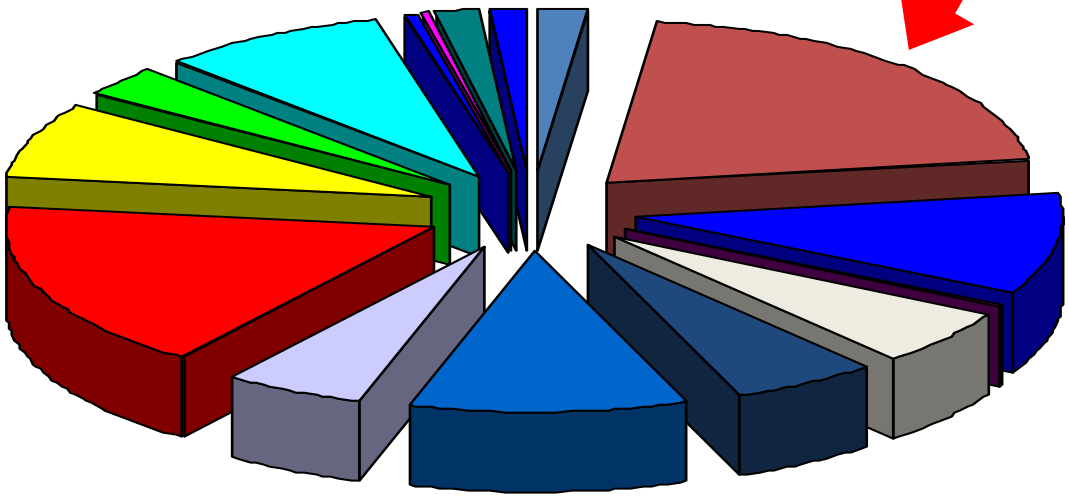
Immunterapi ved Gastrointestinal cancer

Geir Olav Hjortland

Kreft insidens i Norge

Total:
30796 cases

GI: 6430 cases



- Endocrine
- Respiratory organs
- Melanoma
- Breast
- Male genital
- CNS
- Soft tissue
- Mouth-Pharynx
- Digestive organs
- Bone
- Skin
- Gynaecological
- Urinary
- Lymphoid and haematopoietic
- Mesothelioma
- Other

Includes:

-**Oesophageal** (261)

-**Gastric** (464)

-**Small intestine** (134)

-**Colon** (2788)

-**Rectum** (1377)

-**Anus** (73)

-**Hepatobiliary** (448)

-**Pancreas** (747)

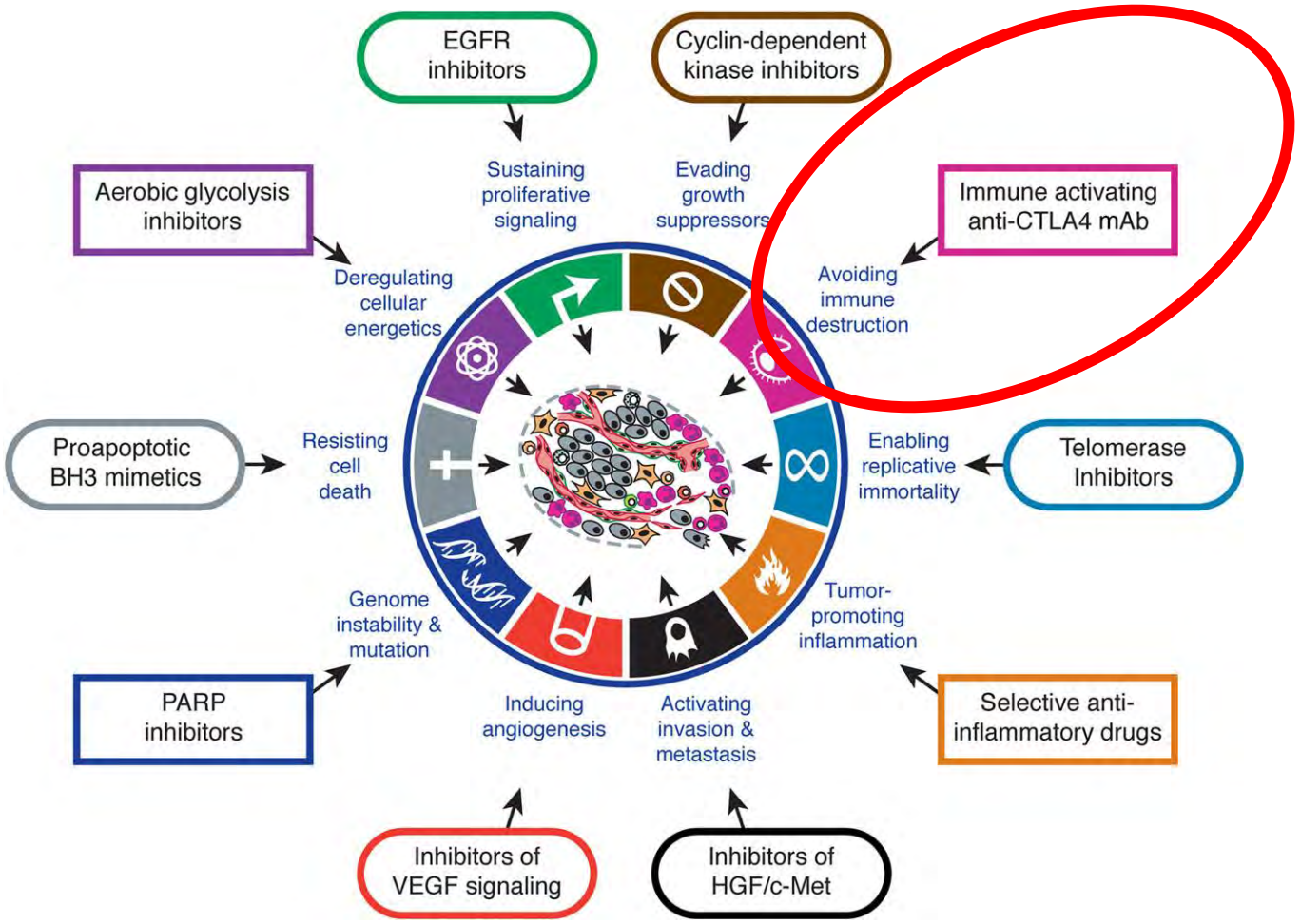
-**Other GI** (138)

Cancer Registry of Norway
(Incidence 2013)

Disposisjon

- Nedre GI
- Midtre GI
- Øvre GI

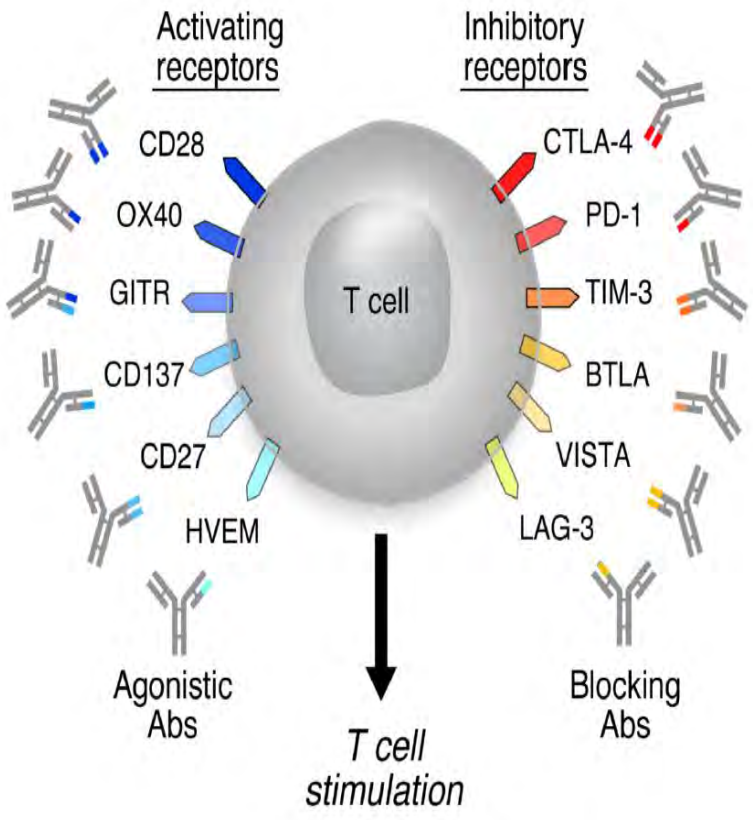
Molecular characteristics of tumors have implications for therapy:



Cell

Hanahan og Weinberg, 2011

«Check-points» in T cell activation



Mellman et al, Nature 2011

Immun-relaterte faktorer av betydning ved GI cancer:

- Mikrosatellitt instabilitet (MSI)
- PDL-1 uttrykk
- Tumor mutasjonsbyrde (TMB)
- Virusinfeksjon (Epstein Barr) (HPV?)
- Tumor infiltrerende Lymfocytter (TILs) /Immunoscore
- Mikrobiomata (?)

Combined positive score (CPS):

$$\text{CPS} = \frac{\text{No. PD-L1–stained cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

(22C3 pharrmDx assay)

Arch Pathol Lab Med—Vol 143, March 2019

Mikrosatellitt instabilitet (MSI)

- Oppstår ved feil i DNA replikasjonen (som ikke blir reparert skikkelig)
- Gir et mønster av hypermutasjon gjennom genomet med repetetive DNA sekvenser (mikrosatelitter) av relativ kort lengde (1-6 bp)
- Oppstår ved defekte mismatch-reparasjon (MMR) proteiner (MLH1/MSH2/MSH6/PMS2)
  - Germline muterte (Lynch syndrom)
  - Somatisk muterte
  - Utslokket genuttrykk (gene silencing) – f.eks hypermetylering av en MMR gen-promotor
- Som regel mest i ikke-kodende DNA

Mikrosatellitt instabilitet - analysemetoder

- PCR metode (Et panel med nukleotid markører, flere kommersielle kit på markedet)
- IHC av MMR proteiner:
- Dybdesekvensering (NGS)

Mikrosatellitt instabilitet (MSI)

- Tidlig stadie CRC : opptil 20% pos MSI-H
- Met CRC: 3-4 % pos
- Disse svulstene er også karakterisert ved:
  - TILs↑
  - TMB↑
  - ICP uttrykk ↑ (PDL1, CTLA4, LAG3)

The prevalence of MSI across 39 human cancer types.

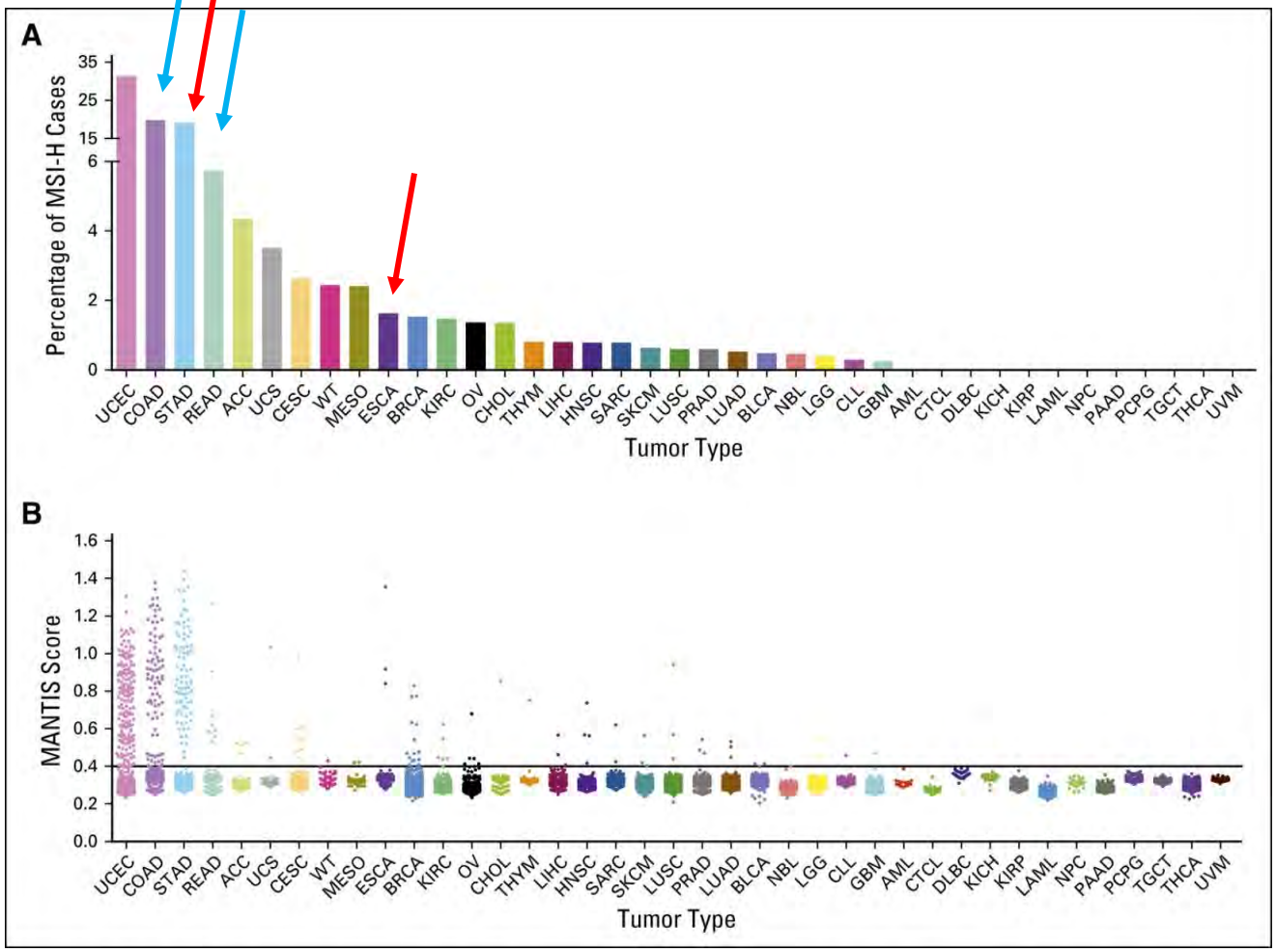
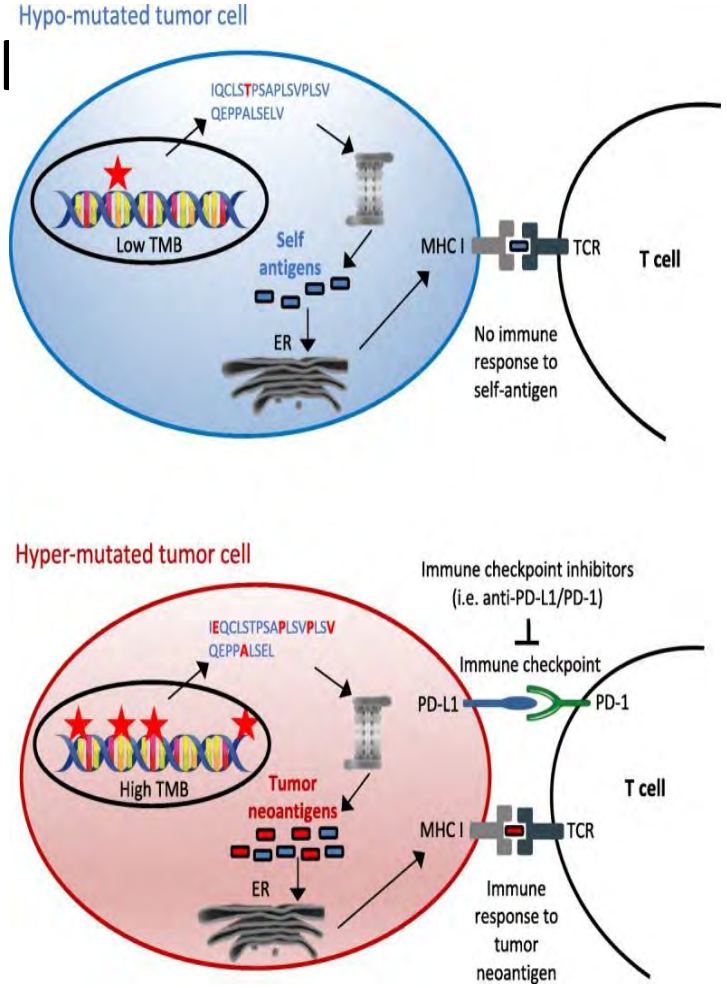


