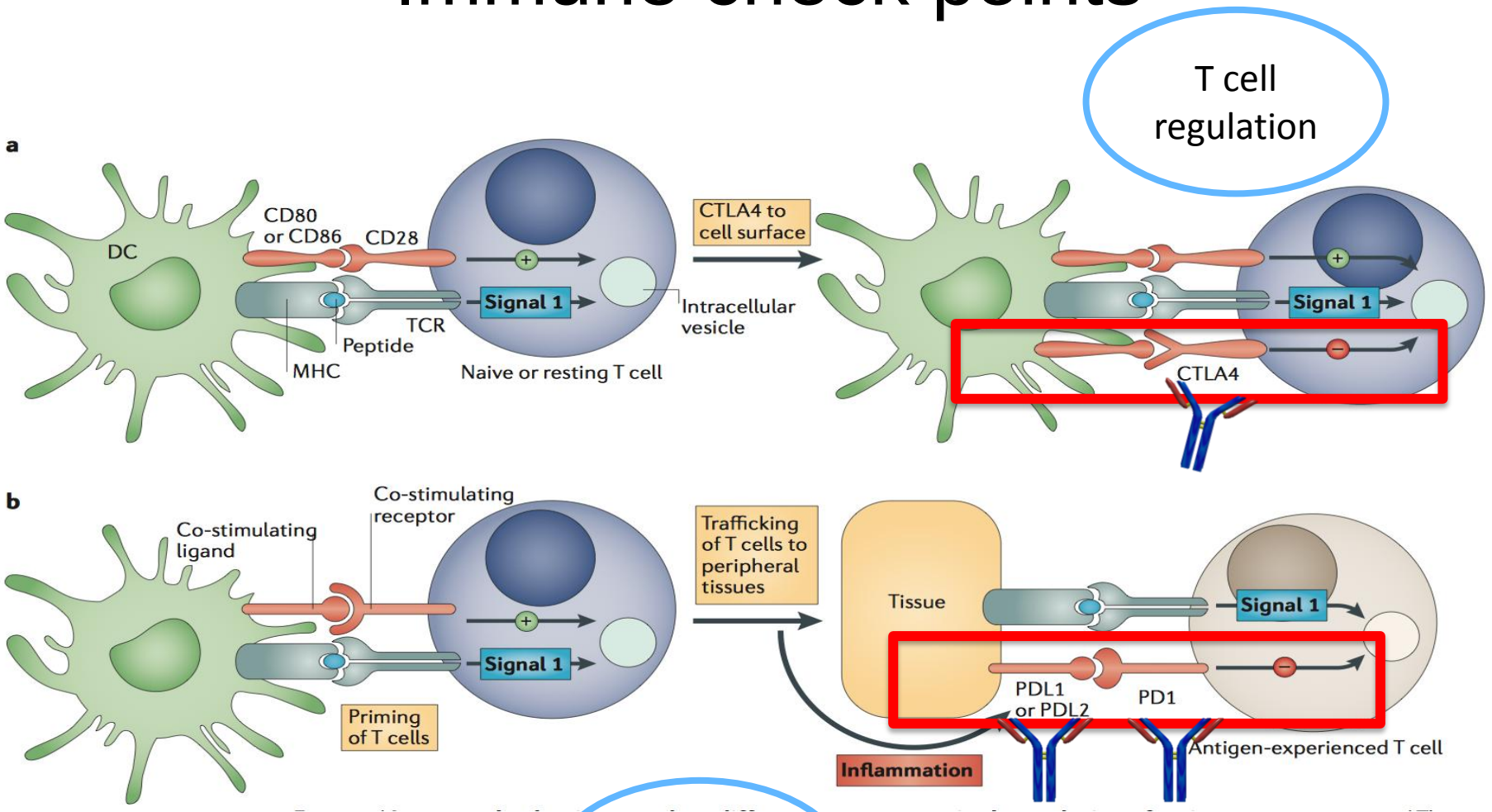
Immunotherapy in GI-Cancer

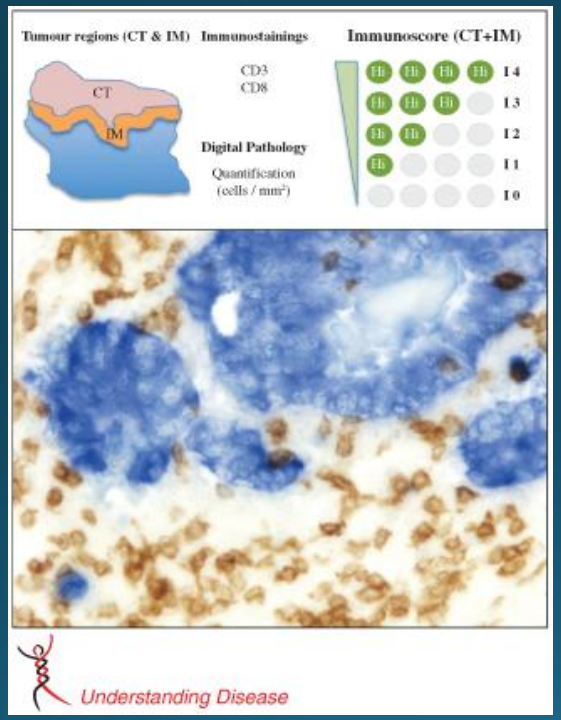
Gerald Prager, M.D.
Professor of Medicine
Comprehensive Cancer Center Vienna
Medical University of Vienna

Immune check points



Pardoll DM et al., *Nat Rev Cancer*, 2012

Immunoscore definition and methodology.

