ASCO GI 2021

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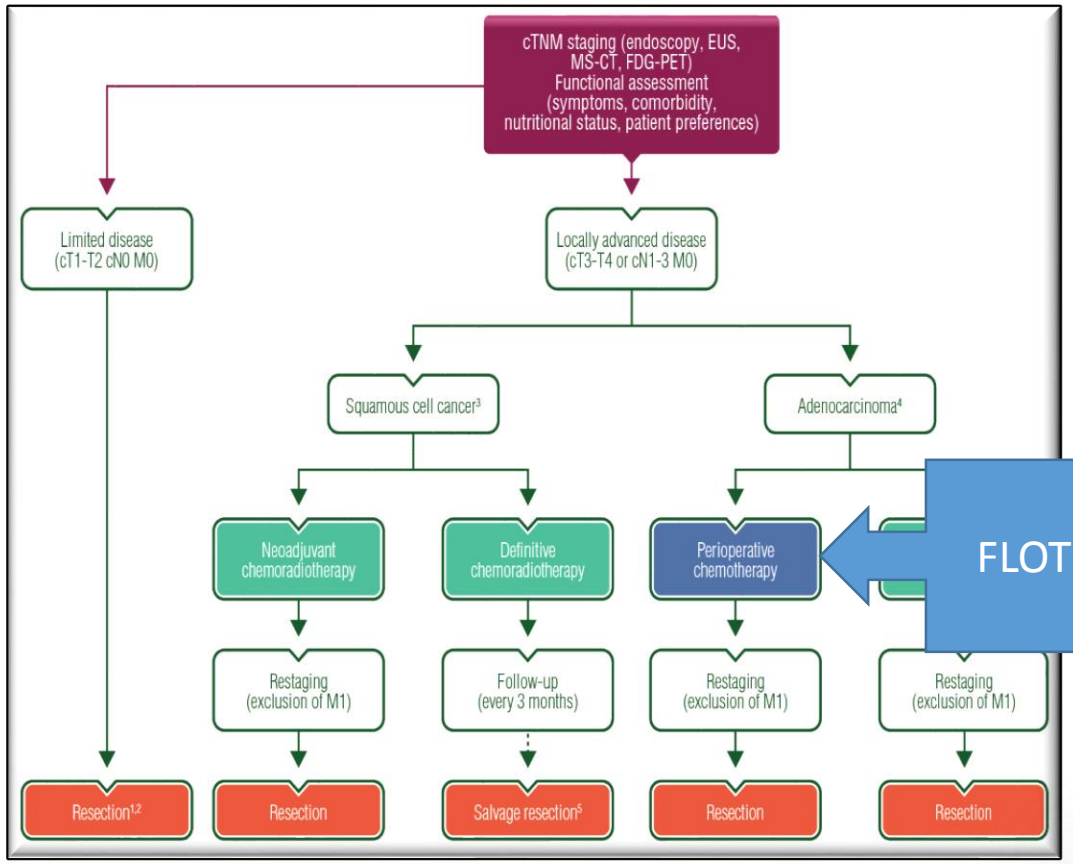
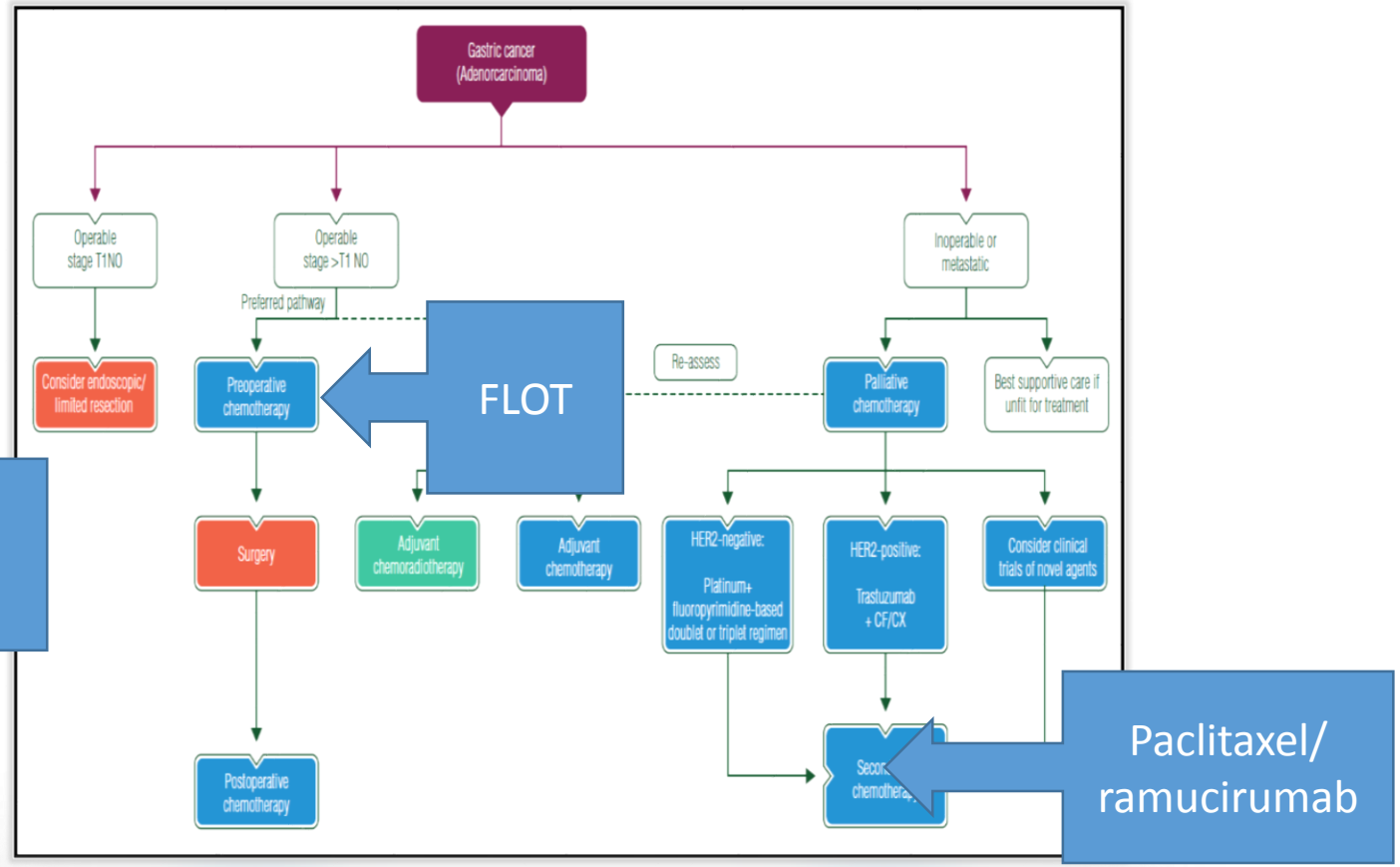
Úvod

- Současná guidlines v ČR
- Imunoterapie u karcinomu jícnu a žaludku
- Cílená terapie v blízké budoucnosti?
- Vybraná data z ASCO GI 2021