Fig 1. Prevalence of microsatellite instability (MSI) across 39 human cancer types. (A) MSI prevalence was detected across 39 tumor types. The total number of tumors and the percentage of cases called MSI-high (MSI-H) in each cohort is listed in Appendix Table A1. (B) The relative level of instability, as measured by MANTIS score, is shown across all 39 tumor types. Note that for chronic lymphocytic leukemia (CLL), the listed MSI prevalence in panel A is out of 279 patients, and all 338 tumors are shown in panel B. MANTIS threshold cutoff of 0.4 is depicted with a dashed line. ACC, adrenocortical carcinoma; AML, pediatric acute myeloid leukemia (TARGET); BLCA, bladder carcinoma; BRCA, breast carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; CTCL, cutaneous T-cell lymphoma; DLBC, diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia (TCGA); LGG, lower-grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; NBL, pediatric neuroblastoma; NPC, nasopharyngeal carcinoma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectal adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TCGT, testicular germ cell tumor; THCA, thyroid carcinoma;

JCO Precision Oncology - Oct, 2017

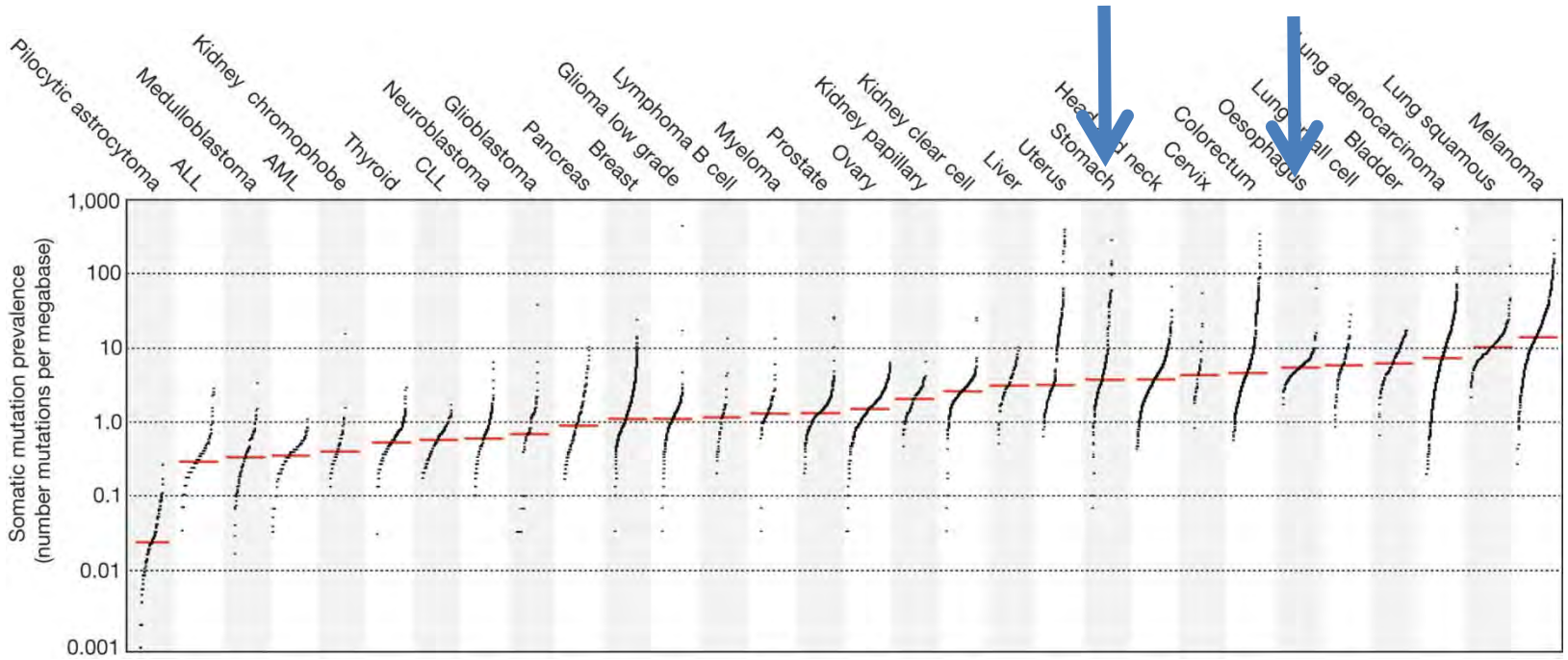
Mutasjons-byrde (TMB) og tumor immunologisk

TMB↑ => Neoantigener
?



J Immunother Cancer. 2019; 7: 183.

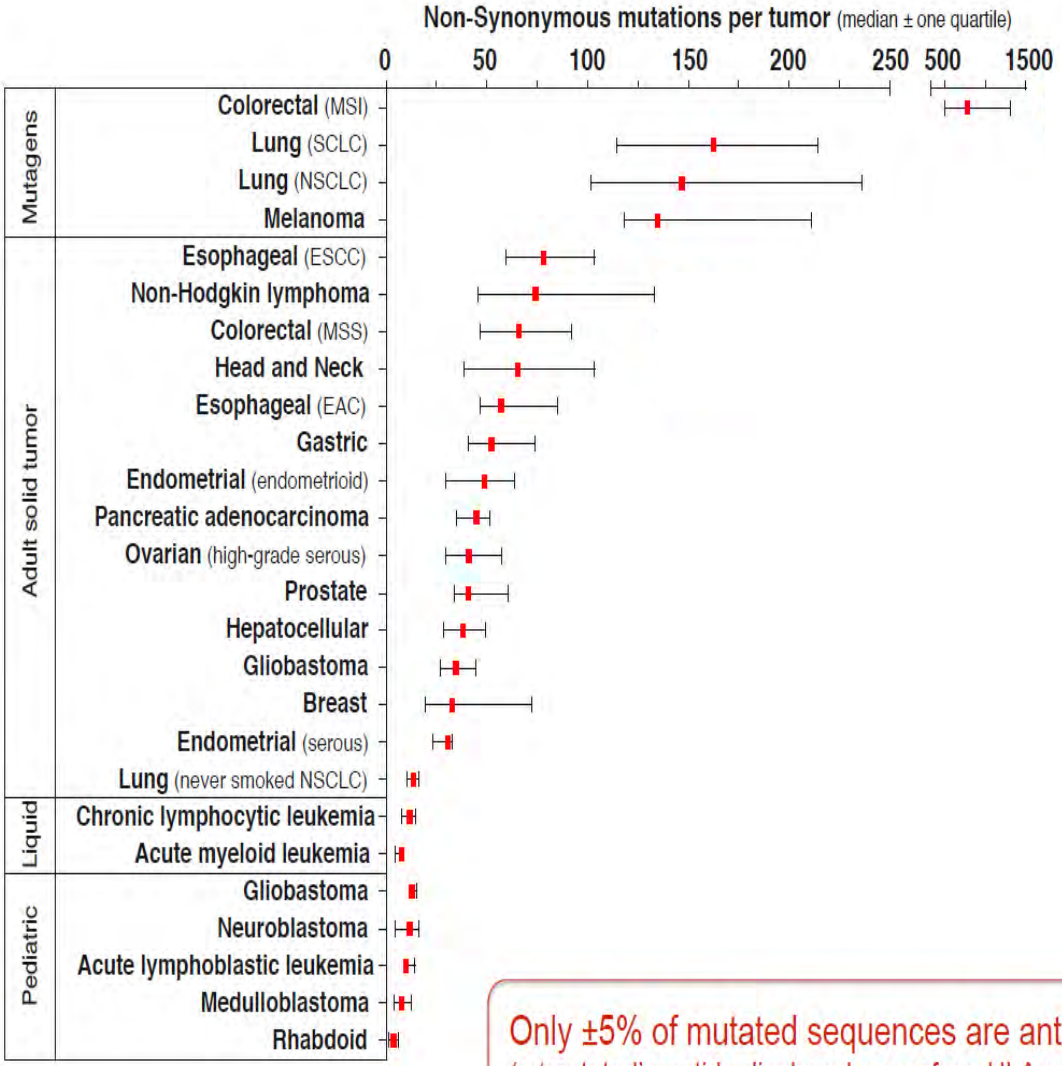
The prevalence of somatic mutations across human cancer types.



LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

nature

Antigens resulting from mutations (single nucleotide variations)

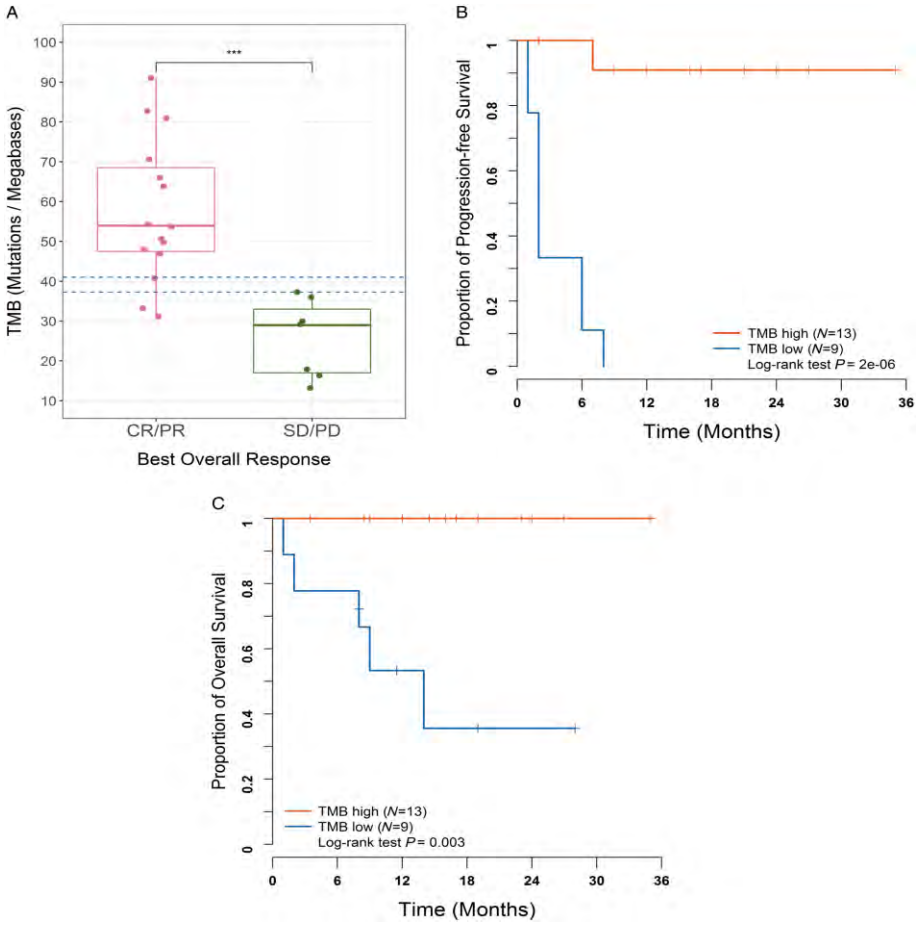


Only ±5% of mutated sequences are antigenic.
(a 'mutated' peptide displayed on surface HLA molecules)

adapted from Vogelstein et al. - 2013 - Science

Modified from: Pierre Couli, WCGI Barcelona 2017

TMB og respons på anti-PD1/PDL1 terapi hos MSI-H CRC:



(19/22 hadde fått pembrolizumab)

Annals of Oncology, Volume 30, Issue 7, July 2019, Pages 1096–1103, https://doi.org/10.1093/annonc/mdz134

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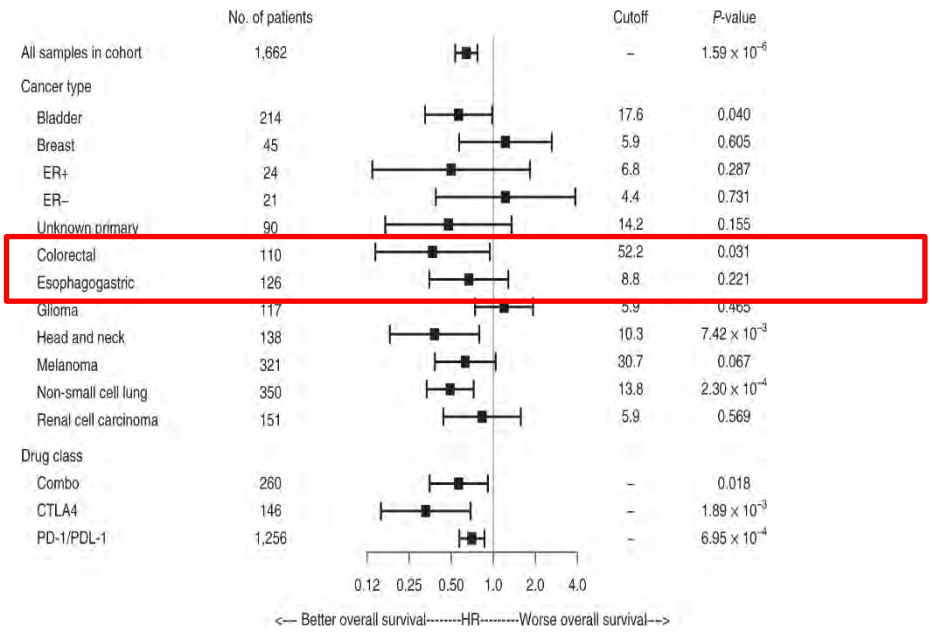
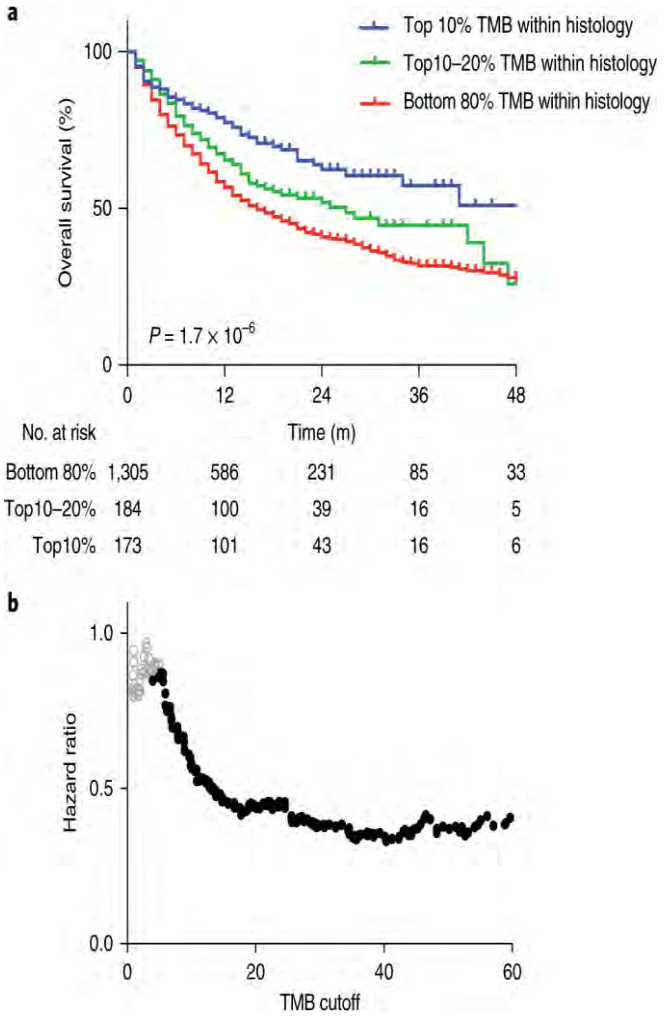
TMB mer usikker som prediktiv markør ved øsofagogastrisk cancer:

Effect of nonsynonymous mutational load on overall survival after ICI treatment, by cancer subtype and drug class



Effect of mutational load on overall survival after ICI treatment:

