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#GI2C

Novinky z ASCO GI 2020 - nádory jícnu a žaludku

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- Abstract 278: Results of the JAVELIN Gastric 100 phase 3 trial: avelumab maintenance following first-line (1L) chemotherapy (CTx) vs continuation of CTx for HER2− advanced gastric or gastroesophageal junction cancer (GC/GEJC). - Markus H. Moehler

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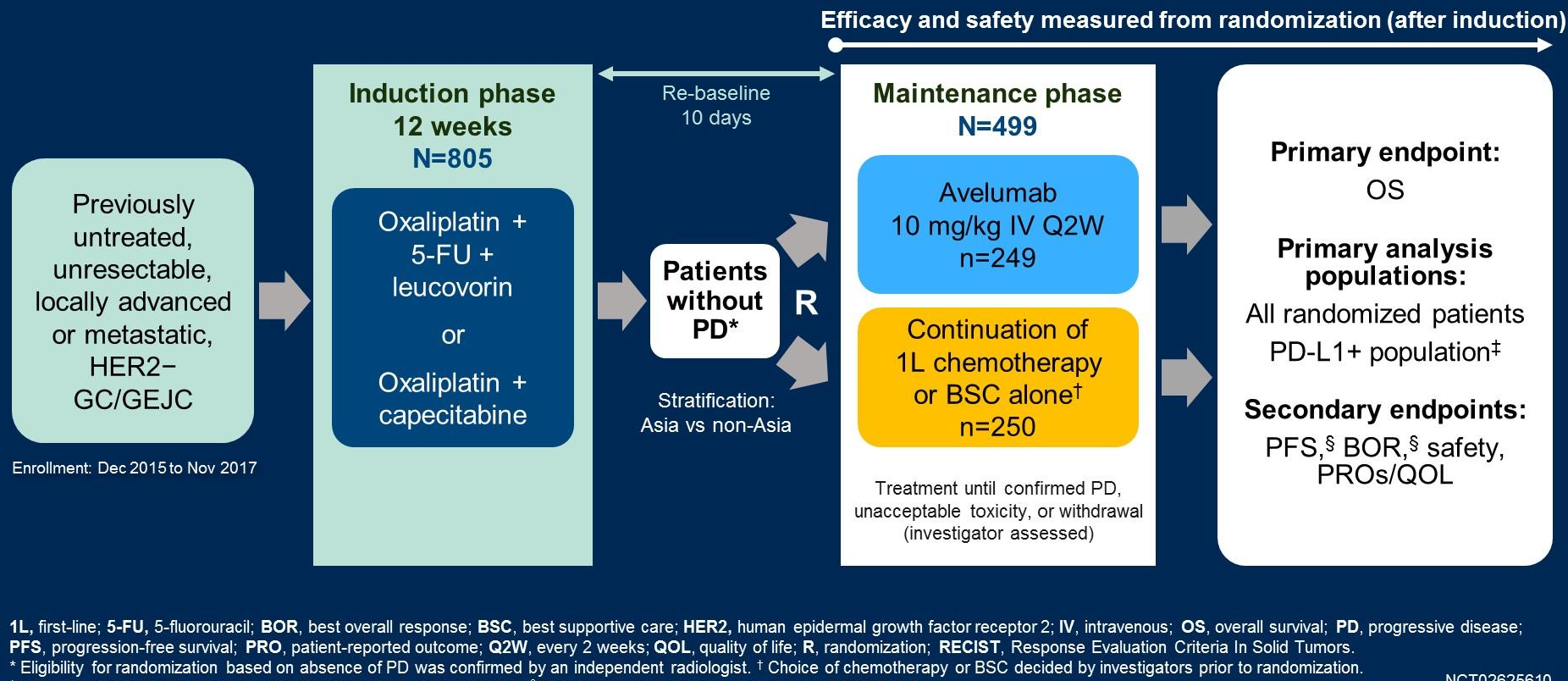

1L, first-line; **5-FU,** 5-fluorouracil; **BOR**, best overall response; **BSC**, best supportive care; **HER2,** human epidermal growth factor receptor 2; **IV**, intravenous; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PRO**, patient-reported outcome; **Q2W**, every 2 weeks; **QOL**, quality of life; **R**, randomization; **RECIST**, Response Evaluation Criteria In Solid Tumors.

* Eligibility for randomization based on absence of PD was confirmed by an independent radiologist. † Choice of chemotherapy or BSC decided by investigators prior to randomization. ‡ ≥1% of tumor cells PD-L1+ using the 73-10 pharmDx assay (Dako). § Based on investigator assessment per RECIST 1.1.

NCT02625610

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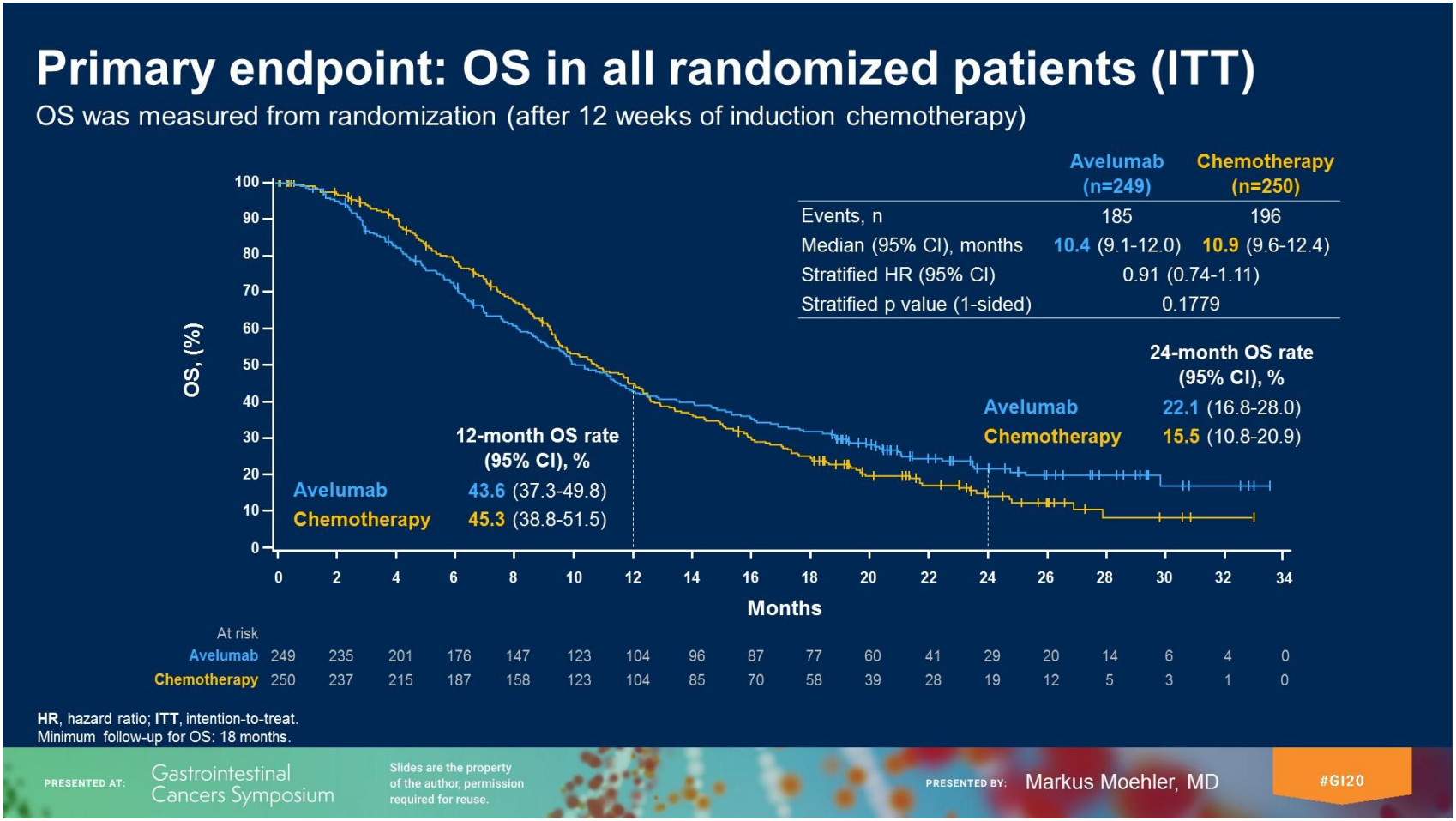