ESMO guidelines- karcinom jícnu a žaludku 2016 a ČR 2021

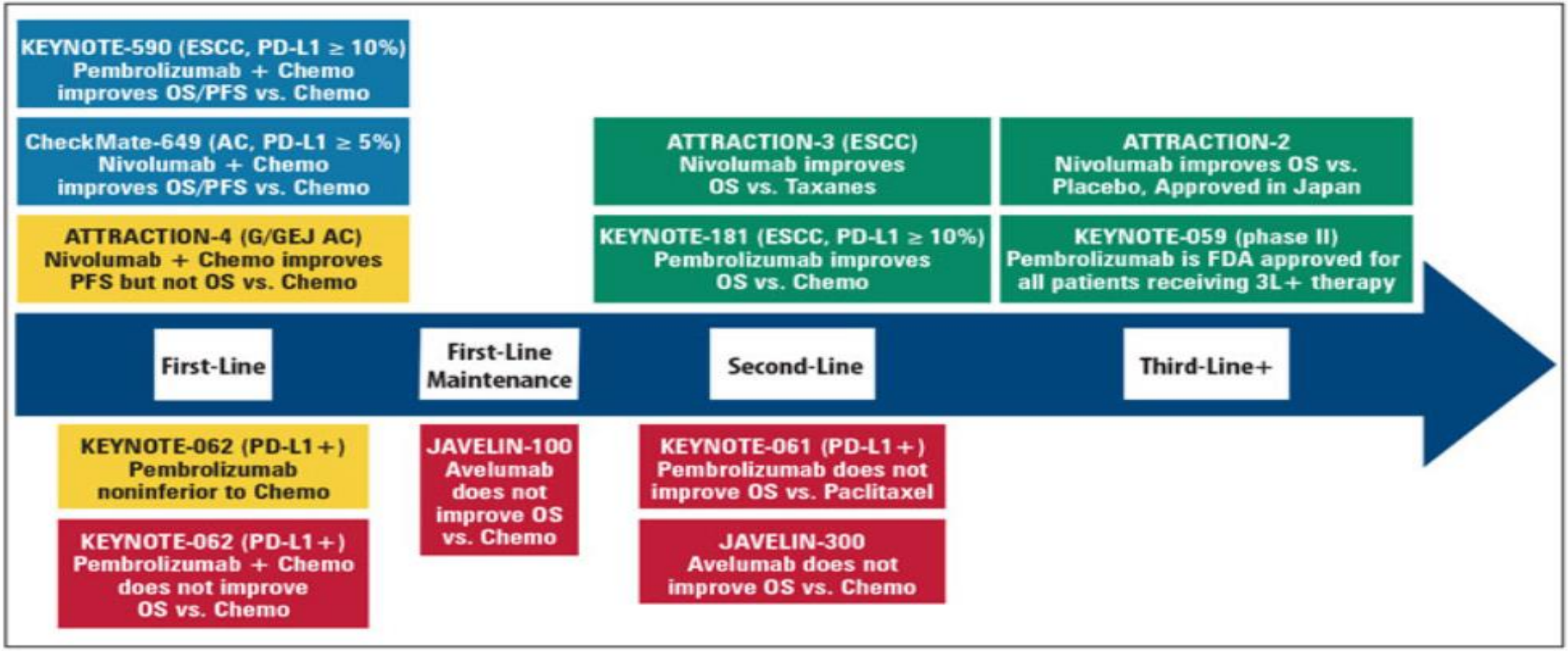




Lordick et al. *Ann Oncol* 2016 Sep;27(suppl 5):v50-v57

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

Imunoterapie v léčbě karcinomu jícnu a žaludku 2021



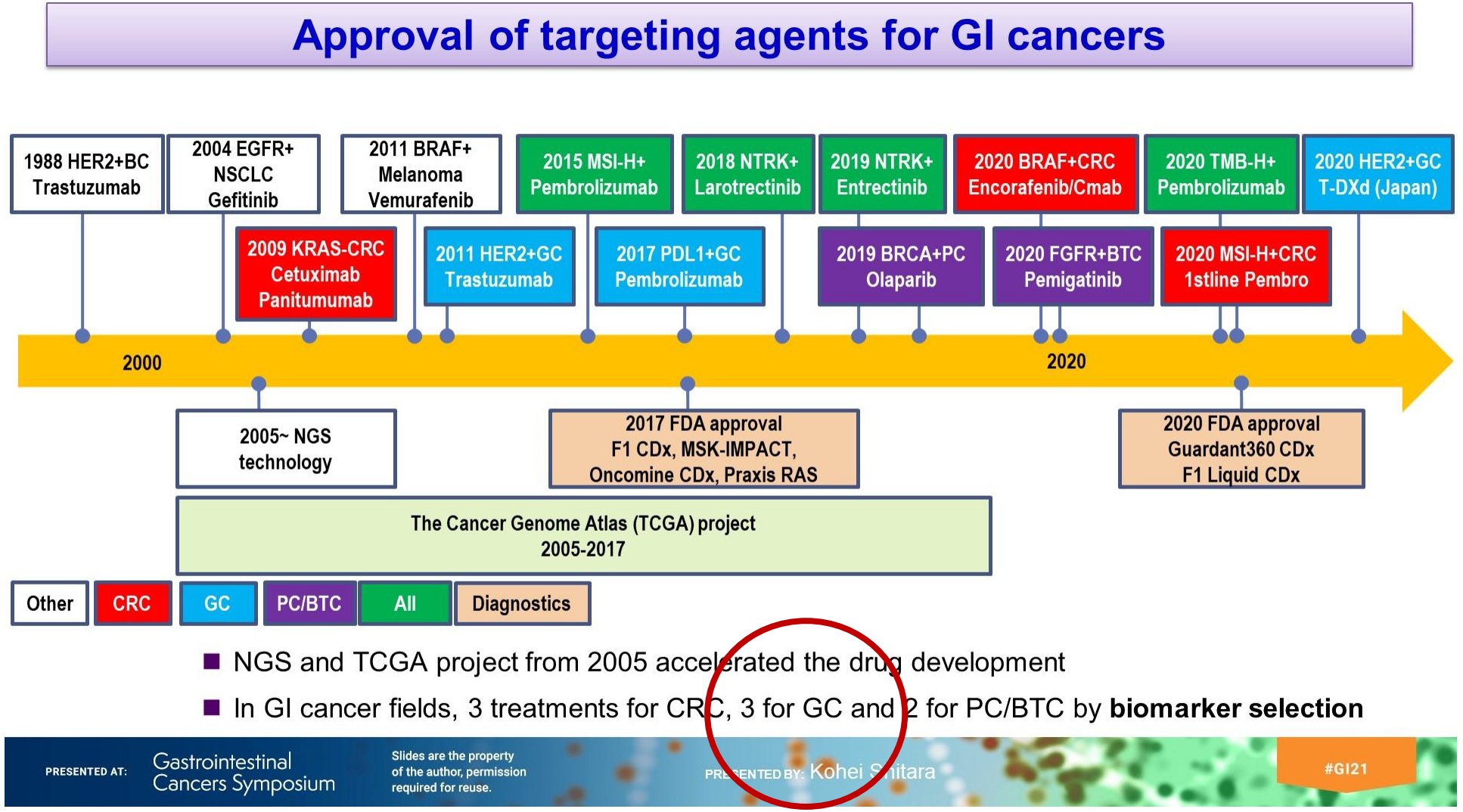
Suneel D. Kamath, *ASCO 2021*

Kdo má zisk z terapie?
- interpretace dat ze studií

- Jedná se o heterogenní onemocnění a ne všichni pacienti mají benefit z imunoterapie

- pacienti s adenokarcinomem žaludku(nikoliv jednoznačně)GEJ
- Pacienti s dlaždicobuněčným karcinomem jícnu
- muži
- asijské etnikum
- pacienti s vyšší PD-L expresí