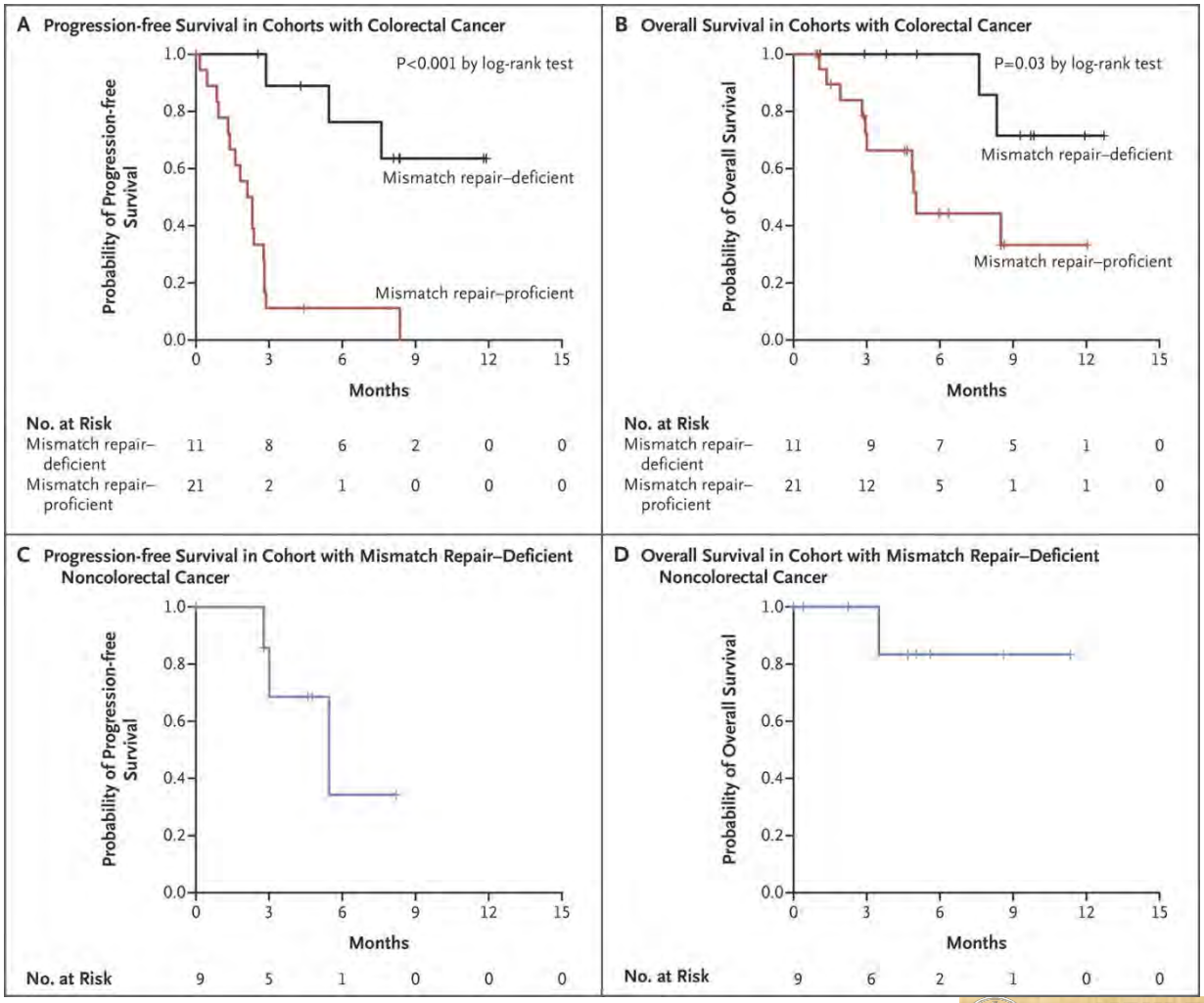


Samstein et al, Nat Genet Jan 2019

Tumor mutasjonsbyrde (TMB)

- Prediktiv for respons på check point hemmere i noen studier
- Noe mer usikre data ved ventrikkelcancer
- Omdiskuterte grenser for definisjon på TMB «high / moderate / low»
- Avhengig av NGS data med relativt store tumor-paneler, alternativt WGS/WES

Clinical Benefit of Pembrolizumab Treatment According to Mismatch-Repair Status.

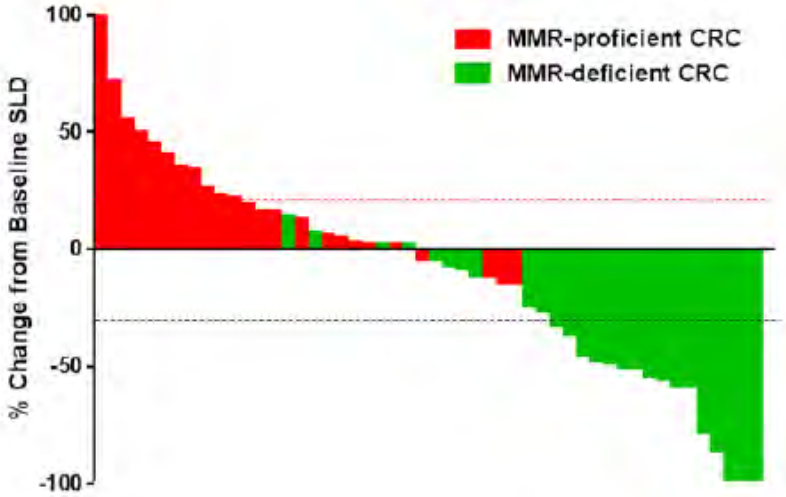


Le DT et al. N Engl J Med 2015;372:2509-2520.

The NEW ENGLAND JOURNAL of MEDICINE

MSI-H CRC – KN016

High Response Rate

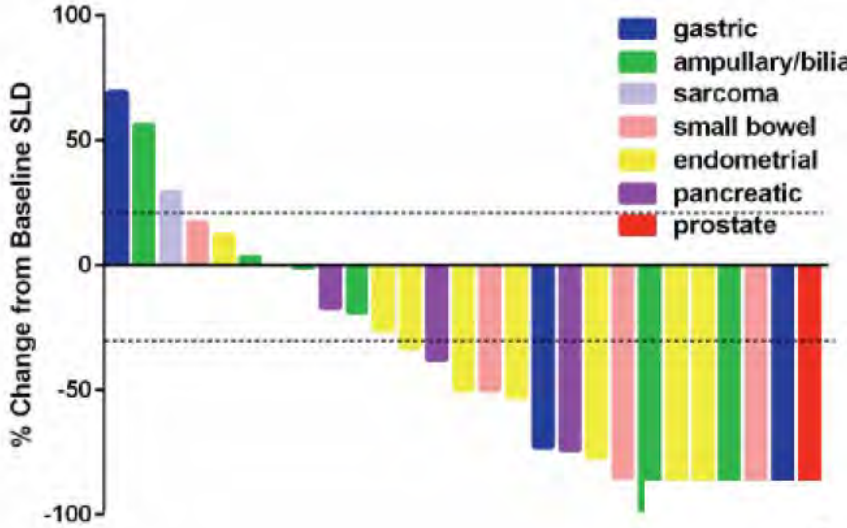


Type of Response-no (%)	MMR-deficient CRC n=28	MMR-proficient CRC n=25
Objective Response Rate (%)	57%	0%
Disease Control Rate (%)	89%	16%
Progression-free Survival (mos)	Not Reached	2.3
Overall Survival (mos)	Not Reached	5.98

Le at al, ASCO 2016

MSI-H non-CRC – KN016

High Response Rate



Type of Response-no (%)	MMR-deficient non CRC n=30
Complete Response	9 (30)
Partial Response	7 (23)
Stable Disease (Week 12)	5 (17)
Progressive Disease	7 (23)
Not Evaluable[1]	2 (7)
Objective Response Rate (%)	16 (53)
95% CI	36-70
Disease Control Rate (%)	21 (70)
95% CI	52 - 83
Median Follow Up	10 mos

[1]Patients were considered not evaluable if they did not undergo a 12 week scan

Le at al, ASCO 2016

MSI-H pasienter og respons på pembrolizumab

Endpoint	n=149
Objective response rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4
Partial response rate	32.2
Response duration	
Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

NR = not reached

Table 25: Response by Tumor Type

	N	Objective response rate n (%)	95% CI	DOR range (months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)
Endometrial cancer	14	5 (36%)	(13%, 65%)	(4.2+, 17.3+)
Biliary cancer	11	3 (27%)	(6%, 61%)	(11.6+, 19.6+)
Gastric or GE junction cancer	9	5 (56%)	(21%, 86%)	(5.8+, 22.1+)
Pancreatic cancer	6	5 (83%)	(36%, 100%)	(2.6+, 9.2+)
Small intestinal cancer	8	3 (38%)	(9%, 76%)	(1.9+, 9.1+)
Breast cancer	2	PR, PR		(7.6, 15.9)
Prostate cancer	2	PR, SD		9.8+
Bladder cancer	1	NE		
Esophageal cancer	1	PR		18.2+
Sarcoma	1	PD		
Thyroid cancer	1	NE		
Retroperitoneal adenocarcinoma	1	PR		7.5+
Small cell lung cancer	1	CR		8.9+
Renal cell cancer	1	PD		

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease
NE = not evaluable

Fra FDA godkjenning, mai-2017

Data supporting pembrolizumab approval

	N	Objective response rate n (%)	95% CI
CRC	90	32 (36%)	(26%, 46%)
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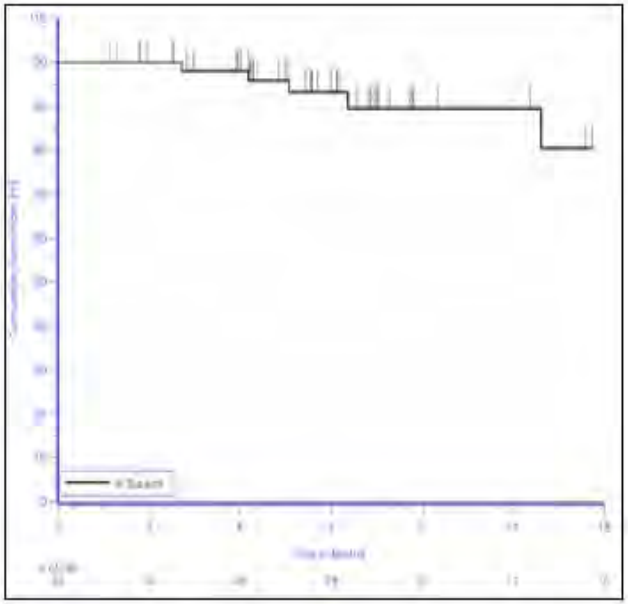
Prostate cancer	2	PR, SD	
Bladder cancer	1	NE	
Esophageal cancer	1	PR	
Sarcoma	1	PD	
Thyroid cancer	1	NE	
Retroperitoneal adenocarcinoma	1	PR	
Small cell lung cancer	1	CR	
Renal cell cancer	1	PD	



KM-DOR in 59 responding patients

Source: Keytruda labeling, BLA submission, FDA review documents

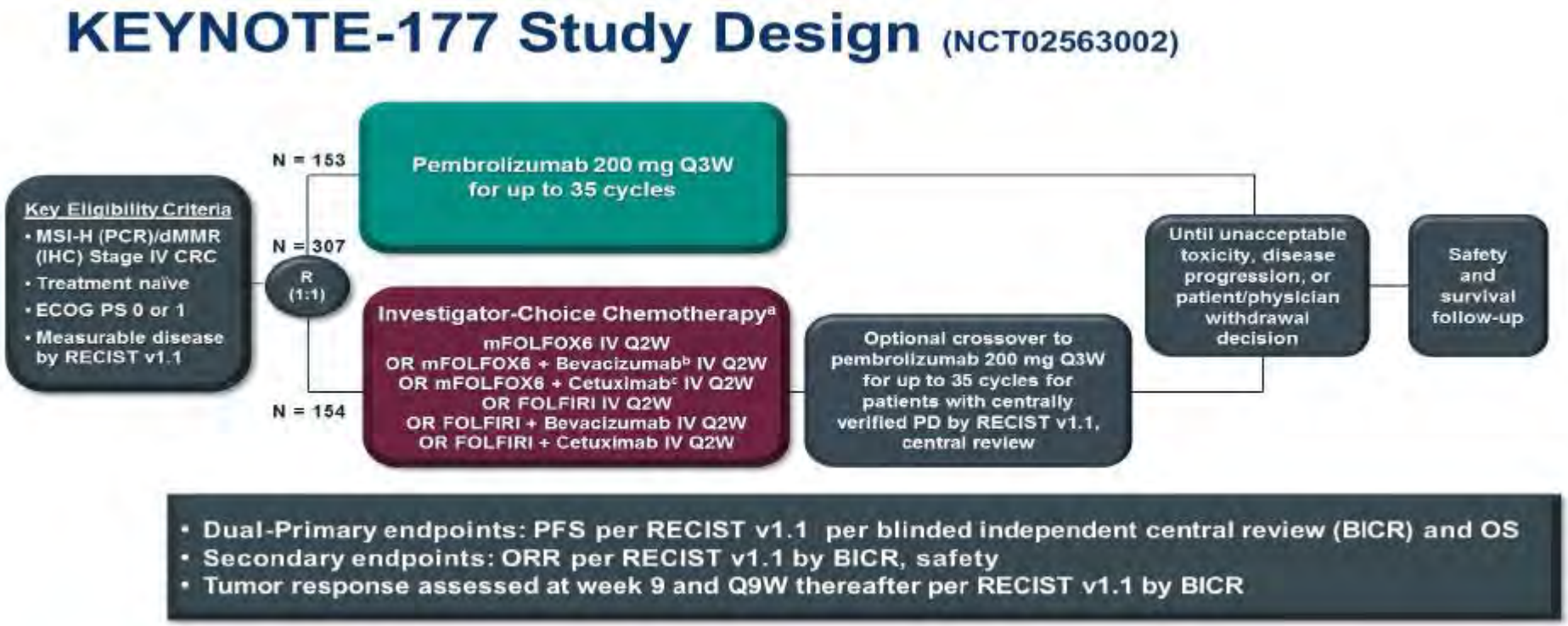
FDA godkjenning, mai-2017

FDA godkjenninger

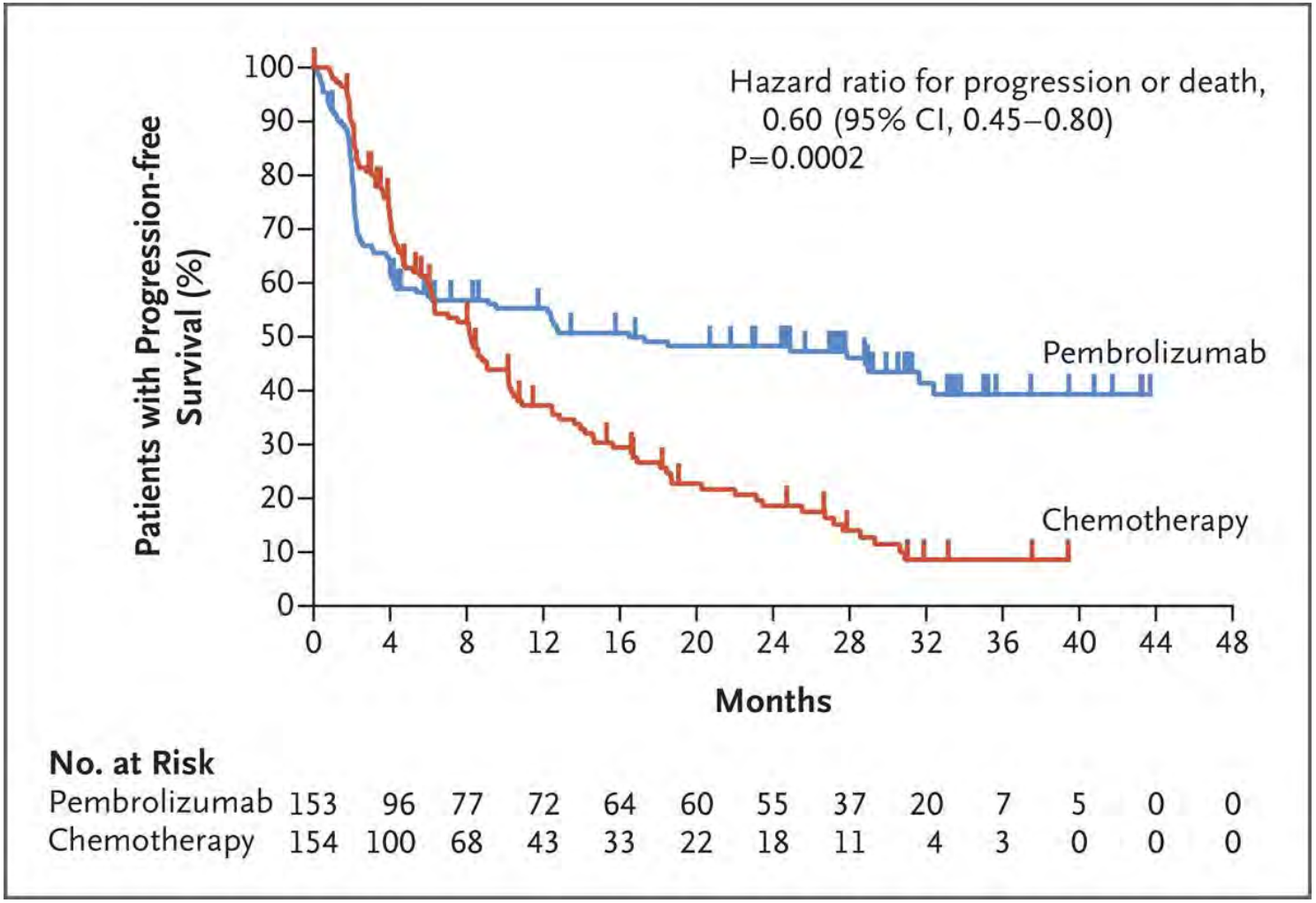
Table 1. Landmark trials leading to FDA approval of immunotherapy in mCRC.