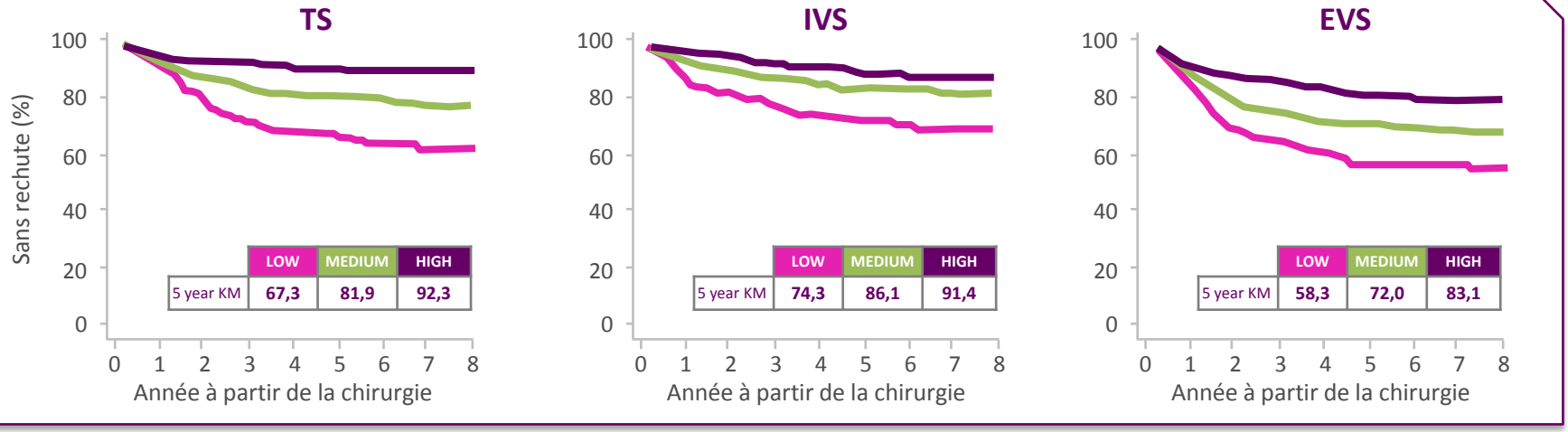


Anitei M et al. Clin Cancer Res 2014;20:1891-1899

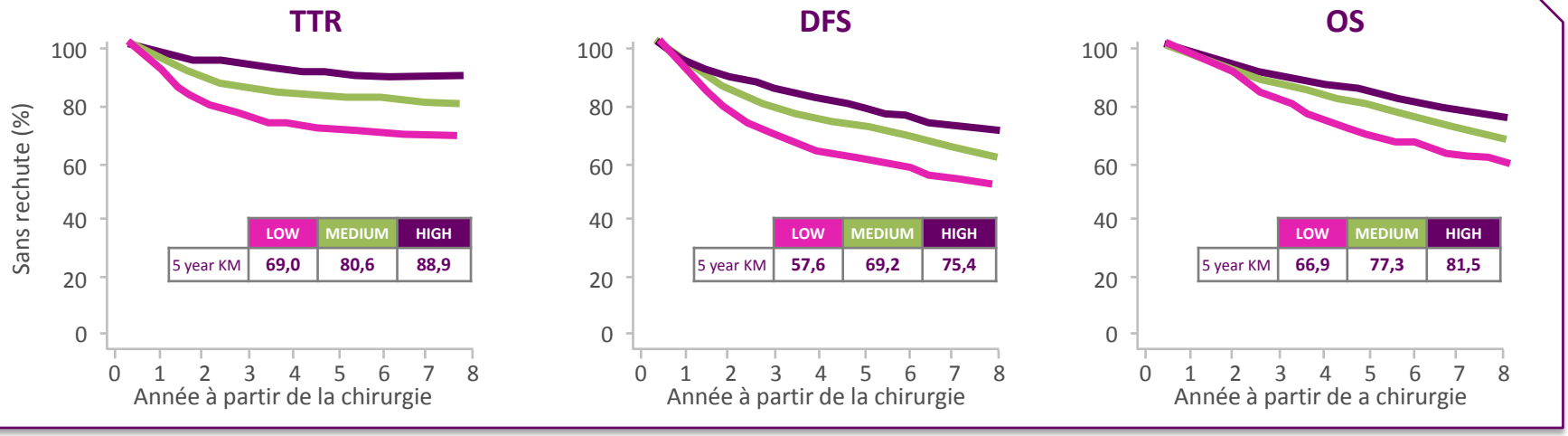
Immunoscore by staining CD_3 and CD8 positive cells in the CT and IM of rectal cancer Immunohistochemistry of a colorectal tumour stained for CD_3 + T cells (brown).