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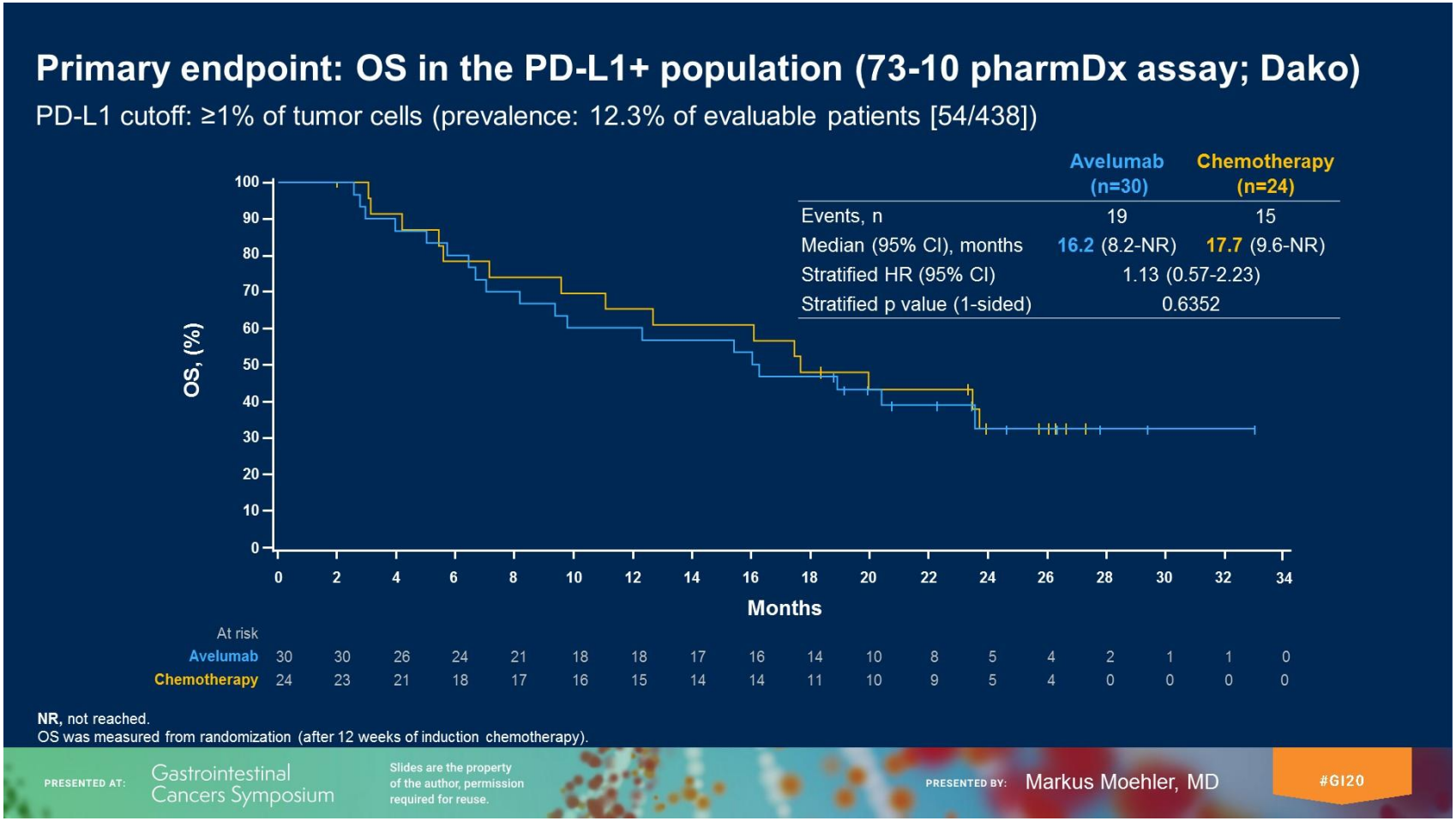

