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Immunotherapy for Gastrointestinal Cancer

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DISCLOSURE SLIDE

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Immunotherapy for gastrointestinal cancer

- **Squamous esophageal cancer**
- **Esophageal, junctional and gastric adenocarcinoma**
- **Hepatocellular Carcinoma**
- **Colorectal Cancer**
- Biliary tract cancer
- Pancreatic Cancer
- Anal cancer

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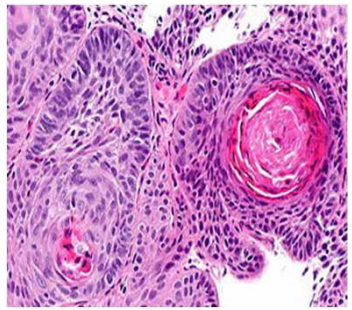
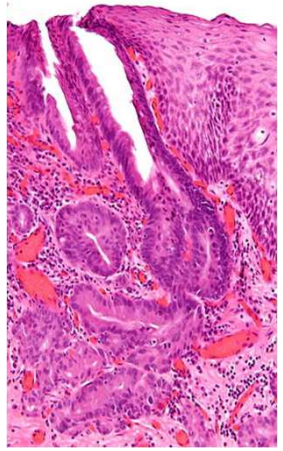
ESOPHAGUEAL CANCERS

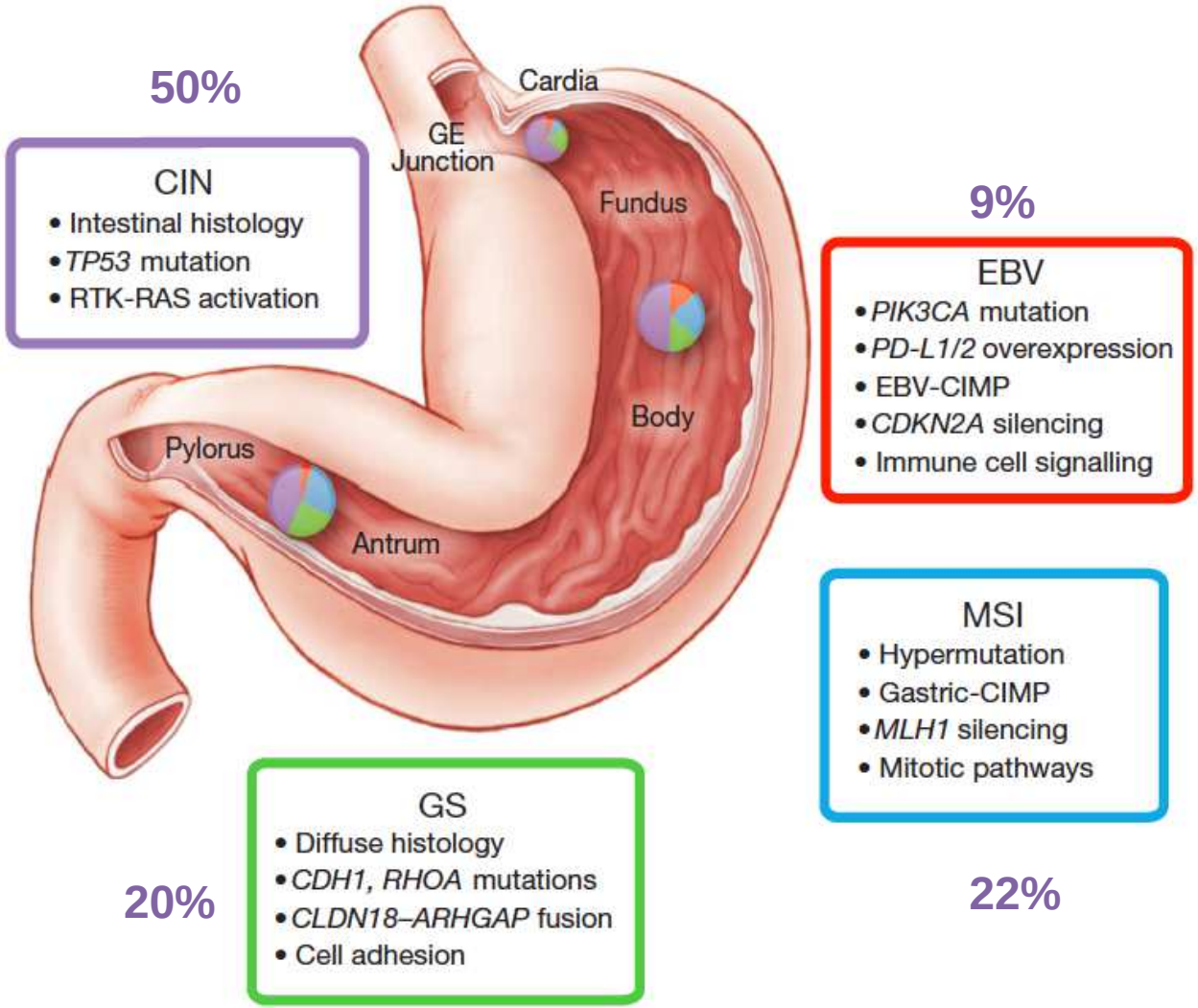
5 YEAR SURVIVAL IN WESTERN COUNTRIES: 10-12%

- Squamous cell carcinomas
  - Upper and mid-esophagus location
  - Smoking and alcohol related in Western countries
  - More prevalent in developing countries



- Adenocarcinomas
  - Lower third and junctional location
  - Related to obesity, smoking, gastric reflux and Barret's esophagus
  - Increasing incidence in Western countries (x4.6 US)





Cancer Genome Atlas Research Network. Nature 2014;513:202–209.

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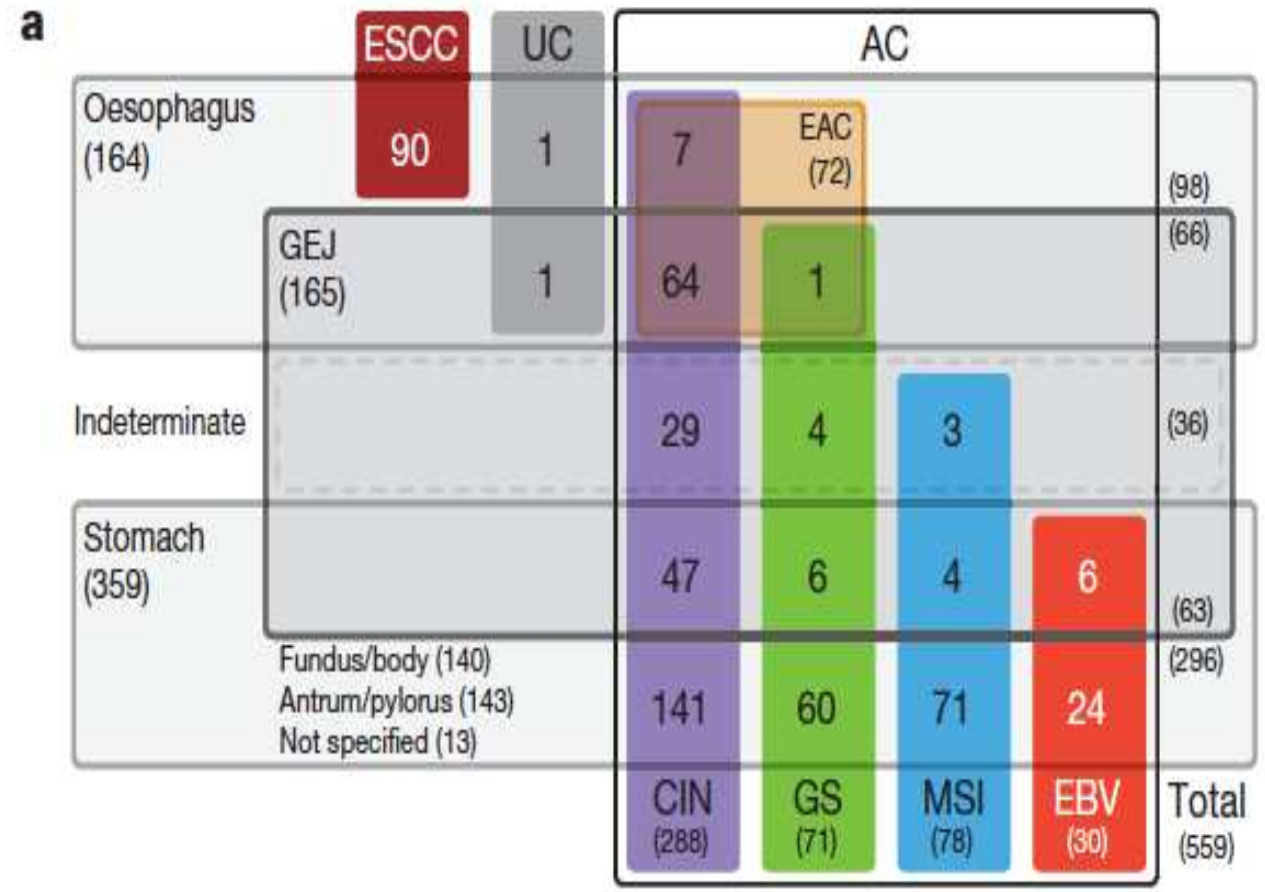
INTEGRATED GENOMIC CHARACTERIZATION OF OESOPHAGEAL CANCERS



Cancer Genome Atlas Research Network. Nature 2017; 541; 169-175.

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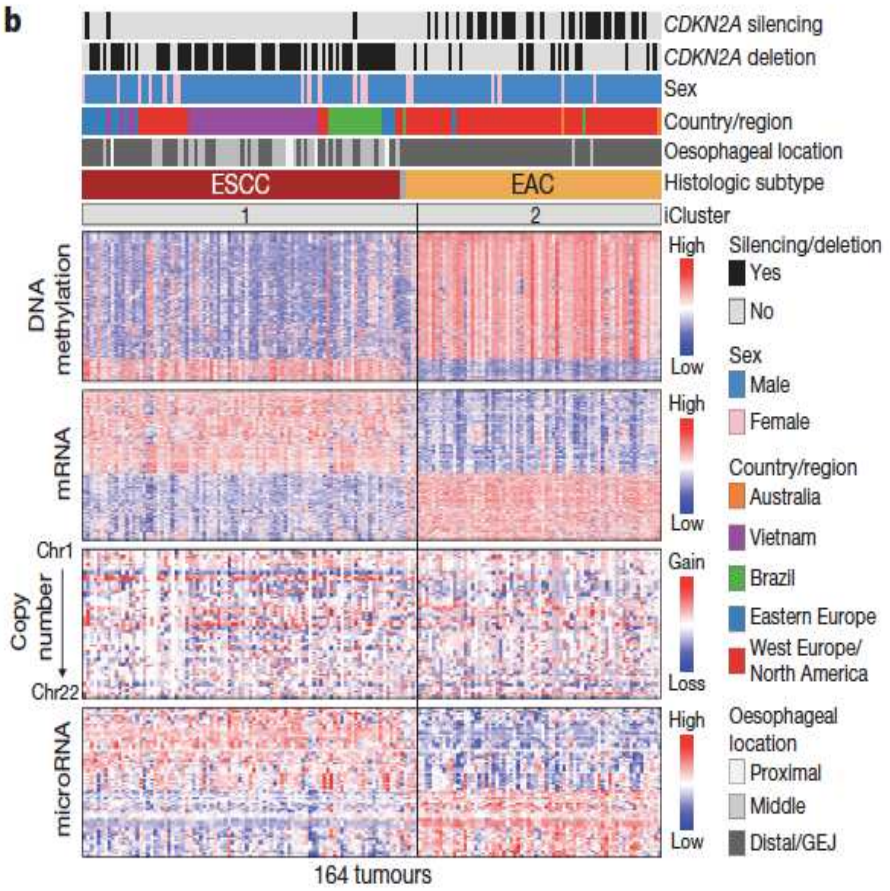
INTEGRATED GENOMIC CHARACTERIZATION OF ESOPHAGEAL CANCERS

Squamous cell cancers

vs

Adenocarcinomas



Cancer Genome Atlas Research Network. Nature 2017; 541; 169-175.

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Europ

Nivolumab treatment for oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial

	Centrally assessed (n=64)	Investigator assessed (n=64)
Best overall response		
Complete response	1 (2%, 95% CI <0·5–8)	2 (3%, 95% CI 1–11)
Partial response	10 (16%, 95% CI 9–26)	12 (19%, 95% CI 11–30)
Stable disease	16 (25%, 95% CI 16–37)	20 (31%, 95% CI 21–43)
Progressive disease	29 (45%)	29 (45%)
Not assessable	8 (13%)	1 (2%)
Objective response*	11 (17%, 95% CI 10–28)	14 (22%, 95% CI 14–33)
Disease controlled†	27 (42%, 95% CI 31–54)	34 (53%, 95% CI 41–65)
Median progression-free survival (months)	1·5 (95% CI 1·4–2·8)	2·3 (95% CI 1·5–3·0)

*Complete or partial response. †Complete response, partial response, or stable disease.

Table 2: Activity of nivolumab

Kudo T et al. Lancet Oncol 2017; 18:631-639

Safety and Antitumor Activity of the Anti–Programmed Death-1 Antibody Pembrolizumab in Patients With Advanced Esophageal Carcinoma

Table 3. Best Overall Response per Response Evaluation Criteria in Solid Tumors, Version 1.1, Assessed by Investigator Review (N = 23)

Response	No.	%	95% CI
Overall response rate	7	30	13 to 53
Complete response	0	0	0 to 15
Partial response	7	30	13 to 53
Stable disease	2	9	1 to 28
Progressive disease	13	57	35 to 77
Nonevaluable	1	4	< 1 to 22

Doi T, et al. J Clin Oncol 2018; 36:61-67

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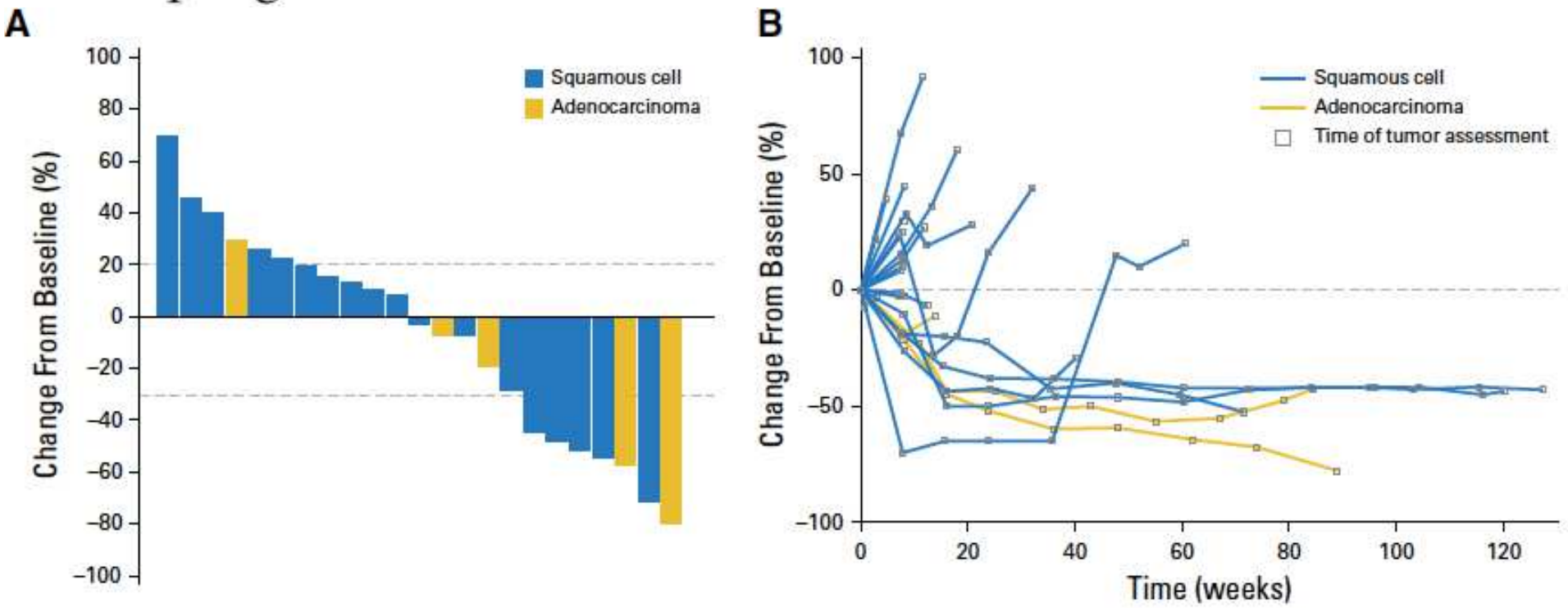
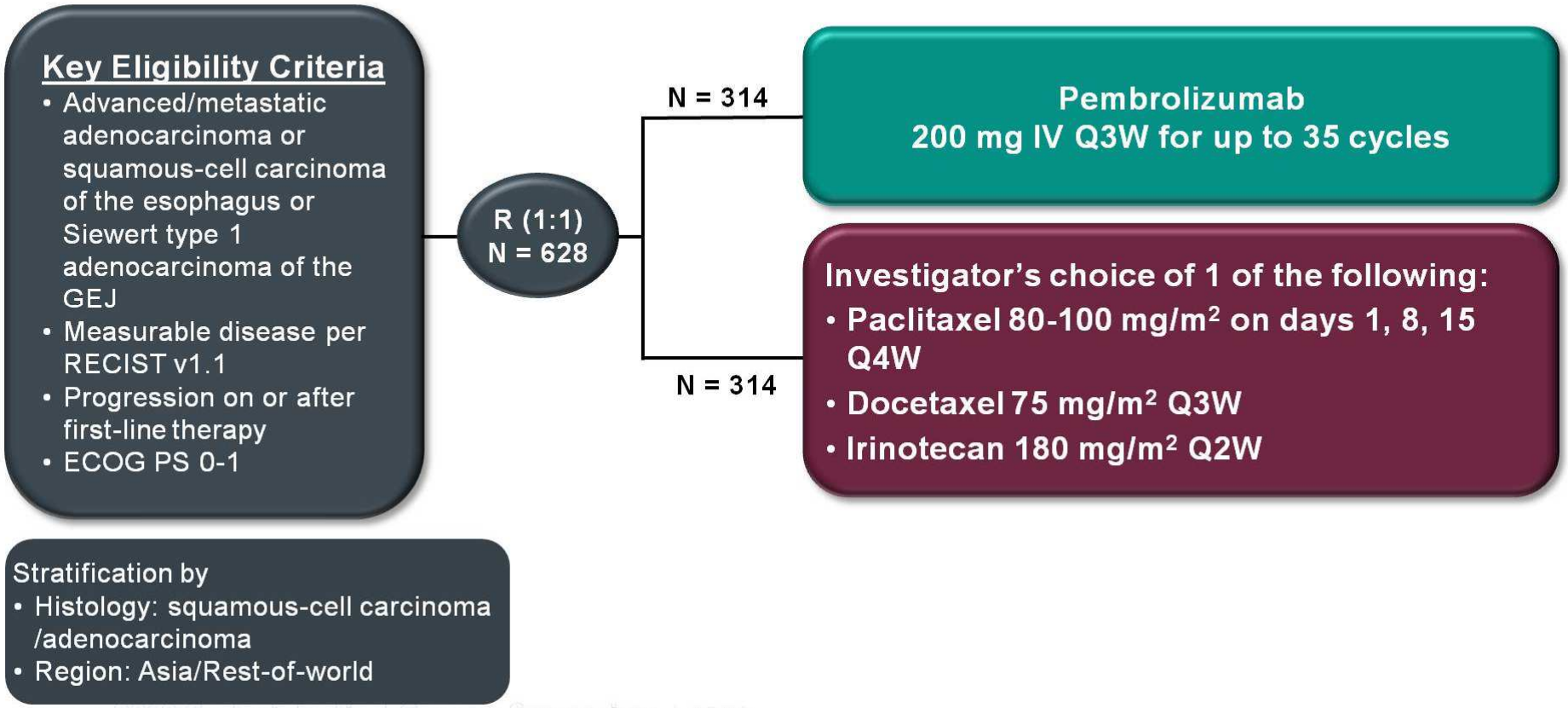
Safety and Antitumor Activity of the Anti–Programmed Death-1 Antibody Pembrolizumab in Patients With Advanced Esophageal Carcinoma