Name of trial	Phase of trial	Drug and dose	Objective response rate in dMMR	Disease control rate >12 weeks in dMMR	FDA approval date
KEYNOTE 028 Le *et al.*[28]	Phase II	Pembrolizumab 10 mg/kg every 14 days	40%	90%	May 2017
CheckMate 142 Overman *et al.*[29]	Phase II	Nivolumab 3 mg/kg every 14 days	31.1%	69%	August 2017
CheckMate 142 (further analysis of subgroup) André *et al.*[30]	Phase II	Nivolumab 3 mg/kg + Ipilumumab 1 mg/kg every 21 days	55%	80%	July 2018

1. Linje Pembro vs kjemoterapi



Progression-free Survival in Patients with MSI-H–dMMR Metastatic Colorectal Cancer.



T André et al. N Engl J Med 2020;383:2207-2218.

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Keynote177

Antitumor Response

	Pembrolizumab N = 153		Chemotherapy N = 154
ORR, n (%)	**67 (43.8)**		**51 (33.1)**
Difference, estimate (95% CI) *P*-value		10.7 (-0.2-21.3) 0.0275	
Best Overall Response, n (%)			
Complete response	17 (11.1)		6 (3.9)
Partial response	50 (32.7)		45 (29.2)
Stable disease	32 (20.9)		65 (42.2)
Disease control rate (CR+PR+SD)	99 (64.7)		116 (75.3)
Progressive disease	45 (29.4)		19 (12.3)
Not evaluable	3 (2.0)		2 (1.3)
No assessment	6 (3.9)		17 (11.0)
Median time to response (range), mo	2.2 (1.8-18.8)		2.1 (1.7-24.9)

Data cut-off: 19Feb2020; Response assessed per RECIST v1.1 by BICR.

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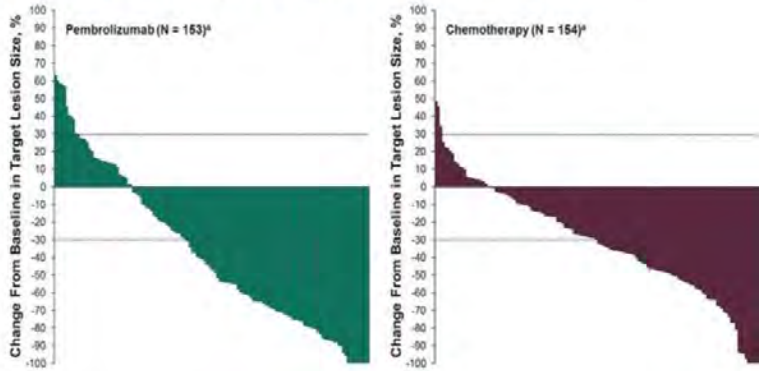
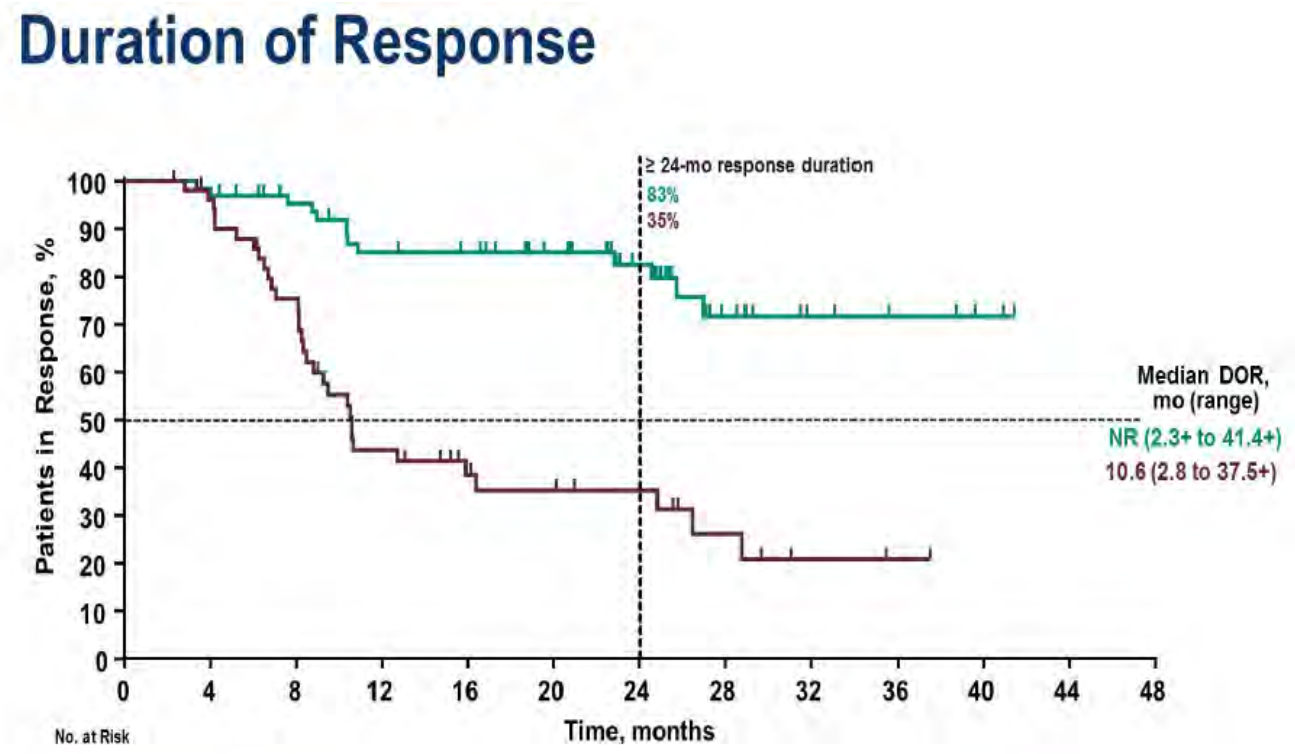
Radiographic Response in Target Lesions



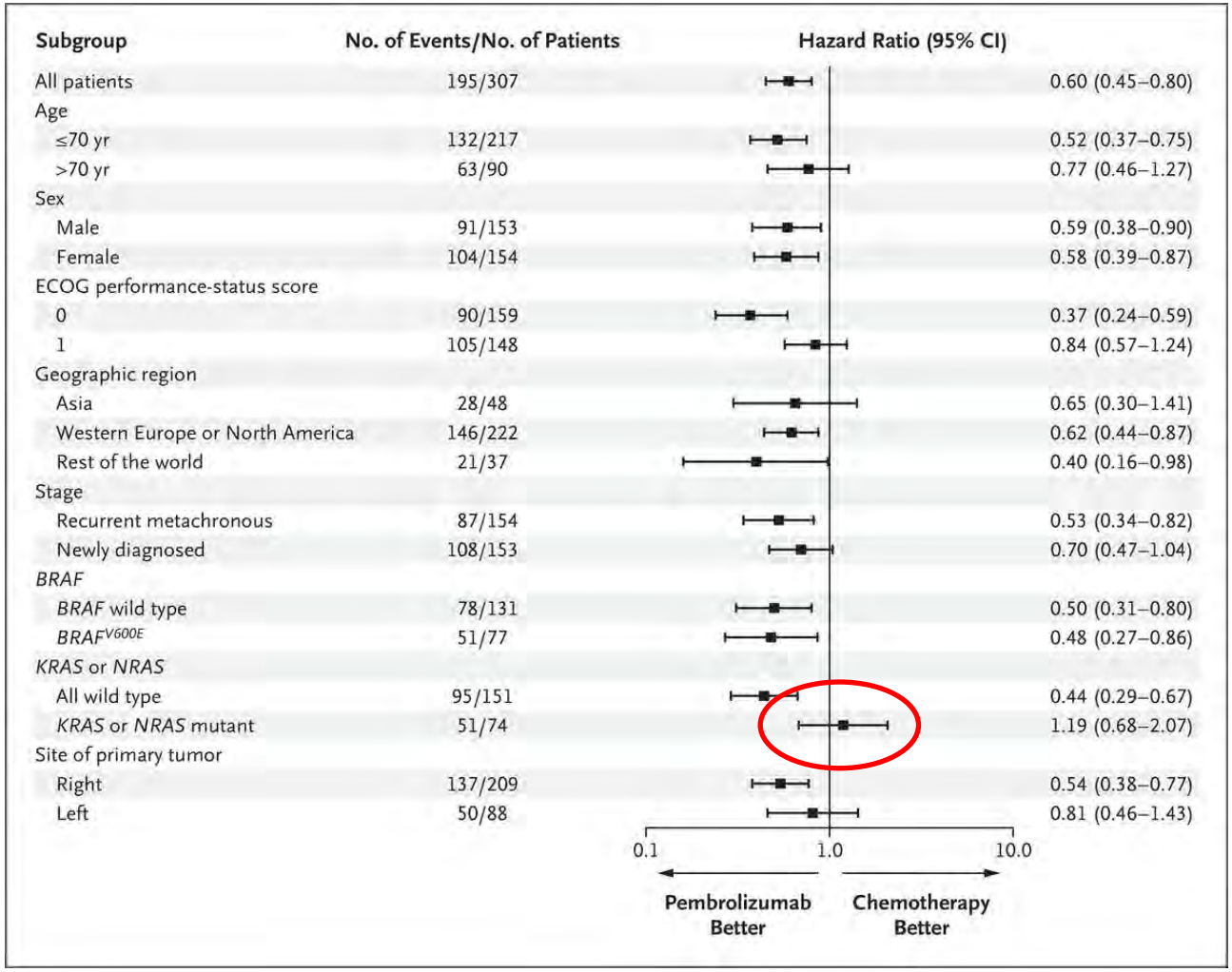
- Higher CR, but also early PD rates with pembrolizumab

Keynote177



Durable Responses in patients who did not progress with Pembrolizumab

Progression-free Survival in Key Subgroups of Patients with MSI-H–dMMR Metastatic Colorectal Cancer.



T André et al. N Engl J Med 2020;383:2207-2218.

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Høy mikrosatellitt instibilitet i tumor (MSI-H) eller Defekt mismatch repair (dMMR):

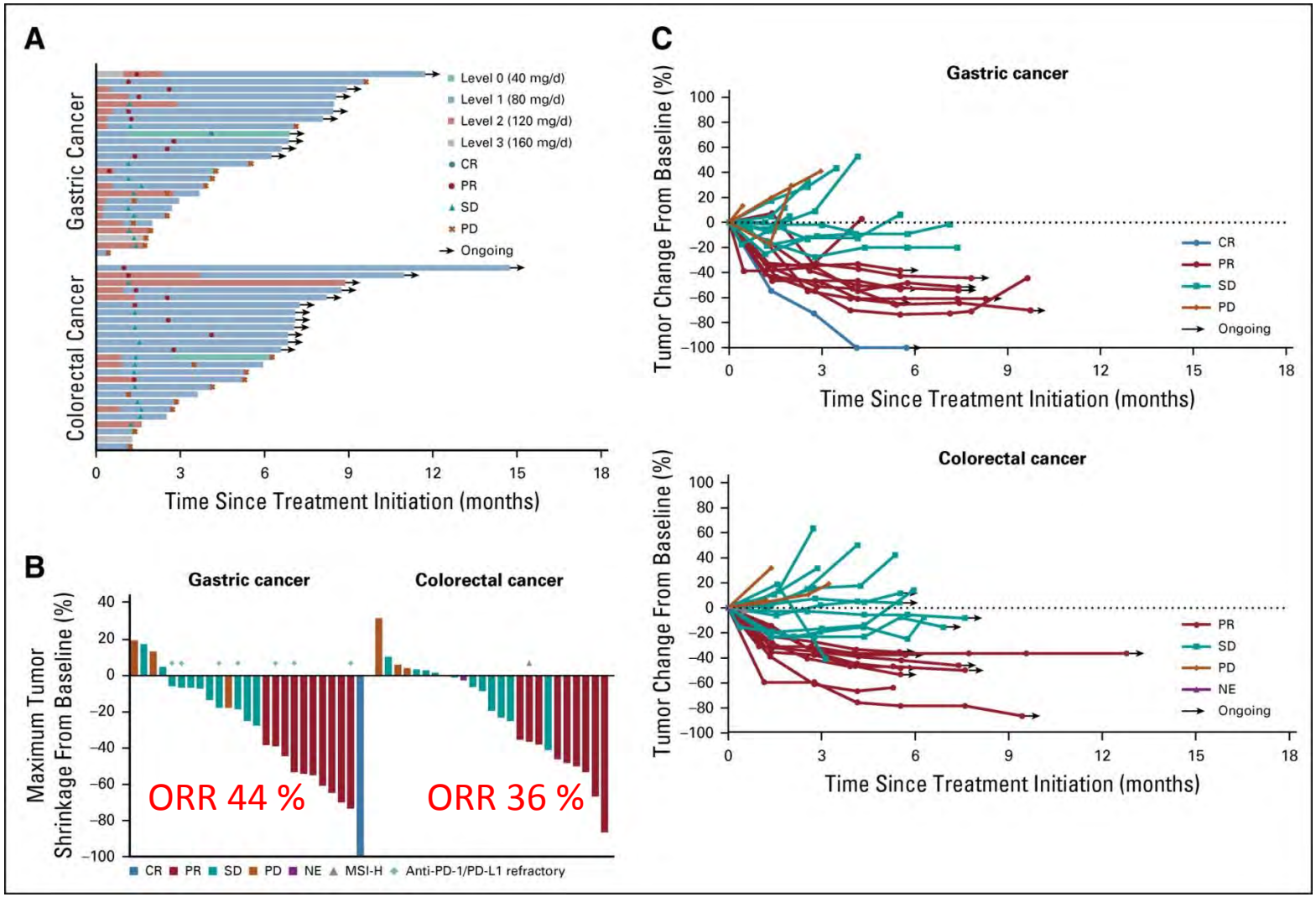
- Prediktiv for respons på check point hemmere i mange studier
- FDA godkjenning (mai-2017):
  - Inoperabel/metastatisk MSI-H eller dMMR (uansett tumordiagnose) ved progresjon på tidligere behandling og ingen annen etablert behandlingsalternativ
  - Inoperabel/metastatisk MSI-H eller dMMR kolorektalcancer som har progrediert på 5-FU, Oxaliplatin og Irinotecan behandling

- EMEA - godkj. Des 2020
  - 2019: Fagdirektører i Norge har gitt bredt unntak for alle tilsvarende kolorektal gruppen over

Hva med MSS CRC ?