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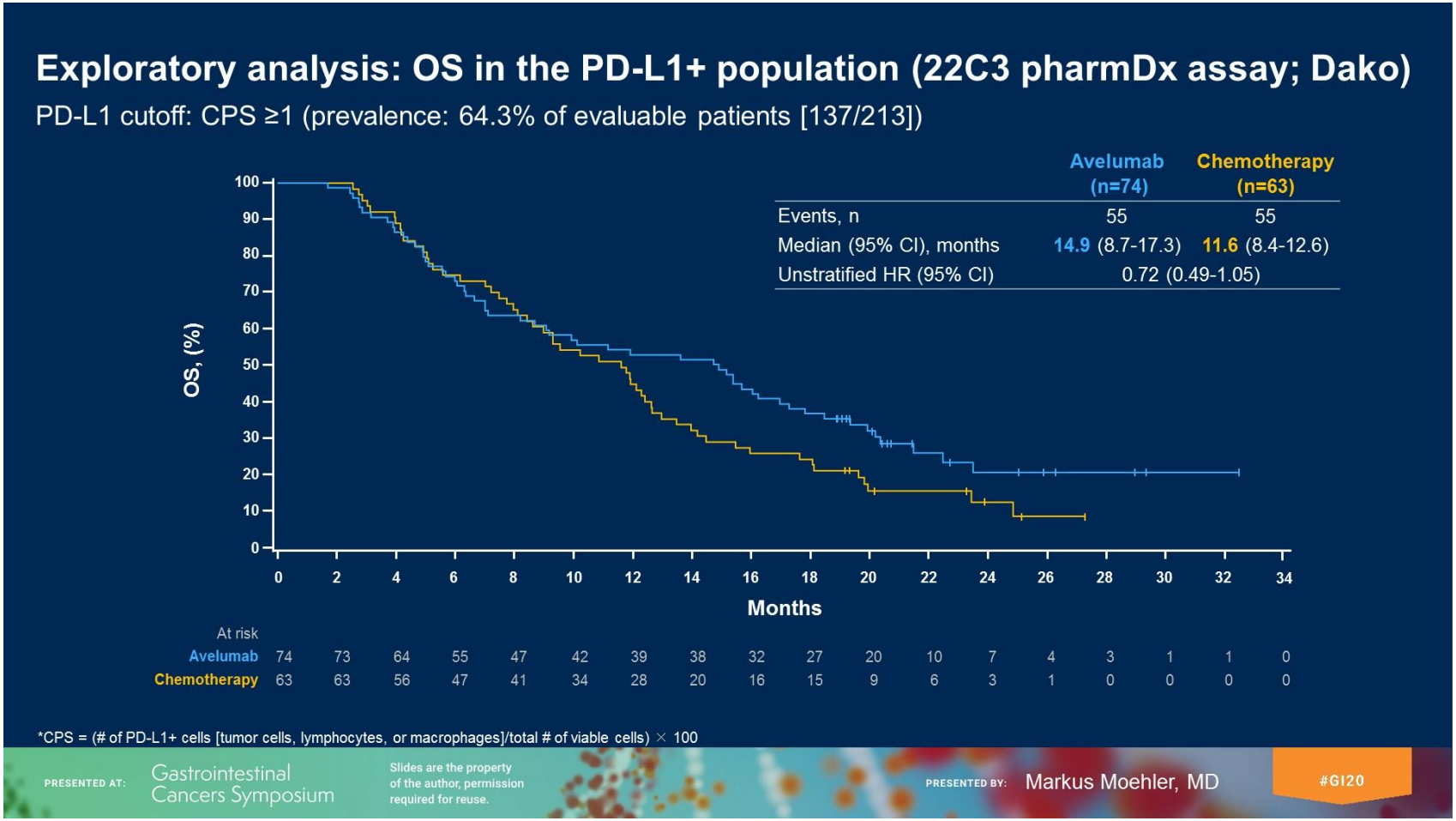

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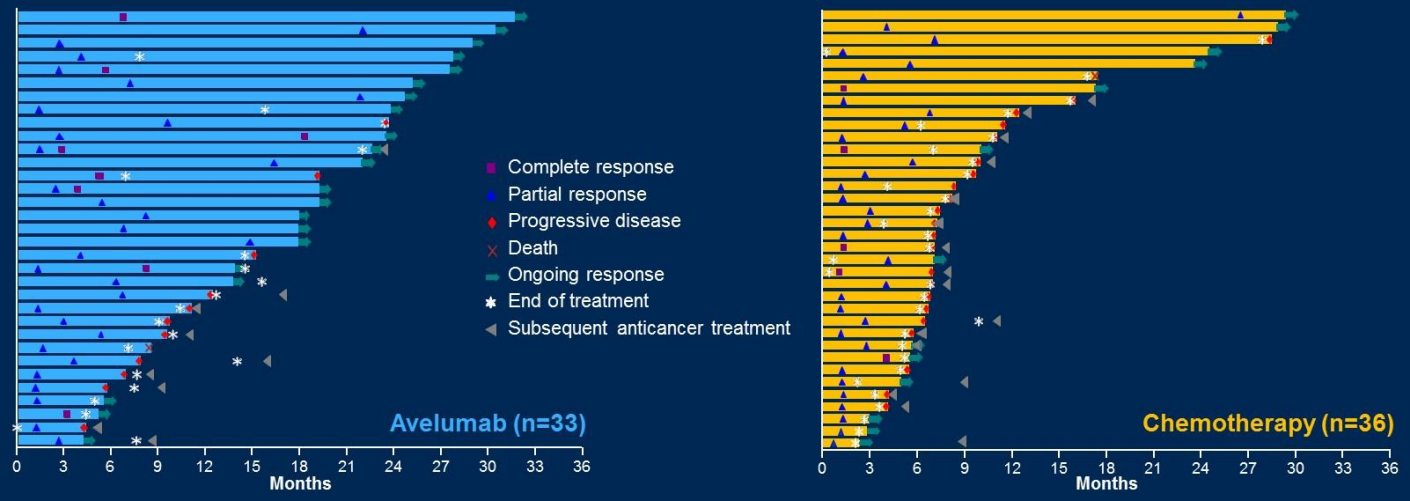
Time to and duration of response from randomization

Responses in patients with PR or SD after induction chemotherapy (excludes 10 patients with CR during induction)



	Avelumab (n=33)	Chemotherapy (n=36)
Median duration of response	Not reached (95% CI: 9.7-NR)	5.9 months (95% CI: 4.5-7.2)
Proportion ongoing		
at 12 months:	62.3% (95% CI: 40.9-77.9)	28.4% (95% CI: 13.2-45.7)
at 24 months:	51.0% (95% CI: 29.0-69.4)	13.5% (95% CI: 3.1-31.6)

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Safety overview

	Avelumab (n=243)	Chemotherapy (n=238)
Any AE (related or unrelated), % (n)	91.8 (223)	89.9 (214)
Grade ≥3	54.3 (132)	53.8 (128)
Any TRAE, % (n)	61.3 (149)	77.3 (184)
Grade ≥3	12.8 (31)	32.8 (78)
TRAE leading to permanent discontinuation, % (n)*	10.3 (25)	27.3 (65)
Serious TRAE, % (n)	7.8 (19)	9.7 (23)
TRAE leading to death, % (n)	0	0.4 (1)
Infusion-related reaction of any grade, % (n)†	19.8 (48)	7.1 (17)

TRAE, treatment-related adverse event.

* TRAEs leading to discontinuation in ≥1% of patients were: avelumab, pneumonitis (1.6%); chemotherapy, peripheral sensory neuropathy (7.6%), peripheral neuropathy (6.7%), neutropenia (2.1%), neurotoxicity (2.1%), thrombocytopenia (1.7%), decreased appetite (1.3%).

† Identified using an expanded definition that included both a prespecified list of MedDRA preferred terms (infusion-related reaction, drug hypersensitivity, anaphylactic reaction, or hypersensitivity reaction) that occurred on the day of infusion or the following day, and prespecified signs/symptoms that occurred on the day of infusion and resolved within 2 days (related or unrelated).