FDA schválená terapie u GI nádorů



Presented By Kohei Shitara at 2021 Gastrointestinal Cancers Symposium

Budoucnost cílené terapie

Candidates of Emerging Targets for GI cancers

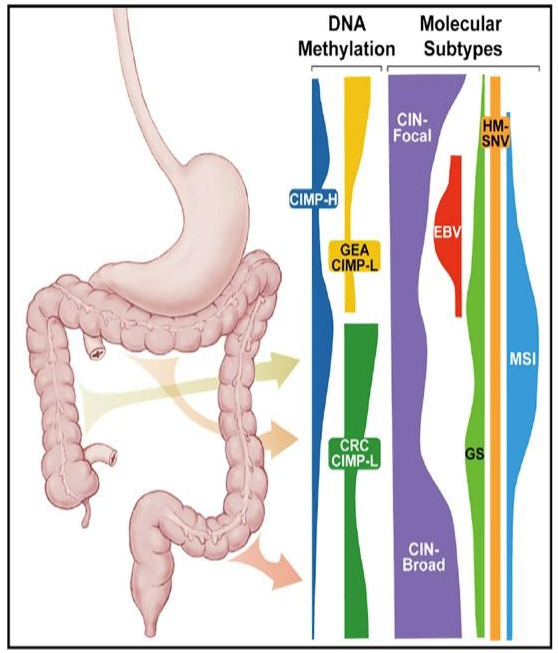
	KRAS mutations	BRAF V600E Mutation	BRACA1/2 Mutation HRD+	HER2 IHC /Amp+	FGFR2 Fusion/ rearrange	FGFR2 IHC/ Amp+	MET Amp+	CLDN 18.2 overexpress	IDH1	Other Fusions	TMB-H MSI-H	NTRK 1-3
Gastric	Sotorasib Combo. Other RAS inhibitors		Pamiparib (all comer, NCT03427814)			Bemarituzumab (NCT03694522) Futibatinib (NCT04189445)	Savolitinib (NCT02449551)	Zolbetuximab (NCT03504397) AMG910 (NCT04260191) CT-04 (NCT04404595)		Zenocutuzumab (NCT02912949) for NRG1 Selpercatinib (NCT03157128) for RET Brigatinib (JapicCTI-194851) for ROS1		
Colorectal							Cabozantinib Savolitinib (NCT03592641)					
Biliary		Dabrafenib +Trametinib (NCT02034110)	Olaparib (NCT04042831)	T-DXd (JMA-IIA00423)								
Pancreas								Zolbetuximab (NCT03816163)				
All (BASKET)			Olaparib (NCT03742895)	T-DXd (NCT04482309)	Futibatinib (NCT04189445)							

Level 1 Approved | Level 2 Standard Care | Level 3 Clinical Evidence | Ongoing/completed trials

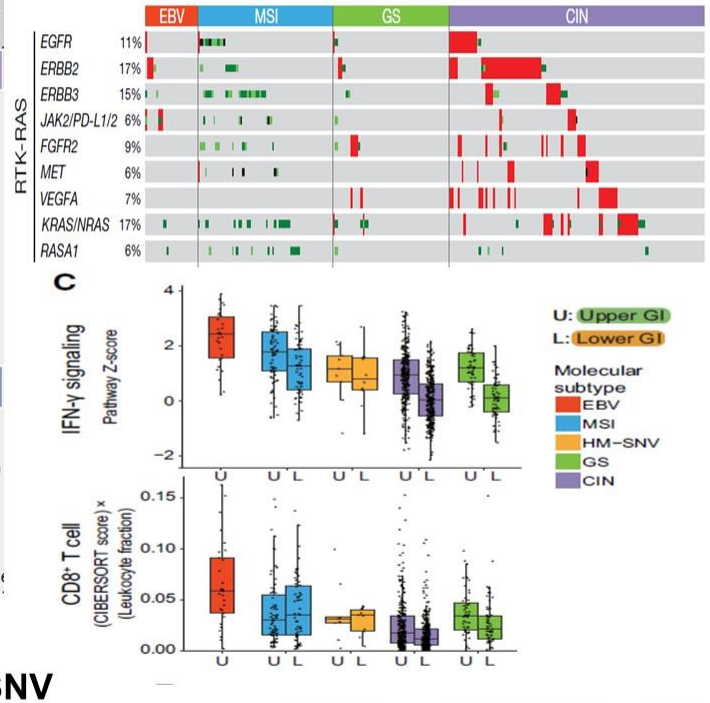
- Profiling by NGS (and IHC) must be important to facilitate drug development.
- Role of ctDNA analysis?

Presented By Kohei Shitara at 2021 Gastrointestinal Cancers Symposium

TCGA subgroups in GI cancer



	GC			
Lauren	Diffuse type	Intestinal type		
TCGA	GS	EBV	MSI	CIN
	• *CDH1* and *RHOA* mutations • *CLDN18–ARHGAP26* fusion • Cell adhesion pathways • Younger patients	• DNA hypermethylation • *PIK3CA* mutation • *PDL1* and *PDL2* overexpression • Recurrent *JAK2* and *ERBB2* amplification • *CDKN2A* silencing • Immune cell signalling • Common in the corpus • Frequent *ARID1A* and *BCOR* mutation • Rare *TP53* mutation	• Hypermutation • *MLH1* silencing • KRAS or NRAS activation • *RASA1* and *PTEN* inactivation • Mitotic pathways • Older patients • Less A->C transversion	• RTK–RAS activation (*ERBB2*, *EGFR*, *MET*, *VEGFA* and *KRAS* or *NRAS*) • *TP53* mutation • Amplifications of cell cycle mediators (*CCNE1*, *CCND1* and *CDK6*), *GATA4* and *GATA6* • Common in GOJ and cardia cancer
ACRG	MSS/EMT	MSS/*TP53*$^+$	MSI	MSS/*TP53*$^-$
	• *CDH1* silencing • Younger patients • Worst prognosis	• Intact *TP53* • *MDM2* amplification • EBV infection • Enrichment with *PIK3CA* or *ARID1A* mutation and cytokine signature in EBV$^+$ tumour	• Common in the antrum • Best prognosis • Hypermutation • *MLH1* silencing • Frequent mutations in *KRAS*, *MTOR*, *PTEN*, *PI3KCA*, *ASL* and *ARID1A*	• *TP53* mutation • Genomic instability • Recurrent amplification (*ERBB2*, *EGFR*, *GATA6*, *MYC*, *CCNE1* and *CCND1*)



- At least 5 types; **EBV, MSI, CIN, GS** and **HM-SNV**
- Distinguished genomic or immunological feature

TCGA Cancer Cell 2018, Nature 2014
Ajani JA,et al. Nat Rev Dis Primers. 2017

CheckMate 577: Health-related quality of life in a randomized, double-blind phase 3 study of nivolumab versus placebo as adjuvant treatment in patients with resected esophageal cancer or gastroesophageal junction cancer

Eric Van Cutsem, MD, PhD[1]; Prianka Singh, PharmD, MPH[2]; James M. Cleary, MD, PhD[3]; Ronan J. Kelly, MD, MBA[4]; Markus Moehler, MD, PhD[5]; Jaroslaw Kudzal, MD, PhD[6]; Guillermo Mendez[7]; Satoru Motoyama, MD, PhD[8]; Elena Elimova MD, M.Sc., FRCPC[9]; Cecile Grootscholten, MD, PhD[10]; Xiaowu Sun, PhD[11]; Fiona Taylor, MBiochem[11]; Rachael Lawrance, CStat[12]; Brad Padilla, MPH[11]; Alejandro Moreno-Koehler, MPH[11]; Jenny Zhang, MD, PhD[2]; Steve I. Blum, MBA, MA[2]; Jaffer A. Ajani, MD[12]

[1]University Hospitals Gasthuisberg, Leuven and KULeuven, Leuven, Belgium; [2]Bristol Myers Squibb, Princeton, NJ; [3]Dana Farber Cancer Institute, Boston, MA; [4]The Charles A. Sammons Cancer Center at Baylor University Medical Center, Dallas, TX; [5]Johannes-Gutenberg University Clinic, Mainz, Germany; [6]Jagiellonian University, John Paul II Hospital, Cracow, Poland; [7]Fundacion Favaloro, Buenos Aires, Argentina; [8]Akita University Hospital, Akita, Japan; [9]Princess Margaret Cancer Centre, Toronto, ON, Canada; [10]Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [11]Adelphi Values, Boston, USA; [12]Adelphi Values, Bollington, UK; [13]The University of Texas MD Anderson Cancer Center, Houston, TX

Health-Related Quality of Life of Pembrolizumab Plus Chemotherapy Versus Chemotherapy as First-Line Therapy in Patients With Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study

Wasat Mansoor,[1] Amit S. Kulkarni,[2] Ken Kato,[3] Jong-Mu Sun,[4] Manish A. Shah,[5] Peter Enzinger,[6] Antoine Adenis,[7] Toshihiko Doi,[8] Takashi Kojima,[8] Jean-Philippe Metges,[9] Zhigang Li,[10] Sung-Bae Kim,[11] Byoung Chol Cho,[12] Patrapim Sunpaweravong,[13] Maria Alsina Maqueda,[14] Eray Goekkurt,[15] Shailaja Suryawanshi,[2] Josephine Norquist,[2] Sukrut Shah,[2] Lin Shen[16]