Doi T, et al. J Clin Oncol 2018; 36:61-67

Phase 3 KEYNOTE-181 Study (NCT02564263)



Analysis Populations and Endpoints

- Analysis populations
  - Efficacy: assessed in patients with PD-L1 CPS ≥10, SCC, and ITT
  - Safety: assessed in all patients who received ≥1 dose of study drug
- 3 primary endpoints
  - Overall survival in
    1. Patients with PD-L1 CPS ≥10
    2. Patients with SCC
    3. All patients (ITT)
- Secondary endpoints
  - Progression-free survival
  - Objective response
  - Safety

SCC, squamous cell carcinoma; ITT, intent-to-treat; PD-L1 CPS: defined as number of PD-L1 positive cells (tumor cells, macrophages, lymphocytes)/total number of tumor cells x 100.

Assessments and Statistical Considerations

- Assessments
  - Response: assessed at week 9 and then every 9 weeks (RECIST, v1.1, BICR)
  - Survival follow-up every 9 weeks
- Statistical considerations
  - **Planned** enrollment: 600; Actual: 628
  - Overall alpha for study: one-sided alpha of 2.5%
    1. α 0.9% ($P \leq 0.0085$) for superiority of OS in PD-L1 CPS ≥10
    2. α 0.8% ($P \leq 0.0077$) for superiority of OS in SCC
    3. α 0.8% ($P \leq 0.0077$[a]) for superiority of OS in ITT
  - Stratified log-rank test used to assess differences between treatment groups for OS and PFS (CPS ≥10, SCC)
  - Stratified maximum weighted log-rank test used to assess differences between treatment groups for OS and PFS (ITT)

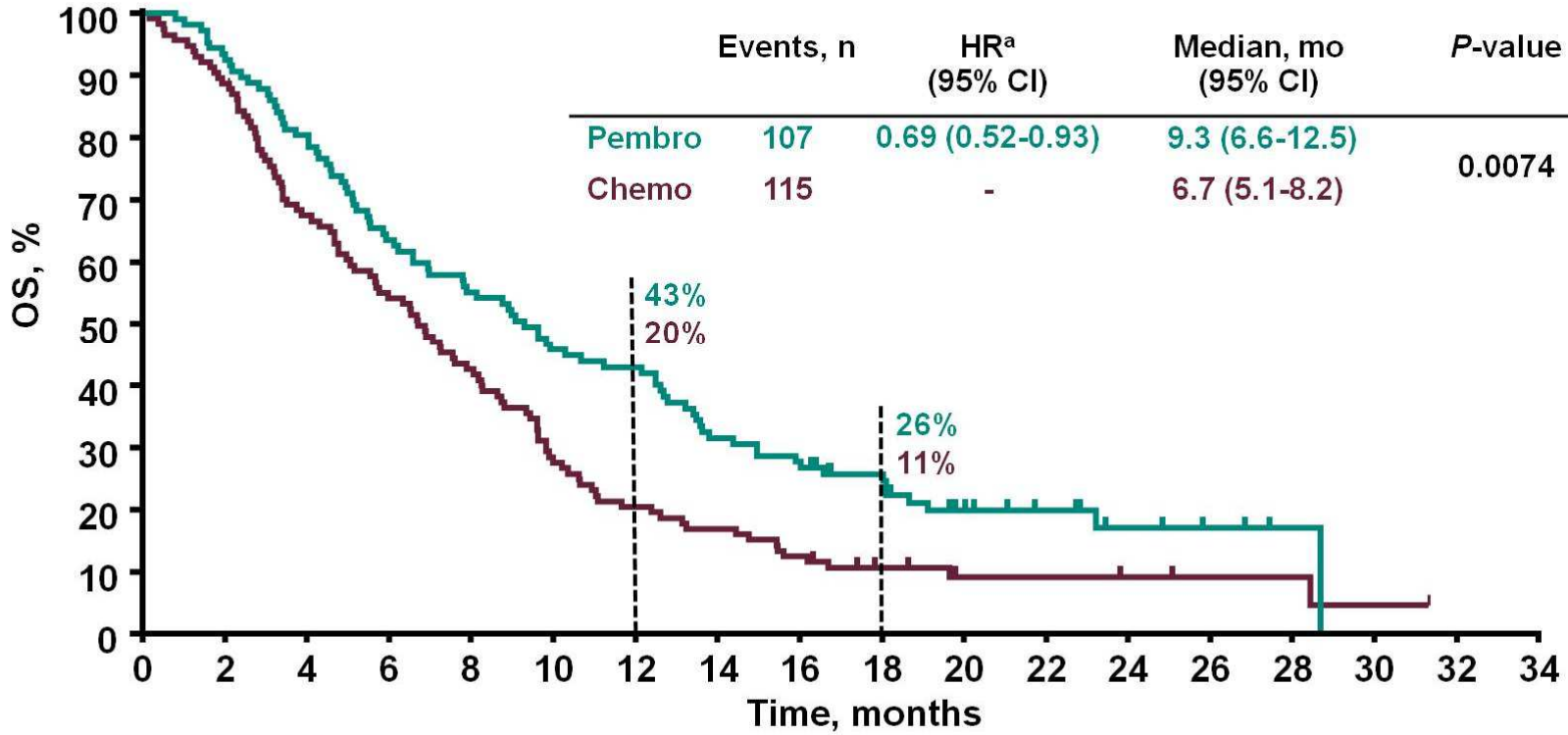
[a]Actual boundary is 0.0162 after alpha passing from OS in PD-L1 CPS ≥10 to OS in ITT (all patients) due to rejected OS in PD-L1 CPS ≥10 hypothesis.
BICR, blinded independent central review; PD-L1 CPS: defined as number of PD-L1 positive cells (tumor cells, macrophages, lymphocytes)/total number of tumor cells x 100.

Baseline Characteristics (ITT)

Characteristic, n	Pembrolizumab N = 314	Chemotherapy N = 314
Median age, years (range)	63 (23-84)	62 (24-84)
≥65 years	139 (44.3)	133 (42.4)
Male	273 (86.9)	271 (86.3)
Asia	121 (38.5)	122 (38.9)
Rest of World	193 (61.5)	192 (61.1)
ECOG PS 1	187 (59.6)	197 (62.7)
Squamous-cell carcinoma	198 (63.1)	203 (64.6)
Adenocarcinoma	116 (36.9)	111 (35.4)
PD-L1 CPS ≥10[a]	107 (34.1)	115 (36.6)
Metastatic disease	290 (92.4)	286 (91.1)
0-1[b] prior therapies	305 (97.1)	310 (98.7)
≥2 prior therapies	9 (2.9)	4 (1.3)

[a]6 patients in pembrolizumab and 3 in chemotherapy group were not evaluable; [b]2 patients in pembrolizumab group had 0 prior therapies; Data cutoff: October 15, 2018.

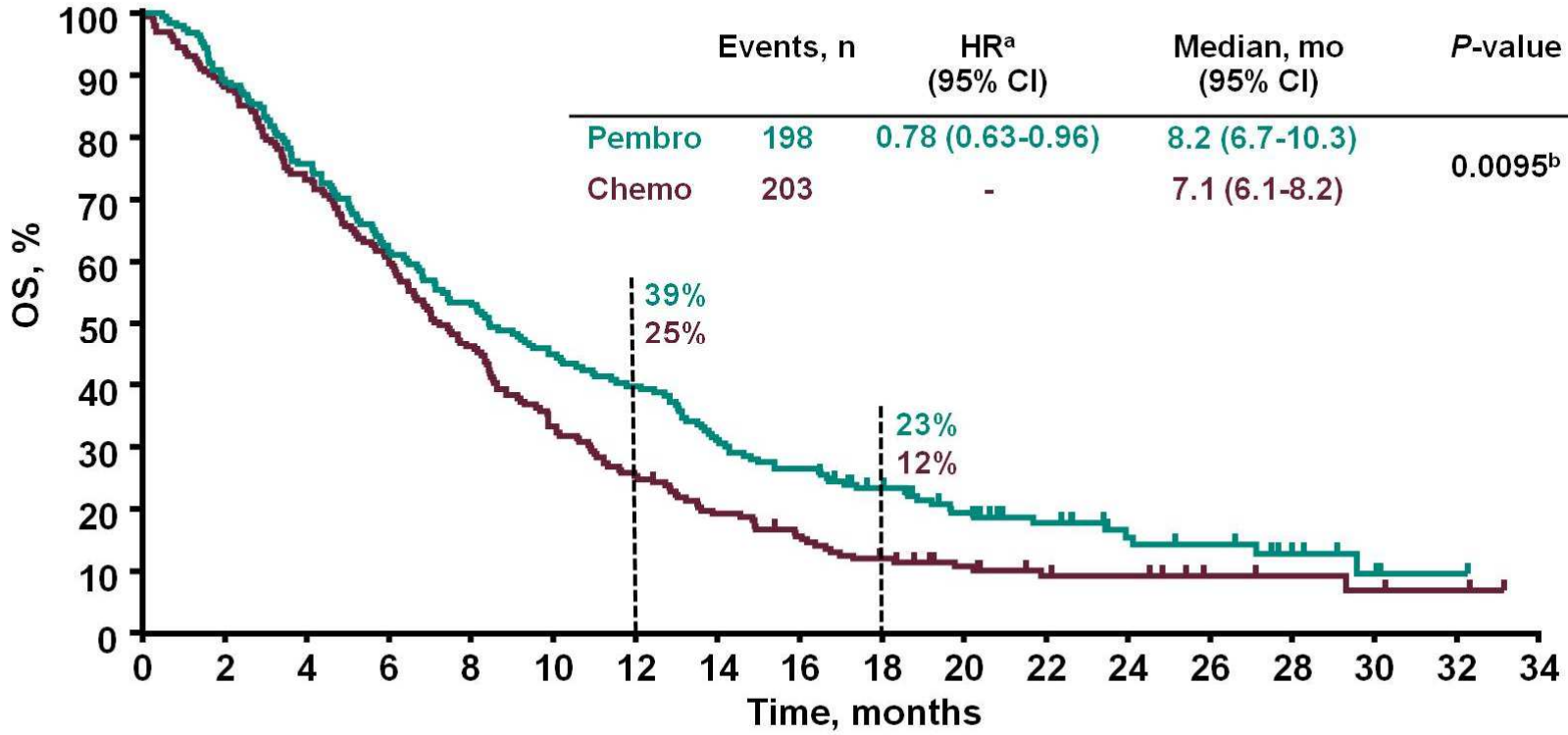
Overall Survival (PD-L1 CPS ≥10)



No. at risk																		
Pembrolizumab	107	100	86	68	59	49	45	33	29	23	13	9	5	3	1	0	0	0
Chemotherapy	115	102	76	61	48	31	23	19	14	8	4	4	3	2	2	1	0	0

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology.
Data cutoff: October 15, 2018.

Overall Survival (SCC)

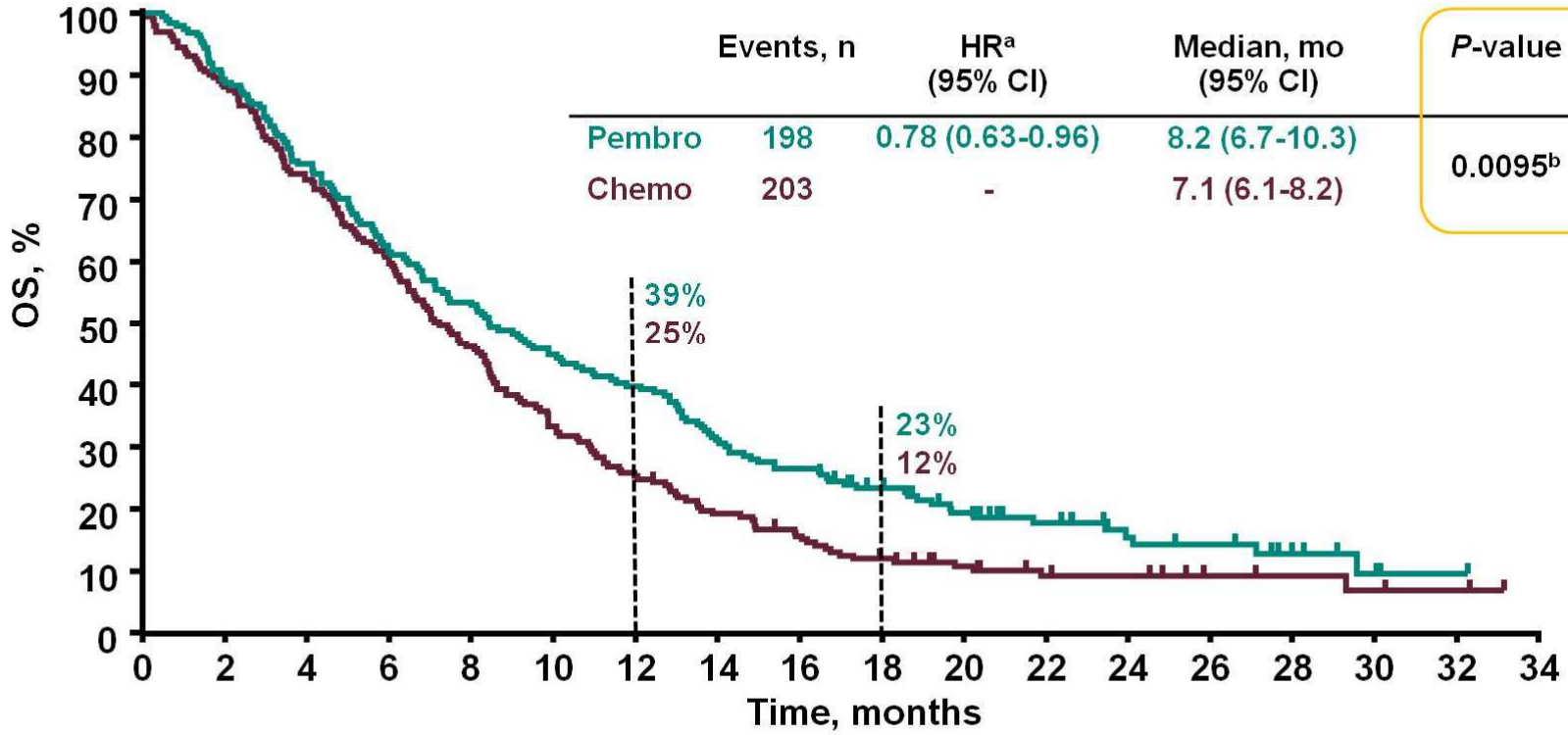


	Events, n	HR[a] (95% CI)	Median, mo (95% CI)	*P*-value
Pembro	198	0.78 (0.63-0.96)	8.2 (6.7-10.3)	0.0095[b]
Chemo	203	-	7.1 (6.1-8.2)	

No. at risk																		
Pembrolizumab	198	177	150	121	103	86	77	57	52	38	24	17	12	10	5	1	0	0
Chemotherapy	203	179	147	118	91	64	50	38	27	20	13	10	8	5	4	2	1	0

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology; [b]Not significant based on pre-specified statistical boundaries of $P \leq 0.0077$ for superiority of OS in SCC; Data cutoff: October 15, 2018.