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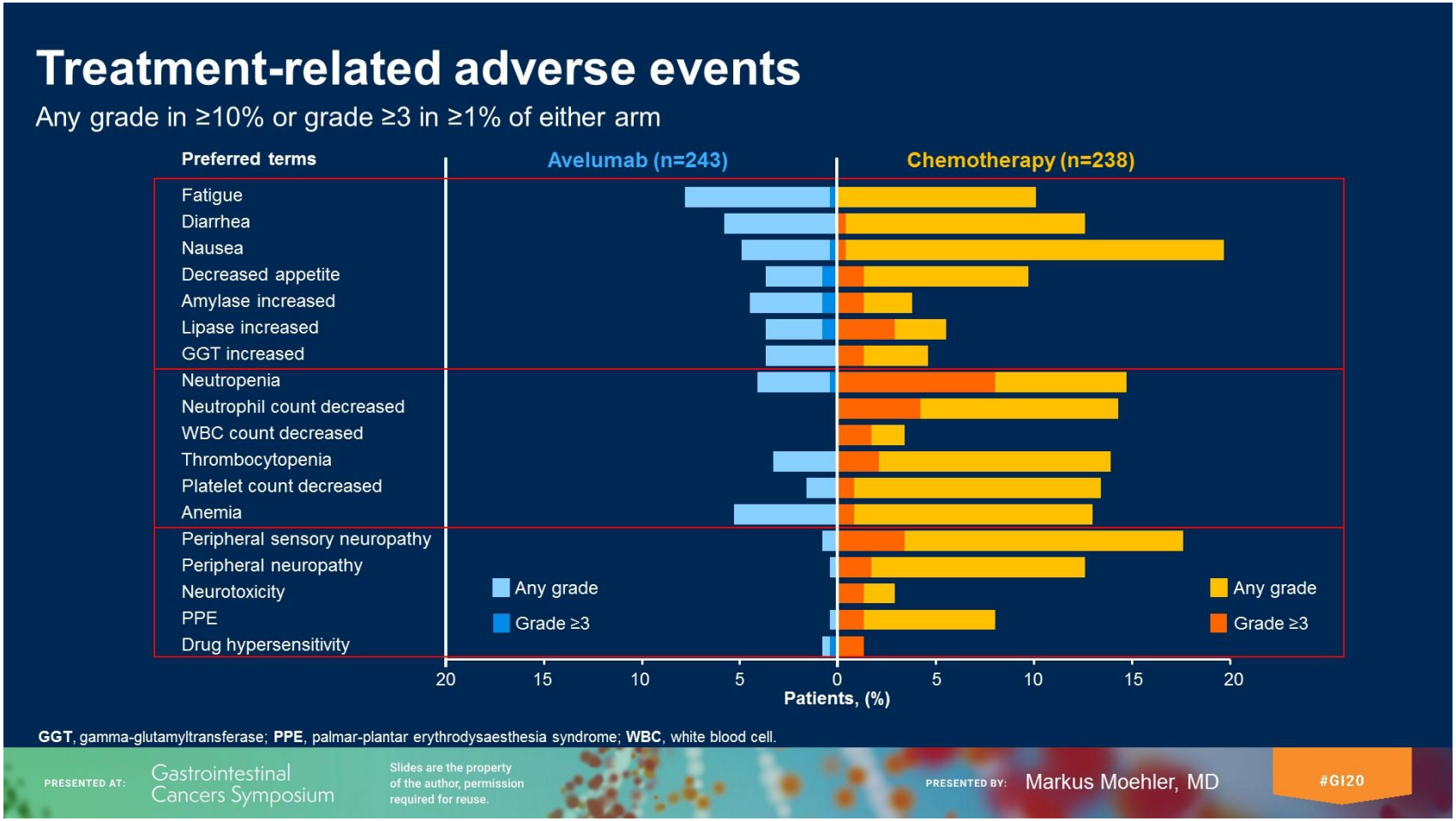

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- Studie JAVELIN 100
  - neprokázala ve srovnání s udržovací chemoterapií zlepšený výsledek OS a to ani se zohledněním PD-L+
  - udržovací léčba avelumabem prokázala však
    - delší trvání RR,
    - menší toxicitu

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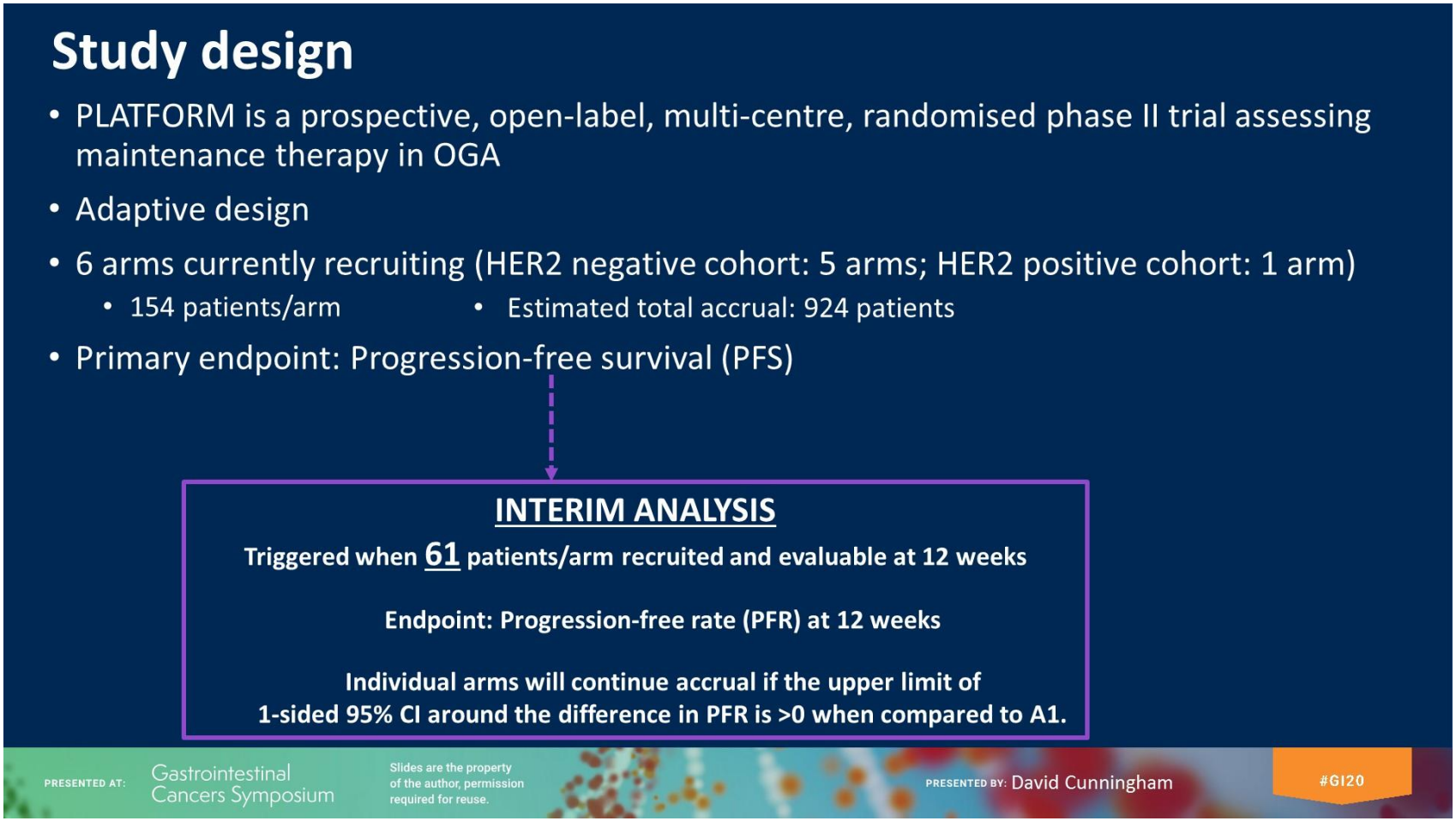

