomy	1	3,5
Total gastrectomy	7	24
4/5 gastrectomy	9	31
Lewis-Santy procedure	11	38
Pancreaticoduodenectomy	1	3,5

ypT stage (N=32)	
ypT0*	19
ypT1a	1
ypT1b	2
ypT2	2
ypT3	5
unknown**	3
ypN stage (N=32)	
ypN0	23
ypN1	6
unknown*	3

TRG Mandard (N=29)	N	%
TRG 1: complete regression/fibrosis with no tumor cells	17	58.6
TRG 2: fibrosis with scattered tumor cells	4	13.8
TRG 3: fibrosis and tumor cells with a dominance of fibrosis	2	6.9
TRG 4: fibrosis & tumor cells with dominance of tumor cells	4	13.8
TRG 5: tumor without evidence of regression	2	6.9
TRG Becker (N=29)		
TRG 1a: complete tumor regression without residual tumor	17	58.6
TRG 1b: < 10% residual tumor per tumor bed	4	13.8
TGR 2: 10% to 50% residual tumor	2	6.9
TRG 3: > 50% residual tumor cells	6	21.7

- * 2 patients ypT0 and ypN1 (residual tumoral cells < 10% in only one node)
- ** 3 patients without surgery, 1 in metastatic PD and 2 in complete response in endoscopy with no tumoral cell on biopsy

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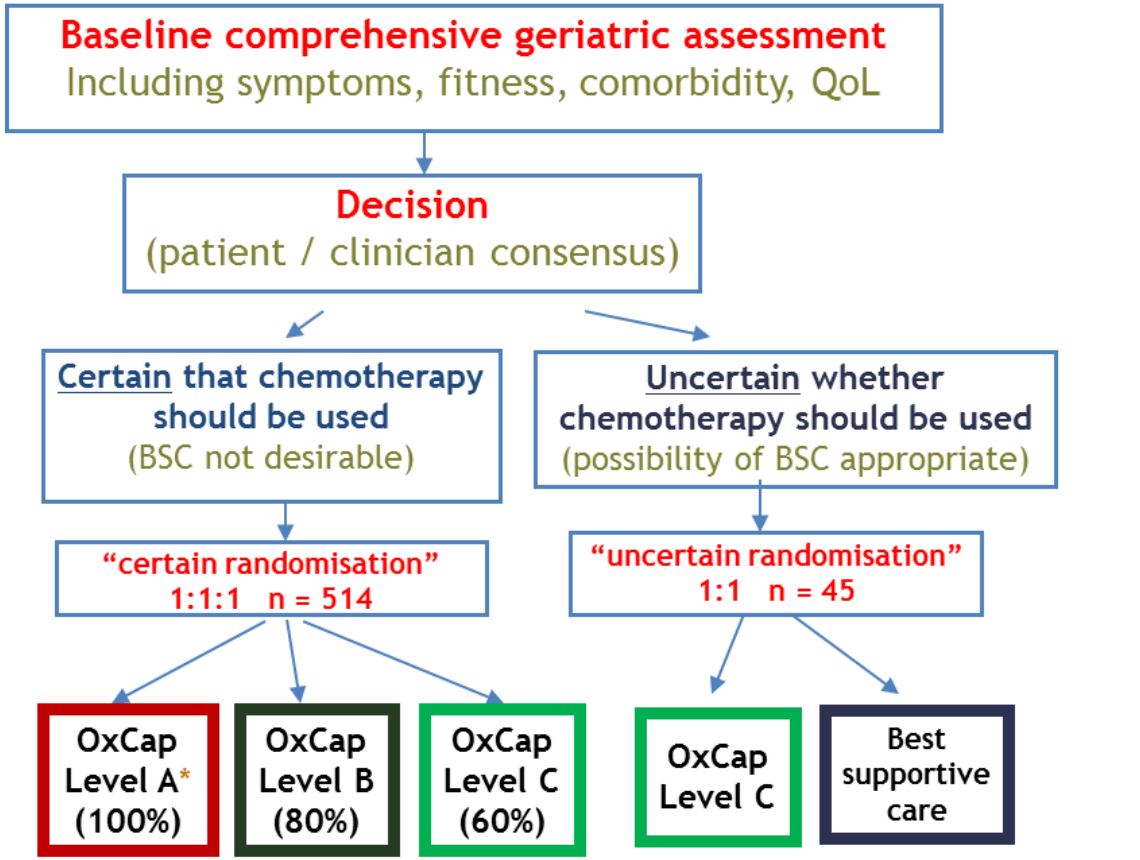
Závěry- NEONIPIGA

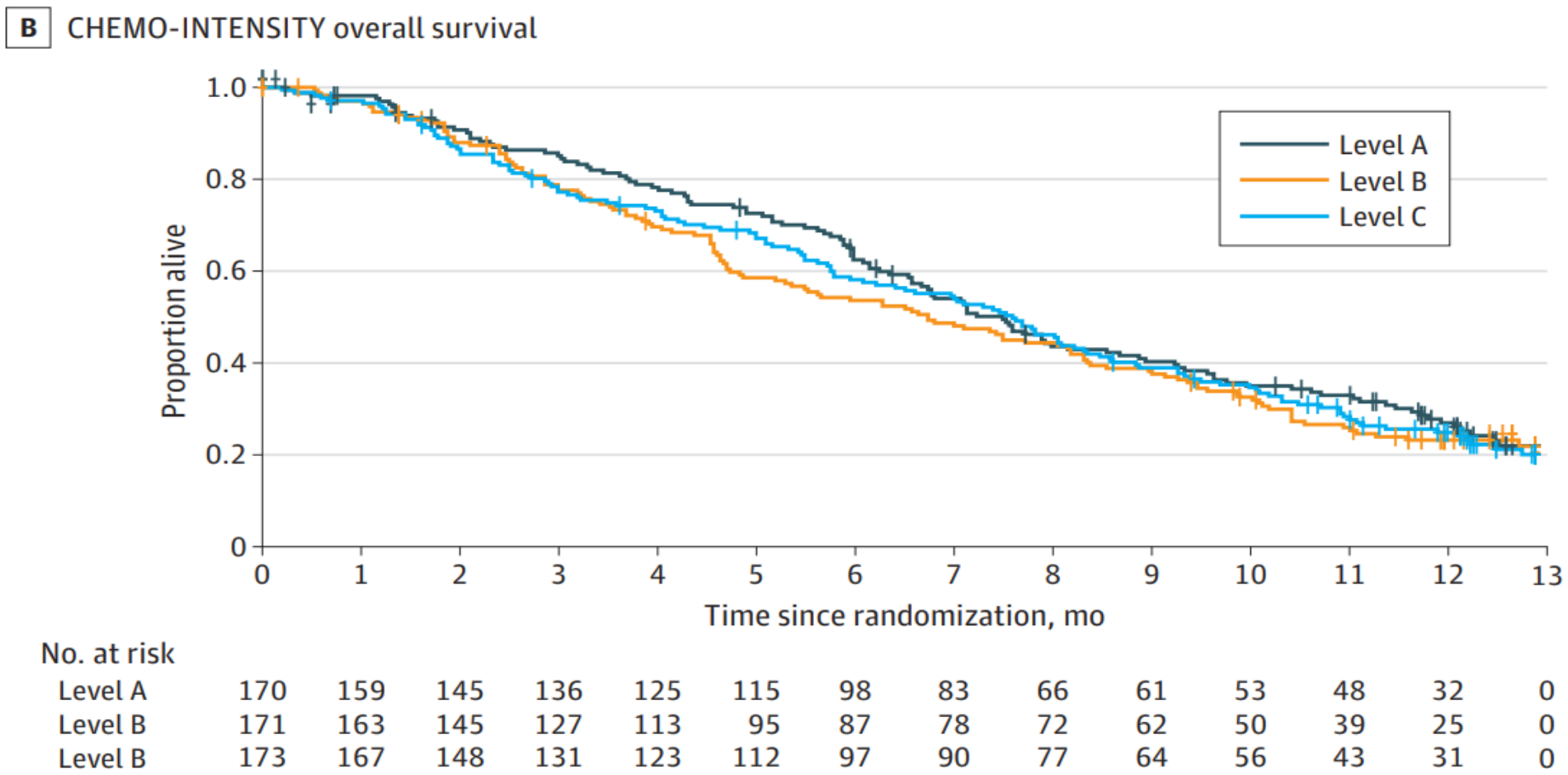
- Splněn primární cíl- 59%patologických kompletních remisí
- Perioperační imunoterapie nezpůsobuje vyšší počet perioperačních komplikací
- Při F-U 12M je 94% pacientů bez relapsu onemocnění
- Stran bezpečnosti- 25% G3-4 TRAE
- Otázkou je, zda a u kterých pacientů lze vynechat operaci