Overall Survival (SCC)

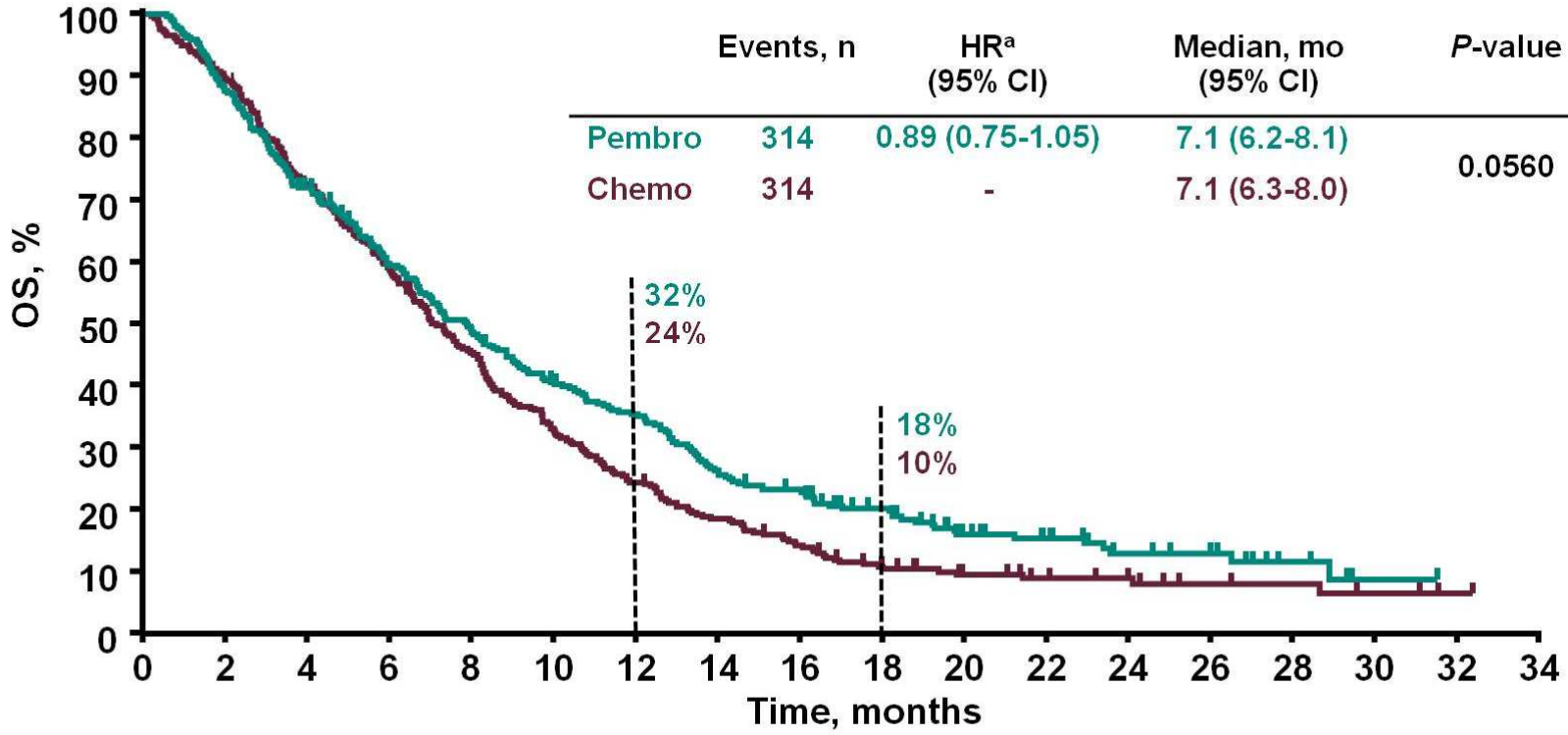


	Events, n	HR[a] (95% CI)	Median, mo (95% CI)	*P*-value
Pembro	198	0.78 (0.63-0.96)	8.2 (6.7-10.3)	0.0095[b]
Chemo	203	-	7.1 (6.1-8.2)	

No. at risk																		
Pembrolizumab	198	177	150	121	103	86	77	57	52	38	24	17	12	10	5	1	0	0
Chemotherapy	203	179	147	118	91	64	50	38	27	20	13	10	8	5	4	2	1	0

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology; [b]Not significant based on pre-specified statistical boundaries of $P \leq 0.0077$ for superiority of OS in SCC; Data cutoff: October 15, 2018.

Overall Survival (ITT)

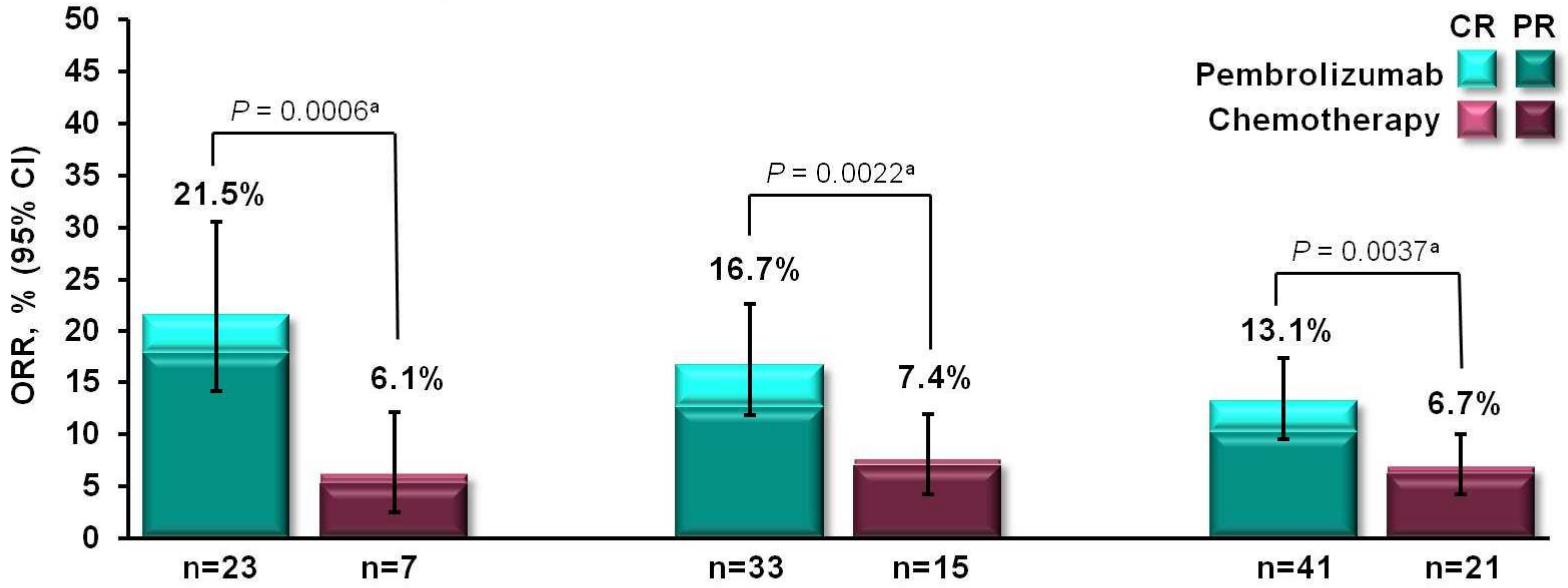


	Events, n	HR[a] (95% CI)	Median, mo (95% CI)	*P*-value
Pembro	314	0.89 (0.75-1.05)	7.1 (6.2-8.1)	0.0560
Chemo	314	-	7.1 (6.3-8.0)	

No. at risk																		
Pembrolizumab	314	275	224	176	143	116	100	73	63	46	28	20	14	10	5	1	0	0
Chemotherapy	314	280	226	181	139	98	75	56	41	26	18	13	9	6	5	3	1	0

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology.
Data cutoff: October 15, 2018.

Response Rate and Duration
(RECIST v1.1, BICR)



Duration	Median, mo (range)	≥ 6 mo, %
Pembro	9.3 (2.1+ to 22.6+)	77
Chemo	7.7 (4.3 to 16.8+)	57

Duration	Median, mo (range)	≥ 6 mo, %
Pembro	8.5 (2.1+ to 25.8+)	68
Chemo	10.7 (2.1+ to 16.8+)	75

Duration	Median, mo (range)	≥ 6 mo, %
Pembro	8.5 (2.1+ to 25.8+)	72
Chemo	10.7 (1.8+ to 16.8+)	62

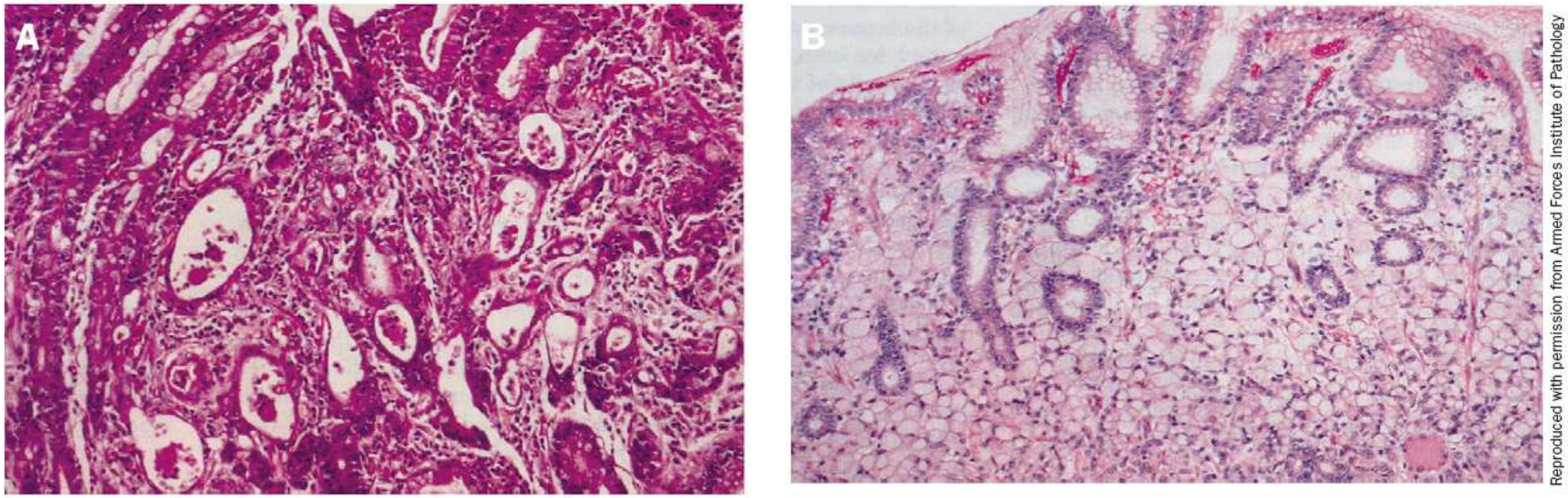
[a]Nominal; one-sided.
Data cutoff: October 15, 2018.

Summary and Conclusions

- Pembrolizumab significantly improved OS in patients with metastatic esophageal cancer and PD-L1 CPS ≥10 that progressed after 1 prior therapy versus chemotherapy
  - Superior OS in patients with PD-L1 CPS ≥10 metastatic esophageal cancer who had progressed after 1 prior therapy (HR 0.69, 95% CI 0.52-0.93)
  - Clinically meaningful increase in OS in patients with SCC (HR 0.78, 95% CI 0.63-0.96)
  - Similar OS in ITT (HR 0.89 95% CI 0.75-1.05)
- ORR higher with pembrolizumab versus chemotherapy
  - 21.5% vs 6.1% (CPS ≥10); 16.7% vs 7.4% (SCC); 13.1% vs 6.7% (ITT)
- More favorable safety profile with pembrolizumab compared with chemotherapy
  - Lower frequency of grade 3-5 treatment-related adverse events with pembrolizumab versus chemotherapy (18.2% vs 40.9%)
  - No new safety signals were observed
- Data suggest that pembrolizumab should be considered a new standard-of-care in the second-line for patients with metastatic esophageal cancer and PD-L1 CPS ≥10

Classification of gastric adenocarcinoma: Pathology

- Intestinal versus diffuse subtypes



Lauren P. et al. Acta Pathol Microbiol Scand 1965;64:31–49

Molecular subtypes of gastric cancer

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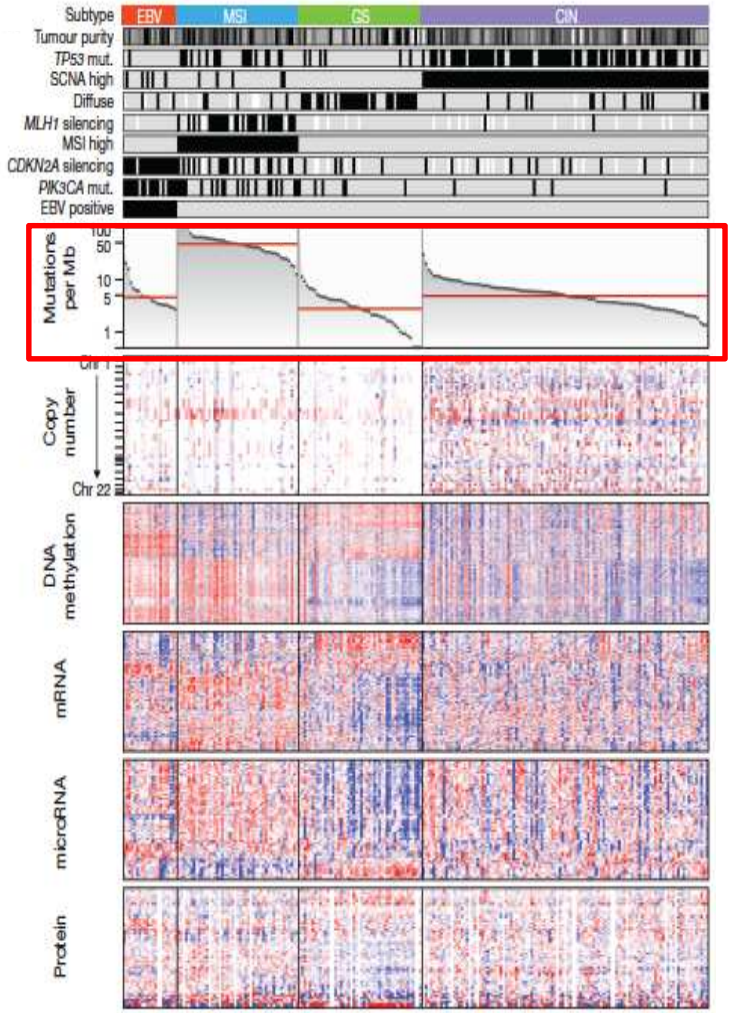

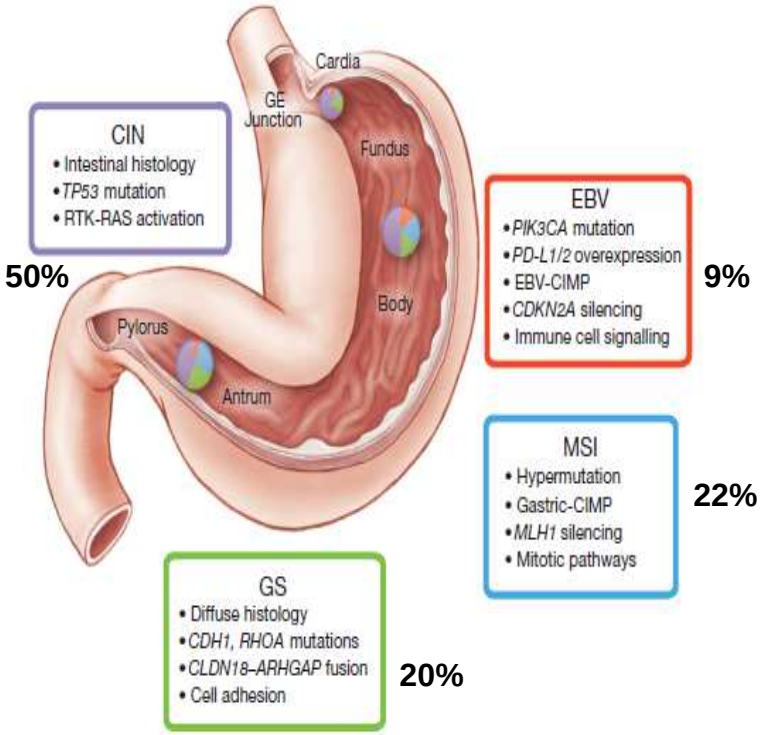

EBV, Epstein–Barr virus (red); MSI, microsatellite instability (blue), GS, genomically stable (green); CIN, chromosomal instability (light purple)

TCGA, Nature 2014

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Immunotherapy in advanced Gastro-esophageal Adenocarcinomas

Pembrolizumab induces responses in chemorefractory gastric cancer: Efficacy in evaluable patients in KEYNOTE-012

		Investigator review N = 39
ORR, % (95% CI)	22.2 (10.1, 39.2)	33.3 (19.1, 50.2)
Best overall response, n (%)		
Complete response[b]	0	0
Partial response[b]	8 (22.2)	13 (33.3)
Stable disease	5 (13.9)	5 (12.8)
Progressive disease	19 (52.8)	21 (53.8)
No assessment[c]	1 (2.8)	—
Not determined[d]	3 (8.3)	—

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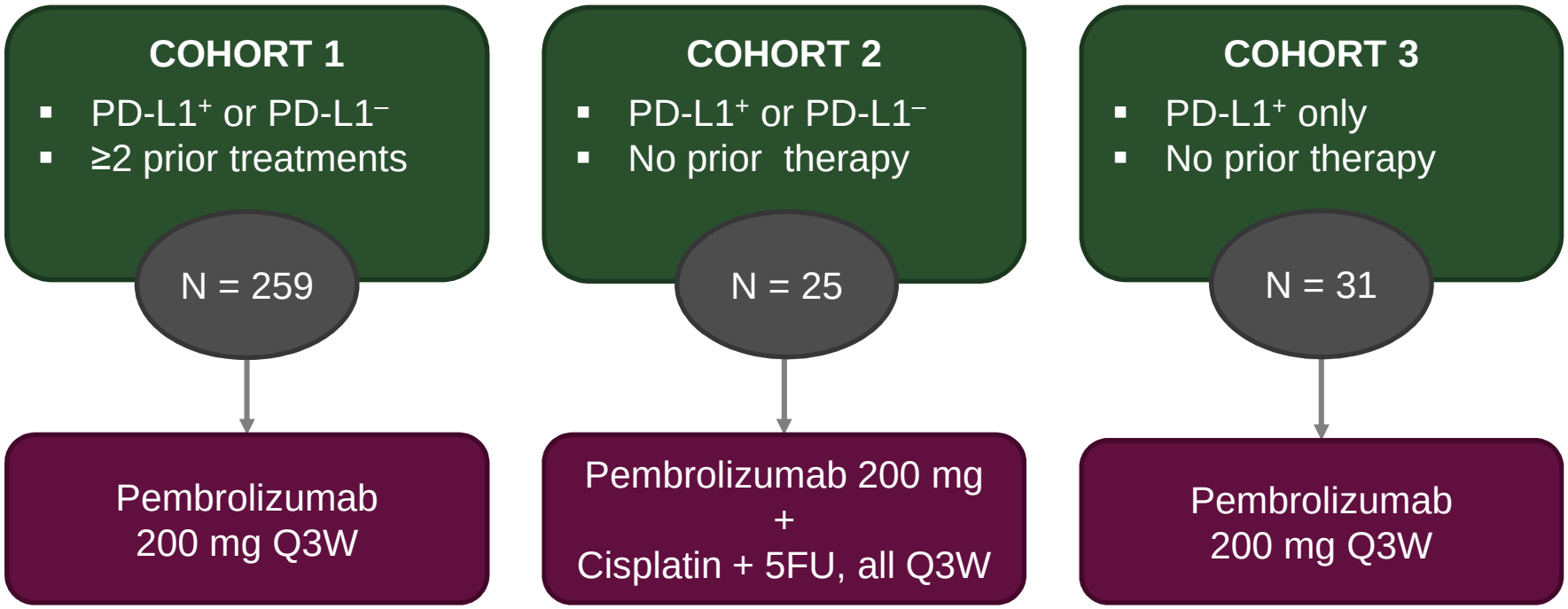
Muro K, *et al.* Lancet Oncol 2016; 17:717-726.