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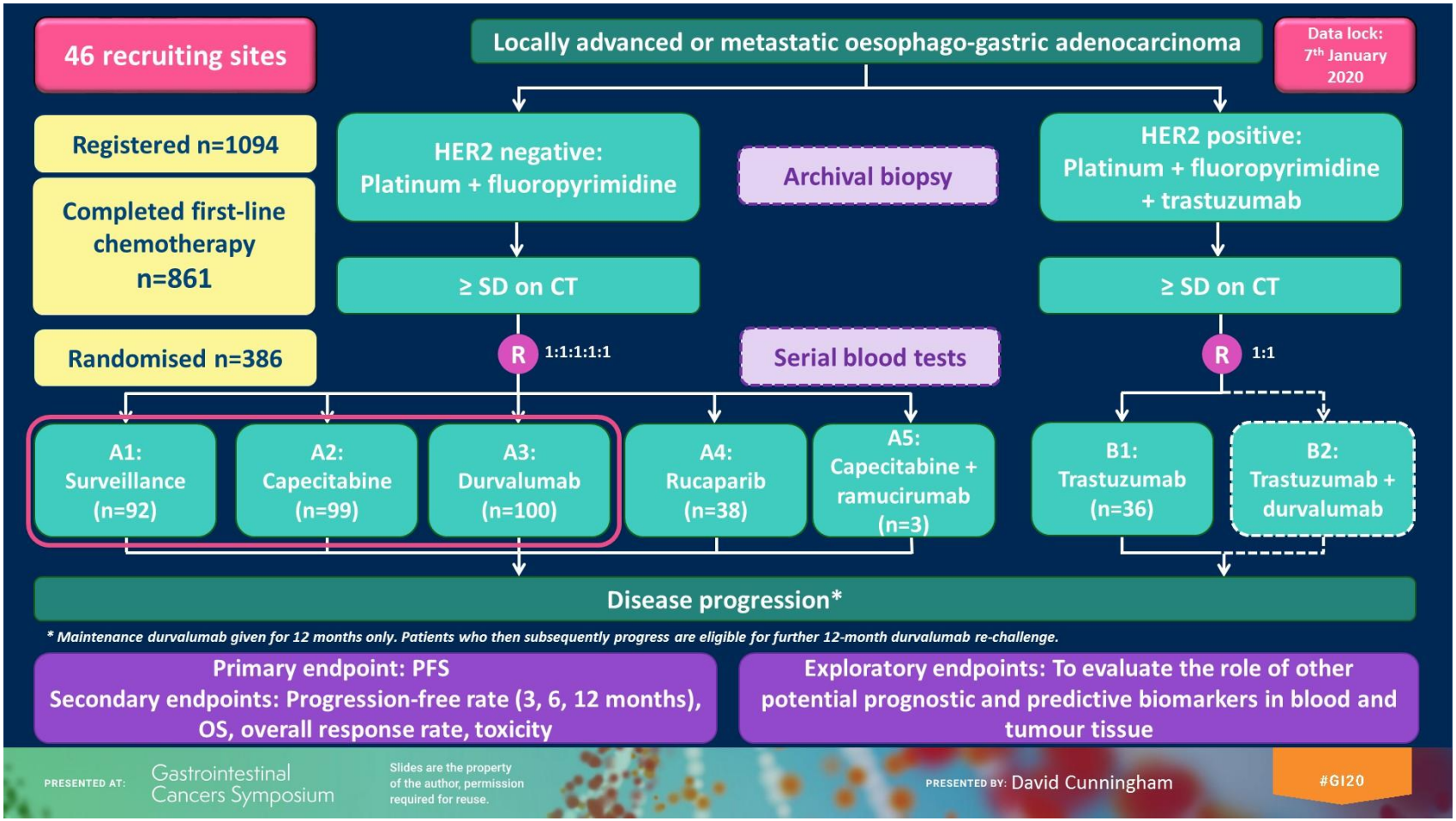

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Progression-free rate (PFR) at 12 weeks from randomisation

Treatment arms	A1: Surveillance (n=61)	A2: Capecitabine (n=61)	A3: Durvalumab (n=61)
PFR at 12 weeks (95% CI)	30 (49%) (39, 60%)	34 (56%) (45, 66%)	29 (48%) (37, 58%)
PFR compared to A1 (95% CI)	Control	+6.6% (-8.3, +21.4%)	-1.6% (-16.5, +13.3%)

Treatment arms	A1: Surveillance (n=61)	A2: Capecitabine (n=61)	A3: Durvalumab (n=61)
Complete response (CR)	0 (0%)	0 (0%)	0 (0%)
Partial response (PR)	0 (0%)	0 (0%)	3 (5%)
Stable disease (SD)	30 (49%)	34 (56%)	26 (43%)
Progressive disease (PD)	28 (46%)	25 (41%)	31 (51%)
Clinical PD	3 (5%)	2 (3%)	1 (2%)

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PFR at 12 weeks by PD-L1 status and tumour mutational burden (TMB)

PD-L1 quantified using Tumor and Tumor-associated Immune Cell (TIC) score

Treatment arm	A1: Surveillance (n=44)		A3: Durvalumab (n=38)	
PD-L1	TIC ≥1 n=28	TIC ≥10 n=7	TIC ≥1 n=22	TIC ≥10 n=4
Progression-free	15 (54%)	3 (43%)	14 (64%)	4 (100%)
Progressive disease	13 (46%)	4 (57%)	8 (36%)	0 (0%)

Median TMB: 5.8 mutations/Mb (range: 1.0-78.1)
Median TMB A1: 5.3 (range: 2.1-78)
Median TMB A3: 5.9 (range: 1.0-53)
Low: 1.0-4.3 Medium: >4.3-8.5 High: >8.5-79

Treatment arm	A1: Surveillance (n=37)			A3: Durvalumab (n=36)		
TMB	Low n=14	Medium n=9	High n=14	Low n=11	Medium n=15	High n=10
Progression-free	9 (64%)	2 (22%)	8 (57%)	7 (64%)	6 (40%)	8 (80%)
Progressive disease	5 (36%)	7 (78%)	6 (43%)	4 (36%)	9 (60%)	2 (20%)