GO2 – „křehcí pacienti“



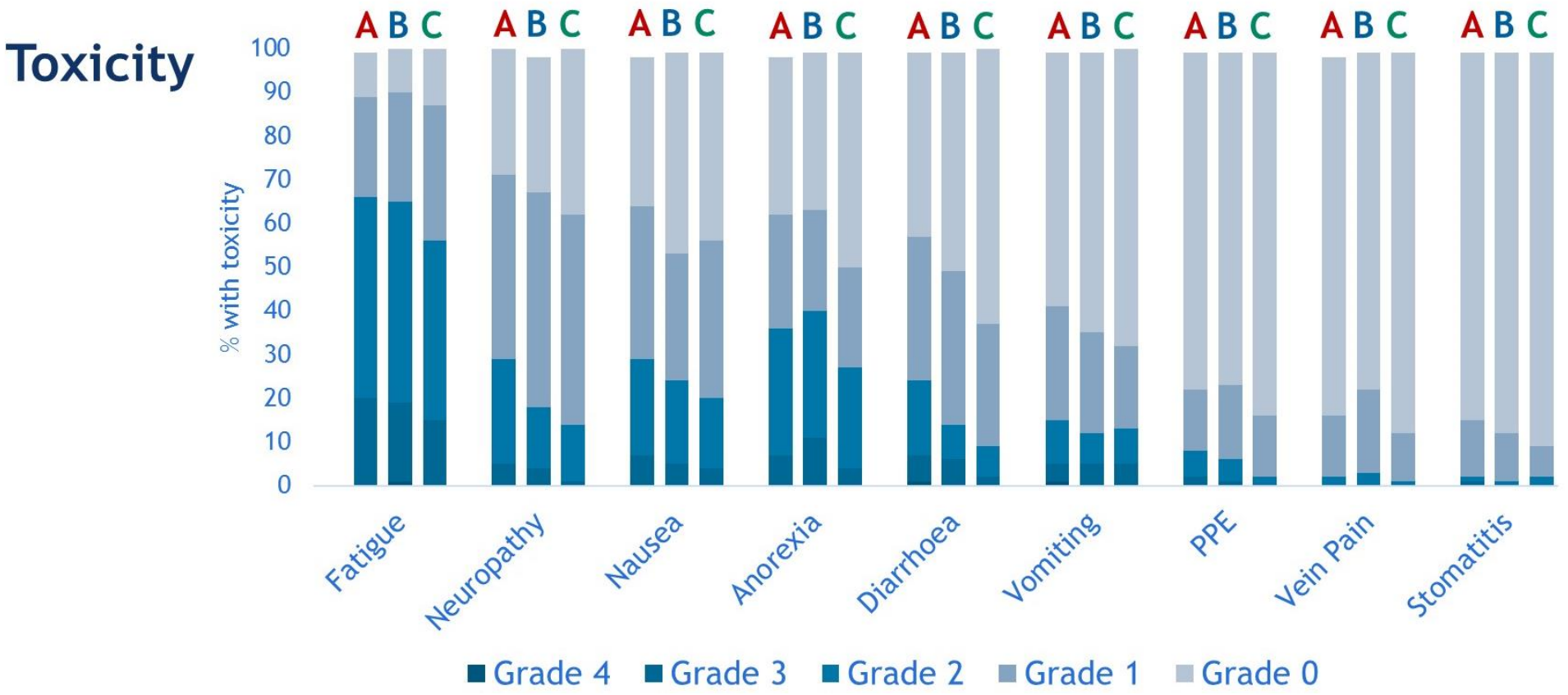
Hall PS et al., JAMA Oncol. 2021 Jun 1; 7(6):869-877