KEYNOTE-059: Phase 2 Study of Pembrolizumab for advanced gastric or GEJ adenocarcinoma

- Primary end point: ORR per RECIST v1.1 by central review



Modified from Muro K, *et al*. ASCO GI 2015; Abstract nr.03

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Pembrolizumab induces responses in chemorefractory gastric cancer: Efficacy in evaluable patients in KEYNOTE-059 Cohort 1

Table 1. Objective Tumor Response

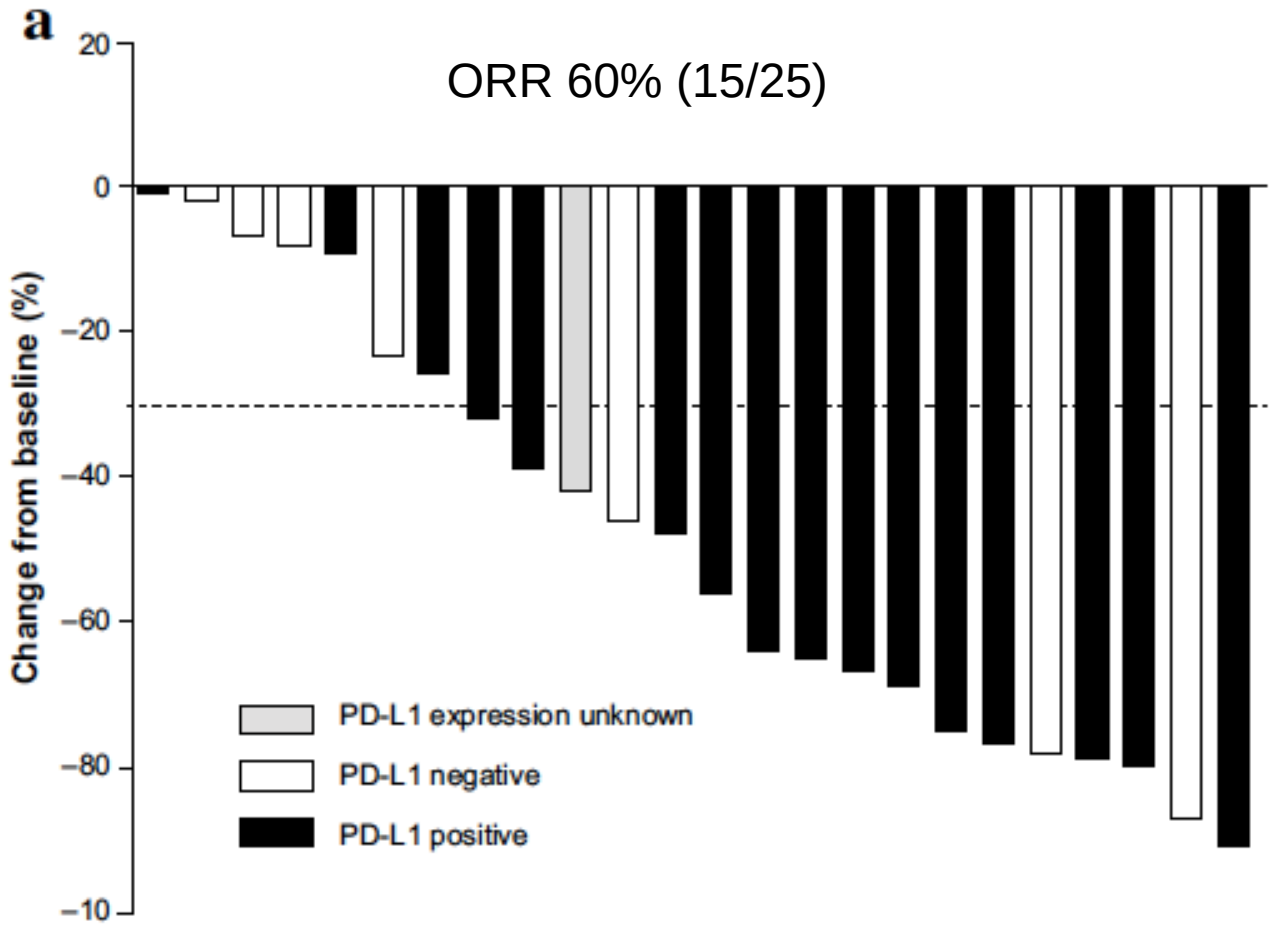
Best Overall Response[a]	Participants (n = 259) No.	% (95% CI)
Objective response (CR+PR)	30	11.6 (8.0-16.1)
Disease control (CR+PR+SD ≥2 mo)	70	27.0 (21.7-32.9)
CR	6	2.3 (0.9-5.0)
PR	24	9.3 (6.0-13.5)
SD	42	16.2 (11.9-21.3)
Progressive disease	145	56.0 (49.7-62.1)
Nonevaluable	7	2.7 (1.1-5.5)
No assessment[b]	35	13.5 (9.6-18.3)
Duration of response, median (range), mo	8.4 (1.6+ to 17.3+)[c]	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

[a] Only confirmed responses are included.

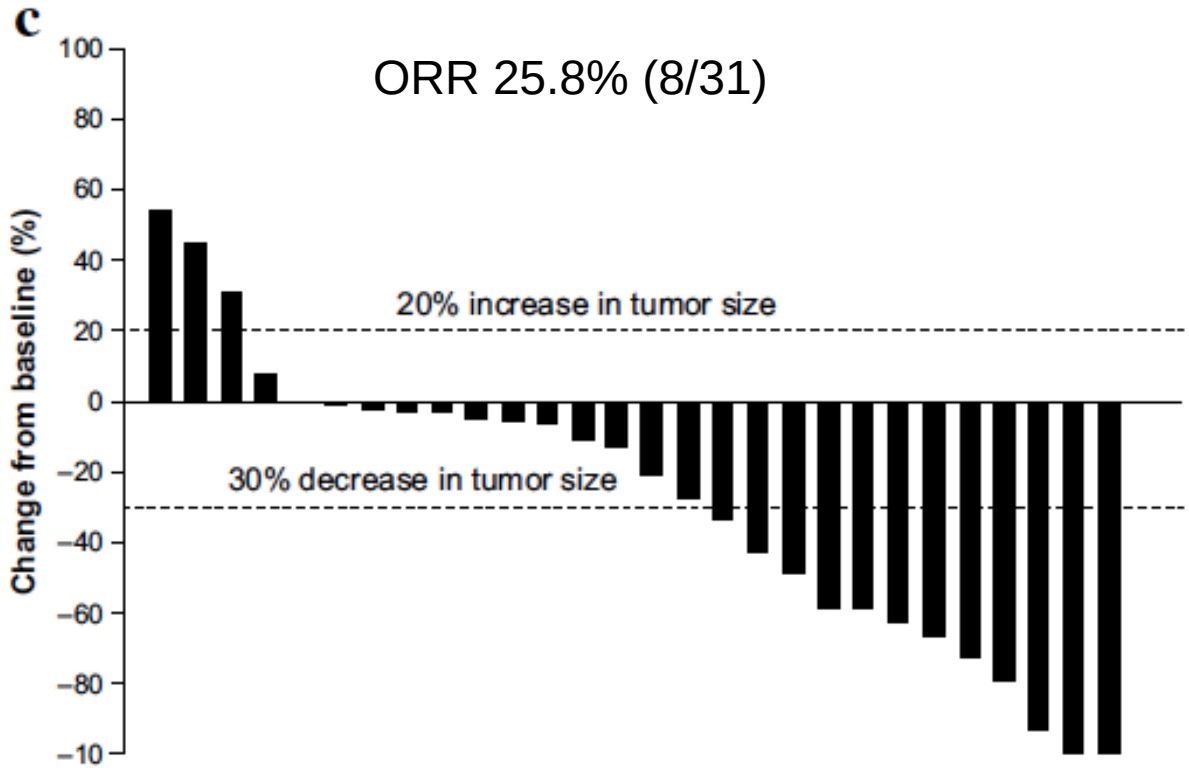
Fuchs CS, et al JAMA Oncol 2018; 4:2180013

Pembrolizumab induces responses in First line gastric Cancer in combination with Chemotherapy Efficacy in evaluable patients in KEYNOTE-059 Cohort 2.



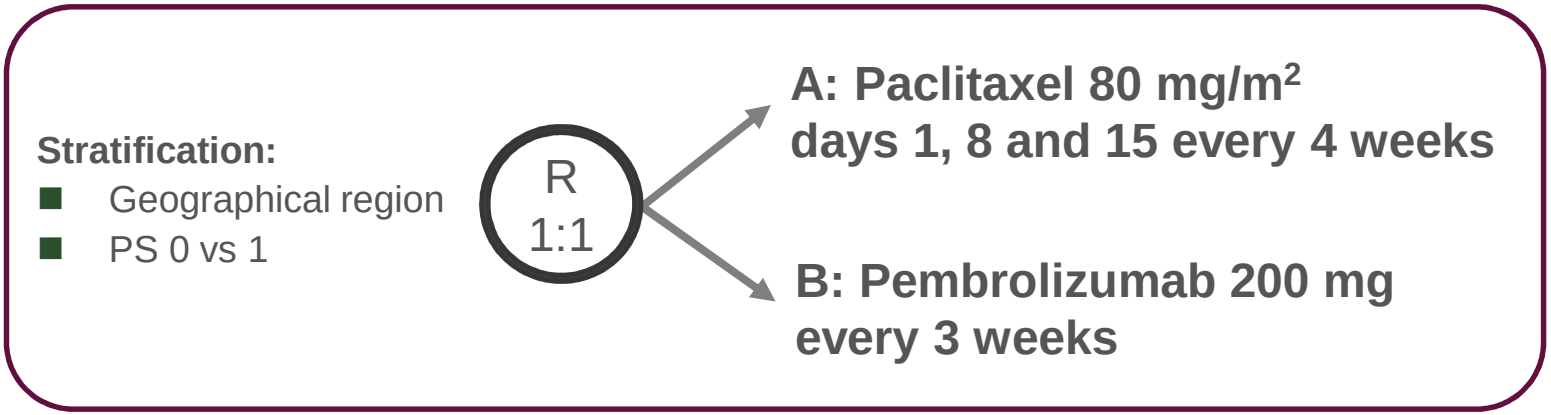
Bang YJ, , et al Gastric Cancer 2019; doi.org/10.1007/s10120-018-00909-5

Pembrolizumab induces responses in First line gastric Cancer as single agent
Efficacy in evaluable patients in KEYNOTE-059 Cohort 3.



Bang YJ, , et al Gastric Cancer 2019; doi.org/10.1007/s10120-018-00909-5

A Phase III Study of Pembrolizumab *vs* weekly Paclitaxel in second line for advanced gastroesophageal adenocarcinoma (KEYNOTE-061)



- **Objective I:** PFS and OS as co-primary end-points in PDL1 Combined Positive Score ≥ 1 patients
- **Objectives II:**
  - Toxicity
  - Response rate
  - Duration of response
  - Time to progression

Shitara, K. et al. Lancet 2018; 392:123–133.

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Pembrolizumab not superior to weekly Paclitaxel in second line for advanced gastroesophageal adenocarcinoma

Trial author	Year	Patients (n)	Treatment	HR OS	P value	Gain in median survival
Hironaka, et al.[1]	2013	223	Irinotecan vs paclitaxel	1.13	0.38	0.9 months For Irinotecam
Wilke et al.[2]	2014	665	Paclitaxel+/- Ramucirumab	0.80	0.017	2.2 months For Ramucirumab
Shitara et al.[3] **KEYNOTE-061**	2018	592 1:1	Pembrolizumab vs wk Paclitaxel	0.82	0.084	0.8 months for Pembrolizumab

1. Hironaka S, et al. J Clin Oncol 2013;31:4438–4444.
2. Wilke H, et al. Lancet Oncol 2014;15:1224–1235.
3. Shitara, K. et al. Lancet 2018; 392:123–133

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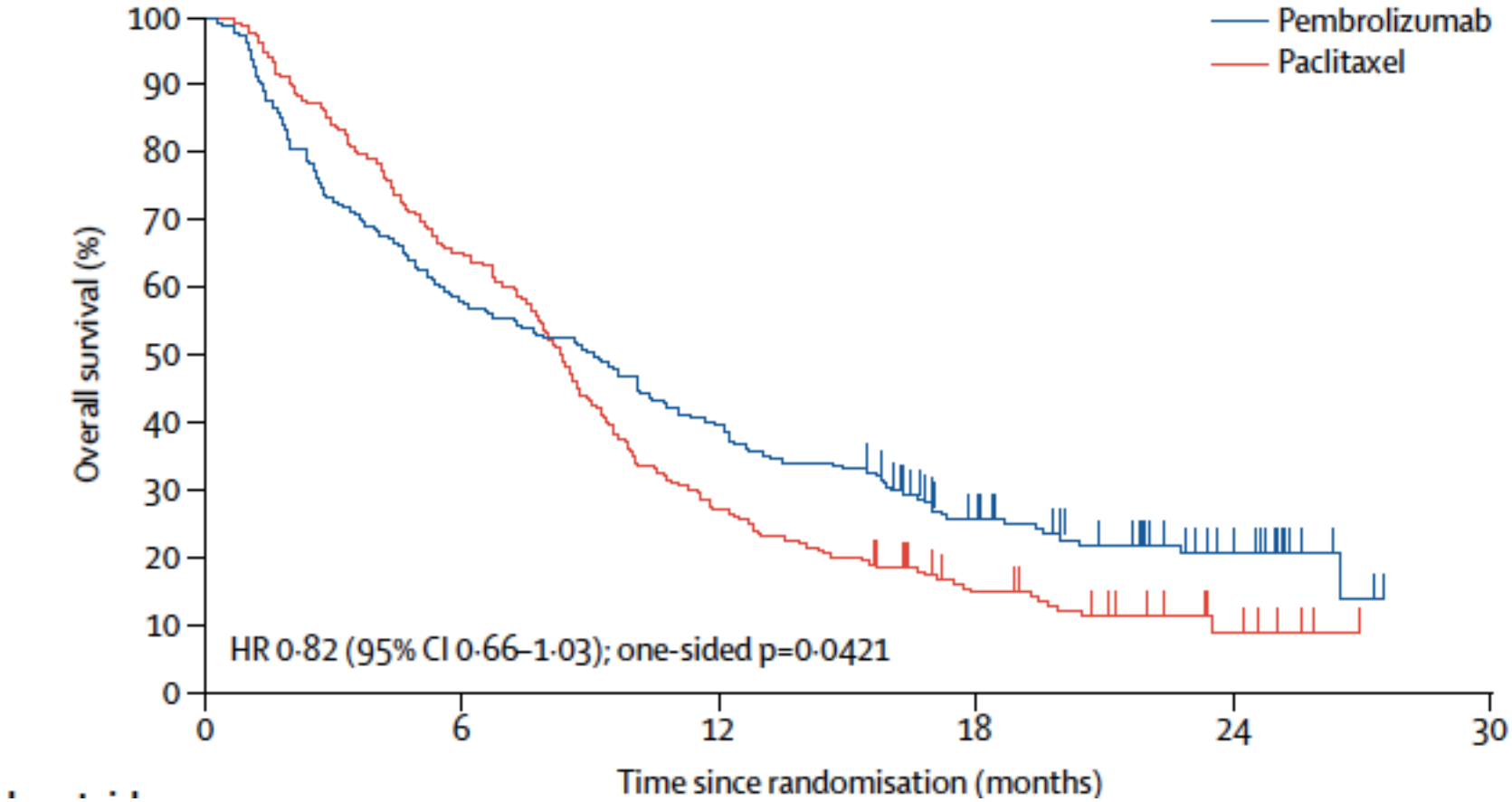
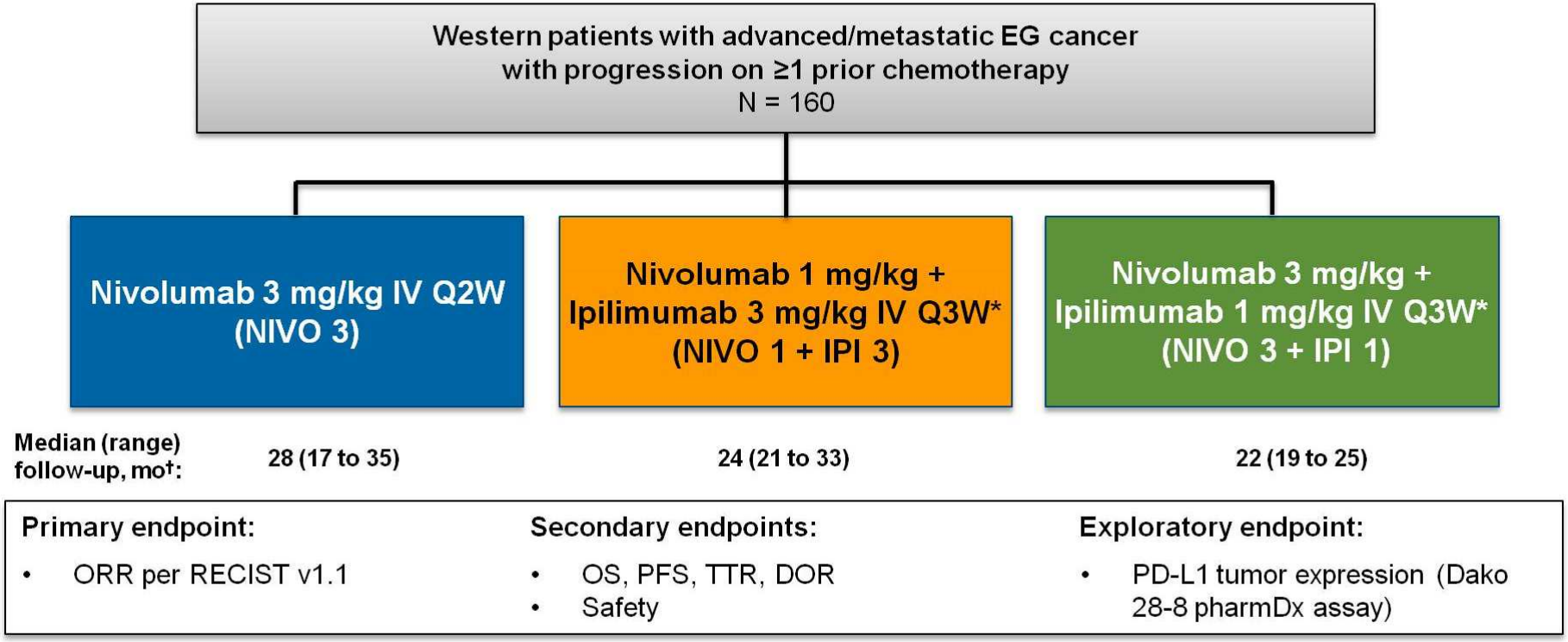
Pembrolizumab not superior to weekly Paclitaxel in second line for advanced gastroesophageal adenocarcinoma in KEYNOTE-061