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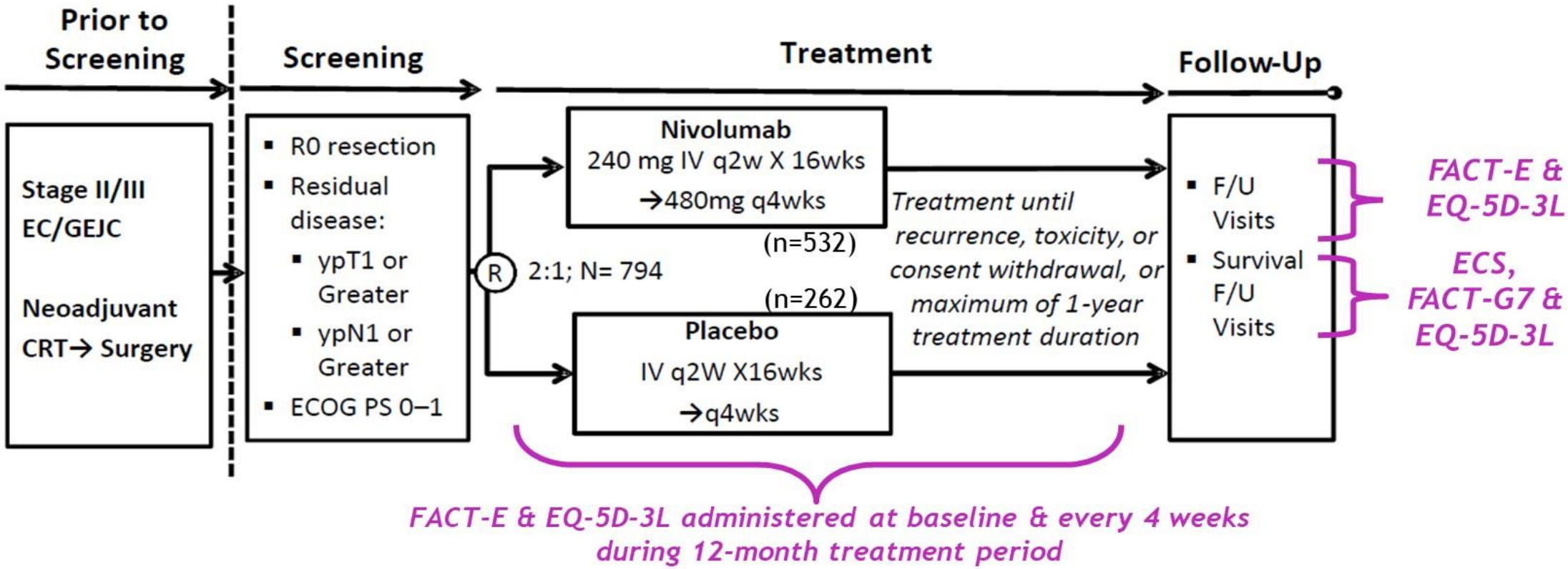
Background

- Nivolumab (NIVO) is the first adjuvant therapy to provide a statistically significant and clinically meaningful improvement in disease-free survival (DFS) versus placebo (PBO) in resected esophageal cancer (EC) / gastroesophageal junction cancer (GEJC) following neoadjuvant chemoradiotherapy as demonstrated by CheckMate 577
  - Median DFS was doubled (NIVO 22.4 versus PBO 11.0 months)[1]
  - HR 0.69 (96.4% CI 0.56–0.86; *P* = 0.0003) at interim analysis[1]
- NIVO was well tolerated with an acceptable safety profile
  - Most treatment-related adverse events (TRAEs) were Grade 1 or 2[1]
  - Frequency of serious TRAEs and TRAEs leading to discontinuation were ≤ 9% with NIVO and 3% with PBO[1]
- Health-related quality-of-life (HRQoL) analyses were incorporated as exploratory endpoints as part of this clinical trial and presented here

[1]Kelly R, et al. *Annals of Oncology* 2020;31(suppl_4):S1193-S1194. Clinicaltrials.gov identifier: NCT02743494

Patient-Reported Outcome (PRO) Administration Schedule in CheckMate 577



Primary endpoint: Disease-free survival

Secondary endpoints: Overall survival, overall survival rates at 1, 2, and 3 years

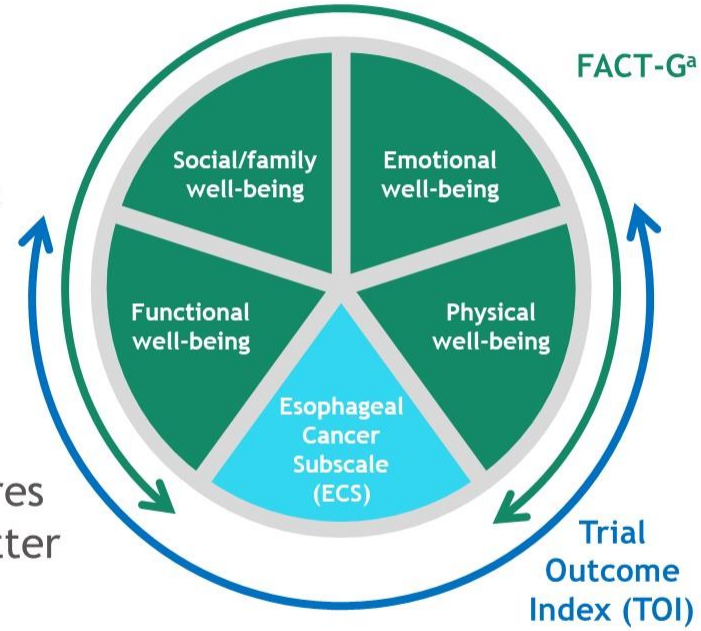
PRO exploratory endpoints: Functional Assessment of Cancer Therapy – Esophageal (FACT-E) questionnaire, EQ-5D-3L, Esophageal Cancer Subscale (ECS), and Functional Assessment of Cancer Therapy – General – 7-Item Version (FACT-G7)

*Follow-up Visit 1 (FU1) = 30 days (± 7 days) from last dose; Follow-up Visit 2 (FU2) = 84 days (± 7 days) from FU1; survival FU visits every 3 months thereafter

PRO Instruments

FACT-E: Cancer-related QoL

- Scale: 0–176 (varies for subscales)
- MID: ≥ 9.5 points (varies for subscales)[1]



Higher scores indicate better QoL

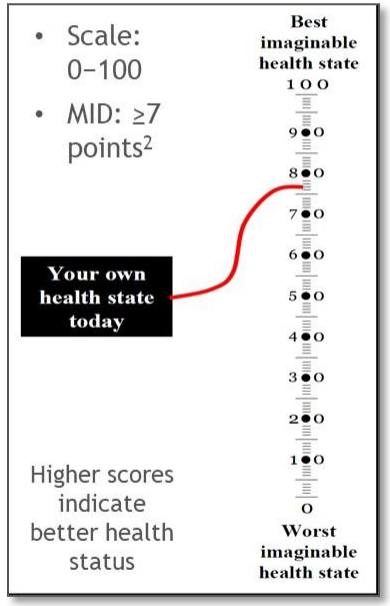
EQ-5D-3L Utility Index: Health status and QoL

- Range: −0.59 to 1
- MID: ≥ 0.08[2]

Higher scores indicate better health status

EQ-5D-3L VAS: Generic measure of health status

- Scale: 0–100
- MID: ≥7 points[2]



MID: minimally important difference; QoL=quality of life; VAS=visual analogue scale