GO2 – „křehcí pacienti“



Hall PS et al., JAMA Oncol. 2021 Jun 1; 7(6):869-877

GO2 – „křehcí pacienti“

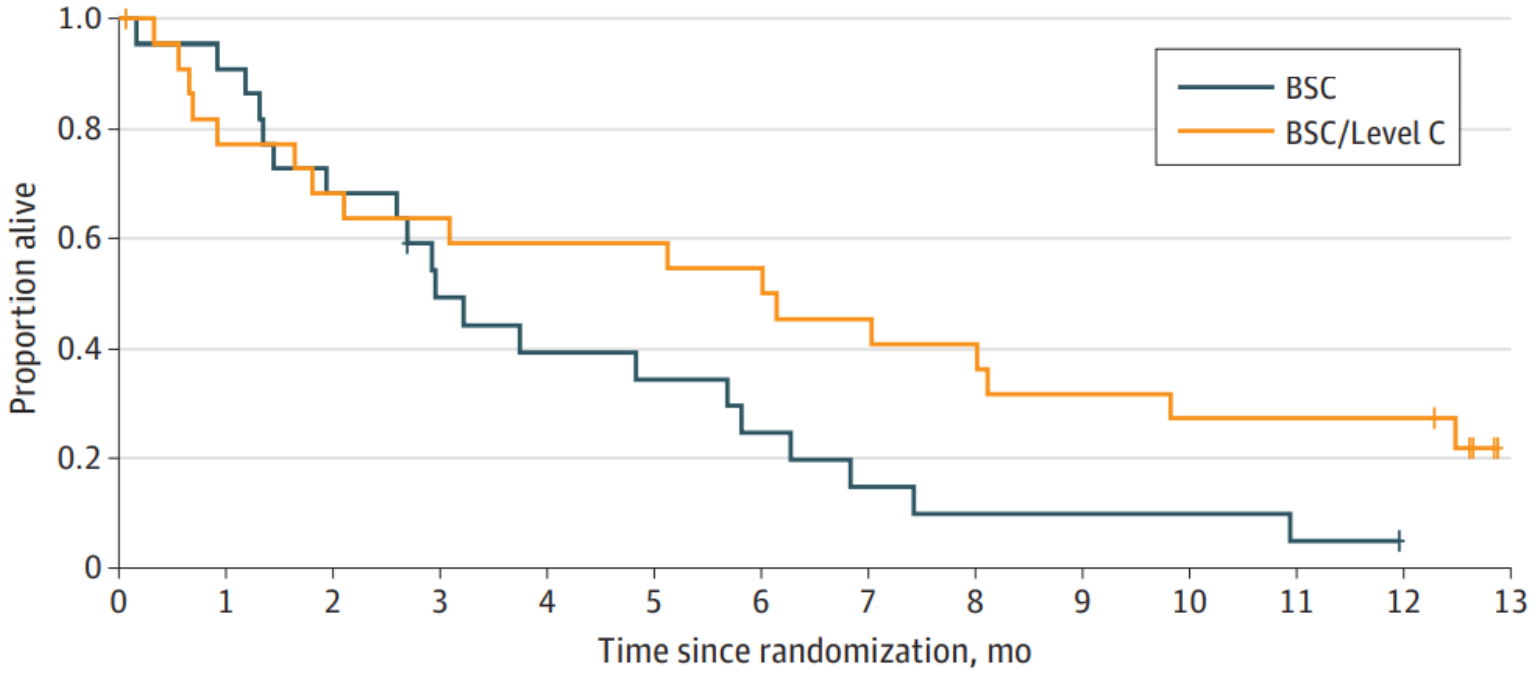


Hall PS et al., JAMA Oncol. 2021 Jun 1; 7(6):869-877

GO2 – „křehcí pacienti“

Skupina- nejisté indikace

C CHEMO-BSC overall survival



No. at risk

BSC	22	20	15	10	8	7	5	3	2	2	2	1	0
BSC/Level C	23	17	15	14	13	13	12	10	9	7	6	6	6	0

Hall PS et al., JAMA Oncol. 2021 Jun 1; 7(6):869-877

Závěry I
Lokálně pokročilý karcinom jícnu a žaludku

- U lokálně pokročilého karcinomu jícnu a a gastroesofageální junkce je u pacientů, u nichž nedošlo k úplné patologické kompletní remisi předoperační terapií, standardem adjuvantní imunoterapie nivolumabem (1 rok)

- Standardem lokálně pokročilého adenokarcinomu jícnu je perioperační chemoterapie nebo předoperační chemoradioterapie

- Standardem léčby lokálně pokročilého adenokarcinomu žaludku je perioperační chemoterapie (otázkou je, zda u MSI-High karcinomů)

Závěry pro praxi
Metastatický karcinom žaludku

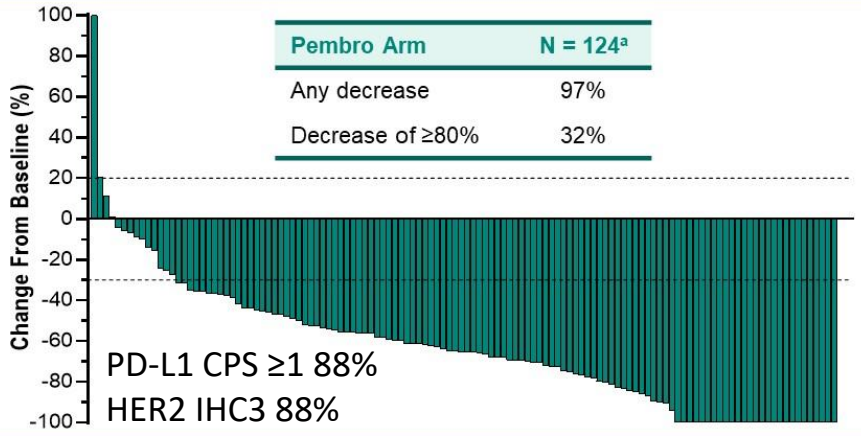
- Nivolumab + chemoterapie = budoucí standard u skupiny HER2 neg a CPS≥5
- Všichni pacienti by měli být testováni na MSI-high/dMMR (*nutnost CHT?)*
- U „křehkých pacientů“ možná redukce dávky na 60% bez kompromitace efektu

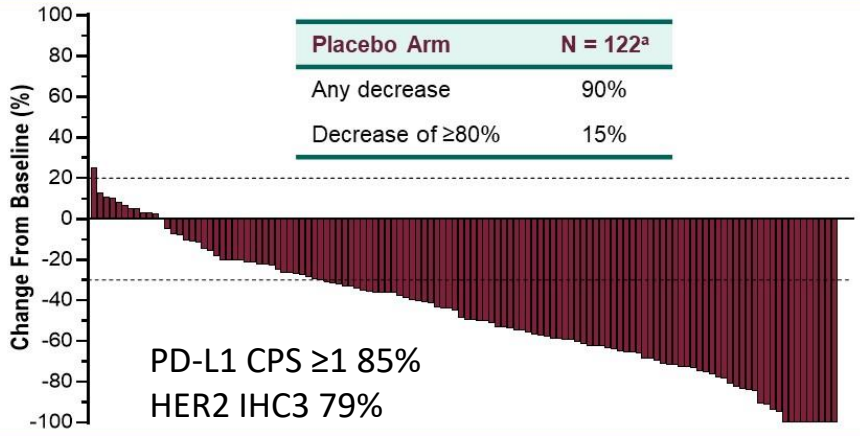
Děkuji za pozornost.