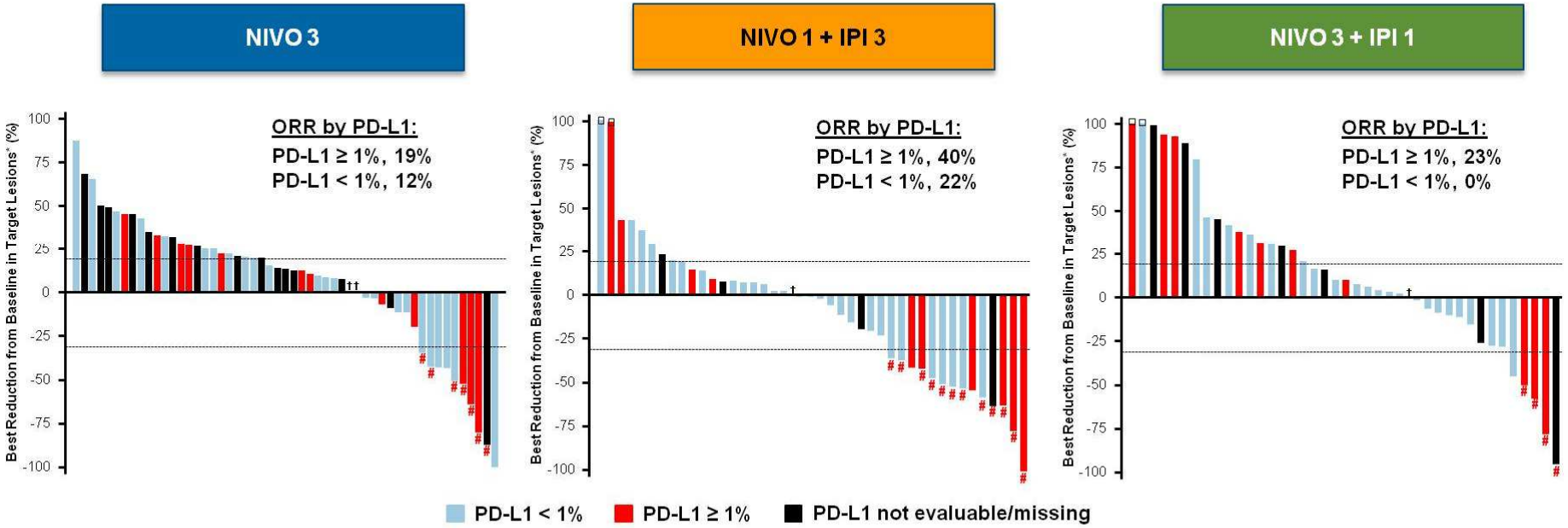
1. Shitara, K. et al. Lancet 2018; 392:123–133

Checkmate 032 EG Cohort



DOR, duration of response; EG, esophagogastric (including gastric/esophageal/gastroesophageal junction cancer); TTR, time to response.
* Nivolumab + ipilimumab administered for 4 cycles followed by nivolumab 3 mg/kg IV Q2W.
†Time from first dose to data cut-off; follow-up was shorter for patients who died prior to data cut-off.

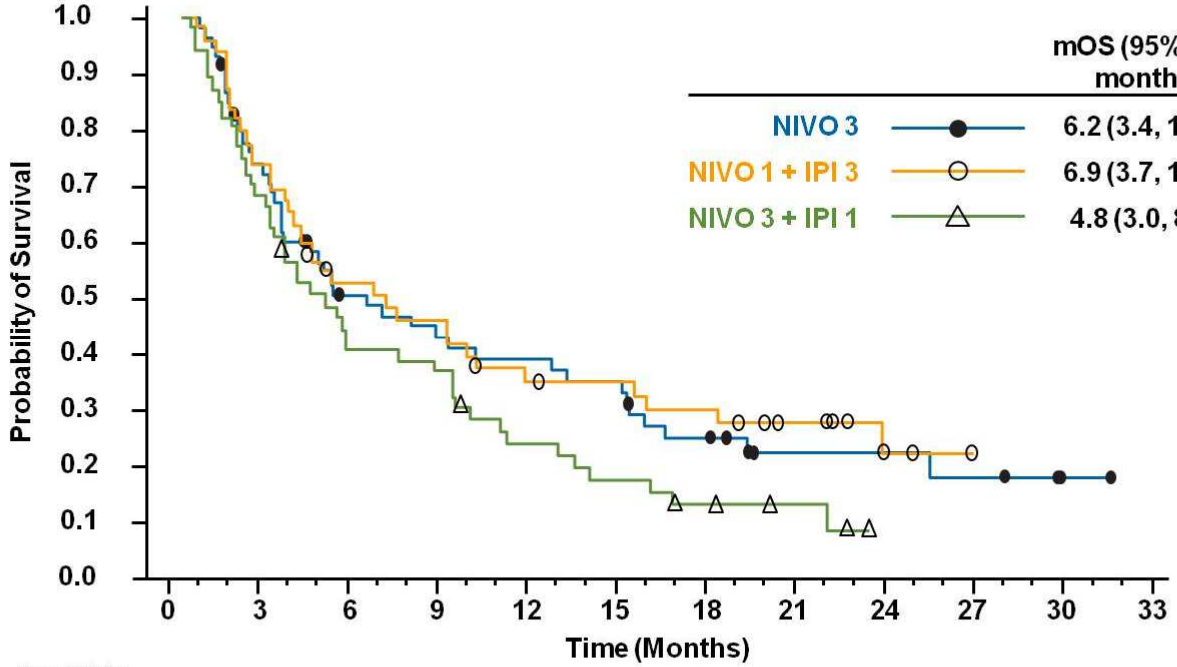
Best Reduction in Target Lesions



- Responses were observed regardless of PD-L1 expression

* Investigator review.
\# Patients with confirmed response (complete or partial response).
† Patients with 0% best reduction in target lesion, including 3 patients with PD-L1 ≥1% (NIVO 3, n=2; NIVO 3 + IPI 1, n=1) and 1 patient with PD-L1 <1% (NIVO 1 + IPI 3).
□ change truncated to 100%

Overall Survival

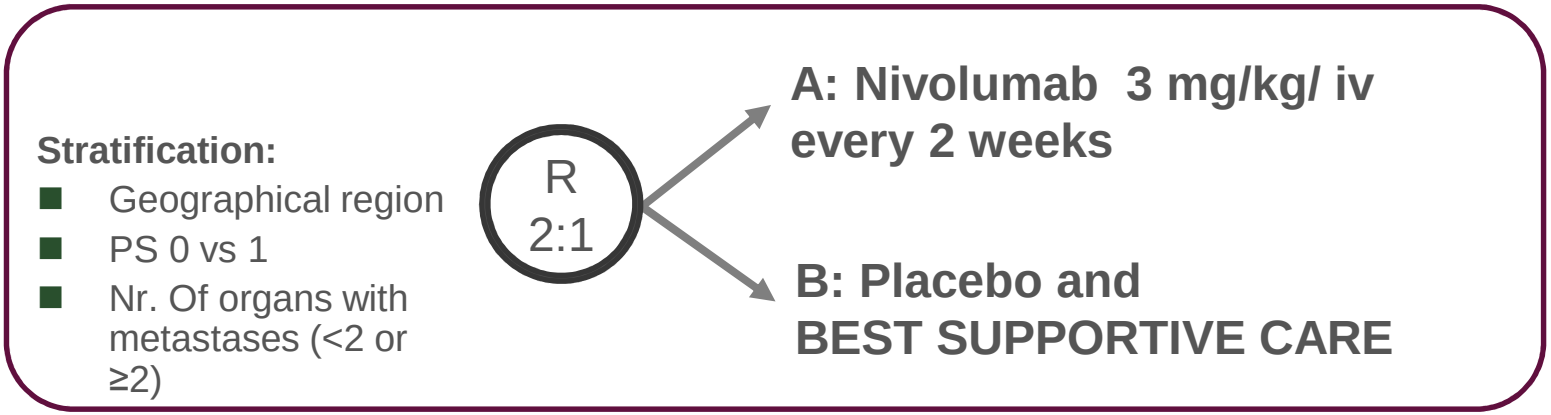


	mOS (95% CI), months	12-month OS rate, %	18-month OS rate, %
NIVO 3	6.2 (3.4, 12.4)	39	25
NIVO 1 + IPI 3	6.9 (3.7, 11.5)	35	28
NIVO 3 + IPI 1	4.8 (3.0, 8.4)	24	13

No. at Risk:											
NIVO 3	59	40	26	21	20	15	11	5	5	4	1	0
NIVO 1 + IPI 3	49	35	24	19	14	14	11	8	3	0	0	0
NIVO 3 + IPI 1	52	33	20	18	11	8	4	3	0	0	0	0

mOS, median OS.

A Phase III Study of Nivolumab *vs* BSC in second line advanced gastroesophageal adenocarcinoma: The ATTRACTION-2 Trial



- **Objective I:** OS
- **Objectives II:**
  - PFS
  - Response rate, Duration of response, Disease Control rate
  - Time to progression
  - Safety

Shitara, K. et al. Lancet 2018; 392:123–133.

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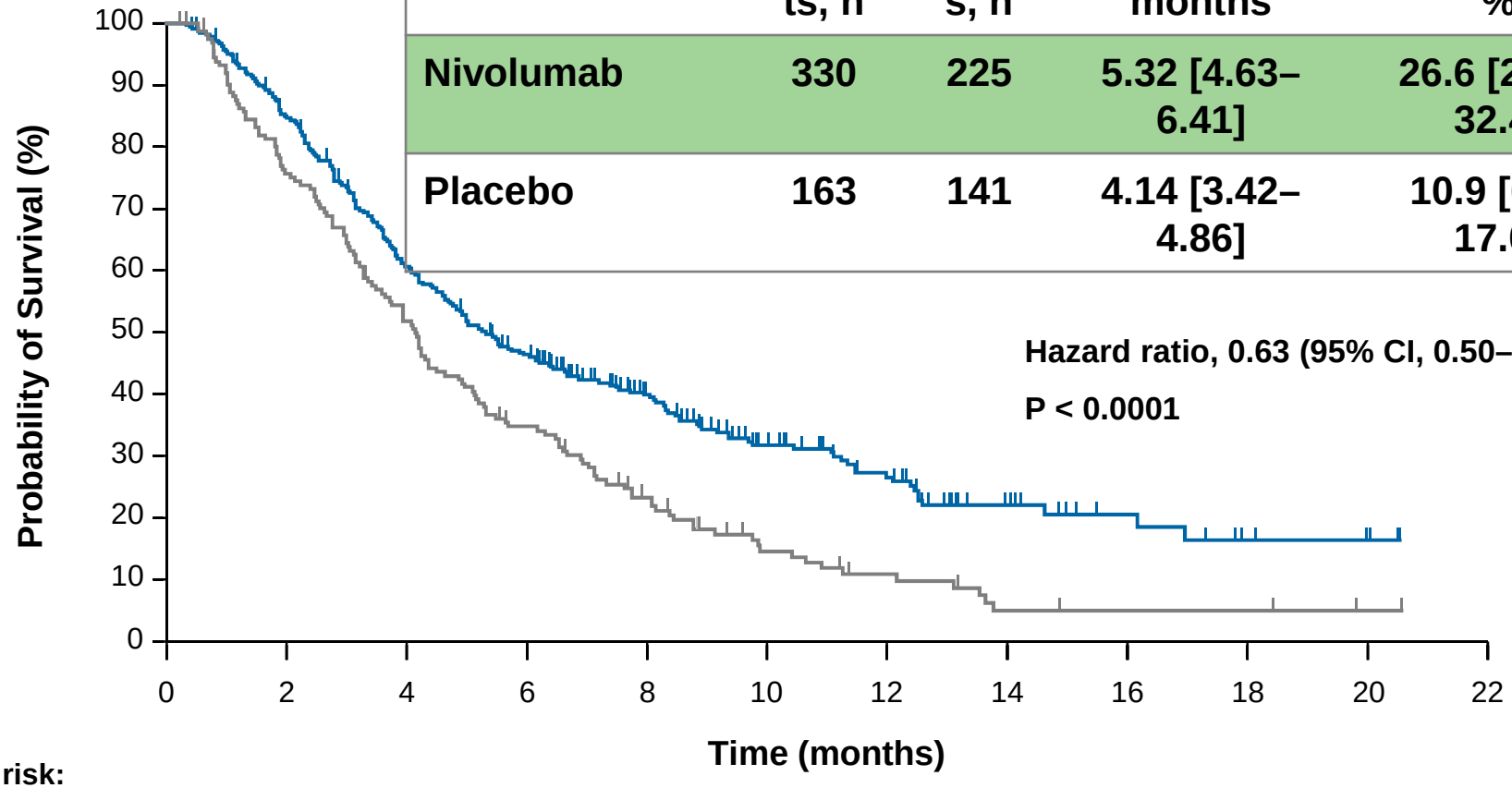
Gastroesophageal Adenocarcinomas: Third or further line therapy. Randomized trials comparing BSC or active treatment

Trial author	Year	Patients random (n)	Treatment	HR OS	P value	mOS and Gain in median survival
Li J, et al.[1] **Apatinib Third line**	2016	273 2:1	**Apatinib** vs Placebo	0,70	0,0149	6.5 vs 4.7 1.8 months
Shitara, et al.[2] **TAGS Third line**	2018	507 2:1	**Trifluridine/Tipiracil** vs BSC	0.69	0.0003	5.7 vs 3.6 2.1 months
Bang, et al.[3] **JAVELIN 300 Third or further lines**	2018	371 1:1	**Avelumab** vs Investigator choice of Chemotherapy	1.10	ns	4.6 vs 5.0 -0.4 months
Kang, et al[4] **ATTRACTION-2 Third or further lines**	2017	493 2:1	**Nivolumab** vs BSC	0.63	0.0001	5.26 vs 4.14 1.12 months

1. Ji L, *et al.* J Clin Oncol 2016:34:1448-1454. 2. Shitara, K. et al. Lancet Oncol 2018; 19:1437–48. 3. Bang YJ, et al. Ann Oncol 2018; 29:2052-60. 4Kang JK, et al. Lancet 2017;390:2461-71.