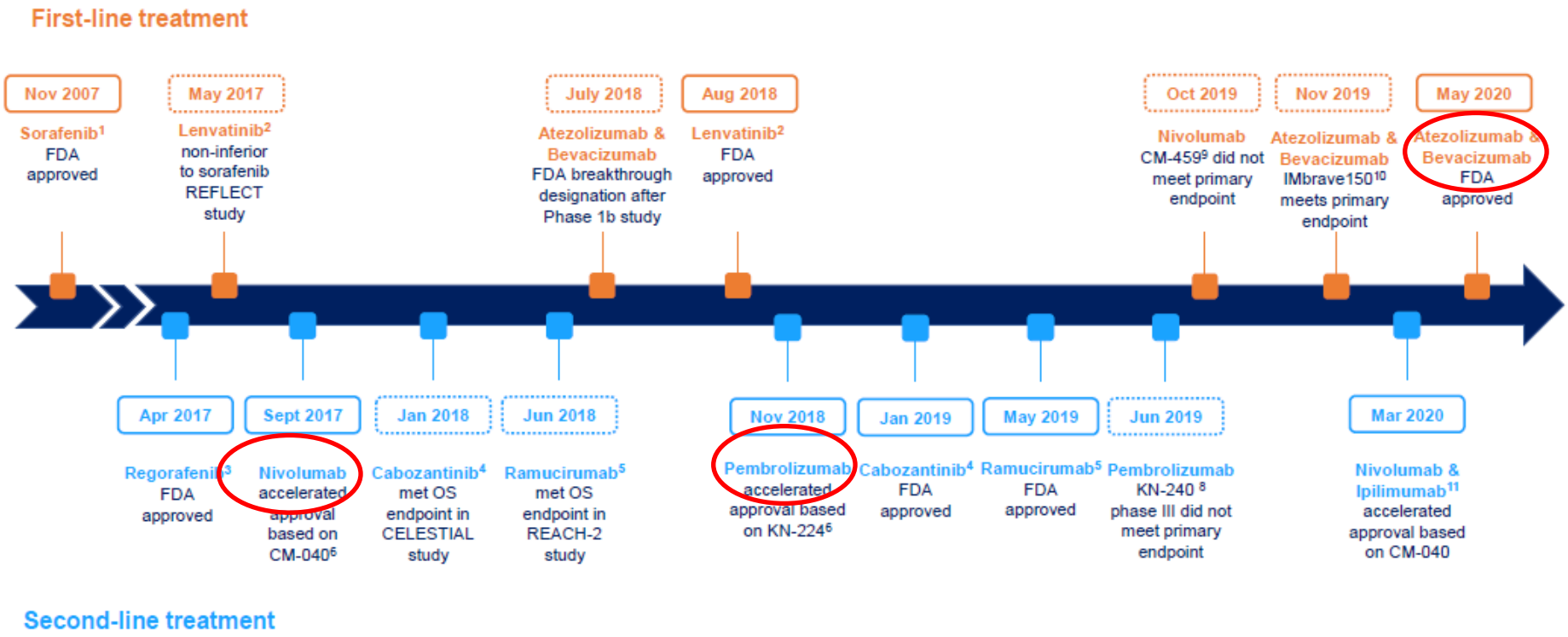
- Studier pågår
- Kombinasjonsbehandlinger

REGONIVO, EPOC1603 (phase Ib)



Journal of Clinical Oncology 38, no. 18 (June 20, 2020) 2053-2061

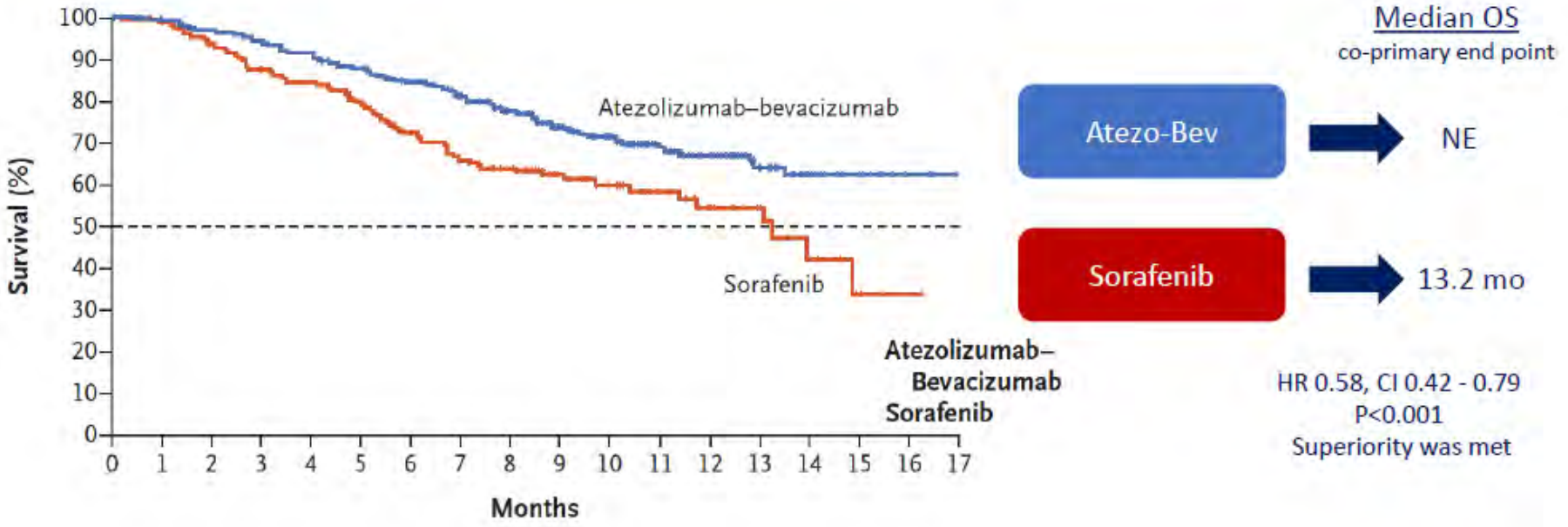
Hepatocellulært carcinom



1. Llovet JM, et al. *N Engl J Med* 2008; 359(4): 378-90. 2. Kudo M et al. *Lancet* 2018; 391(10126): 1163-73. 3. Bruix J et al. *Lancet* 2017; 389(10064): 56-66. 4. Abou-Alfa GK et al. *N Engl J Med* 2018; 379(1): 54-63. 5. Zhu AX et al. *Lancet Oncol* 2019; 20(2): 282-96. 6. Zhu AX et al. *Lancet Oncol* 2018; 19(7): 940-52. 7. El-Khoueiry AB et al. *Lancet* 2017; 389(10088): 2492-502. 8. Finn et al. ASCO (Abs). 2019. 9. Yau et al. ESMO (abs). 2019.10. Finn et al. NEJM. 2020;382:1894-905. 11. Yau et al. ASCO 2019. Abs 4012.

Hepatocellulært carcinom

IMbrave150 (Atezolizumab + Bevacizumab) – 1st line therapy

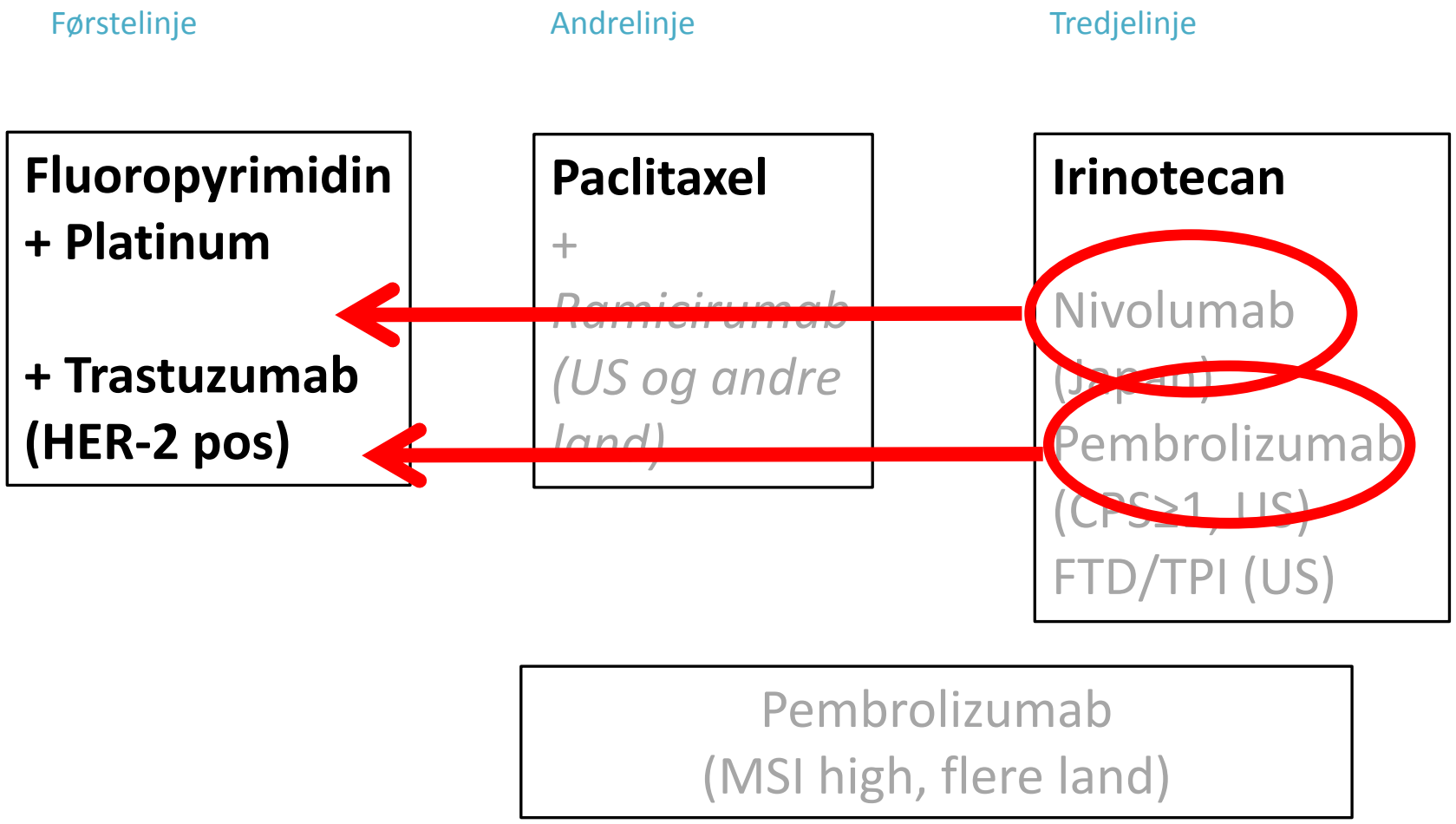


May 14, 2020

N Engl J Med 2020; 382:1894-1905

Gastroøsofageal cancer

Standardbehandling avansert/metastatisk Øsofagus & Ventrikkelkreft



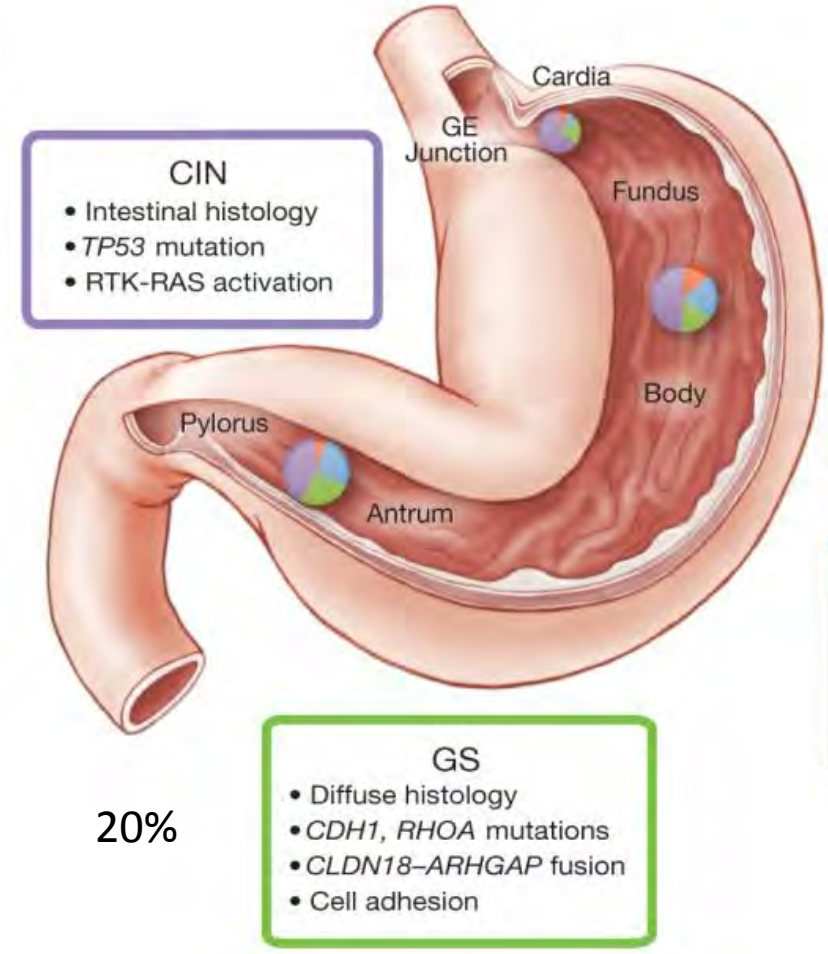
Combined positive score (CPS):

$$\text{CPS} = \frac{\text{No. PD-L1–stained cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

(22C3 pharrmDx assay)

Arch Pathol Lab Med—Vol 143, March 2019

TCGA network's molecular classification of 295 primary gastric cancers



50%

CIN
- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

EBV
- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

9%

MSI
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

22%

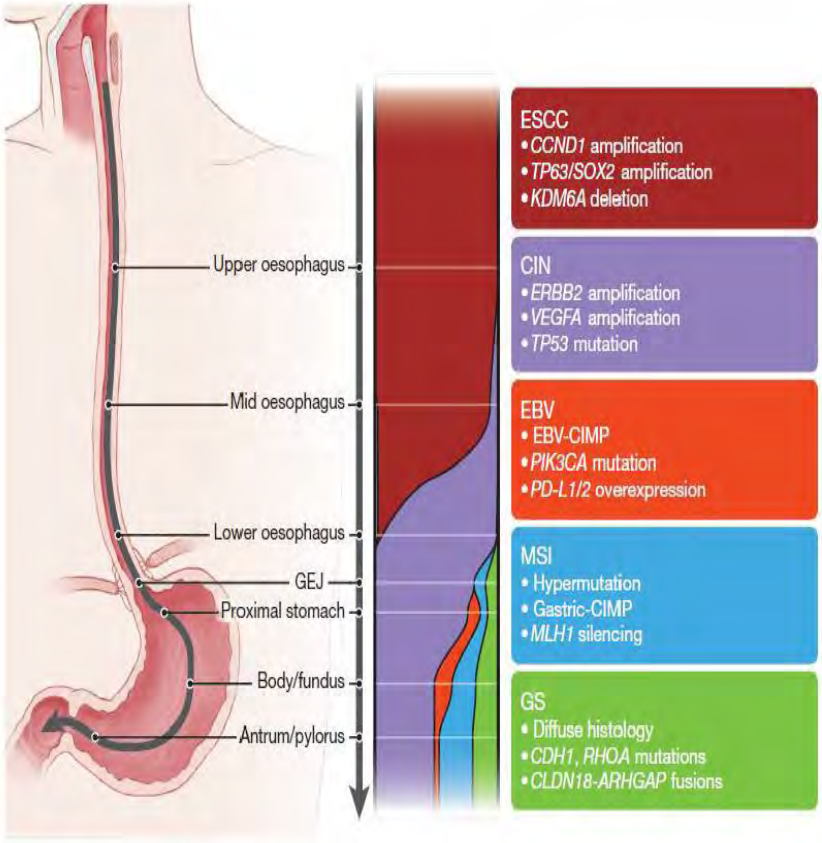
GS
- Diffuse histology
- *CDH1, RHOA* mutations
- *CLDN18–ARHGAP* fusion
- Cell adhesion