obermannova@mou cz

TRASTUZUMAB + PEMBROLIZUMAB – KEYNOTE-811

Confirmed Response at IA1





ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	**74.4% (66.2-81.6)**	**51.9% (43.0-60.7)**
ORR difference[b]	**22.7% (11.2-33.7) *P* = 0.00006**	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
CR	**15 (11%)**	**4 (3%)**
PR	**84 (63%)**	**64 (49%)**
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

Duration of Response[c]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median[d]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥6-mo duration[d]	70.3%	61.4%
≥9-mo duration[d]	58.4%	51.1%

[a]Participants with RECIST-measurable disease at baseline and ≥1 post-baseline measurement evaluable for change from baseline in target lesions. [b]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [c]Calculated in participants with best response of CR or PR. [d]Kaplan-Meier estimation. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Janjigian YY et al. ASCO 2021; abstract 4013

Conclusions

- The primary objective with **59% pathological complete Response Rate was met (17/29 pts evaluable for** pCRR**)**
- Neo-adjuvant nivolumab & ipilimumab is feasible in pts with MSI/dMMR resectable OGJ/gastric adenocarcinoma
- No new safety concerns: with 25% of grade 3-4 TRAE (max/pts)
- Surgical complications are as expected with this type of surgeries
- 94% of pts included are free of events with 12 months follow-up
- Neonipiga raises the question whether the surgery can be delayed or avoided for some pts with localized MSI/dMMR G-OGJ adenocarcinoma if immune-check point inhibitors are effective.

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NEONIPIGA: Background

- Locally advanced OGJ/gastric adenocarcinoma (OGA) MSI/dMMR have better prognosis compared to MSS/pMMR
- Perioperative chemotherapy with fluoropyrimides and platinum salt offers questionable benefit in MSI/dMMR and might decrease both DFS and OS[1].
- MSI/dMMR status is predictive for the efficacy of immune checkpoint inhibitors.
- Use of immune checkpoint inhibitors in this population before and/or after radical surgery might improved outcomes

1 Pietrantonio, F et al. *J Clin Oncol* 2019

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IMUNOTERAPIE
KeyNote 062-1.linie adenokarcinom žaludku- update po dalších 25 M

ASCO GI22

Pembrolizumab With or Without Chemotherapy Versus Chemotherapy Alone for Patients With PD-L1–Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma: Update From the Phase 3 KEYNOTE-062 Trial

Z. A. Wainberg[1]; K. Shitara[2]; E. Van Cutsem[3]; L. Wyrwicz[4]; K. W. Lee[5]; M. Garrido[6]; H. C. Chung[7]; J. Lee[8]; H. R. Castro[9]; W. Mansoor[10]; M. I. Braghiroli[11]; N. Karaseva[12]; E. Goekkurt[13]; H. Satake[14]; J. Chao[15]; U. Kher[16]; S. Shah[16]; P. Bhagia[16]; J. Tabernero[17]

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Background

- The global phase 3 KEYNOTE-062 study (NCT02494583) evaluated pembrolizumab as monotherapy and with chemotherapy versus chemotherapy as first-line therapy for PD-L1–positive (combined positive score [CPS] ≥1) advanced gastric/gastroesophageal junction adenocarcinoma[1]
  - Pembrolizumab was noninferior to chemotherapy (overall survival [OS] HR, 0.91; 99.2% CI, 0.69-1.18; noninferiority margin, 1.2) with fewer adverse events (AEs) observed
  - Pembrolizumab or pembrolizumab + chemotherapy was not superior to chemotherapy for OS and progression-free survival (PFS) end points tested

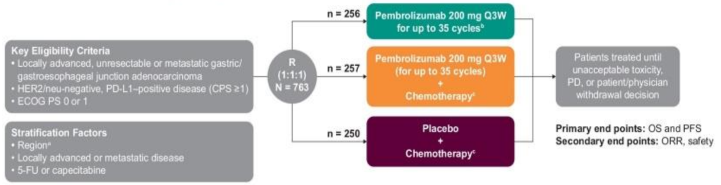
Objective

- To evaluate results from KEYNOTE-062 after ~25 additional months of follow-up

Methods

Study Design

Figure 1. KEYNOTE-062 Study Design



5-FU, 5-fluorouracil; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; PD, progressive disease; Q3W, every 3 weeks; R, random assignment.

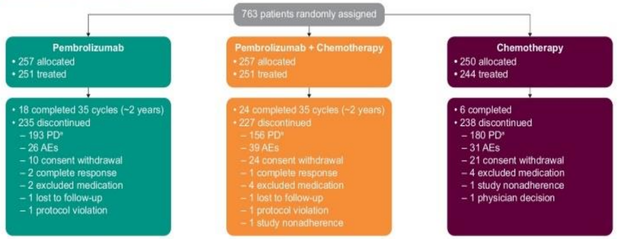
[a]EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, and Japan), or rest of world (including South America).

[b]Administration of pembrolizumab monotherapy was not blinded.

[c]Chemotherapy: cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/d for 5 days Q3W or capecitabine BID d1-14 Q3W (cisplatin may be capped at 6 cycles per country guidelines).

Results

Figure 2. Disposition of Study Treatment



[a]Defined as clinical progression or PD.

- Median time from randomization to data cutoff was 54.3 months (range, 46.8-66.1)
  - Database cutoff date: April 19, 2021

Figure 3. Kaplan-Meier Estimates of Overall Survival in Patients with Untreated Gastric/Gastroesophageal Junction Cancer by PD-L1 Expression

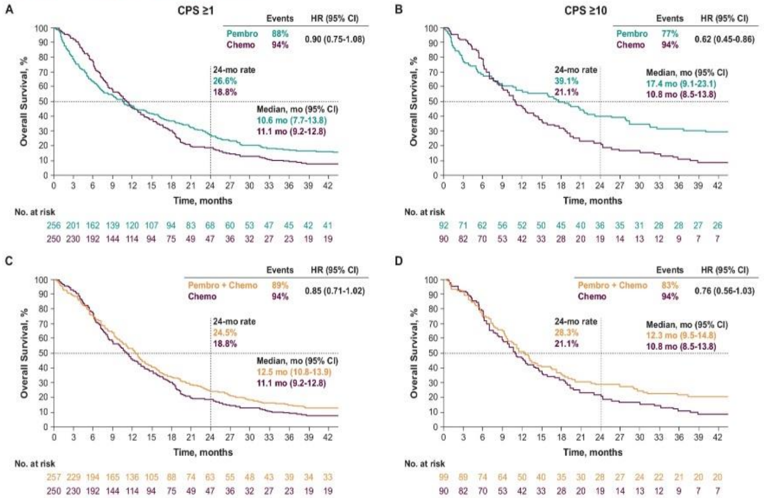


Figure 4. Kaplan-Meier Estimates of Progression-Free Survival in Patients with Untreated Gastric/Gastroesophageal Junction Cancer by PD-L1 Expression