Overall Survival Nivolumab *vs* BSC in ATTRACTION-2 Trial

	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]



At risk:

Nivolumab	330	275	193	142	95	57	39	19	10	5	3	0
Placebo	163	121	82	53	32	16	10	4	3	3	1	0

Kang YK, et al Lancet Oncol 2017; 390:2461-2471

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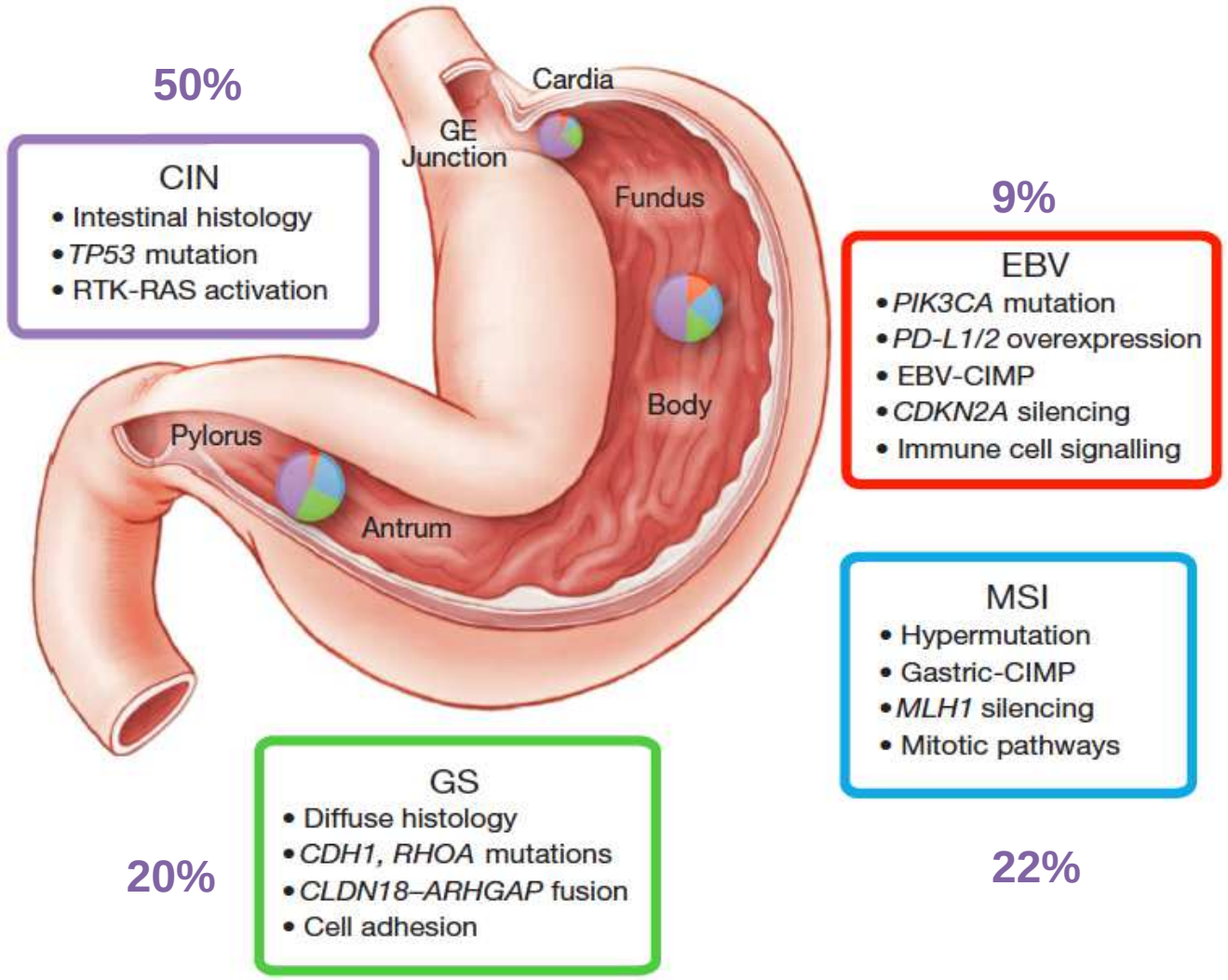

Cancer Genome Atlas Research Network. Nature 2014;513:202–209

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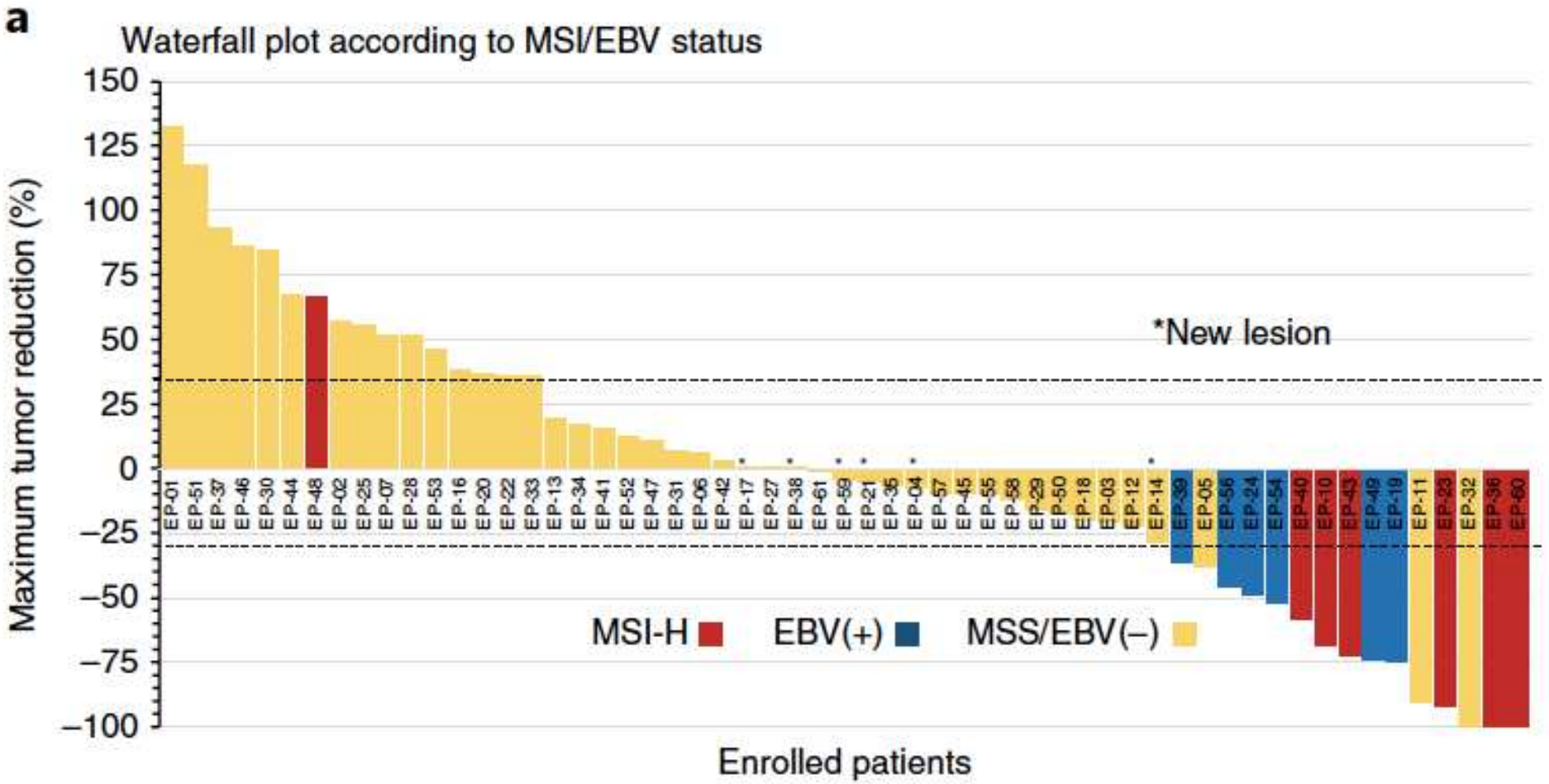
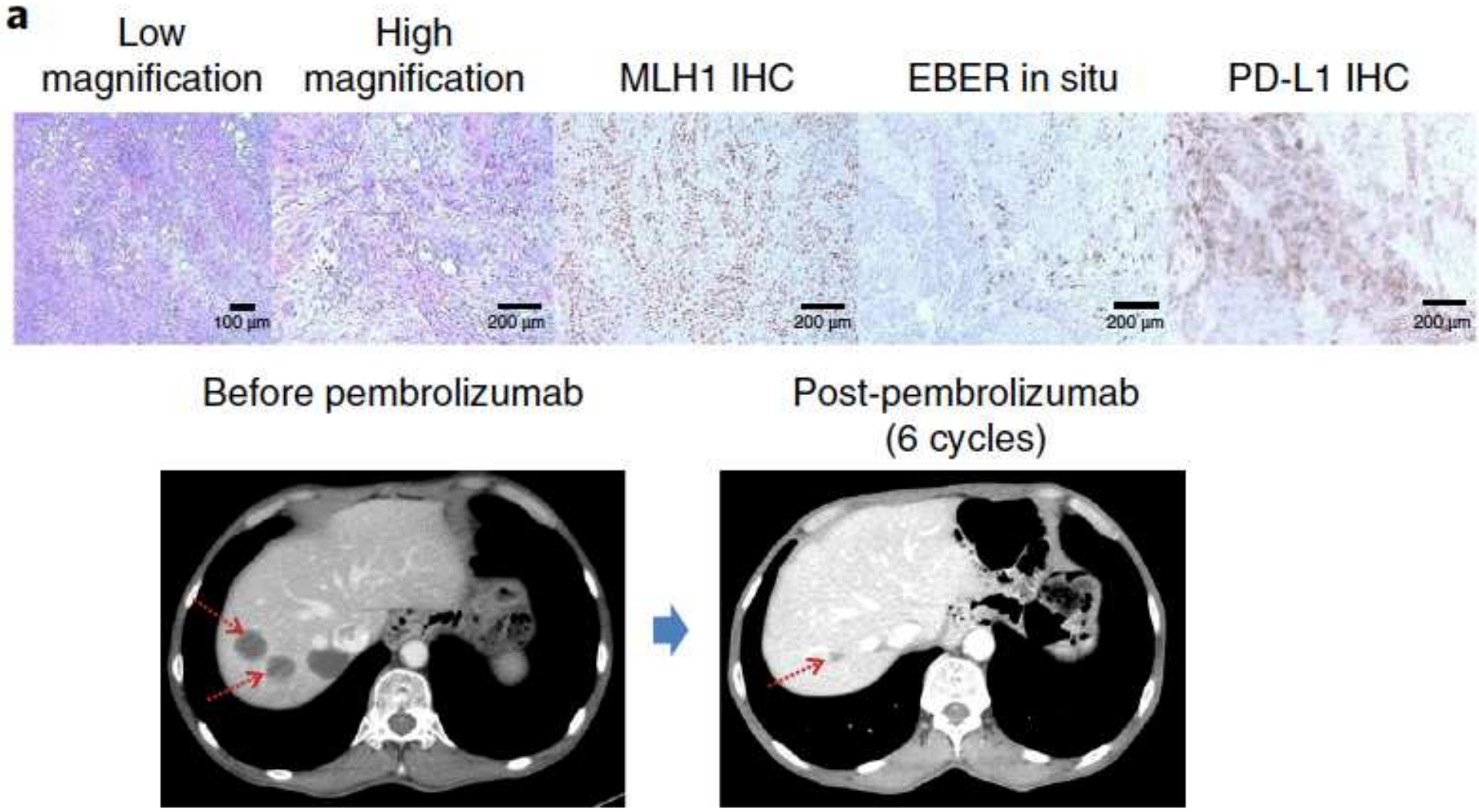
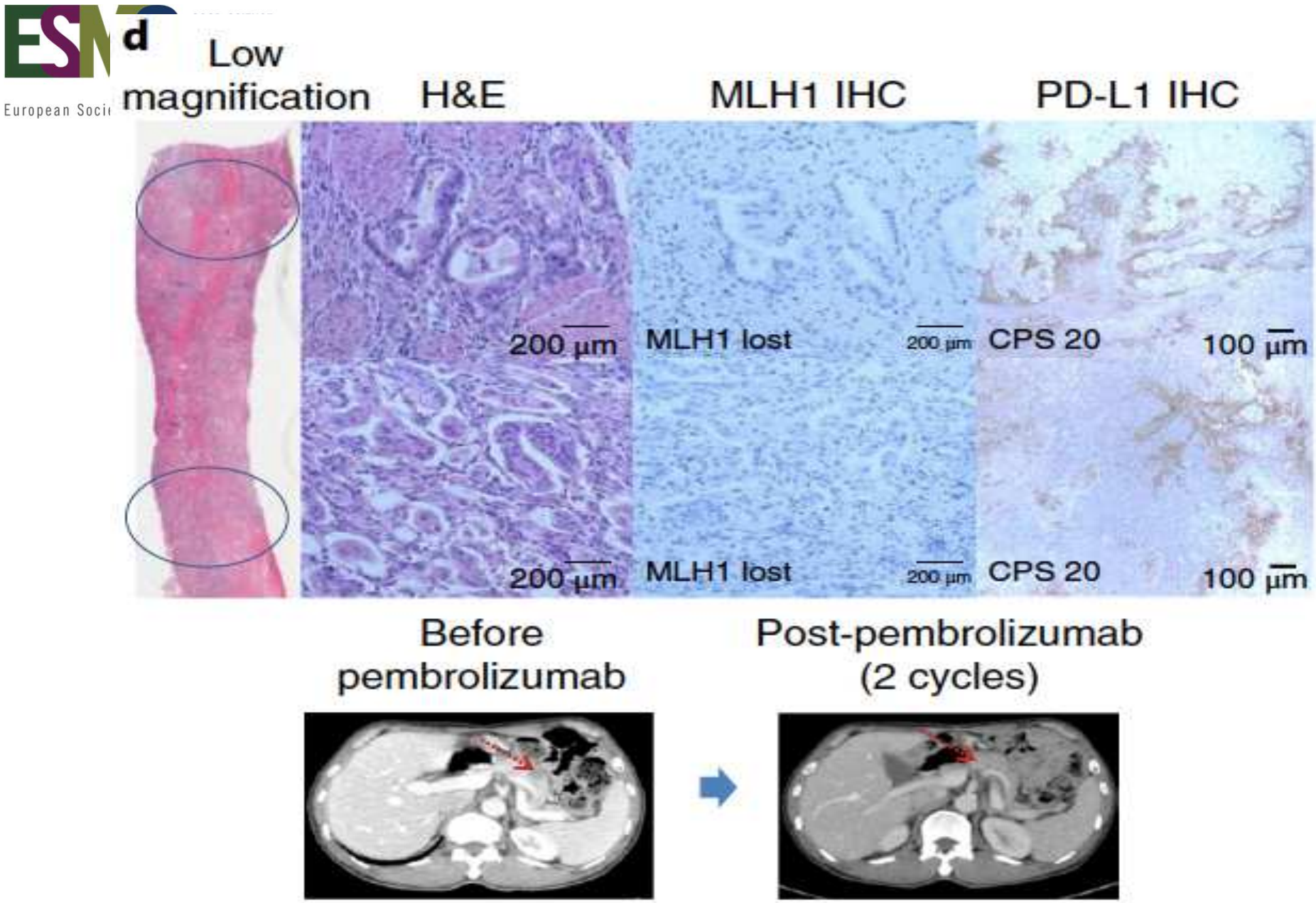
Pembrolizumab induces responses mainly in MSI or EBV+ gastric cancer



Kim ST, et al. Nature Med 2018;24:1449–1458.



Kim ST, et al. Nature Med 2018;24:1449–1458.



Kim ST, et al. Nature Med 2018;24:1449–1458.

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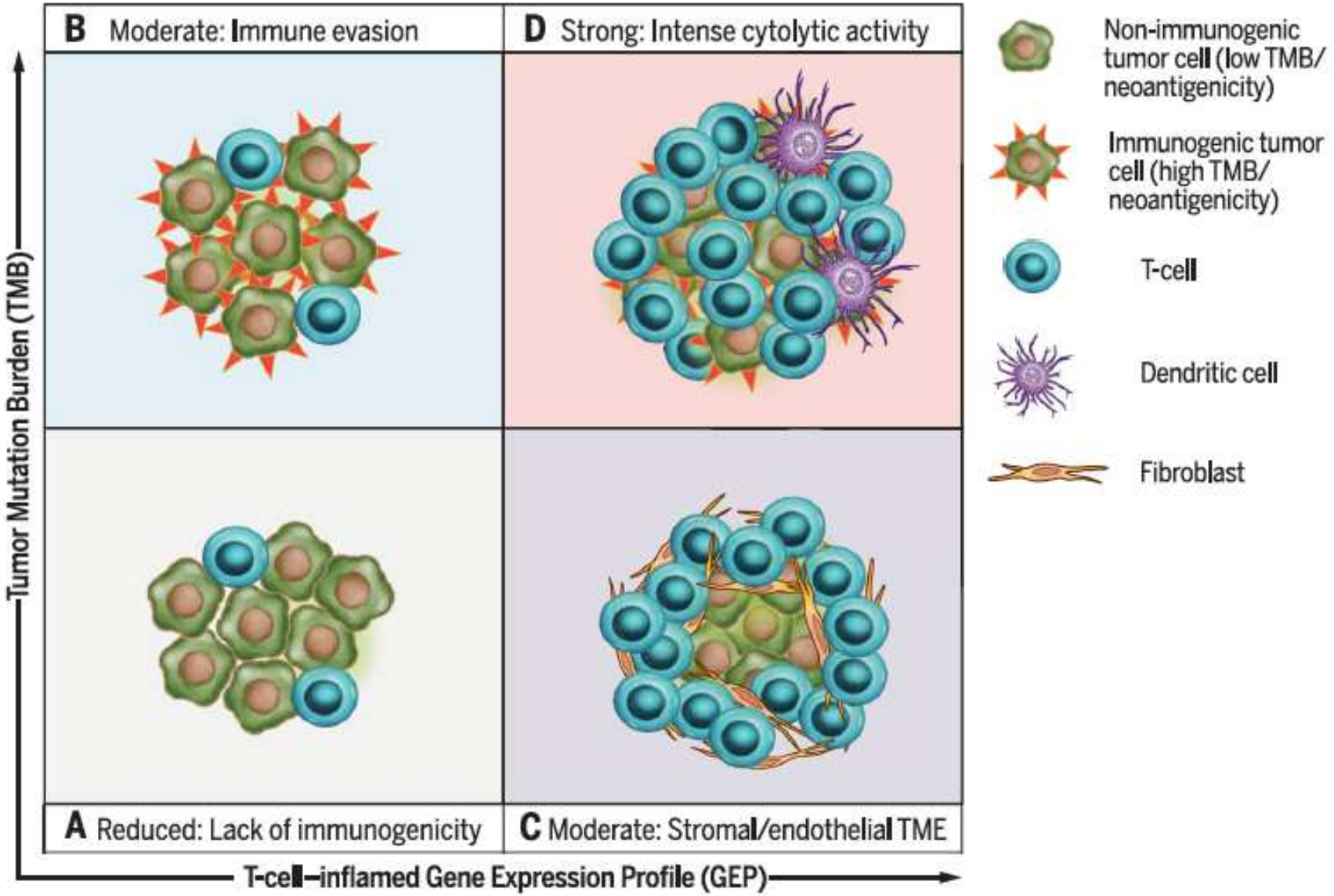
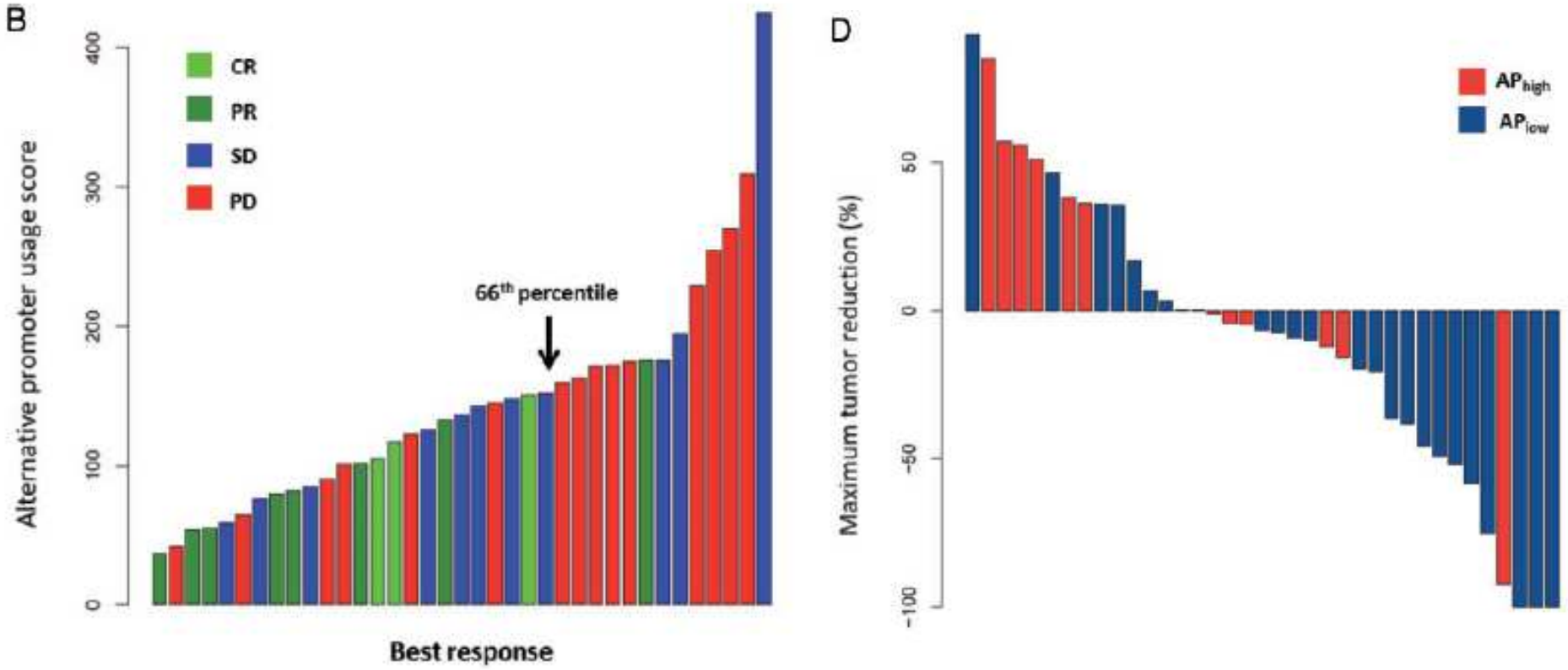
Pan-tumor genomic biomarkers for PD-1 checkpoint blockade–based immunotherapy