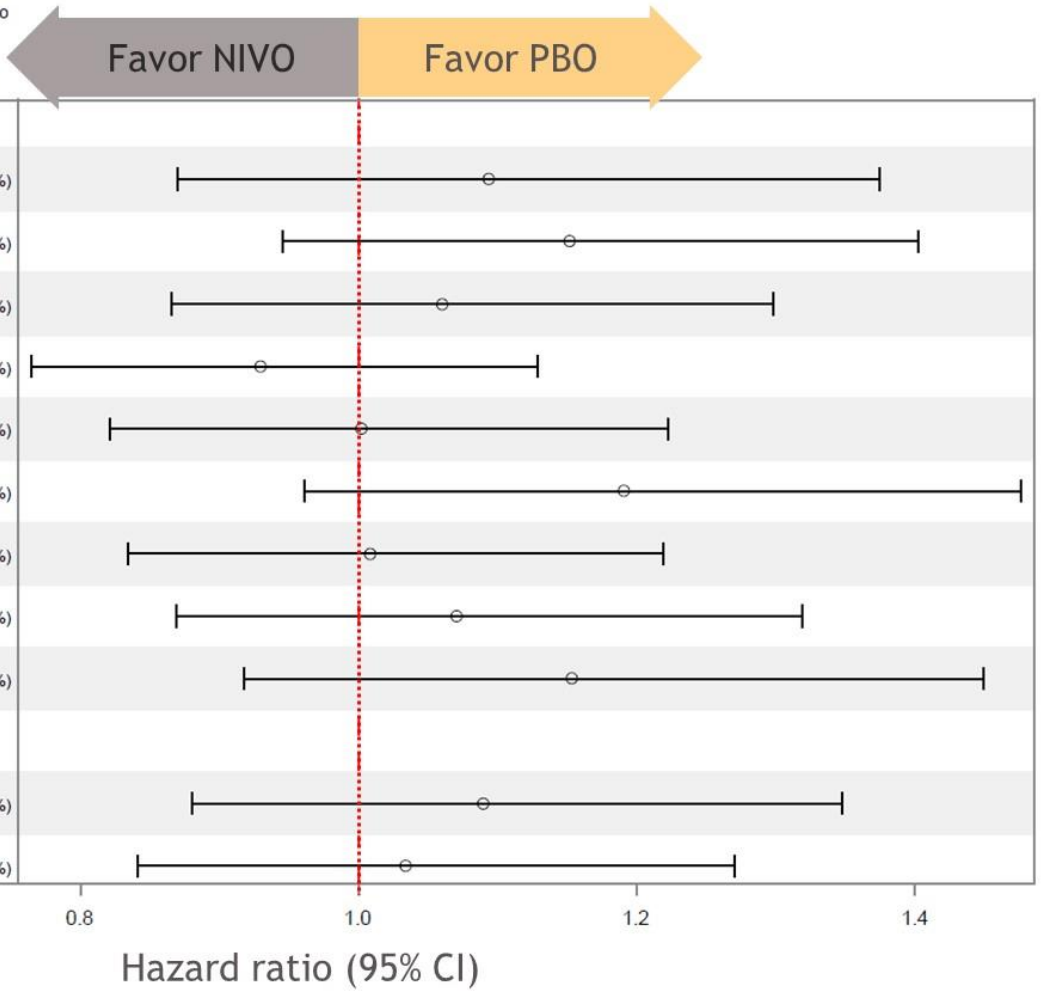
[1]FACT MIDs from Yost & Eton. *Eval Health Prof*. 2005;28(2):172-191, Ringash et al. *Cancer* 2007;110(1):196-202, Yount et al. *Qual Life Res* 2007;16(10):1615-1626, or based on distributional statistics from Darling et al. *Cancer* 2006;107(4):854-863 and Yanez et al. *Ann Oncol* 2013;24(4):1073-1078.

[2]EQ-5D-3L MID from Pickard et al. *Health Qual Life Outcomes* 2007;5:70

[a]FACT-G7 consists of a subset of seven items from three FACT-G domains: three items from Physical well-being (lack of energy, pain, and nausea), one item from Emotional well-being (condition will get worse), and three items from Functional well-being (sleep, enjoy life, content with quality of life)

Time to First Deterioration: Quality-of-Life Metrics*

PRO Measure	No. of Nivolumab (N=532) Patients with Event N(%)	No. of Placebo (N=262) Patients with Event N(%)
FACT-E:		
Total Score (MID=9.5)	228 (42.9%)	109 (41.6%)
Physical well-being (MID=2)	309 (58.1%)	146 (55.7%)
Social/family well-being (MID=2)	284 (53.4%)	140 (53.4%)
Emotional well-being (MID=2)	301 (56.6%)	155 (59.2%)
Functional well-being (MID=2)	289 (54.3%)	146 (55.7%)
Esophageal Cancer Subscale (ECS) (MID=4)	274 (51.5%)	121 (46.2%)
FACT-G Total Score (MID=3)	314 (59.0%)	163 (62.2%)
FACT-G7 Total Score (MID=2.5)	273 (51.3%)	130 (49.6%)
Trial Outcome Index (MID=6.1)	234 (44.0%)	108 (41.2%)
EQ-5D-3L:		
VAS (MID=7)	266 (50.0%)	125 (47.7%)
Index Score (UK weights) (MID=0.08)	274 (51.5%)	135 (51.5%)



- Time to first deterioration of HRQoL was not found to be statistically significant between NIVO and PBO
- No significant differences were seen for sub-group analyses

*Time to first PRO deterioration defined as the time from randomization until the first deterioration in PRO score meeting or exceeding the MID/responder definition threshold corresponding to that score. Additionally, time to deterioration analysis is considered an exploratory objective, and was not a pre-specified analysis in clinical SAP.

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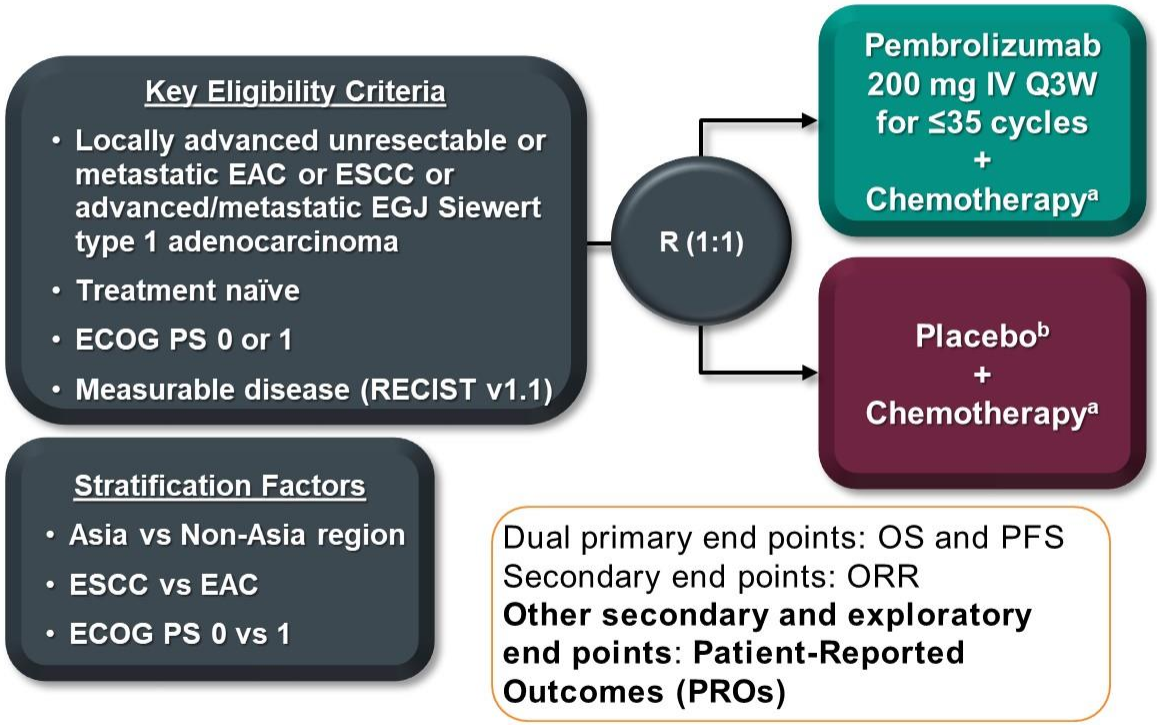
Presented By Wasat Mansoor at 2021 Gastrointestinal Cancers Symposium