CD4 and CD8 infiltration according to PD-L1 and TMB

Biomarker	T cells		
	Low	Medium	High
PD-L1 TIC ≥10	3/29 (10%)	2/17 (12%)	6/28 (21%)
TMB high	13/26 (50%)	6/15 (40%)	3/24 (13%)

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Grade ≥3 Treatment-related adverse events (TrAEs)

Maximum reported grade of TrAEs (Grades ≥3 only)			
Grade	**A1: Surveillance (n=61)**	**A2: Capecitabine (n=61)**	**A3: Durvalumab (n=61)**
3	0 (0%)	8 (13%)	7 (11%)
4	0 (0%)	0 (0%)	2 (3%)
5	0 (0%)	0 (0%)	0 (0%)

A2: Capecitabine Grade 3 TrAEs:

- Fatigue (5%), peripheral sensory neuropathy (3%), anaemia (2%), dysgeusia (2%), hand-foot syndrome (2%), hypoalbuminaemia (2%), hyponatraemia (2%), pain (2%).

A3: Durvalumab Grade 3/4 TrAEs:

- Raised ALT (5%), hyperbilirubinaemia (4%), diarrhoea (3%), raised AST (2%), raised GGT (2%), anaemia (2%), hypoalbuminaemia (2%), fatigue (2%), ascites (2%), chills (2%), hypertension (2%), hypophosphataemia (2%), pleural effusion (2%)

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- Interní analýza studie PLATFORM
  - Studie pokračuje
  - Radiologická RR byla jen v rameni durvulumabem
  - Efekt byl výraznější ve skupině PD-L + a TMB

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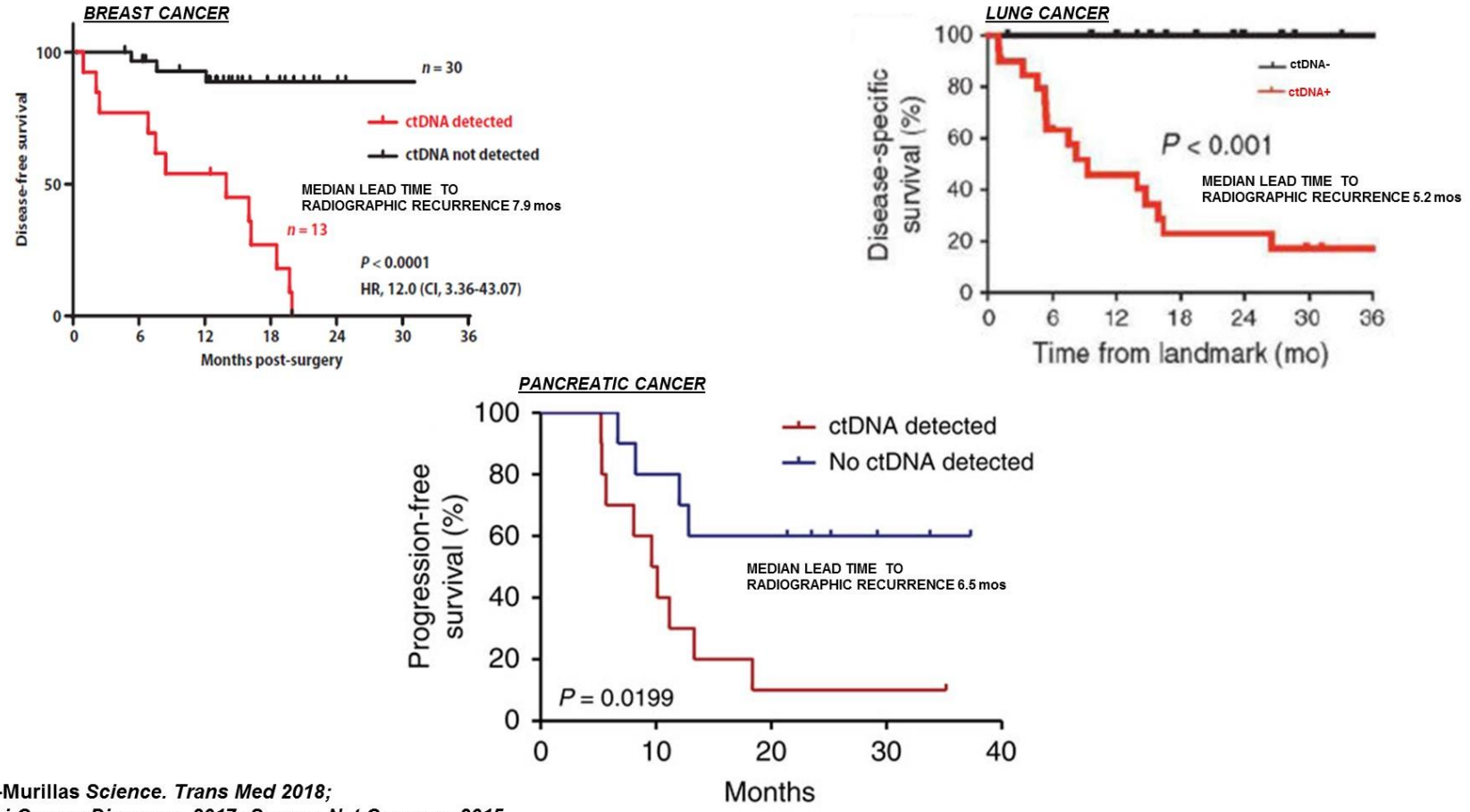
ctDNA POST-SURGERY PREDICTS RECURRENCE



Garcia-Murillas *Science. Trans Med 2018;*
Chaudri Cancer Discovery 2017; Sausen Nat Commun 2015

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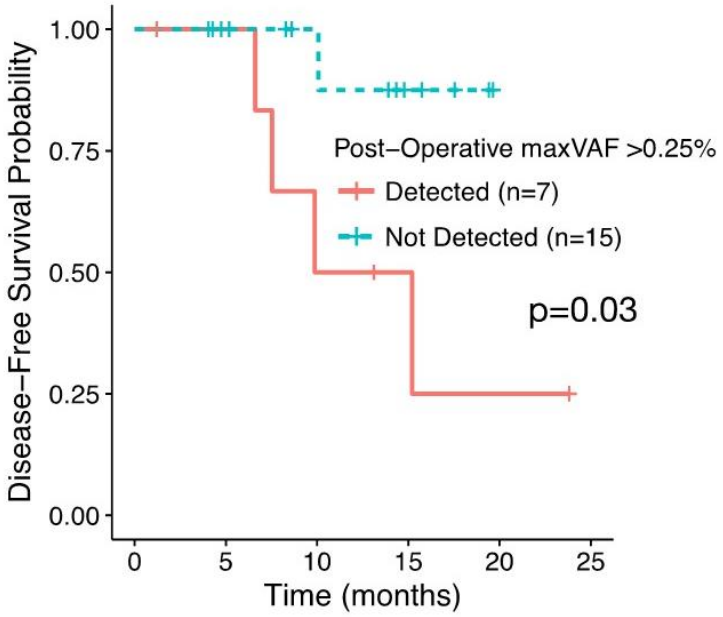
ctDNA PREDICTS RECURRENCE IN GASTRIC CANCER