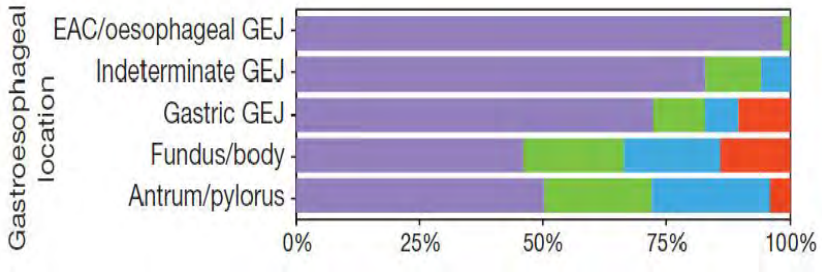
20%

AJ Bass *et al. Nature* **000**, 1-8 (2014) doi:10.1038/nature13480

nature

Gradienter av typer i esofagogastrisk karsinom

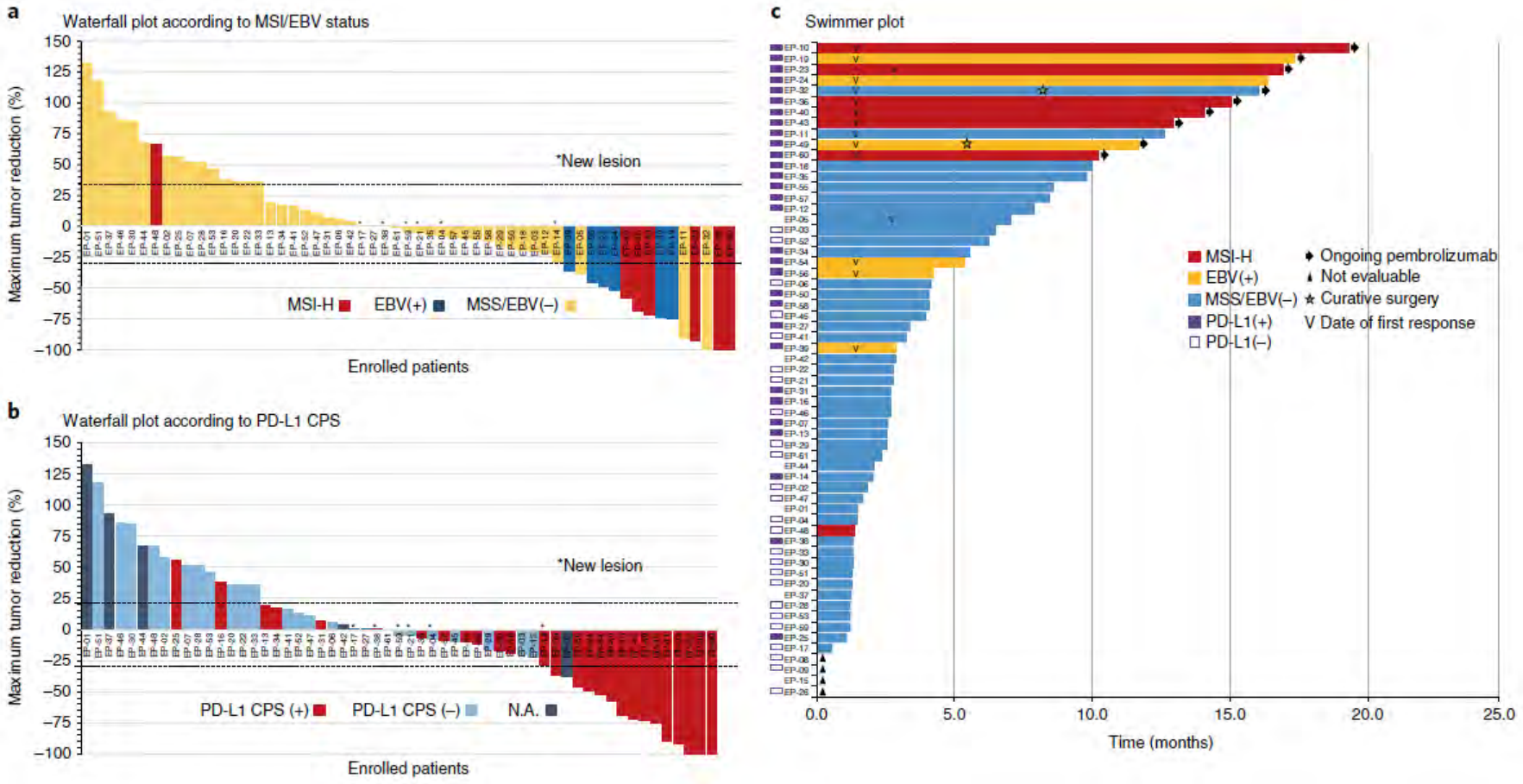




J Kim *et al. Nature* 1–9 (2017)
doi:10.1038/nature20805

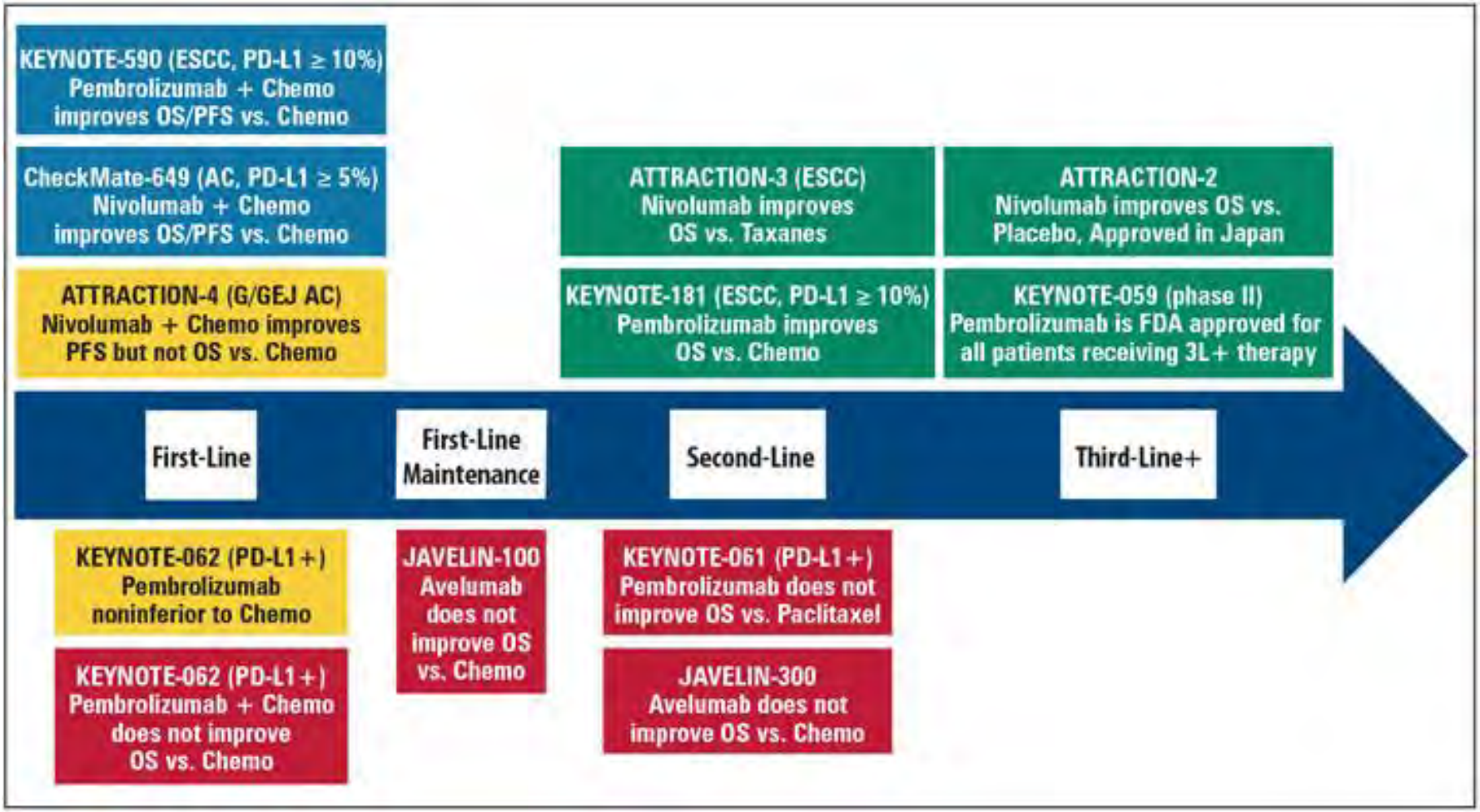
nature

Pembrolizumab ved ventrikkel-ca



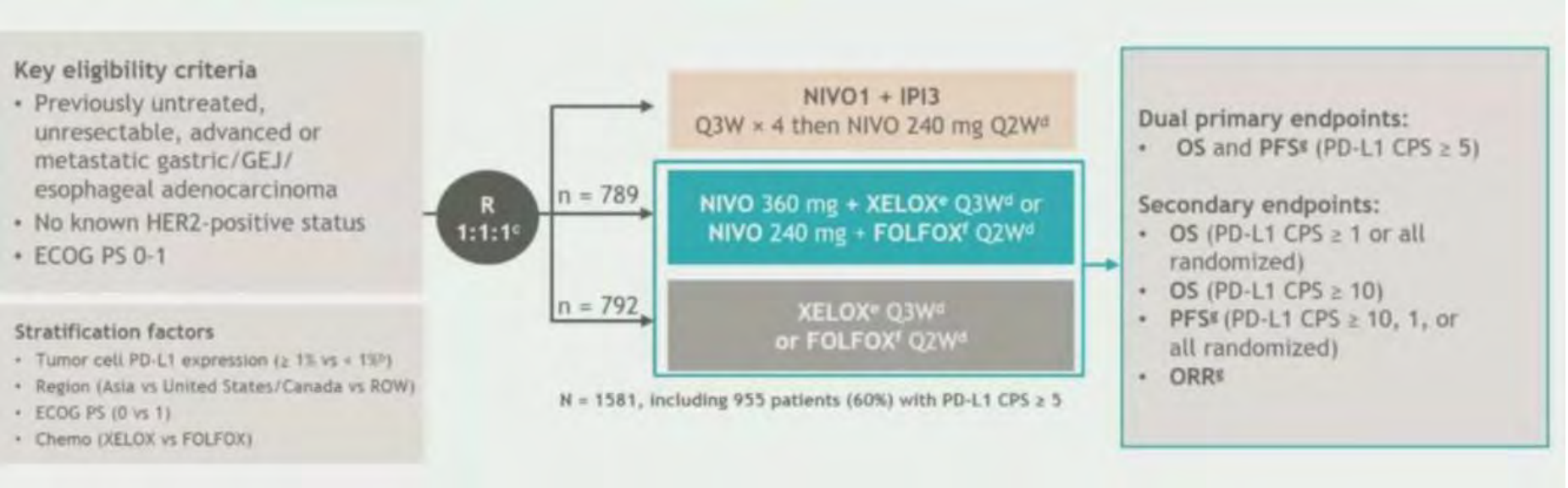
Kim et al. , Nat Med , Vol 24, 2018

ICPI studier
øsofagus- og ventrikkel cancer



Suneel D. Kamath, MD, and Alok A. Khorana, MD, ASCO Daily News nov 2020

CheckMate 649



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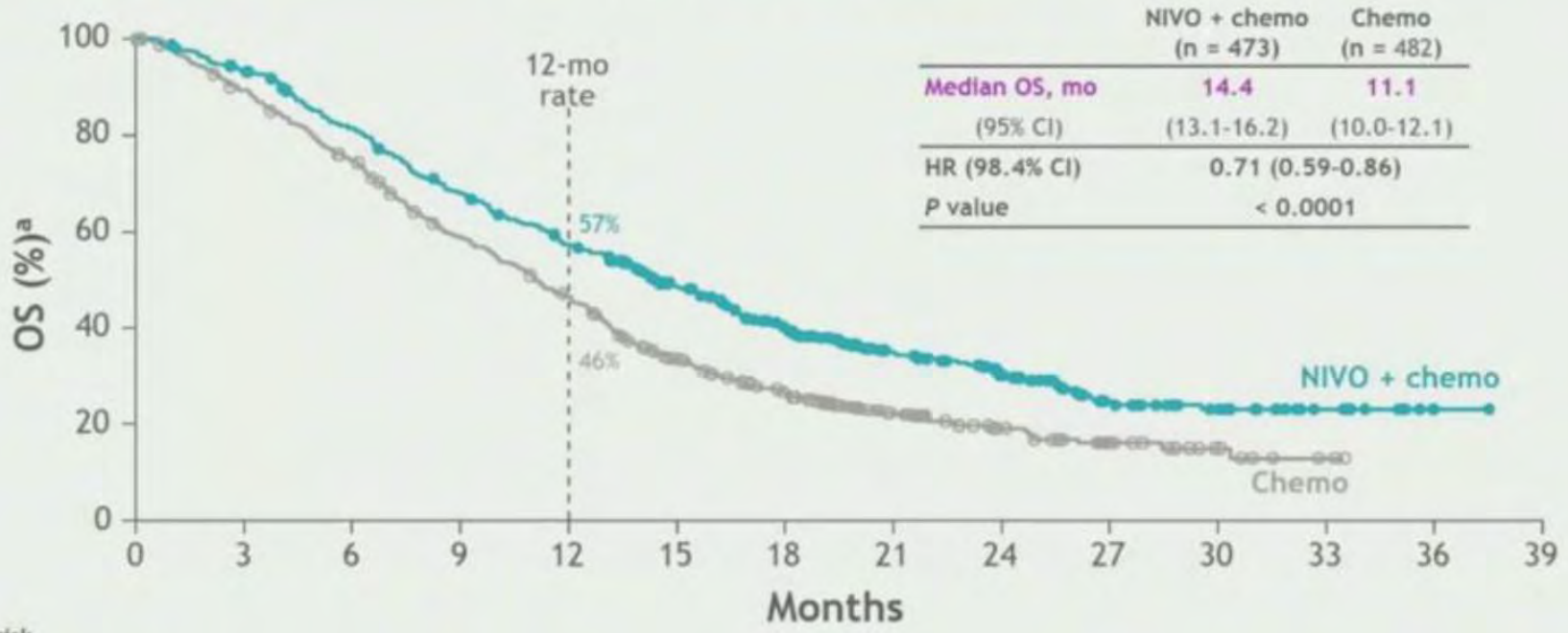
Overall survival

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

[a]Minimum follow-up 12.1 months.

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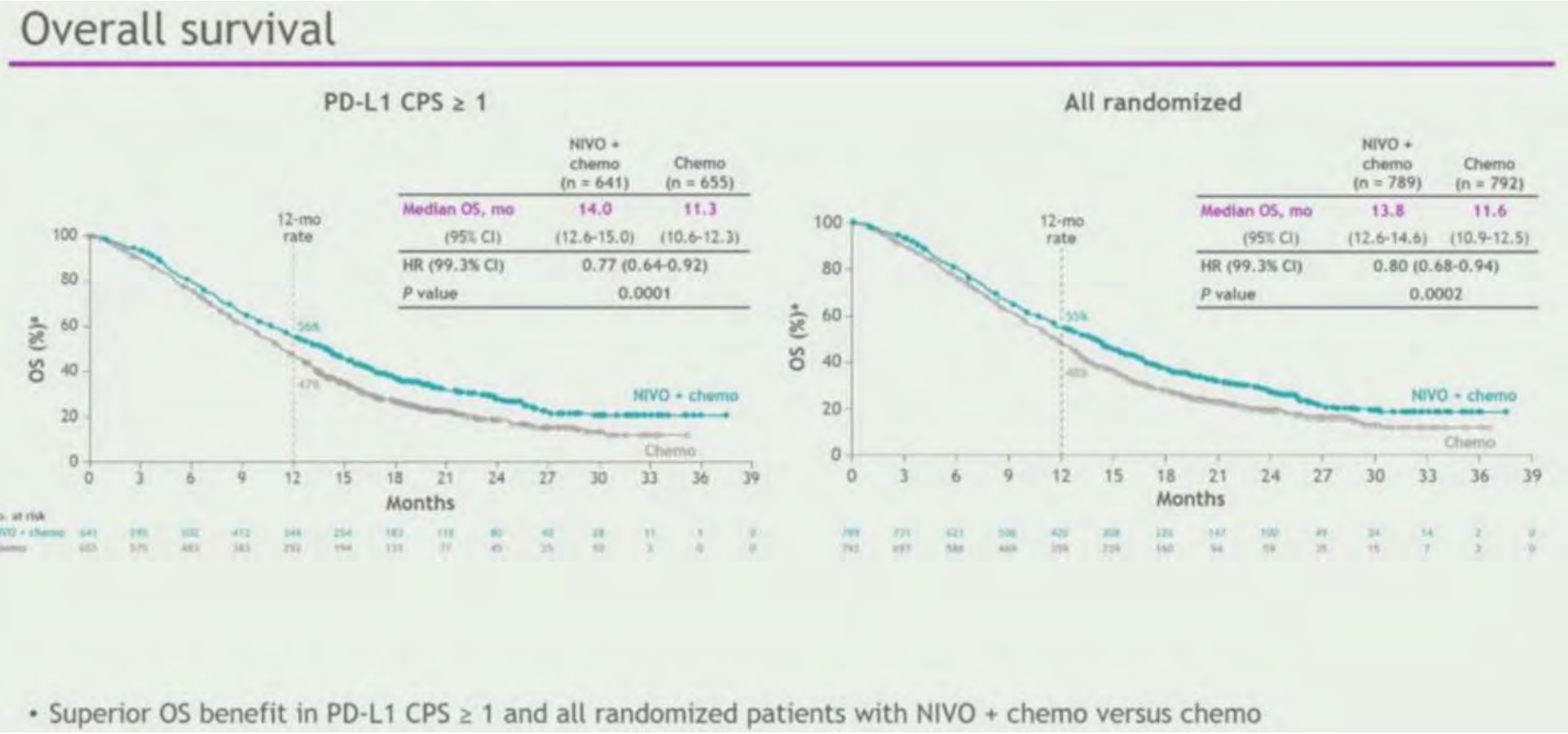

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CheckMate 649

Overall survival subgroup analysis

Category (PD-L1 CPS ≥ 5)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 955)		14.4	11.1	0.70	
Age, years	< 65 (n = 552)	14.8	11.0	0.69	
	≥ 65 (n = 403)	14.3	11.2	0.72	
Sex	Male (n = 680)	14.4	10.8	0.67	
	Female (n = 275)	14.4	12.1	0.78	
Race	Asian (n = 236)	16.1	11.5	0.63	
	White (n = 655)	14.0	11.1	0.71	
	Other (n = 64)	9.8	10.6	0.93	
Region	Asia (n = 228)	15.6	11.8	0.64	
	US/Canada (n = 137)	16.8	12.6	0.67	
	ROW (n = 590)	13.6	10.4	0.74	
ECOG PS[a]	0 (n = 397)	17.6	13.8	0.79	
	1 (n = 557)	12.6	8.8	0.63	
Primary tumor location	GC (n = 667)	15.0	10.5	0.66	
	GEJC (n = 170)	14.2	13.1	0.84	
	EAC (n = 118)	11.2	11.3	0.78	
Tumor cell PD-L1[b] expression	< 1% (n = 724)	14.2	11.6	0.75	
	≥ 1% (n = 230)	16.2	8.8	0.56	
Liver metastases	Yes (n = 408)	13.1	9.8	0.63	
	No (n = 518)	15.5	12.0	0.76	
Signet ring cell carcinoma	Yes (n = 141)	12.1	9.0	0.71	
	No (n = 814)	15.1	11.3	0.69	
MSI status[c]	MSS (n = 846)	14.4	11.1	0.73	
	MSI-H (n = 34)	Not reached	8.8	0.33	
Chemotherapy regimen	FOLFOX (n = 479)	14.3	11.3	0.71	
	XELOX (n = 454)	15.0	11.0	0.69	

- OS consistently favored NIVO + chemo versus chemo across multiple pre-specified subgroups

[a]Not reported, n = 1; [b]Unknown, n = 1; [c]Not reported/invalid, n = 75.