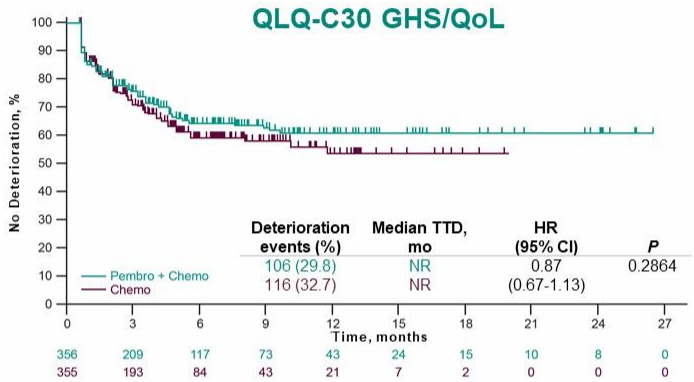
KEYNOTE-590 Study Design (NCT03189719) and Primary Study Results

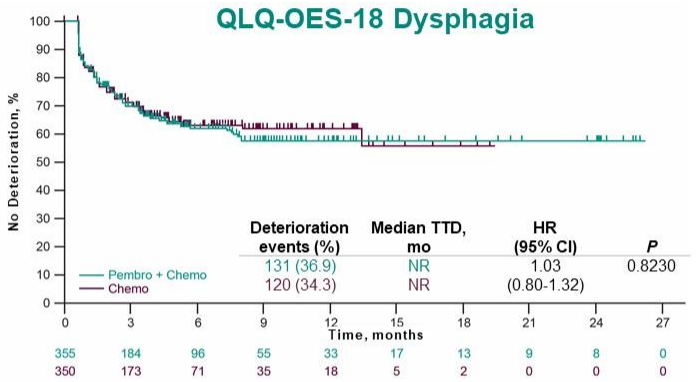


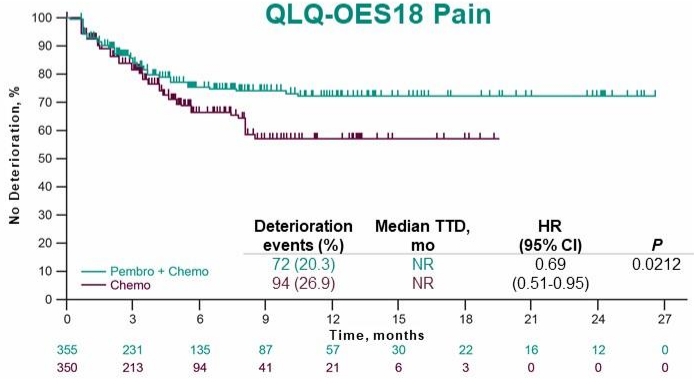
- Pembro + chemo provided statistically significant and clinically meaningful improvements over placebo + chemo
  - OS (HR, 0.73, $P < 0.0001$)
  - PFS (HR, 0.65, $P < 0.0001$)
  - ORR (% difference, 15.8, $P < 0.0001$)
- Comparable safety profiles between the two treatment groups; no new safety signals detected
- Mean (SD) time on therapy was 7.7 months (6.84) for pembro + chemo versus 5.8 months (4.76) for placebo + chemo

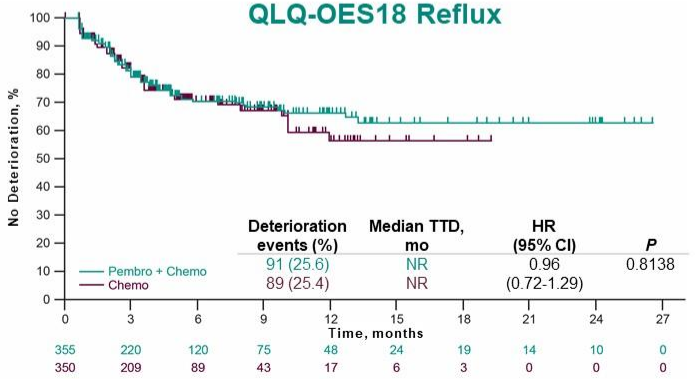
[a]5-FU 800 mg/m^2 IV for days 1-5 Q3W for ≤35 cycles + cisplatin 80 mg/m^2 IV Q3W for ≤6 cycles.
[b]Saline IV Q3W for ≤35 cycles.
All treatments were continued for the specified number of cycles or until disease progression, intolerable toxicity, withdrawal of consent, or physician decision.

Time to Deterioration: Total HRQoL Population



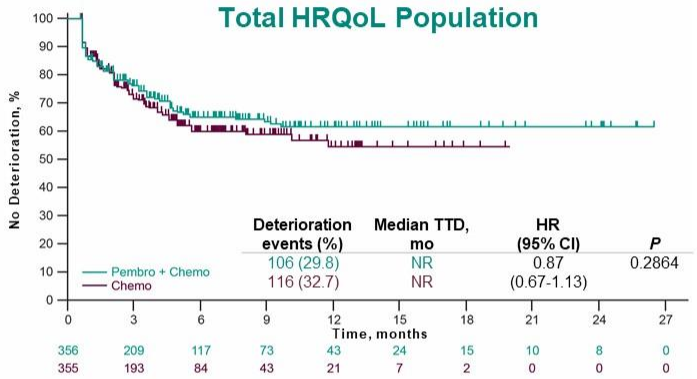


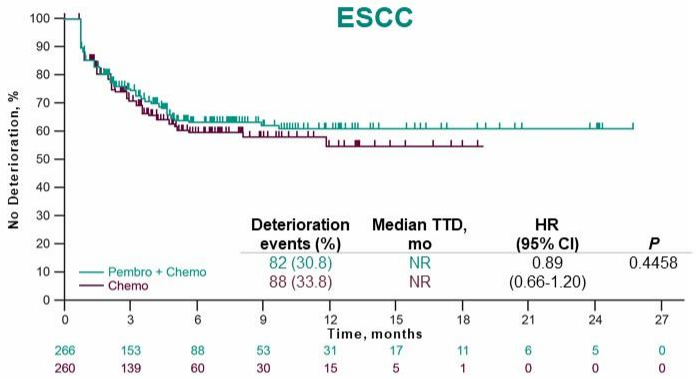


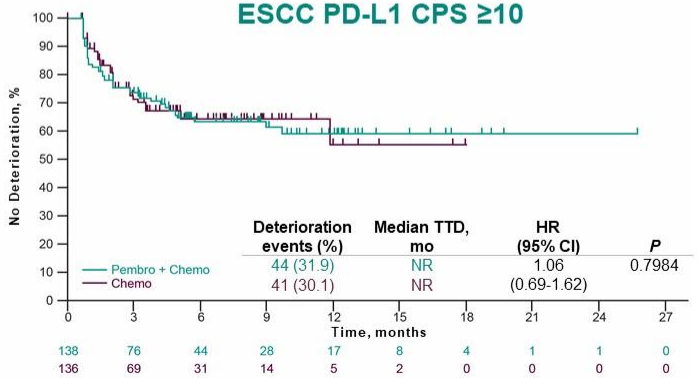


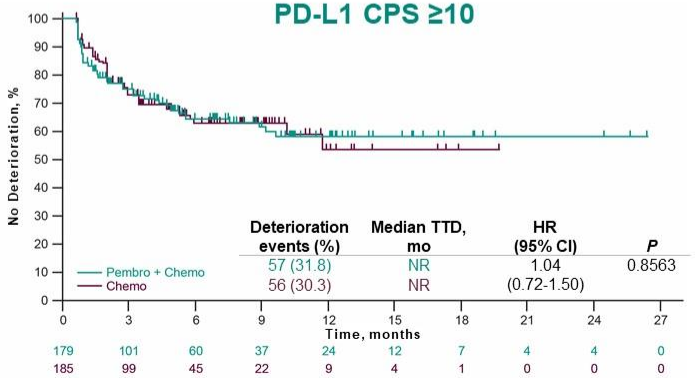
P values are nominal and two-sided.
Data cutoff: July 2, 2020