Within 6 months after surgery



Median mDFS
12.5 months vs. NR

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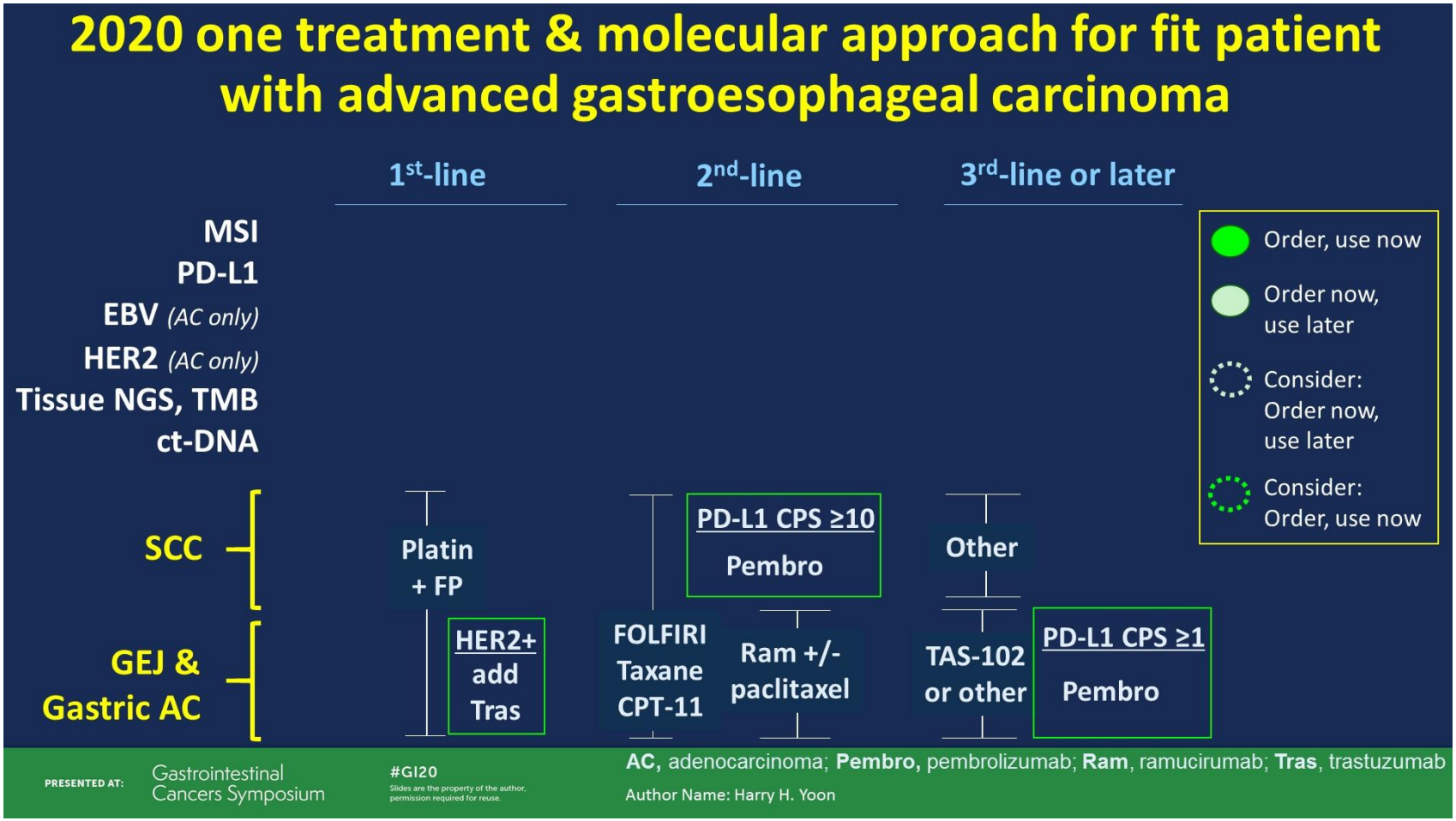

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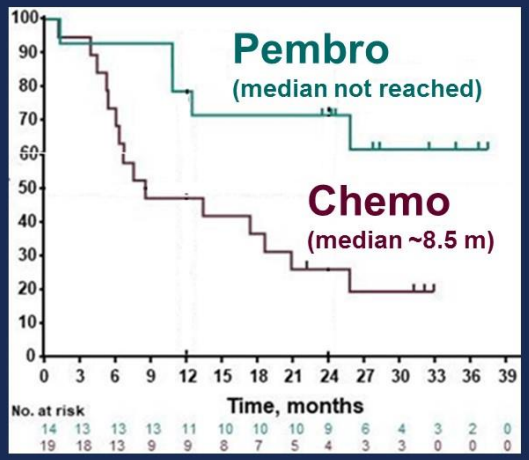
Pembro confers OS benefit in MSI gastric/GEJ adenoca in 1st line setting

Secondary analyses of phase III KN-062

1st-line (n = 23, all MSI-high)



- **HR 0.29 (95% CI 0.11 – 0.81)**
- **Duration of response on Pembro = 21.2 m**

Shitara et al KN-062 ESMO 2019

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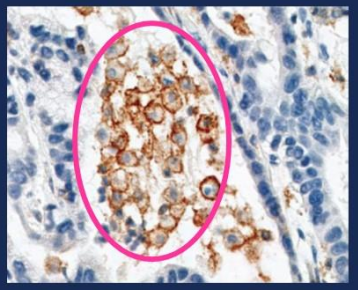
CPS (combined positive score), the only PD-L1 method predictive of immunotherapy benefit in gastroesoph cancer

$$\text{CPS} = \frac{\#\text{ of } \textit{macrophages}, \textit{lymphocytes}, \text{ or tumor cells that express PD-L1}}{\#\text{ of tumor cells evaluated}} \times 100$$

In gastroesoph adenoca microenvironment, PD-L1 is expressed most commonly in immune cells (not tumor cells)



Take home message

Verify on path report that immune cells were counted.

If they were not, scoring must be repeated.