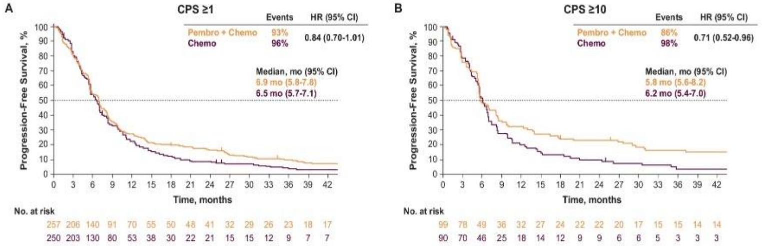


Table 1. Adverse Event Summary

n (%)	Pembro n = 254	Pembro + Chemo n = 250	Chemo n = 244
AE			
Any	242 (95.3)	244 (97.6)	240 (98.4)
Grade 3-5	128 (50.4)	212 (84.8)	201 (82.4)
Led to discontinuation	29 (11.4)	85 (34.0)	58 (23.8)
Led to death	25 (9.8)	17 (6.8)	13 (5.3)
Treatment-related AE			
Any	139 (54.7)	235 (94.0)	224 (91.8)
Grade 3-5	44 (17.3)	183 (73.2)	169 (69.3)
Led to discontinuation	11 (4.3)	69 (27.6)	44 (18.0)
Led to death	3 (1.2)	5 (2.0)	3 (1.2)

Conclusions

- Efficacy and safety outcomes with first-line pembrolizumab or pembrolizumab + chemotherapy versus chemotherapy, with an additional 25 months of follow-up, were consistent with data from the final analysis of KEYNOTE-062
  - Pembrolizumab was noninferior to chemotherapy for OS in patients with PD-L1 CPS ≥1 tumors with a clinically meaningful OS benefit observed in patients with PD-L1 CPS ≥10 tumors
  - Pembrolizumab + chemotherapy was not superior to chemotherapy for OS in the CPS ≥1 or the CPS ≥10 population
- Treatment with pembrolizumab resulted in fewer treatment-related AEs
- Pembrolizumab + chemotherapy will be further investigated in the first-line setting in KEYNOTE-859 (NCT03675737)

References

1. Shitara K et al. *JAMA Oncol.* 2020;6:1571-1580.

Acknowledgments

The authors thank the patients and their families and caregivers for participating in this trial as well as all investigators and site personnel. Medical writing and/or editorial assistance was provided by Holly C. Cappelli, PhD, CMPP, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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Presented at ASCO Gastrointestinal Cancers Symposium; January 20-22, 2022, San Francisco, California

Update po 25M

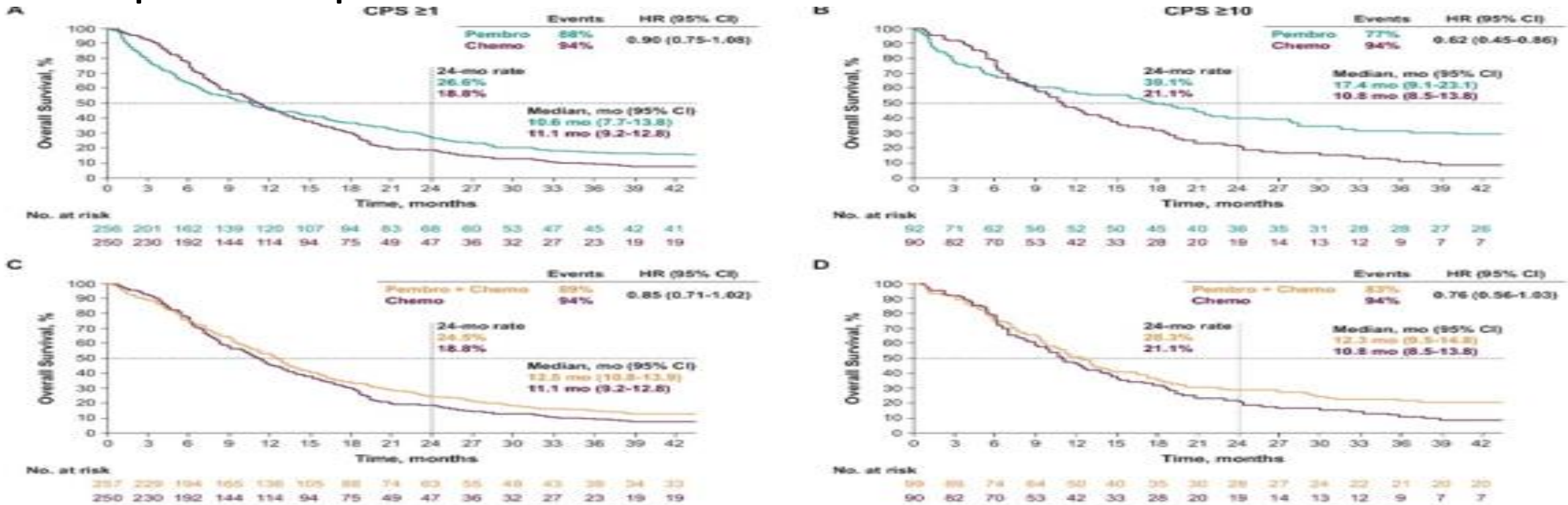
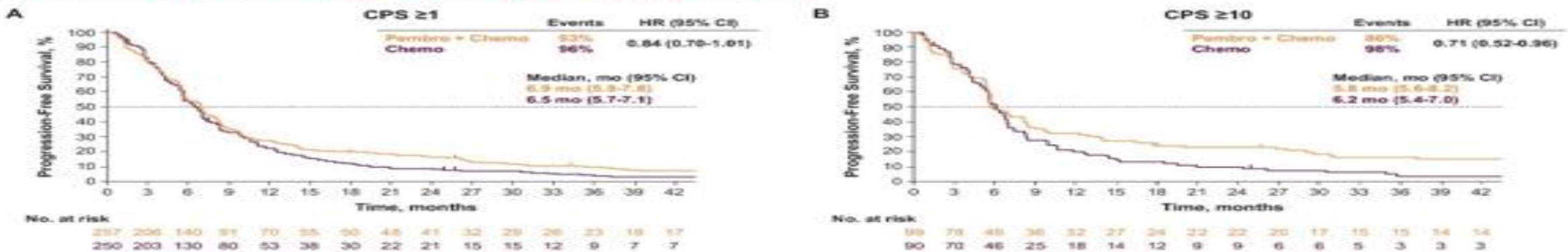


Figure 4. Kaplan-Meier Estimates of Progression-Free Survival in Patients with Untreated Gastric/ Gastroesophageal Junction Cancer by PD-L1 Expression