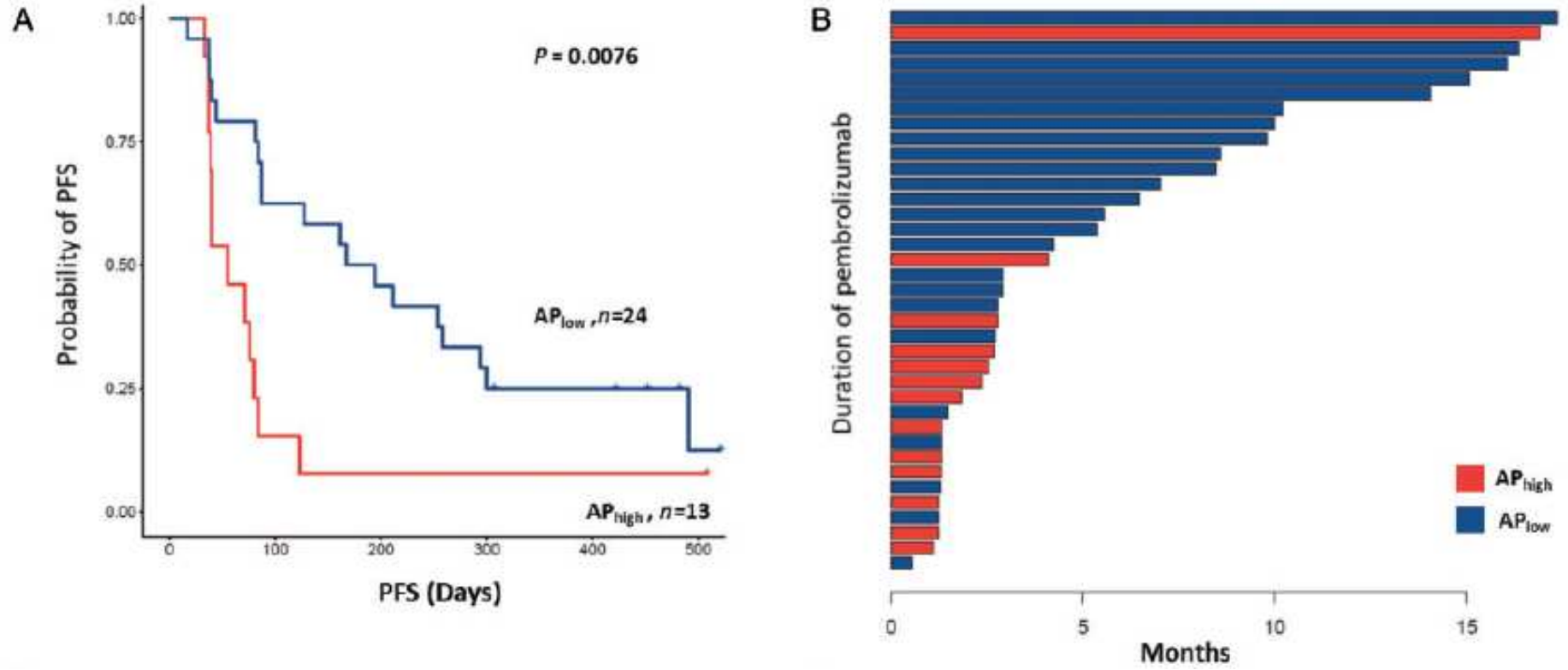
Cristescu R, et al Science 2018; 362:eaar3593

Epigenomic promoter alterations predict for benefit from immune checkpoint inhibition in metastatic gastric cancer



Sundar R, et al. Ann Oncol 2019; 30:424-430

Epigenomic promoter alterations predict for benefit from immune checkpoint inhibition in metastatic gastric cancer



Sundar R, et al. Ann Oncol 2019; 30:424-430

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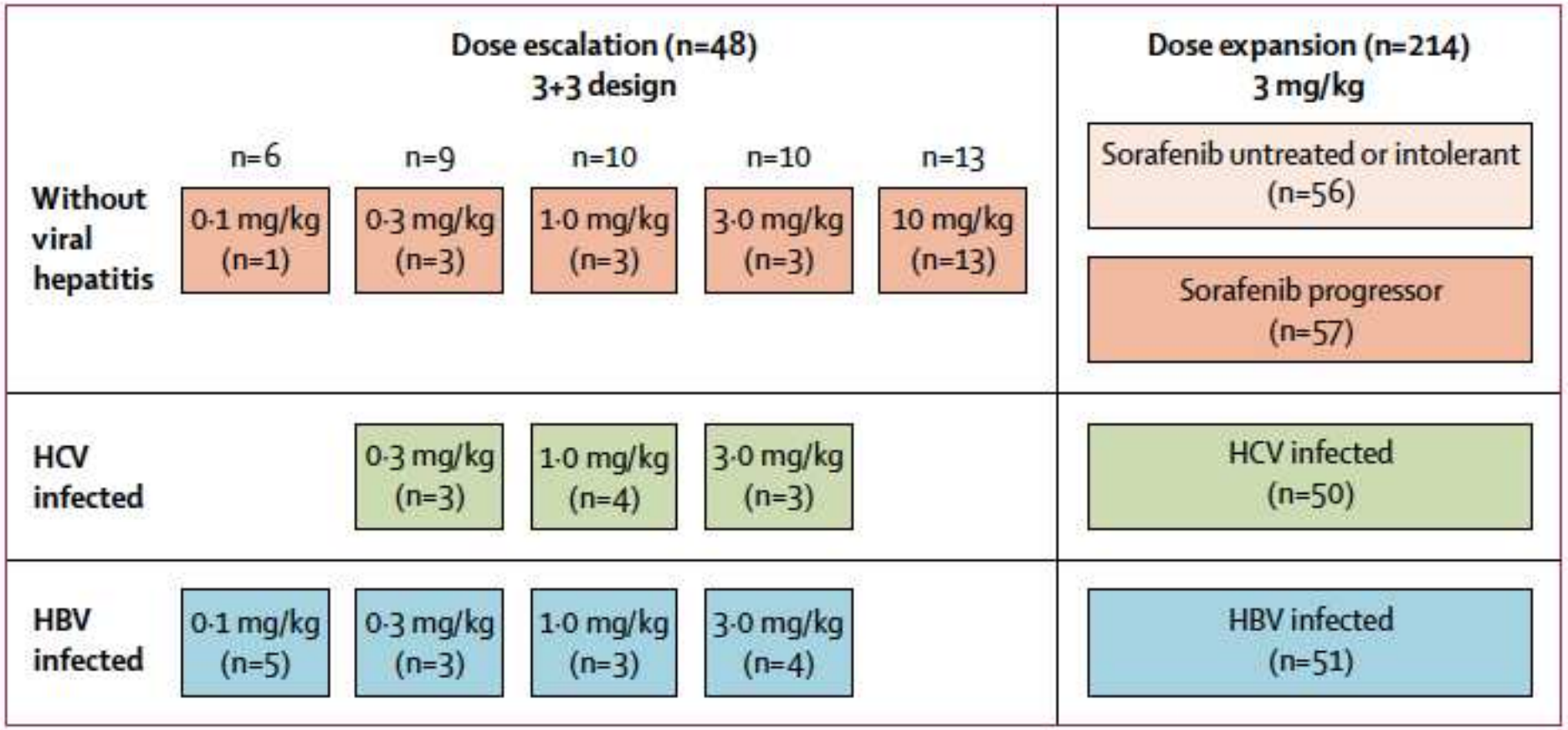
Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial



El-Khoueri AB, et al Lancet 2017; 389:2492-2502

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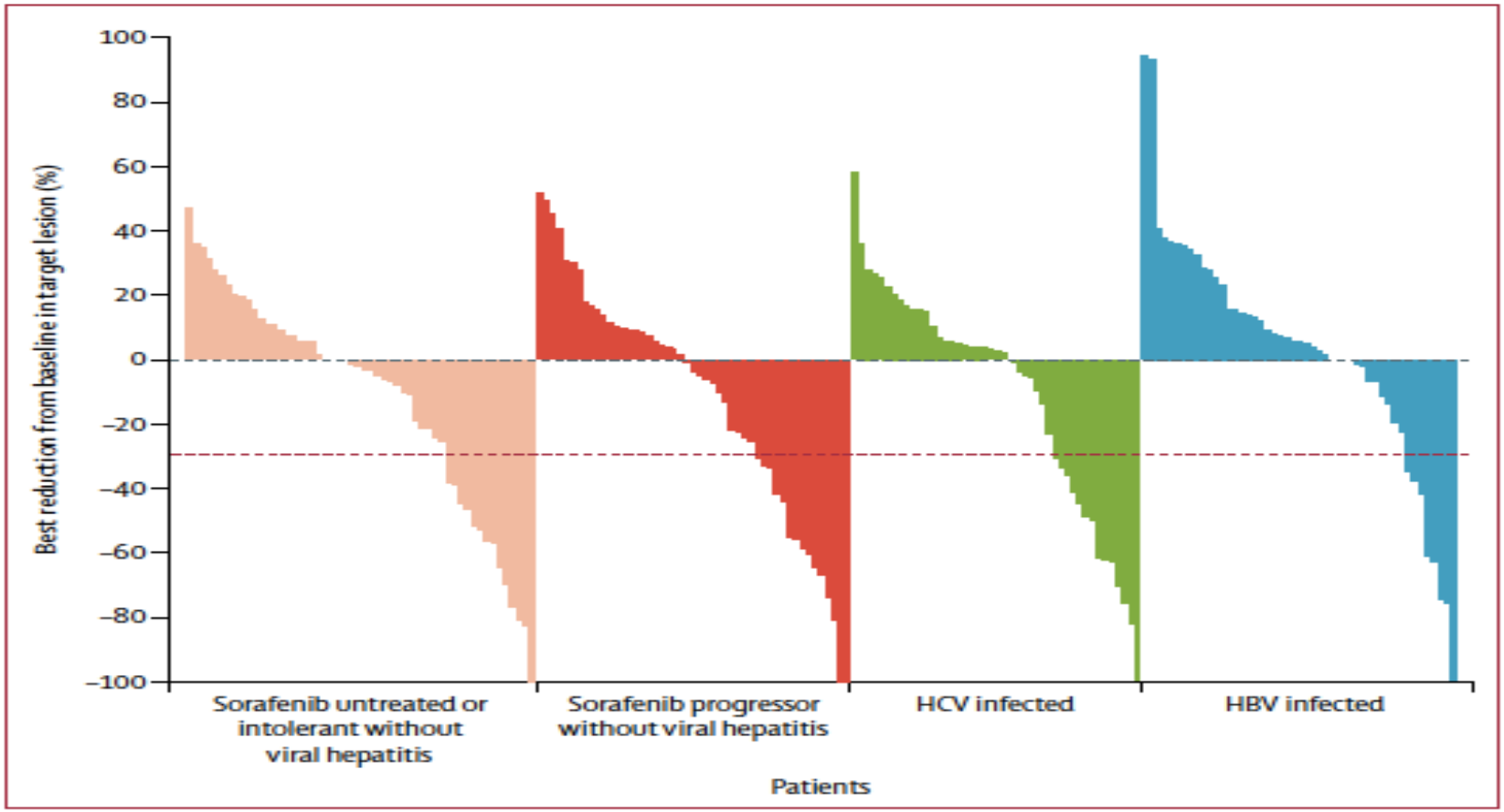

***Figure 4*: Best percentage change in tumour burden**
Best percentage change in tumour lesion size from baseline over time in the dose-expansion phase (n=202). Red dash indicates a 30% reduction. HCV=hepatitis C virus. HBV=hepatitis B virus.

El-Khoueri AB, et al Lancet 2017; 389:2492-2502

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Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial

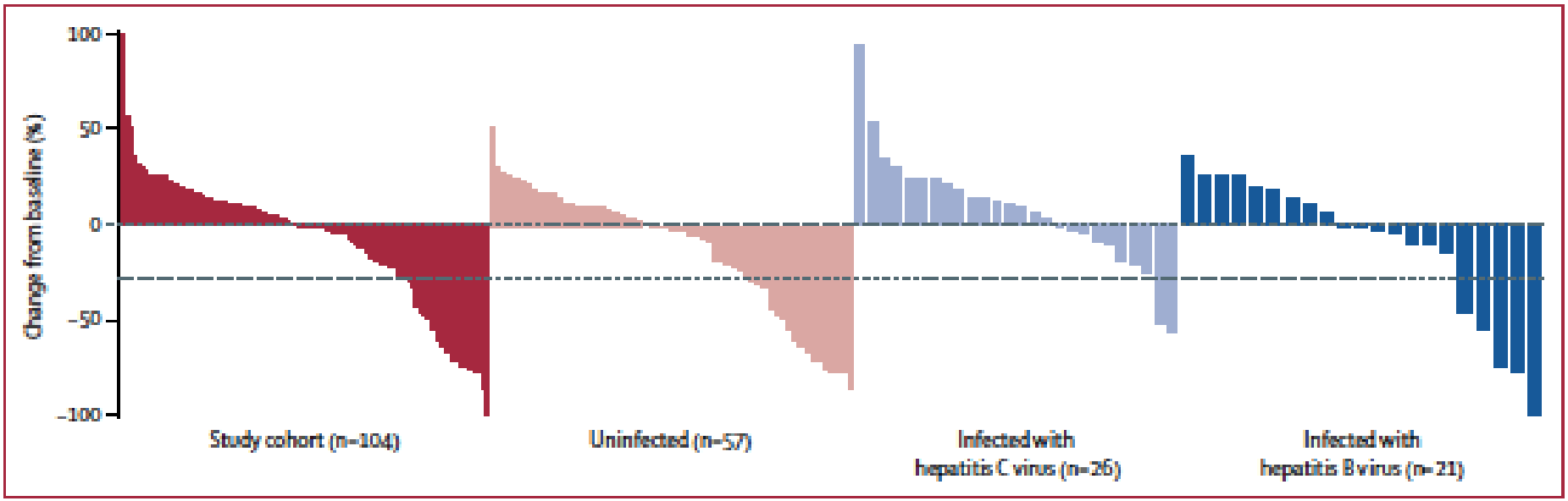

Figure 5: **Best percentage changes from baseline in size of target lesions**
Assessed with RECIST by central radiology review in patients with image measurements before and after treatment. The horizontal dashed line represents the threshold for response according to RECIST version 1.1.