Inter-lab agreement for PD-L1 scoring (CPS 1 *vs* 0) is >90%

Kulangara et al Arch Pathol Lab Med 2019

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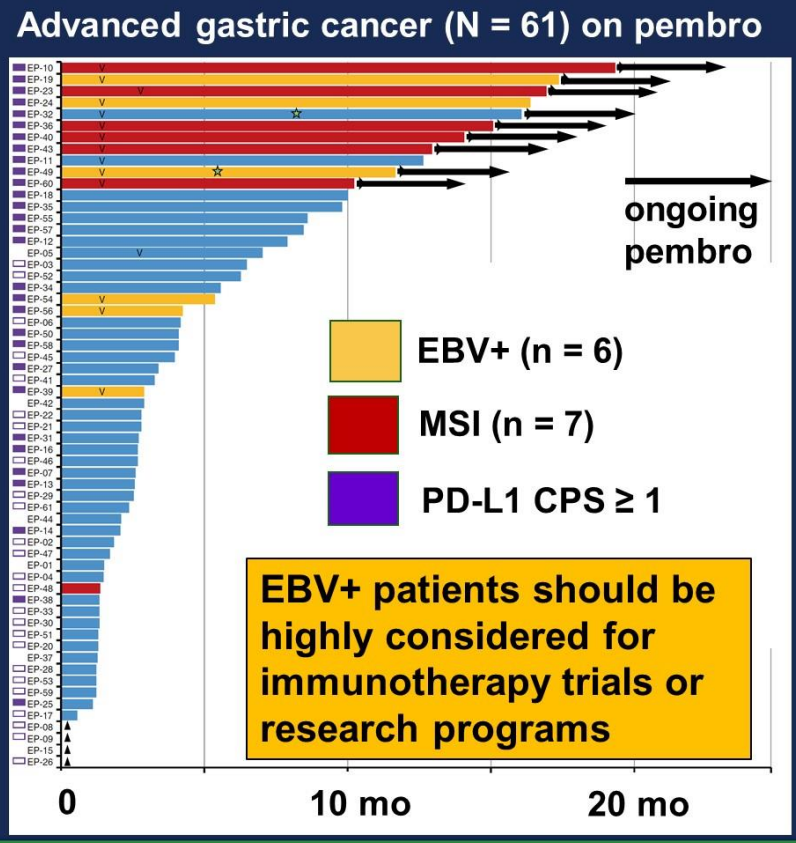
EBV+ gastric ca seems responsive to anti-PD-1 (comparable to MSI)

- All 6 (of 6) EBV+ patients had PR/CR with anti-PD-1 monotherapy
  - Response duration >10 mo in 3 patients
- Every EBV+ tumor was PD-L1 CPS ≥ 1
  - Usually NOT due to *PD-L1* amp
  - Enriched with IFN gene signature
- PD-L1 CPS level in EBV+ tumor may not correlate response benefit
  - 3 longest responders: CPS 1, 5, 80
  - Other 3 patients had CPS 15 to 80



Kim ST et al 2018 *Nature Medicine*; Derks et al 2016 *Oncotarget*
V = date of first response

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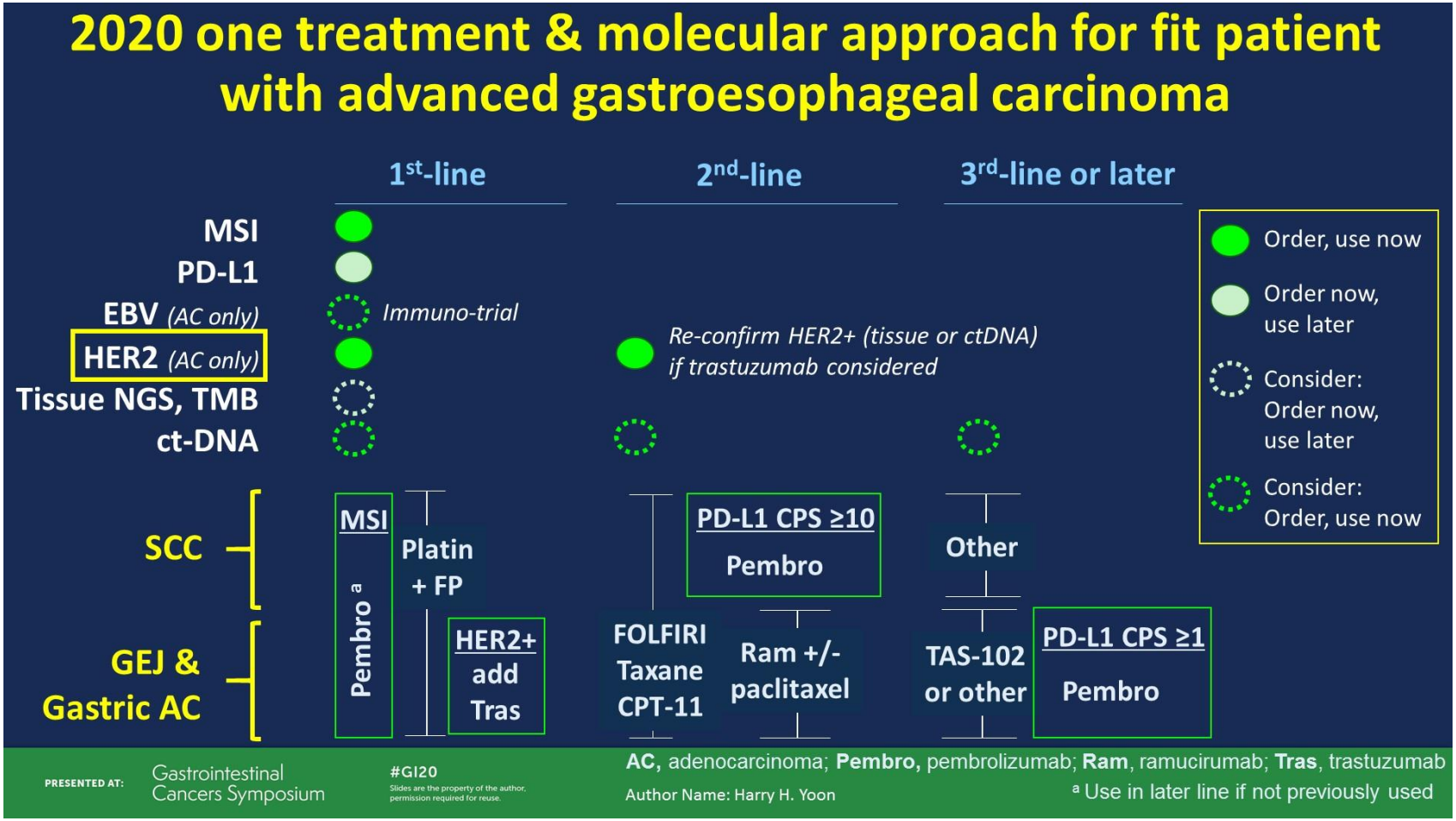

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- MSI a PD-L1 před 1 lininií
  - PD-L1 musí zahrnovat i bb imunitního systému
  - Využití i v 2. a 3. linii
- EBV+ využití pro stratifikaci pacientů do klinických studií s imunoterapií
- HER2 status znovu vyšetření po selhání léčby s HER2i


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lizumab)
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Děkuji za pozornost