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ATTRACTION-4

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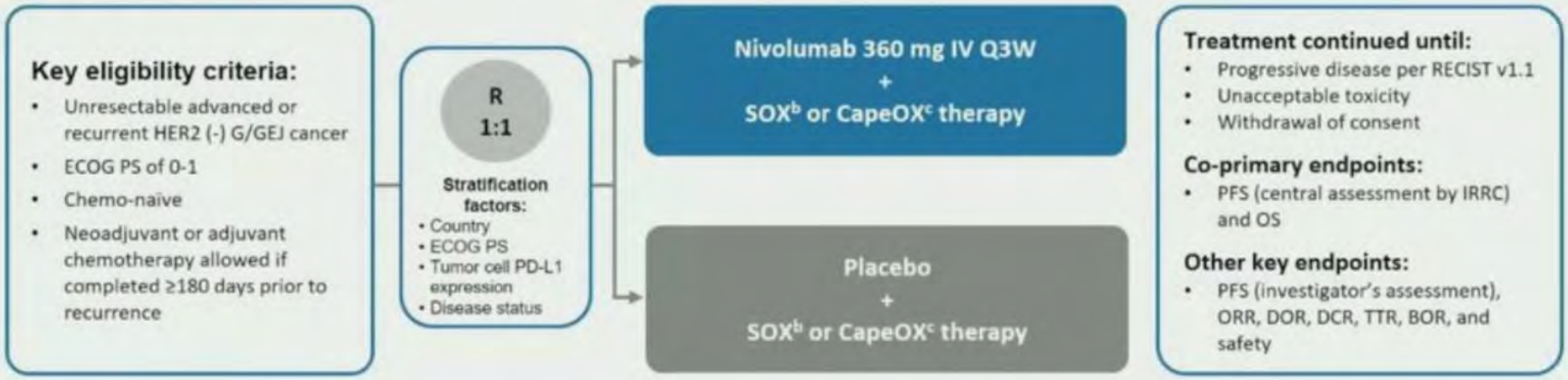
Phase 3 part of ATTRACTION-4: Study Design

- Phase 3 part of ATTRACTION-4 is a double-blind, randomized controlled study conducted at 130 centers in Japan, Korea, and Taiwan[a]



- At data cutoff for interim analysis of PFS (31 Oct 2018), the median follow-up period was 11.6 months
- At data cutoff for final analysis of OS (31 Jan 2020), the median follow-up period was 26.6 months
- A total of 724 patients were randomized between Mar 2017 and May 2018

ATTRACTION-4

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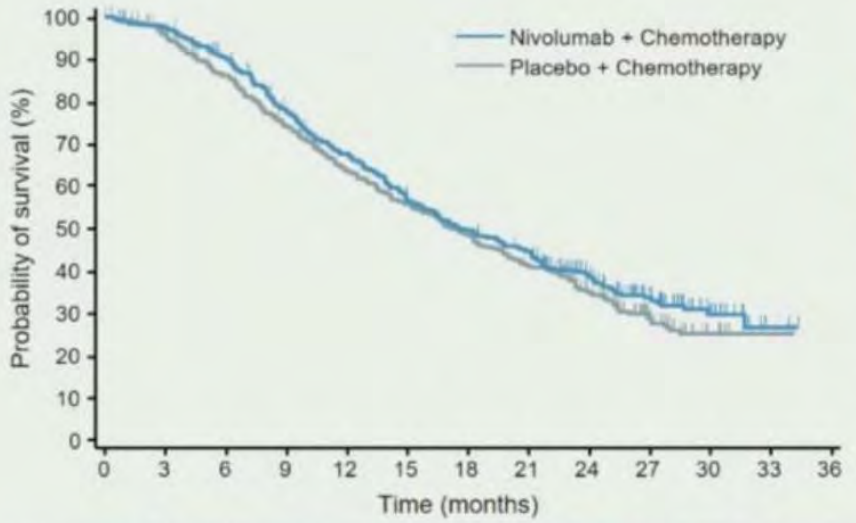
Overall Survival (Final Analysis)



At Risk													
Nivolumab + Chemotherapy	362	346	318	269	232	193	169	150	102	58	23	2	0
Placebo + Chemotherapy	362	342	301	259	219	192	167	141	97	48	16	5	0

	Nivolumab + Chemotherapy N = 362	Placebo + Chemotherapy N = 362
Median OS, months (95% CI)	17.45 (15.67-20.83)	17.15 (15.18-19.65)
Hazard ratio (95% CI)	0.90 (0.75-1.08)	
P value	0.257	

Data cut off : 31 Jan 2020 at final analysis

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ATTRACTION-4

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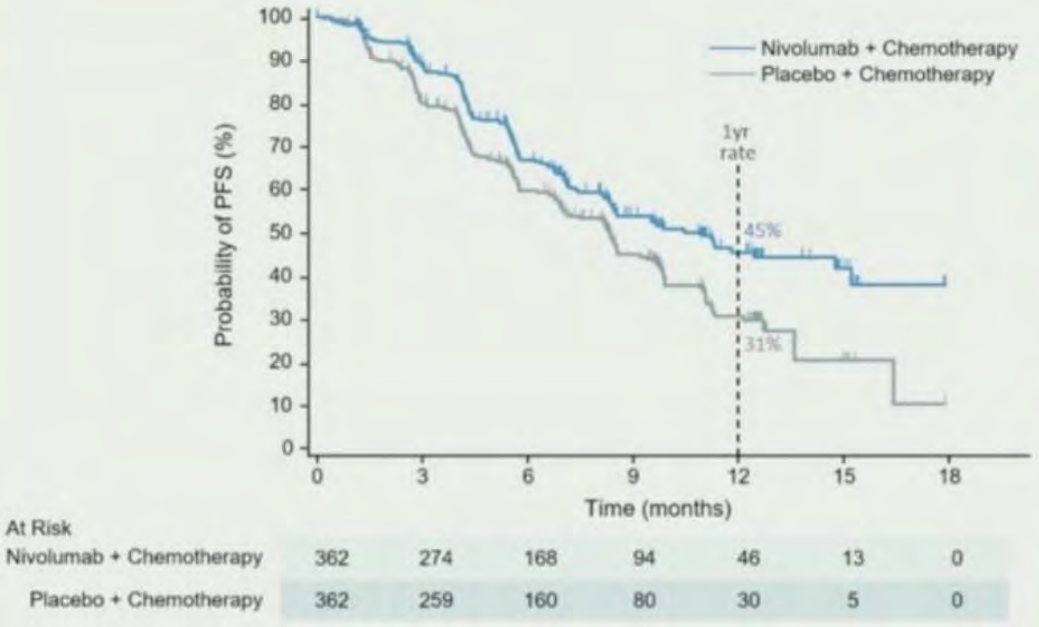
Progression-Free Survival (Interim Analysis)



	Nivolumab + Chemotherapy N = 362	Placebo + Chemotherapy N = 362
Median PFS, months (95% CI)	10.45 (8.44-14.75)	8.34 (6.97-9.40)
Hazard ratio (98.51% CI)	0.68 (0.51-0.90)	
P value	0.0007	
1yr PFS rate (%)	45.4	30.6

Data cut off : 31 Oct 2018 at interim analysis

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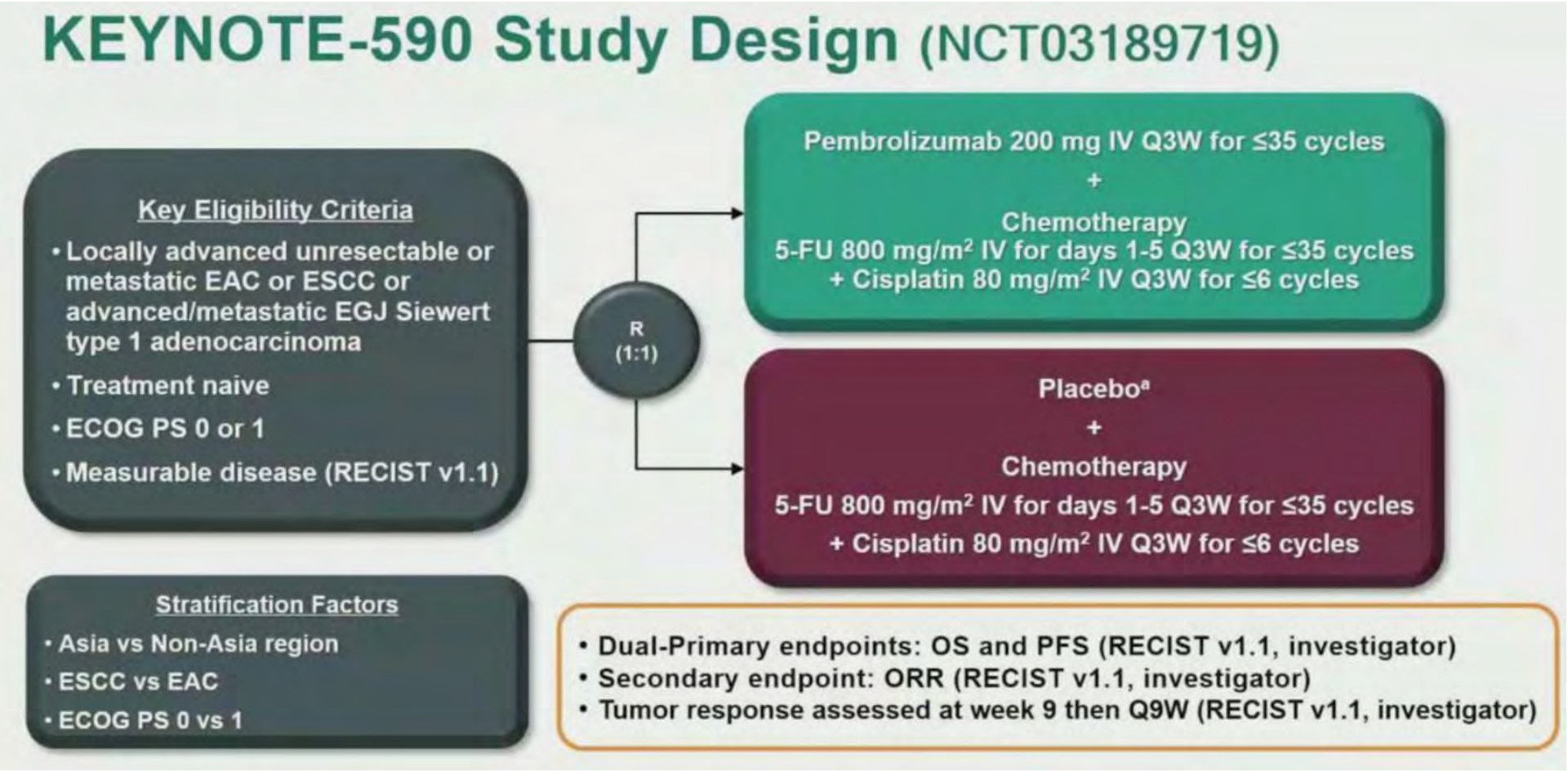
ATTRACTION-4
Baseline characteristics

		Nivolumab + Chemotherapy N = 362	Placebo + Chemotherapy N = 362
Age (years)	Median (range)	63.5 (25-86)	65.0 (27-89)
Sex, n (%)	Male	253 (69.9)	270 (74.6)
	Female	109 (30.1)	92 (25.4)
Country, n (%)	Japan	198 (54.7)	197 (54.4)
	Korea	148 (40.9)	143 (39.5)
	Taiwan	16 (4.4)	22 (6.1)
ECOG PS, n (%)	0	195 (53.9)	194 (53.6)
	1	167 (46.1)	168 (46.4)
Disease status, n (%)	Advanced	280 (77.3)	279 (77.1)
	Recurrent	82 (22.7)	83 (22.9)
Perioperative chemotherapy, n (%)	No	294 (81.2)	303 (83.7)
	Yes	68 (18.8)	59 (16.3)
Number of organs with metastases, n (%)	≤ 1	108 (29.8)	105 (29.0)
	≥ 2	254 (70.2)	257 (71.0)
Histology, n (%)	Intestinal type	139 (38.4)	154 (42.5)
	Diffuse type	192 (53.0)	176 (48.6)
	Others	11 (3.0)	12 (3.3)
	Unknown	20 (5.5)	20 (5.5)
Tumor cell PD-L1 expression, n (%)	< 1%	304 (84.0)	306 (84.5)
	≥ 1%	58 (16.0)	56 (15.5)
Chemotherapy regimen, n (%)	SOX	232 (64.1)	232 (64.1)
	CapeOX	130 (35.9)	130 (35.9)

KN 590



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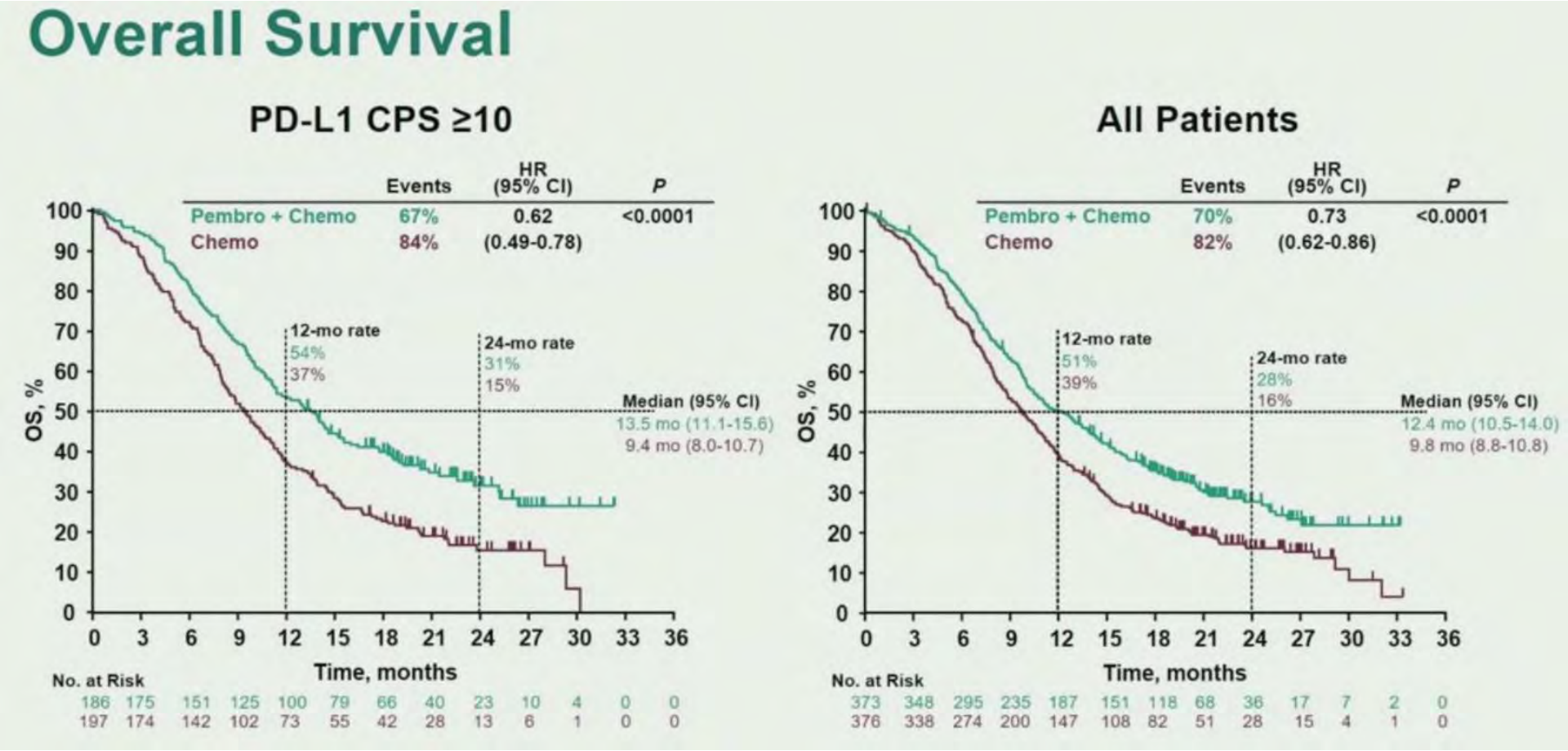
KN 590