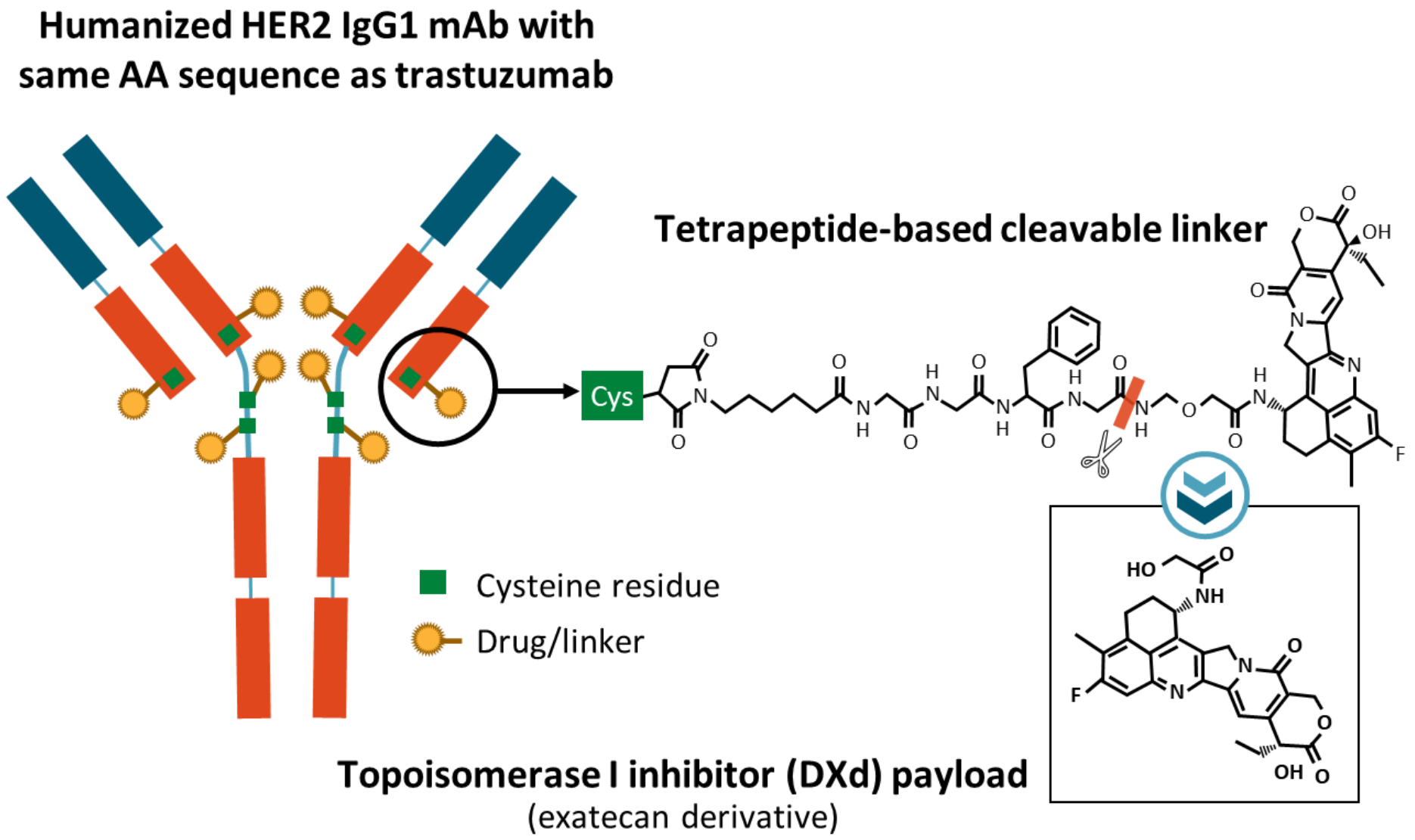
Shrnutí KeyNote 062- UPDATE po dalších 25 M- ASCO GI 22

- Kombinace pembrolizumab a chemoterapie nebyla lepší než chemoterapie samotná pro pacienty s karcinomem GEJ/G s CPS ≥1 a CPS ≥10

- Pembrolizumab samotný nebyl lepší než CHT v OS u CPS ≥1 a byl zaznamenán benefit u skupiny CPS ≥10

- Pembrolizumab a chemoterapie bude nadále studována v KeyNote 859

TRASTUZUMAB DERUXTECAN



Nakada et al. *Chem Pharm Bull (Tokyo).* 2019;67:173

TRASTUZUMAB DERUXTECAN

- Multicenter, open-label, randomized phase II study

Stratified by region (Japan vs Korea), ECOG PS (0 vs 1), HER2 status (IHC 3+ vs IHC 2+/ISH+)

Adult patients with HER2+* locally advanced or metastatic gastric or GEJ cancer that progressed on ≥ 2 prior regimens† (N = 188)

Randomized 2:1

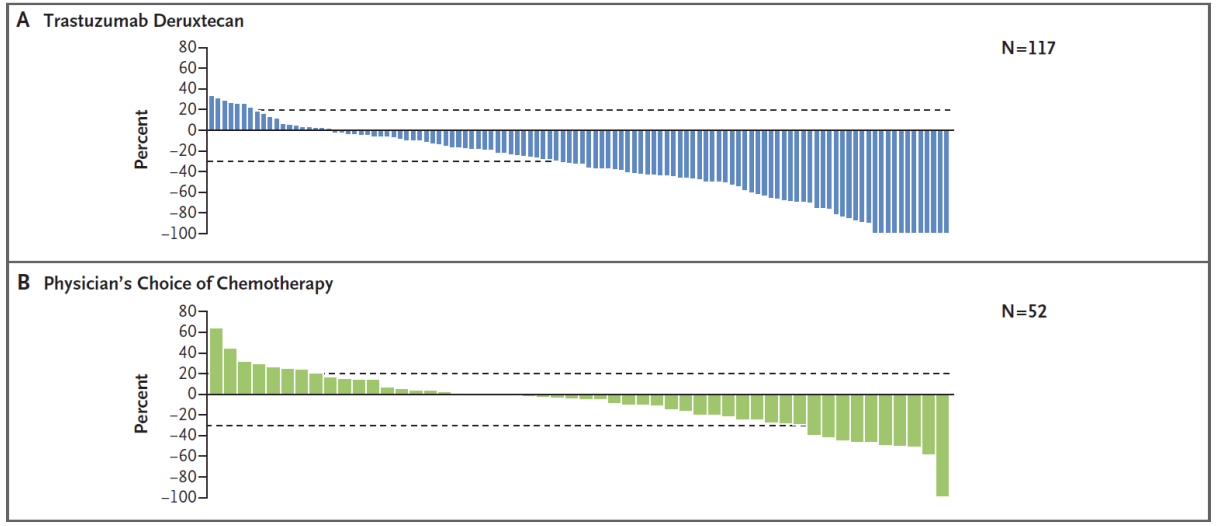
T-DXd 6.4 mg/kg, 3-week cycles (n = 126)