Zhu A, et al Lancet Oncol 2018; 19:940-952

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Comparison of Toxicity / Efficacy Profiles CPI in HCC.

	n	ORR %	PFS months	OS months	AE leading to discont.
Camrelizumab[1]	217	14 [9 -19]	2.3 [2.0 – 3.2]	14.4 [13.8 – NR]	3%
Nivolumab[2]	214	15 [6 – 28]	4.0 [2.9 – 5.4]	15.0 [9.6 – 20.2]	6%
Pembrolizumab[3]	104	17 [11 – 26]	4.9 [3.4 – 7.2]	12.9 [9.7 – 15.5]	5%

[1]Qin S et al. ESMO 2018
[2]El-Khoueiry AB et al. Lancet Oncol 2017;389:2492-502
[3]Zhu A et al. Lancet Oncol 2018.19:940-52

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Competitive Landscape for Immunotherapy in HCC

Monotherapy (checkpoint inhibitors – mostly in 2L)

Atezolizumab (Ph1b) *Anti-PDL1*	Nivolumab (Ph3) *Anti-PD1*	Camrelizumab (Ph2) *aPD-1*
Pembrolizumab (Ph1/2) *Anti-PD1*	Durvalumab (Ph1/2) *Anti-PDL1*	Avelumab (Ph2) *aPD-L1*
	Spartalizumab (Ph1b/2) *Anti-PD1*	Tislelizumab (Ph3) *aPD-1*

Combinations of checkpoint inhibitors + anti-VEGF

Atezolizumab + Bevacizumab (Ph3) *Anti-PDL1 + anti-VEGF*	Nivolumab + Avastin (Ph1) *Anti-PD1 + anti-VEGF*	Camrelizumab + Apatinib (Ph2) *Anti-PD1 + TKI*
Pembrolizumab + lenvatinib (Ph1b) *Anti-PD1 + TKI*	Nivolumab + sorafenib (Ph3) *Anti-PD1 + TKI*	Avelumab + Axitinib (Ph1b) *Anti-PDL1 + TKI*
Pembrolizumab + regorafenib (Ph1b) *Anti-PD1 + TKI*	Nivolumab + lenvatinib (Ph1b) *Anti-PD1 + TKI*	Spartalizumab + sorafenib (Ph2) *Anti-PD1 + TKI*

Combinations of two checkpoint inhibitors

Durvalumab + tremelimumab (Ph3) *Anti-PDL1 + anti-CTLA4*	Nivolumab + relatlimab (Ph1/2) *Anti-PD1 + anti-LAG3*	Nivo + Ipilimumab (Ph2) *aPD-1 + aCTLA-4*

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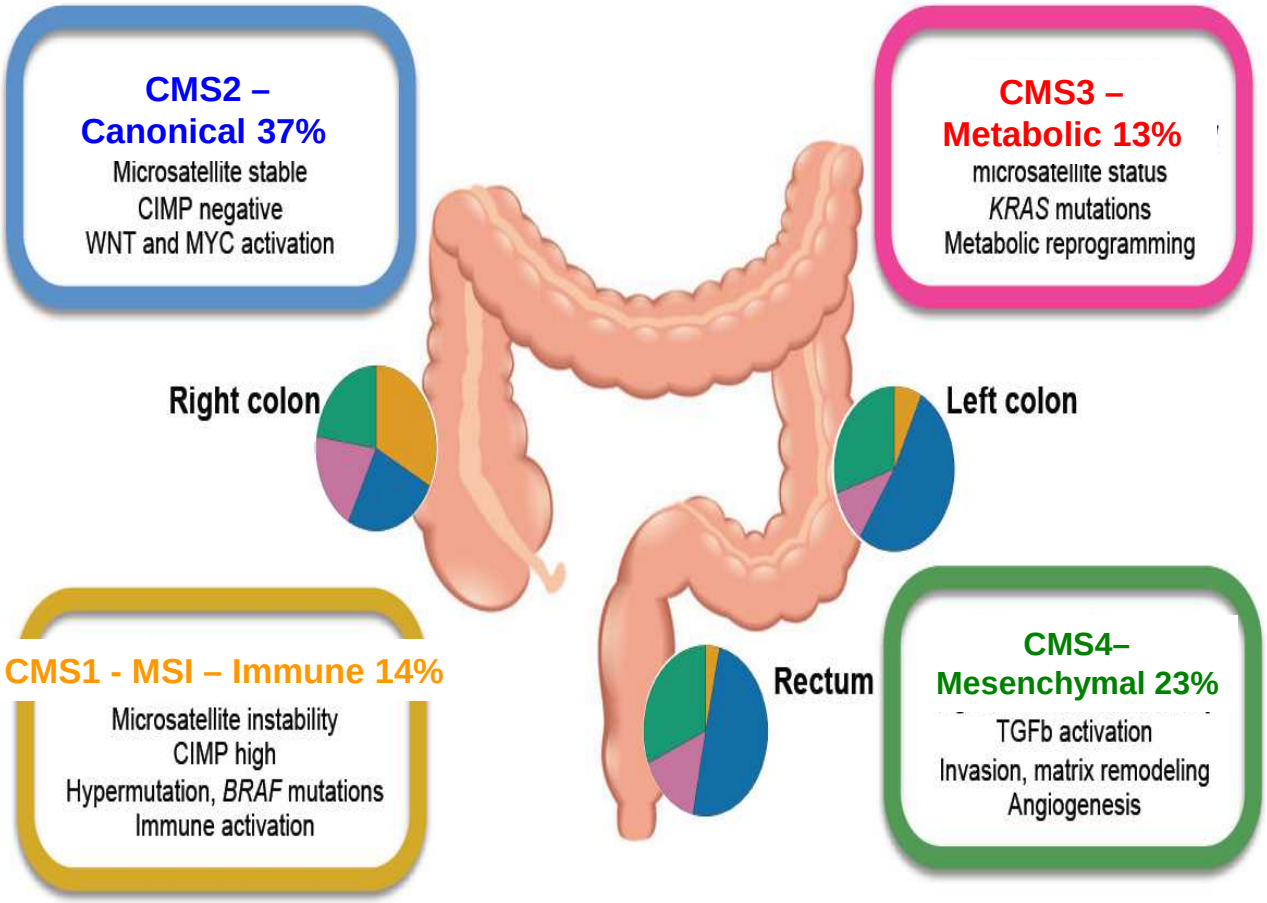
CMS subtypes – clinical and molecular correlates



Guinney J, Dienstmann R et al. Nat Med 2015

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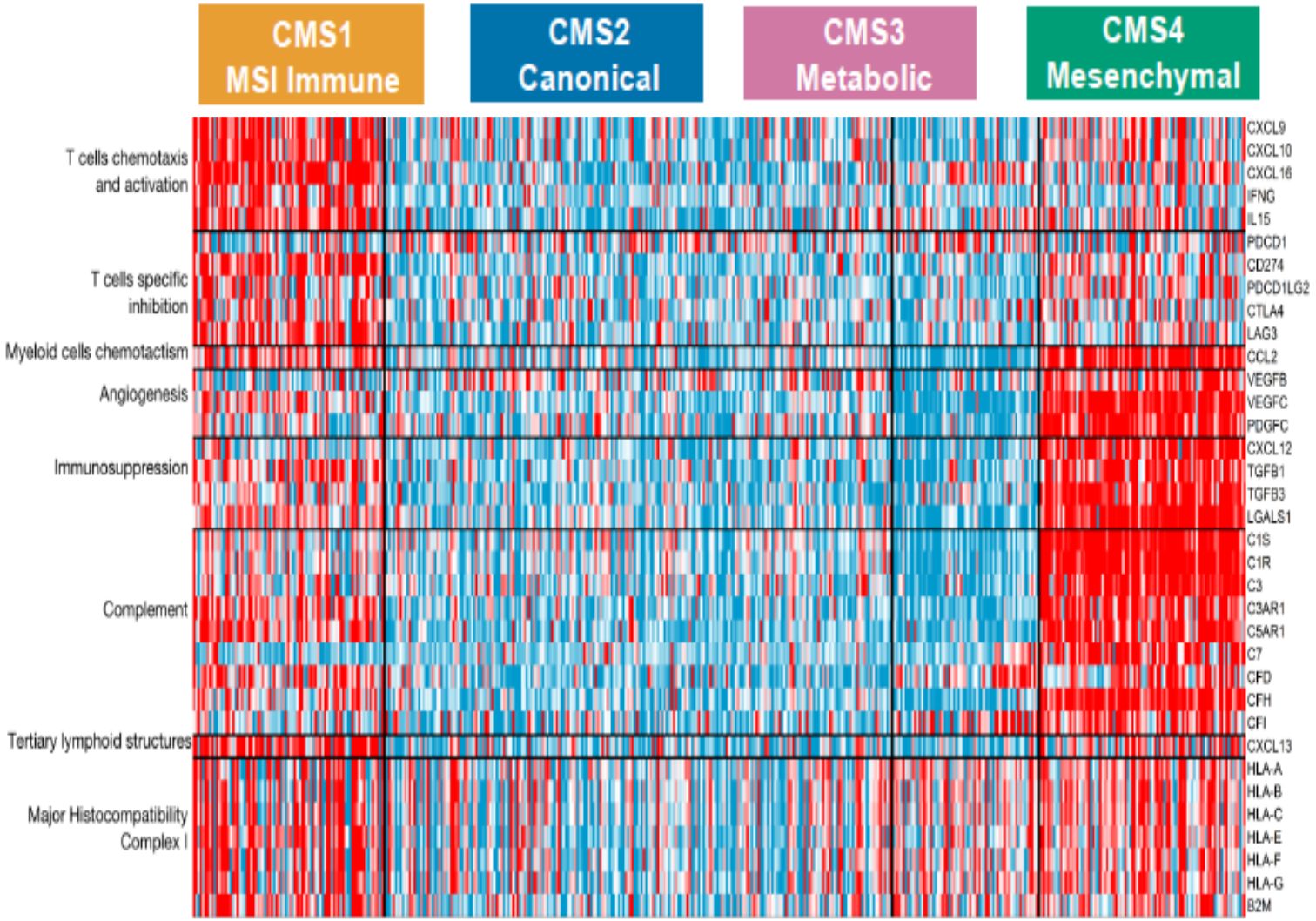
Immune vs Transcriptomic subtypes of CRC

Supervised immune infiltration analysis

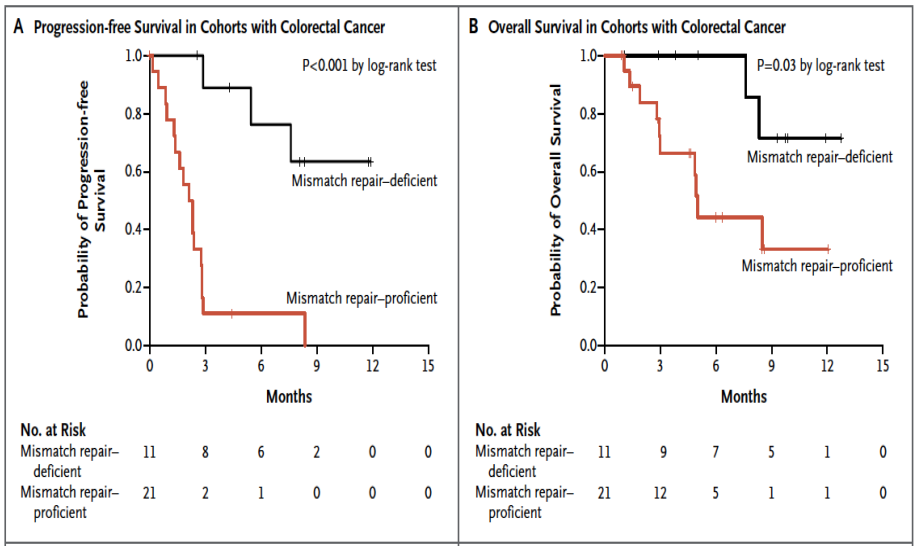


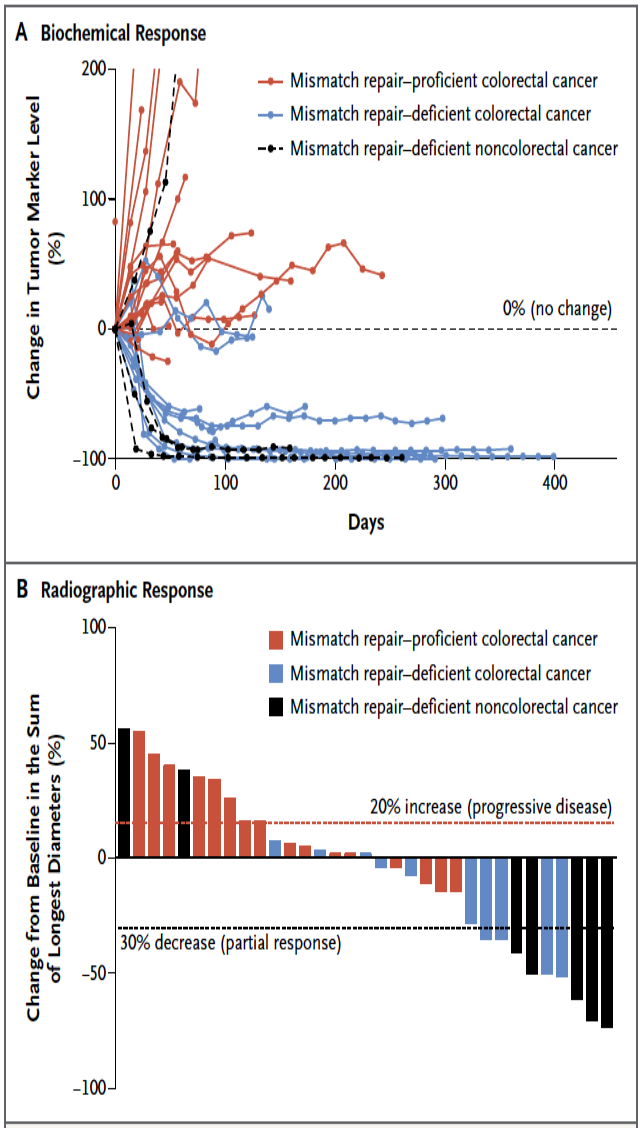
Becht E et al, Clin Cancer Res 2016

Pembrolizumab (anti-PD1) in mismatch repair-deficient/-proficient CRC: phase II

Table 2. Objective Responses According to RECIST Criteria.

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)





Le DT et al. ASCO 2015, Le DT NEJM 2015

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Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

Table 2. ORR, Best Overall Response, and DCR per Investigator Assessment (N = 119)

Response	No. (%)	95% CI
ORR	65 (55)	45.2 to 63.8
Best overall response		
Complete response	4 (3)	
Partial response	61 (51)	
Stable disease	37 (31)	
Progressive disease	14 (12)	
Not determined	3 (3)	
Disease control for ≥ 12 weeks	95 (80)	71.5 to 86.6

Abbreviations: DCR, disease control rate; ORR, objective response rate.

Overman MJ et al. J Clin Oncol 2018; 36:773-779

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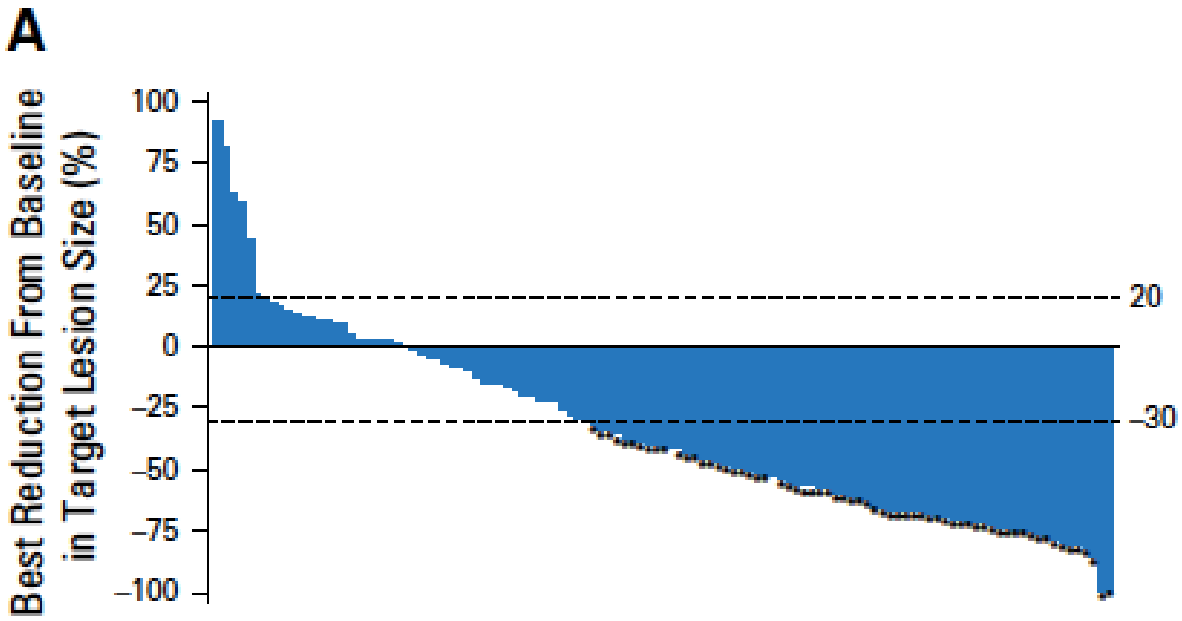

Overman MJ et al. J Clin Oncol 2018; 36:773-779

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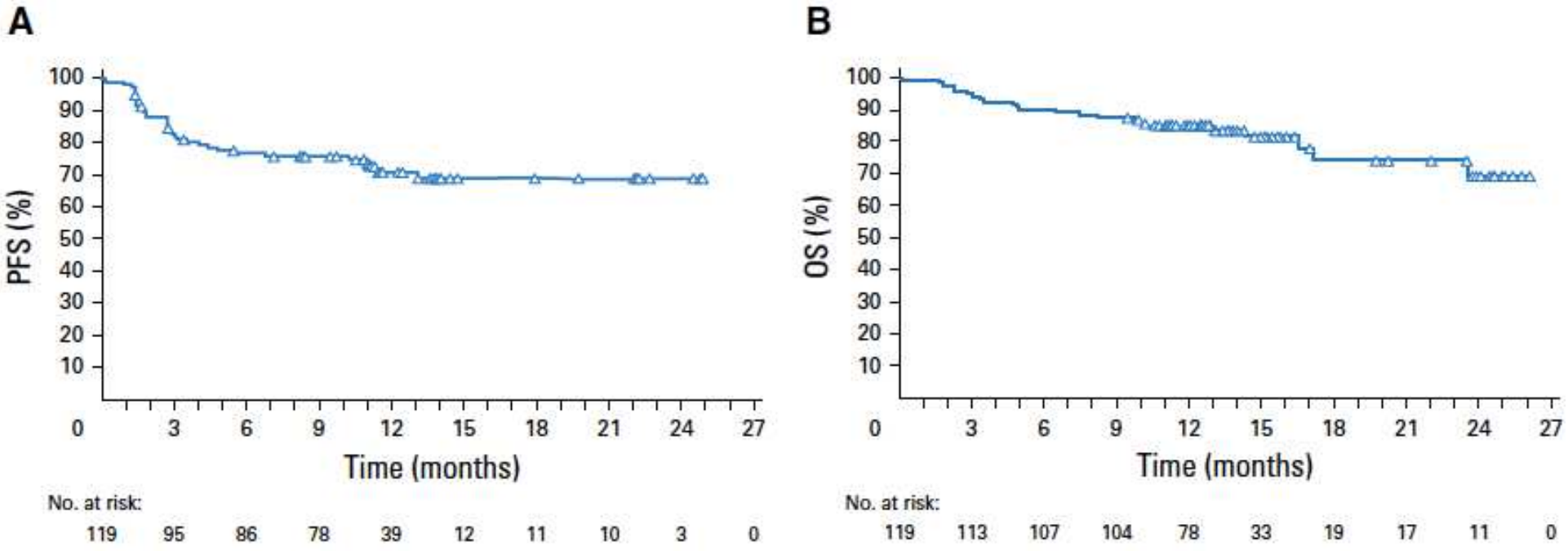

Overman MJ et al. J Clin Oncol 2018; 36:773-779

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THANK YOU