Time to Deterioration in QLQ-C30 GHS/QoL: Patient Subgroups









P values are nominal and two-sided.
Data cutoff: July 2, 2020

Conclusions

- In the primary analysis, pembrolizumab plus chemotherapy provided superior OS, PFS, and ORR versus placebo and chemotherapy and a manageable safety profile
- All HRQoL measures remained stable and similar over 18 weeks in the pembrolizumab plus chemotherapy and placebo plus chemotherapy treatment group, with no difference between groups
- The addition of pembrolizumab to chemotherapy maintained HRQoL measures relative to baseline and did not worsen HRQoL compared with chemotherapy alone
- These results support the use of pembrolizumab plus chemotherapy as first-line therapy for locally advanced and metastatic esophageal cancer or Siewert type 1 EGJ adenocarcinoma

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Nivolumab in advanced esophageal squamous cell carcinoma (ATTRACTION-1/ONO-4538-07): Minimum of 5-year follow-up

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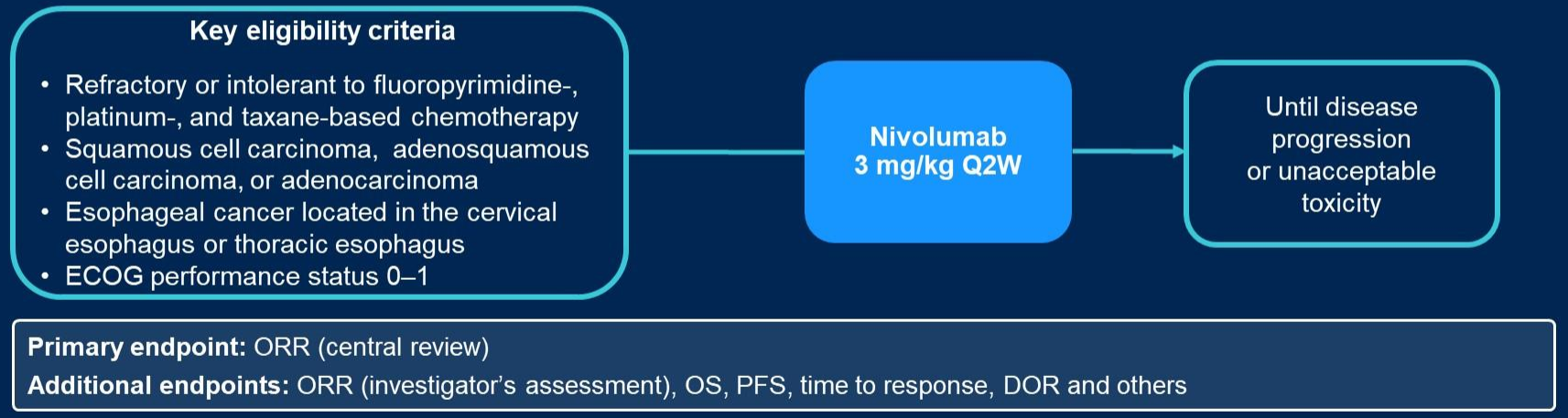
ATTRACTION-1: Study design

- ATTRACTION-1 is an open-label, single-arm, multicenter, phase 2 clinical trial evaluating the efficacy and safety of nivolumab in patients with advanced esophageal squamous cell carcinoma (ESCC) [ONO-4538-07/JapicCTI-No.142422]. Here, we report the findings of ATTRACTION-1 based on a minimum follow-up of five years.



Primary endpoint: ORR (central review)
Additional endpoints: ORR (investigator's assessment), OS, PFS, time to response, DOR and others

- All enrolled patients (N = 65) had ESCC and the median (range) age was 62 (49–80) years.

DOR, duration of response; ECOG; Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every two weeks

ATTRACTION-1: Overall response and safety

Activity of nivolumab

Best overall response (Central review)	All (N= 64)	2-year survivors (N = 11)	3-year survivors (N = 7)	5-year survivors (N = 4)
Complete response	3 (4.7)	3 (27.3)	3 (42.9)	3 (75.0)
Partial response	8 (12.5)	3 (27.3)	2 (28.6)	0
Stable disease	16 (25.0)	3 (27.3)	1 (14.3)	0
Progressive disease	29 (45.3)	1 (9.1)	0	0
Not assessable	8* (12.5)	1 (9.1)	1 (14.3)	1 (25.0)

*including subjects who had no target lesion. FAS full-analysis set

Adverse events and treatment-related adverse events

	Adverse events		Treatment-related adverse events	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Overall	**56 (86.2)**	**21 (32.3)**	**41 (63.1)**	**13 (20.0)**
Diarrhea	15 (23.1)	0	11 (16.9)	0
Pneumonia	14 (21.5)	6 (9.2)	5 (7.7)	2 (3.1)
Decreased appetite	12 (18.5)	2 (3.1)	6 (9.2)	2 (3.1)
Rash	9 (13.8)	0	7 (10.8)	0
Cough	8 (12.3)	0	1 (1.5)	0
Nasopharyngitis	8 (12.3)	0	0	0
Fatigue	7 (10.8)	1 (1.5)	5 (7.7)	1 (1.5)
Pruritus	7 (10.8)	0	6 (9.2)	0
Malaise	7 (10.8)	0	3 (4.6)	0
Constipation	7 (10.8)	0	1 (1.5)	0

No Grade 5 adverse events were observed

Presented By Ken Kato at 2021 Gastrointestinal Cancers Symposium

Conclusions

- Nivolumab demonstrated durable efficacy in patients with advanced ESCC based on a minimum of 5-year update of ATTRACTION-1 study.
- No new safety signals with nivolumab were identified.
- Long-term survivors tended to show the deeper response (e.g., complete response) of nivolumab in this study.

For additional information, see poster # 207

Abstract 201

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Perioperative FLOT plus anti-PD-L1 Avelumab (FLOT-A) in resectable oesophagogastric adenocarcinoma (OGA): Interim safety analysis results from the ICONIC trial

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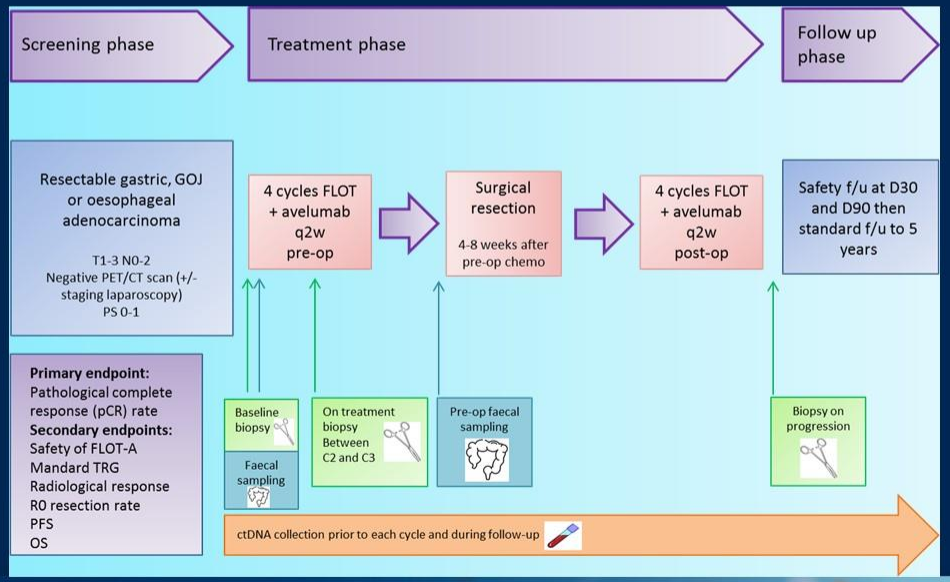
Background

ICONIC is a single-arm phase II trial investigating the safety and efficacy of perioperative FLOT-A in resectable OGA.

Following a 3+3 design safety run-in phase, standard dose FLOT* with 10mg/kg IV Avelumab administered every 2 weeks was taken forward into the main study.

The aims of this pre-planned interim analysis were to assess perioperative safety and R0 resection rates.

Trial schema



Methods

Key eligibility criteria:

- Histologically confirmed localised and operable OGA
- PS 0-1
- Considered fit for surgery
- No prior therapy for OGA
- No prior antibody targeting T-cell co-stimulation or checkpoint pathways

The interim analysis occurred after the 15th patient treated at the above dose reached 30 days post-surgery.