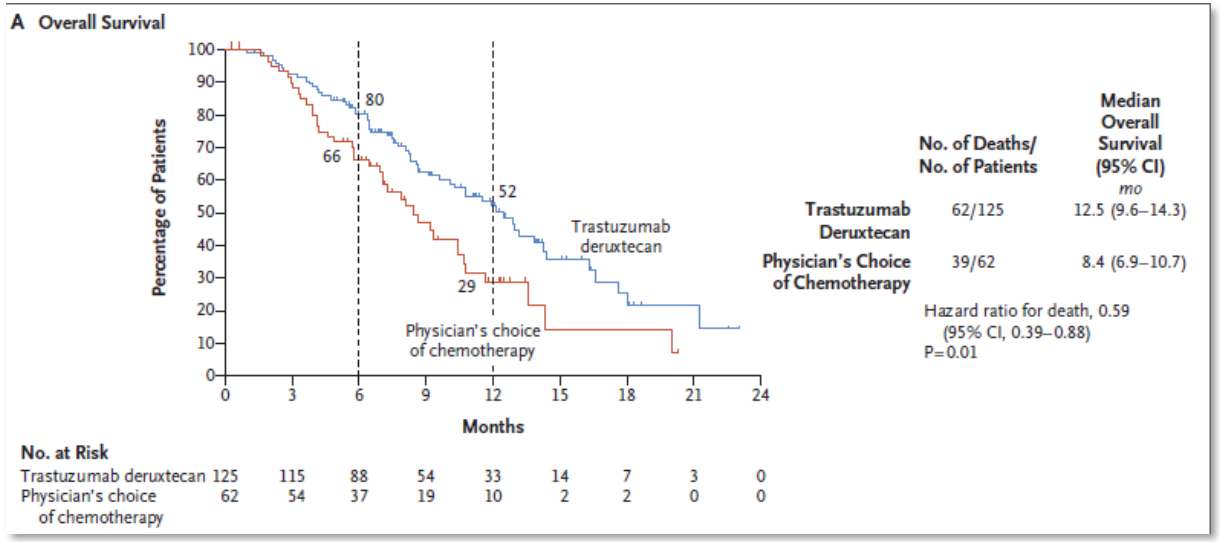
Physician's choice:
Irinotecan 150 mg/m² every 2 weeks or
Paclitaxel 80 mg/m² Days 1, 8, 15 every 4 weeks
(n = 62)

Until PD, unacceptable AEs, or pt withdrawal

*HER2+ based on IHC 3+ or IHC 2+/ISH+ according to ASCO/CAP guidelines.
†Prior regimens included fluoropyrimidine, a platinum agent, and trastuzumab or approved biosimilar.

- Primary endpoint: ORR by ICR (RECIST v1.1)
- Secondary endpoints: OS (key), DoR, PFS, DCR, confirmed ORR, safety





Shitara K et al. *N Engl J Med 2020* Jun 18;382(25):2419-2430

ESOPHAGEAL CANCER - ATTRACTION-3

Attraction-3: Randomized global Phase III – Second-line esophageal squamous cell cancer

N=419

Advanced or relapsed

Squamous cell cancer

Previously treated with Platin-Fluoro-pyrimidine

RANDOM

Nivolumab
240 mg 30 min q2w
monotherapy

Primary endpoint: survival

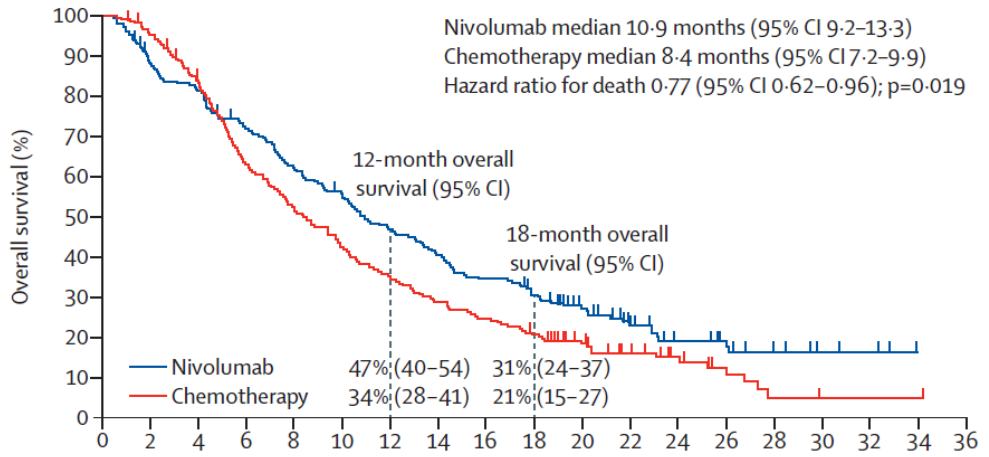
Taxane
Paclitaxel 100 mg/m² weekly x 6,
then 1 week pause; or Docetaxel 75 mg/m² q3w

Kato K et al., Lancet Oncol. 2019 Nov;20(11):1506-1517

ESOPHAGEAL CANCER - ATTRACTION-3

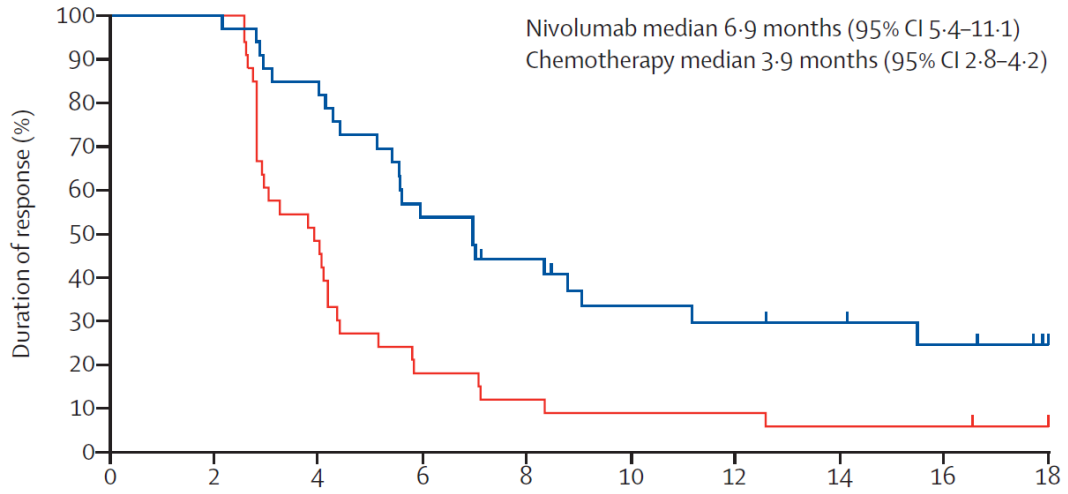
Attraction-3: Randomized global Phase III – Second-line esophageal squamous cell cancer