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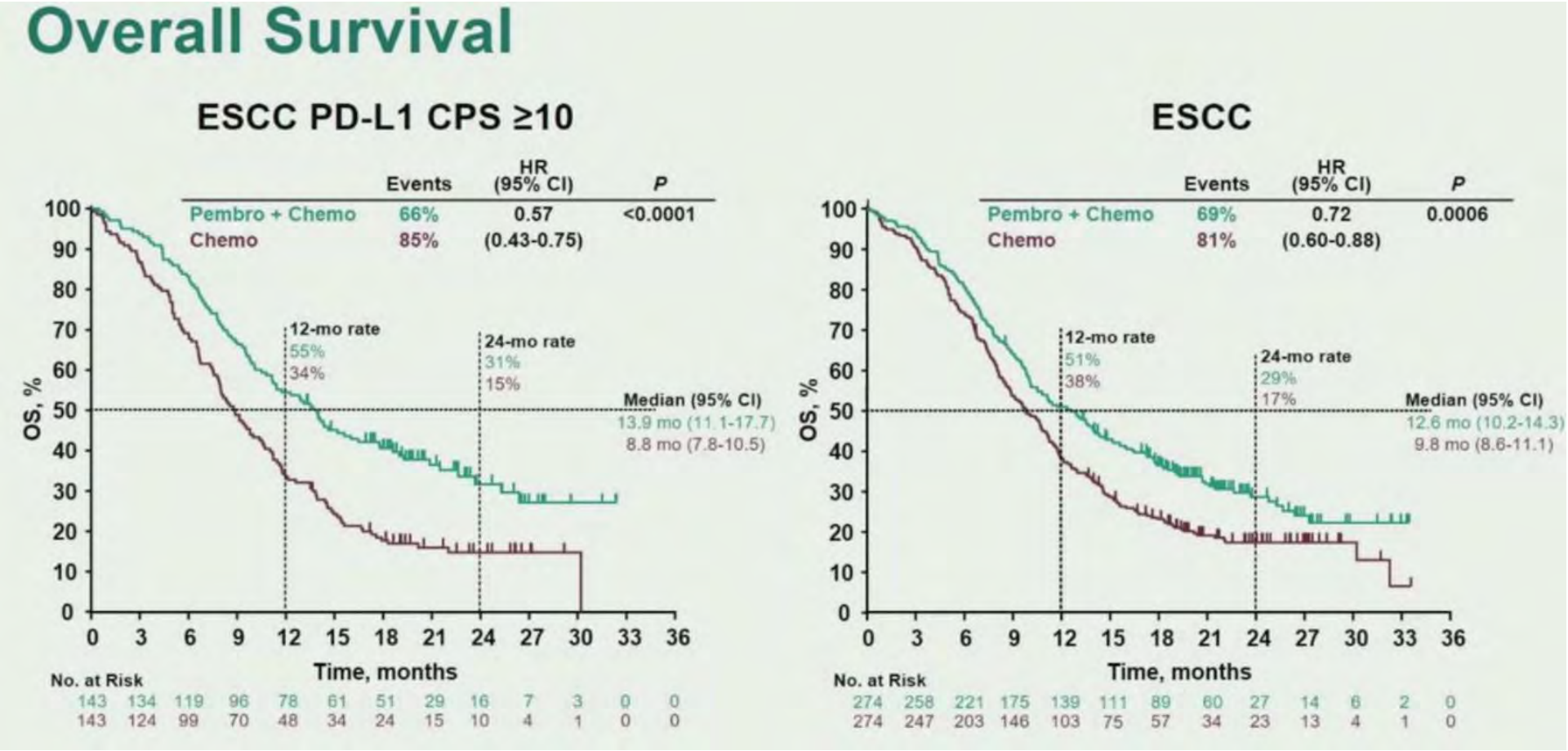

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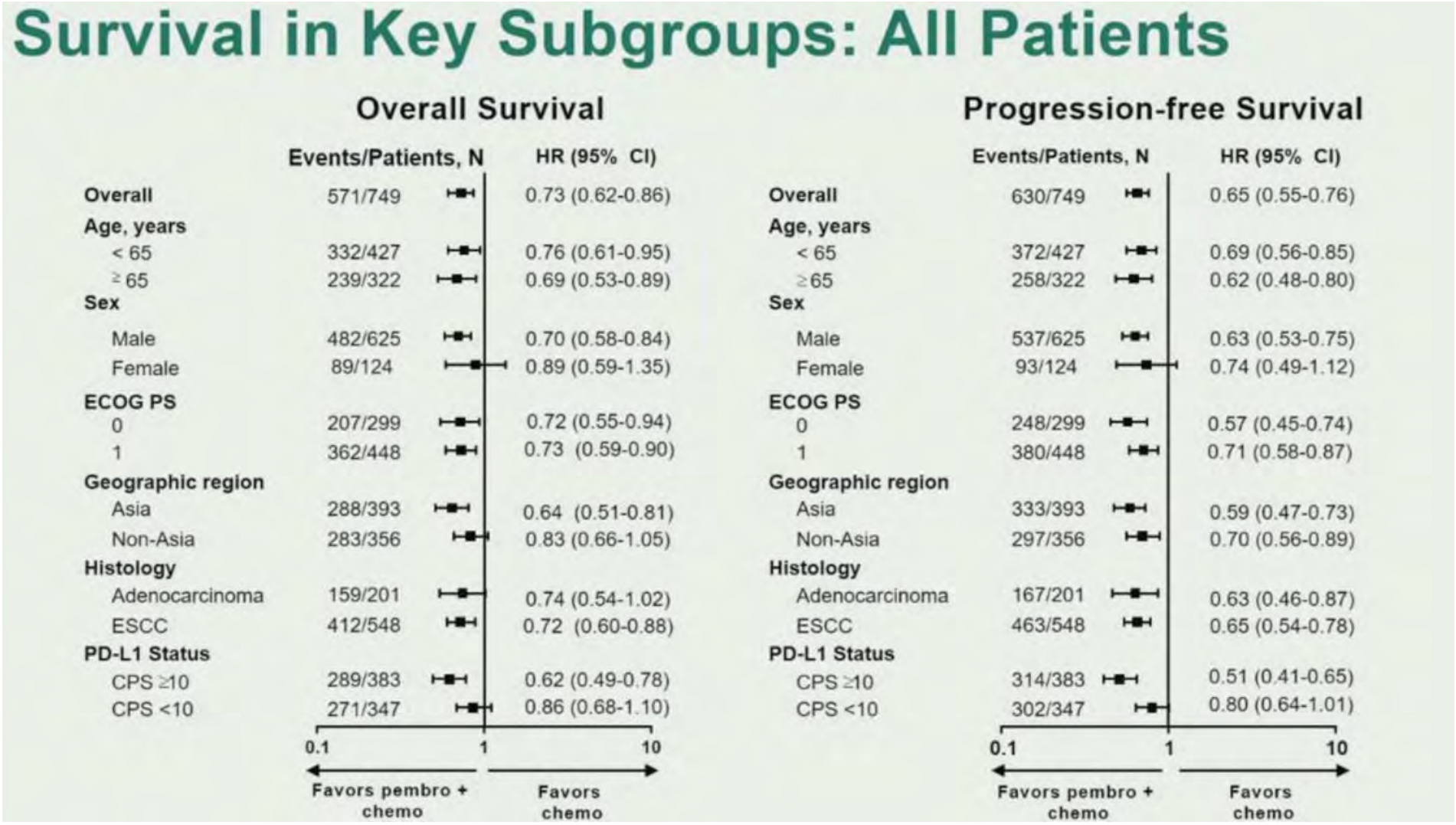
KN 590

Survival in Key Subgroups: All Patients



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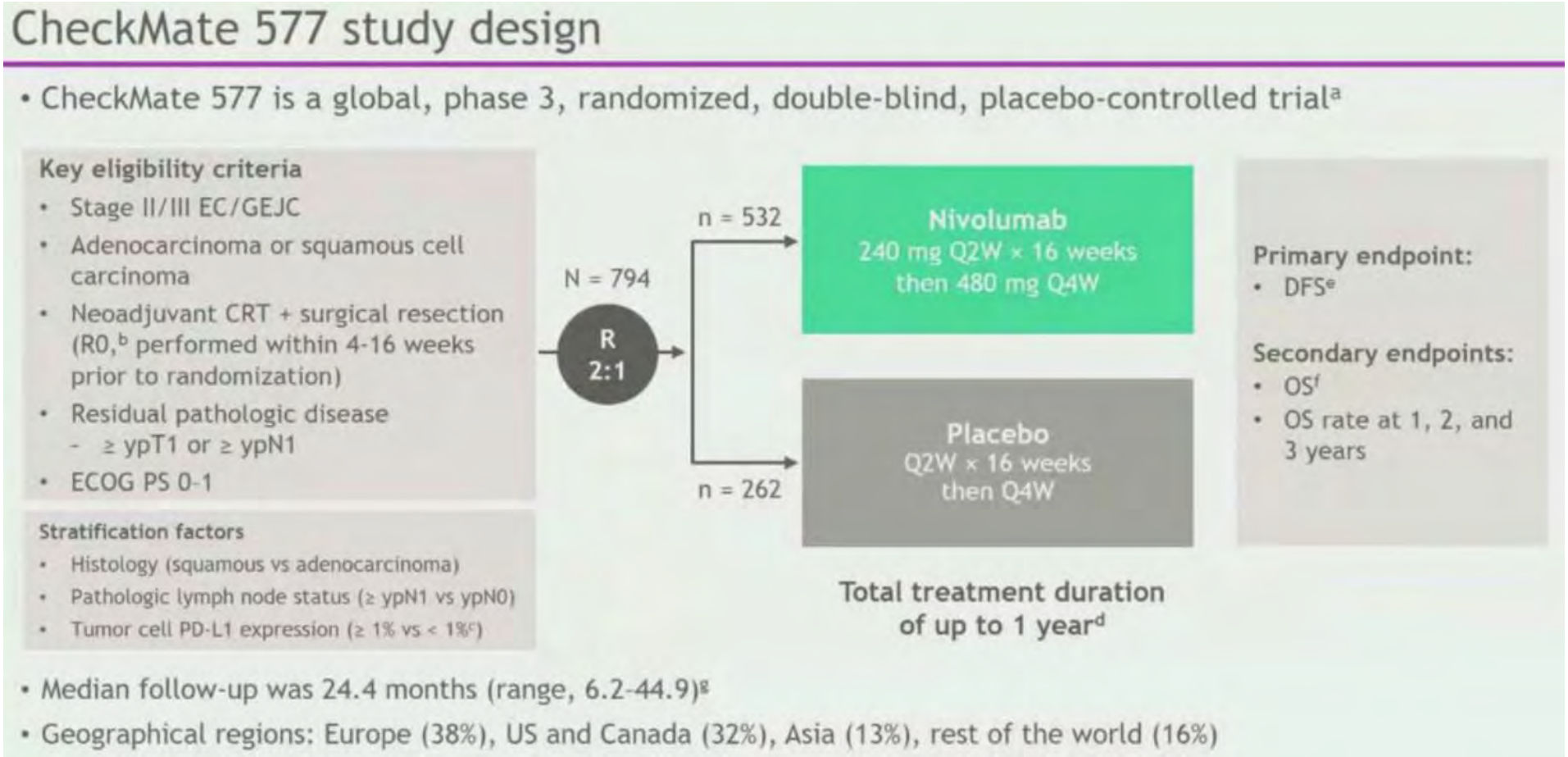
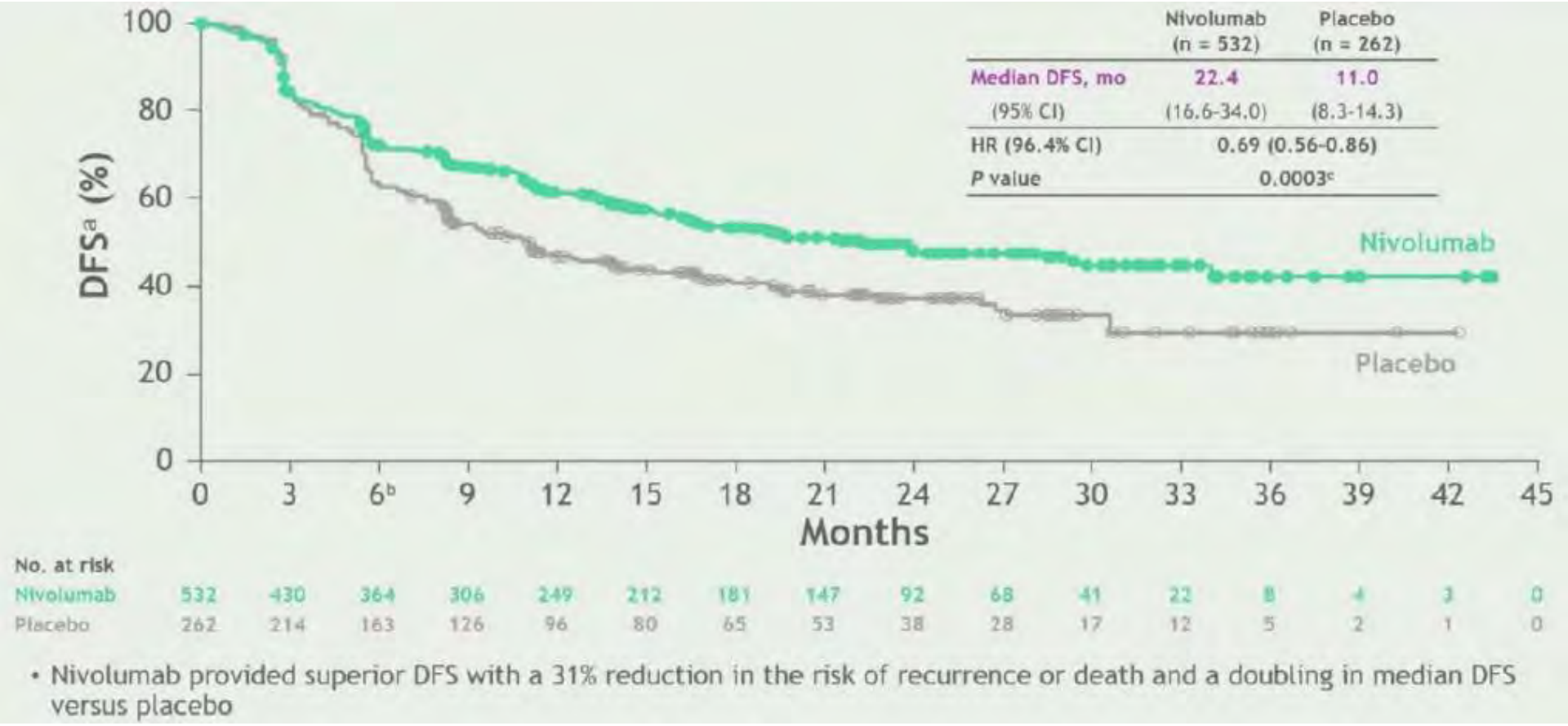
Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer after CROSS chemoradiotherapy *(excl. ypT0N0)*



CheckMate 577 study; Presentation by Ronan Kelly, ESMO Sep 2020

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer after CROSS chemoradiotherapy *(excl. ypT0N0)*



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

CheckMate 577 study; Presentation by Ronan Kelly, ESMO Sep 2020

Konklusjoner:

- Nivolumab og Pembrolizumab kan bli aktuelle i førstelinjes behandling ved mage –og spiserørskreft (avventer MT-søknader/evt godkjenninger)
- Nivolumab kan bli aktuell adjuvant behandling etter neoadjuvant radiokjemoterap for EAC og ESCC *(ikke ypT0N0)*
- Nivo/Pembro aktuelle ved MSI-H CRC på generell unntaksbestemmelse (HF-beslutn), må søkes for non-CRC
- Atezolizumab/Bevacizumab kan bli aktuelle i førstelinjes beh av HCC
- MSI / MMR, CPS, evt TMB, EBV er aktuelle molekylære tumor-analyser.