*5-FU 2600mg/m^2 over 24 hours, Oxaliplatin 85mg/m^2, Docetaxel 50mg/m^2, Folinic acid 200mg/m^2, Primary prophylactic GCSF.

Discussion/Conclusions

- This is the first interim safety data of combining FLOT chemotherapy with an anti-PD-L1 inhibitor in the perioperative setting in OG adenocarcinoma.
- In these 15 patients treated with FLOT-A, no intra-operative complications have occurred and no unexpected complications have been identified post-operatively.
- The ICONIC trial will continue recruitment until 40 patients have been treated and undergone surgery.
- Biomarker analysis (tumour mutation burden, immune cell infiltration, immunotherapy response signatures) in pre-operative and on-treatment biopsies and ctDNA is ongoing.

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Results: Surgical outcomes

- Median time from last chemotherapy to surgery = 6.4 weeks.
  - Reason for delay (>8 weeks following pre-operative treatment) in 3/15 patients = fitness for surgery.
- All patients (100%) achieved an R0 resection.
- No intra-operative complications were reported.
- There were no emergency re-operations.

Table 5: Post-operative complications in N=14 patients from whom data was available at interim analysis

Complication (8 patients)	Clavien-Dindo grade	Timing of complication Early (≤3 days) Intermediate (4-30 days) Late (>30 days)	Outcome	Action taken
Anastamosis/conduit leak	IIIa	Intermediate	Resolved	Percutaneous drainage and Esosponge
Supraventricular tachycardia	II	Intermediate	Resolved	No action taken
Pleural effusion	IIIa	Intermediate	Resolved	Percutaneous drainage
Chest infection	IIIa	Late	Resolved	Prolonged antibiotics
Sub-acute bowel obstruction	II	Late	Resolved	NG tube and conservative management
Clostridium Difficile diarrhoea	II	Intermediate	Resolved	No action taken
Chest infection and pyrexia	II	Early	Resolved	Prolonged antibiotics
Infection unknown source	II	Early	Resolved	Prolonged antibiotics
Chest infection	II	Intermediate	Resolved	Prolonged antibiotics

Table 4: Surgical procedures and metrics (N=15 patients)

	No of patients (%)
Procedure	
• Minimally invasive Ivor-Lewis oesophagogastrectomy with two-field radical lymphadenectomy	10 (67)
• Left thoracoabdominal oesophago-gastrectomy	1 (7)
• Gastrectomy with D2 lymphadenectomy	4 (27)
ASA pre-operative risk score	
• I	1 (7)
• II	7 (47)
• III	7 (47)
Inotropic support required	
• Yes	12 (80)
• No	3 (20)
Blood transfusion required	
• Yes	1 (7)
• No	14 (93)
Operation time in minutes (median [IQR])	300 [260-380]
Time to extubation in hours (median [IQR])	6 [4-24]
Days on vasopressors/inotropes (median [IQR])	0 [0-1]
APACHE score D1 post-op (median [IQR])	12 [10-15]
Days in CCU (ITU/HDU) (median [IQR])	3 [2-4]
Days in hospital (median [IQR])	13 [11-16]

Discussion/Conclusions

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The interaction between microsatellite instability high (MSI-high) resectable gastric cancer and chemotherapy on survival

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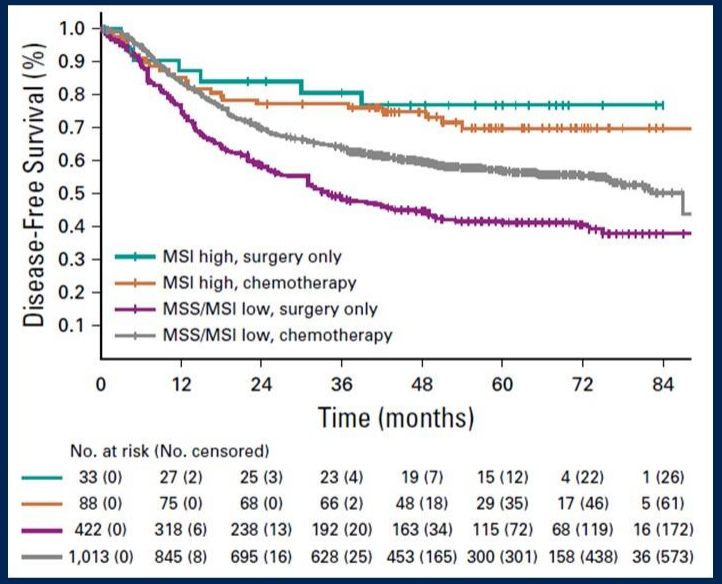
Introduction

- Meta-analysis of 4 trials found:
  - patients with MSI-high gastric cancer did not benefit from chemotherapy
- Our aim:
  - retrospectively study interaction between MSI status and chemotherapy (neoadjuvant or adjuvant) on prognosis

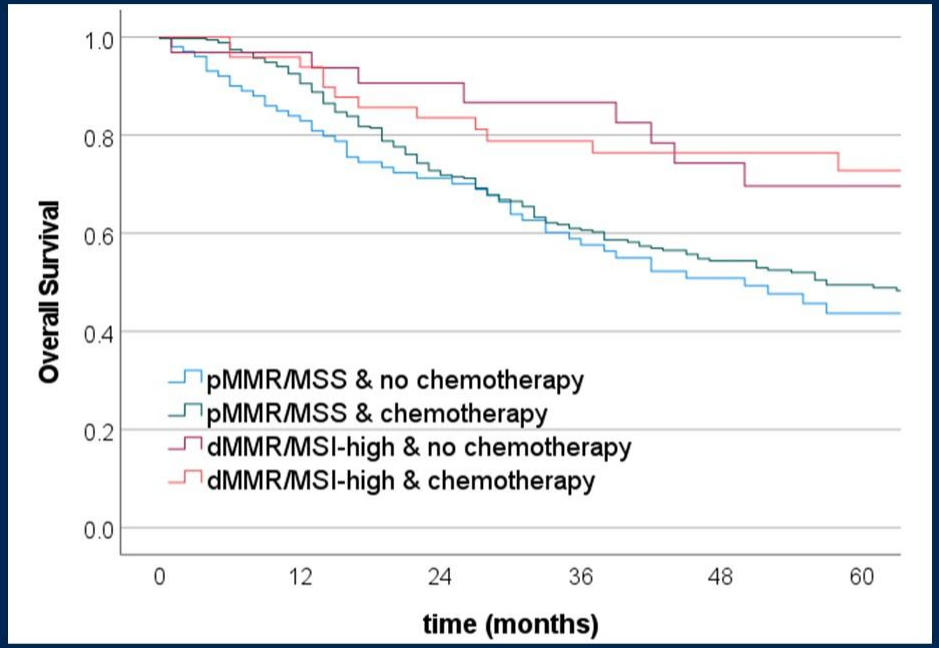


Pietrantonio et al. J Clin Oncol 2019;37:3392-3400

Results

- Clinically locally advanced gastric adenocarcinoma with resection 2000-2018 > N=1770
  - MSI status by next-generation-sequencing (NGS) or immunohistochemistry (IHC) > N=535
    - 82/535 (15.3%) mismatch repair deficient (dMMR) or MSI-high

- Pathological neoadjuvant chemotherapy response grade 1 (90-100%):
  - 0/40 dMMR/MSI-high vs 43/274 (16%) pMMR/MSS, P=0.007



No. at risk						
pMMR/MSS & no chemotherapy	102	82	64	47	34	22
pMMR/MSS & chemotherapy	351	321	237	160	123	92
dMMR/MSI-high & no chemotherapy	32	31	26	21	17	14
dMMR/MSI-high & chemotherapy	50	47	36	33	27	19

Adjusted for age and clinical tumor stage:

- Chemotherapy for dMMR/MSI-high: HR 1.03 95%CI 0.40-2.66

Conclusions

- Incidence of MSI-high tumors in clinically locally advanced, resectable, gastric cancer: 15%
- In patients with MSI-high tumors:
  - pathological response to neoadjuvant chemotherapy is worse
  - overall survival (OS) is better
  - OS was not altered by neoadjuvant/adjuvant chemotherapy
- We recommend assessing MSI status in gastric cancer

Děkuji
za pozornost.