Overall Survival



Number at risk (number censored)																			
Nivolumab	210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
	(0)	(4)	(4)	(5)	(5)	(6)	(6)	(6)	(6)	(8)	(19)	(31)	(35)	(38)	(43)	(46)	(47)	(50)	(50)
Chemotherapy	209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0
	(0)	(3)	(7)	(8)	(8)	(9)	(9)	(9)	(9)	(10)	(19)	(26)	(30)	(33)	(34)	(35)	(35)	(35)	(36)

Duration of Response



Number at risk (number censored)										
Nivolumab	33	33	27	17	13	9	8	7	5	0
	(0)	(0)	(0)	(1)	(2)	(3)	(3)	(4)	(5)	(10)
Chemotherapy	34	34	16	6	4	3	3	2	2	0

Kato K et al., Lancet Oncol. 2019 Nov;20(11):1506-1517

ESOPHAGEAL CANCER - ATTRACTION-3

Attraction-3: Randomized global Phase III – Second-line esophageal squamous cell cancer

Side Effects

	Nivolumab (n=209)				Chemotherapie (n=208)			
	Grad 1-2	Grad 3	Grad 4	Grad 5	Grad 1-2	Grad 3	Grad 4	Grad 5
Alle	99 (47%)	33 (16%)	5 (2%)	0	65 (31%)	85 (41%)	46 (22%)	2 (1%)
SAE‘s	13 (6%)	16 (8%)	4 (2%)	0	6 (3%)	31 (15%)	8 (4%)	2 (1%)

Kato K et al., Lancet Oncol. 2019 Nov;20(11):1506-1517

ADVANCED ESOPHAGEAL CANCER 2ND LINE – EMA APPROVAL

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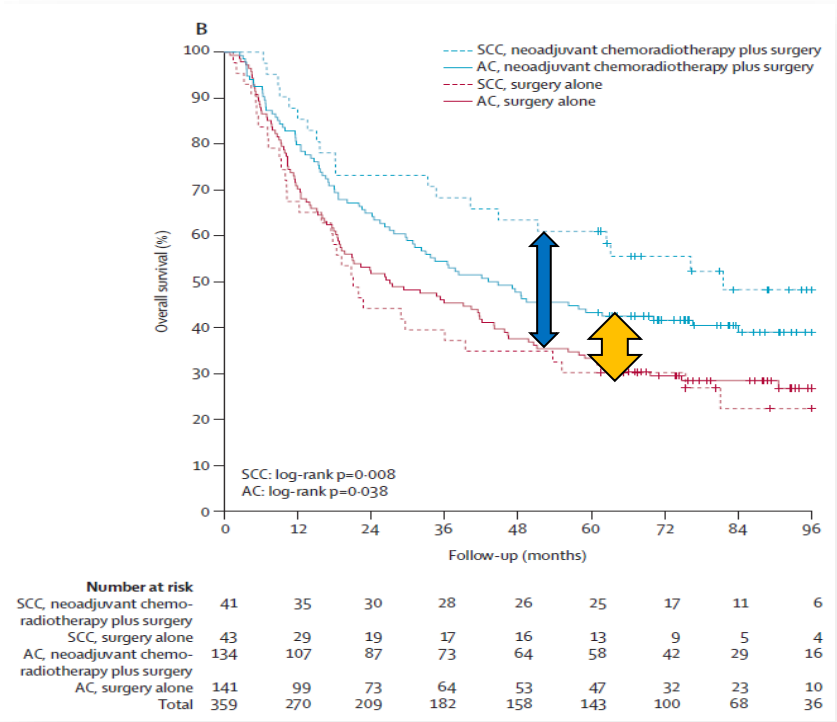
nivolumab

AUTHORISED
This medicine is authorised for use in the European Union.

Nivolumab is approved as monotherapy for 2nd-line treatment of advanced esophageal squamous cell cancer independent of the PD-L1 expression status

https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo accessed 6 September 2021

Neoadjuvantní CHT/RT(CROSS)



Medián F-U 84,1M – mOS 48,6 vs 24M,
SCC mOS 81,6 vs 21,1M
adenoCa mOS 43,2 vs 27,1M

T2-T3N0-1M0, N=366, SCC 23%, adenoCa 75%

		CHT/RT (n=178)	Operace (n=188)
mOS(M)		49	24
R0(%)		92	69
3-letý OS(%)		58	44
5-letý OS(%)		47	34
pCR	SCC	49%	
	adenoCa	23%	
Počet rekurencí po F-U m24 M(%)		35%	58%
Počet lokálních rekurencí(%)		14%	34%
Peritoneální diseminace		4%	14%

Shapiro J et al., Lancet Oncol 2015; 16: 1090–98

Safety Summary

Neo-adjuvant treatment before surgery	Patients, N (%) (N=32)			
	Any Grade		Grade 3-4	
Any treatment related AE max/patients	27	84	8	25
Any AE leading to discontinuation	5	16	5	16
Type of AE				
Diarrhea	5	7	1	3
Colitis/ileitis	2	6	2	6
Fatigue	9	28	0	0
Pruritus	8	25	0	0
Pyrexia/Fever/Chills	2	6	0	0
Hepatitis (=Increased AST/ALAT)	3	9	2	6
Adrenal insufficiency/ Hypophysitis	1	3	1	3
Vomiting	2	6	1	3
Nausea	2	6	0	0
Rash	4	12	0	0
Hypothyroidism	2	6	0	0
Hyperthyroidism	7	22	0	0
Decreased appetite	3	9	2	6
Pancreatitis	1	3	0	0
Other	20	28,	2	6*

* Other grade 3-4(hyperglycemia, anemia in relation with hemorrhage)

Per and/or post-op complications (until 90 days post op)	Population with surgery (N=29) N/%	
No	12	41.5
Yes	17	58.5
Postoperative general complications (for some patients more than one)	22	
Clavien-Dindo grade (max/patient)		
I-II	11	38
III-IIIB	4	14
IV	1	3.5
V	1	3.5
Complication term**	22	
Fistula	6	-
Pancreatitis	3	-
Ileus	2	-
Pneumonia	2	-
Atrial fibrillation	2	-
Death	1	-
Other	6	-

** Some patients had more than one complication

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