Immunity seems important in CRC immunoscore ASCO 2016

Time to recurrence for immunoscore



Immunoscore (n=2667 patients)



Galon J. *et al.*, ASCO 2016, OS 3500

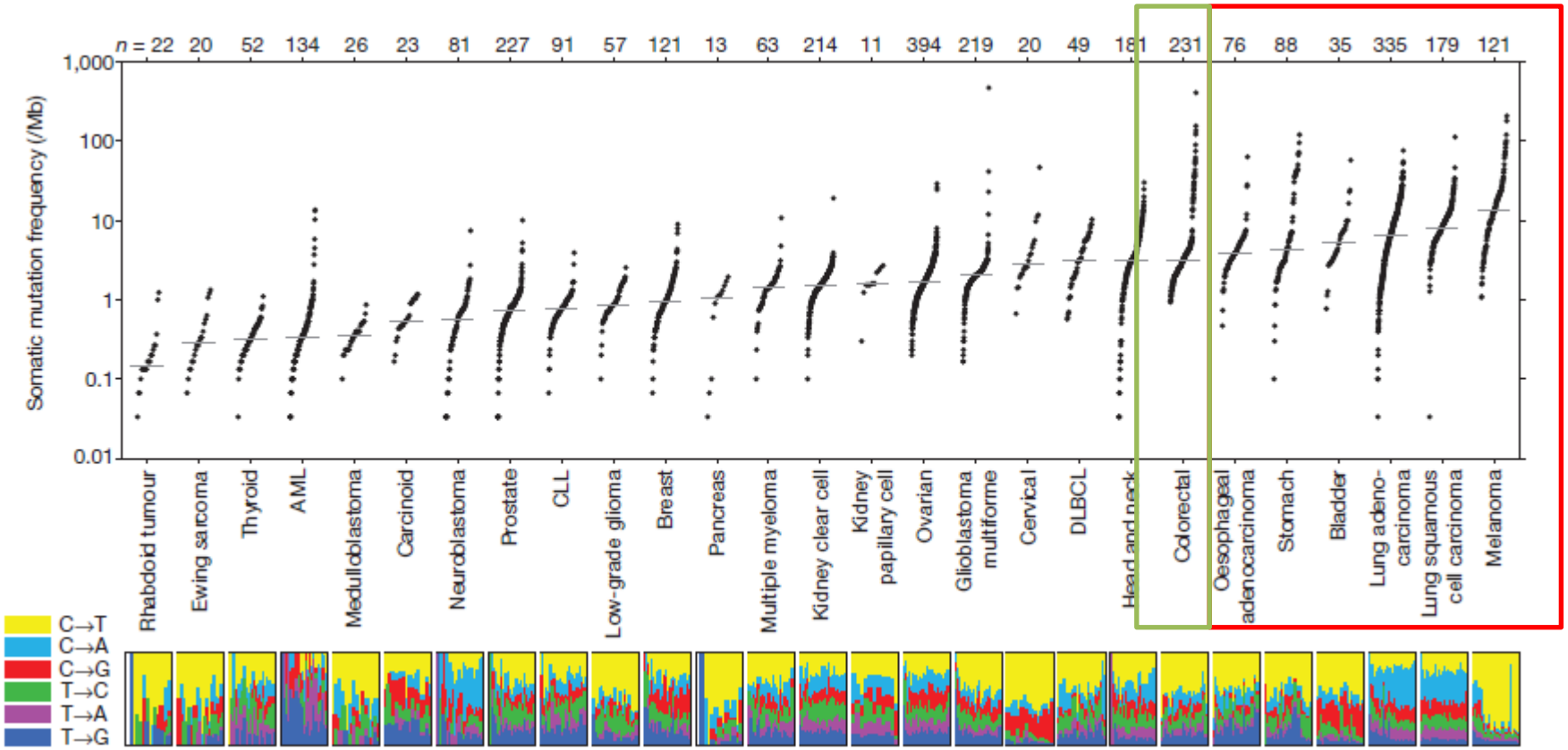
J Taieb WCGIC Barcelona 2016

Mutational load

LETTER

doi:10.1038/nature12213

Mutational heterogeneity in cancer and the search for new cancer-associated genes



Lawrence MS, et al. Nature 2013;499:214–218

Immunotherapy in MSI-high mCRC

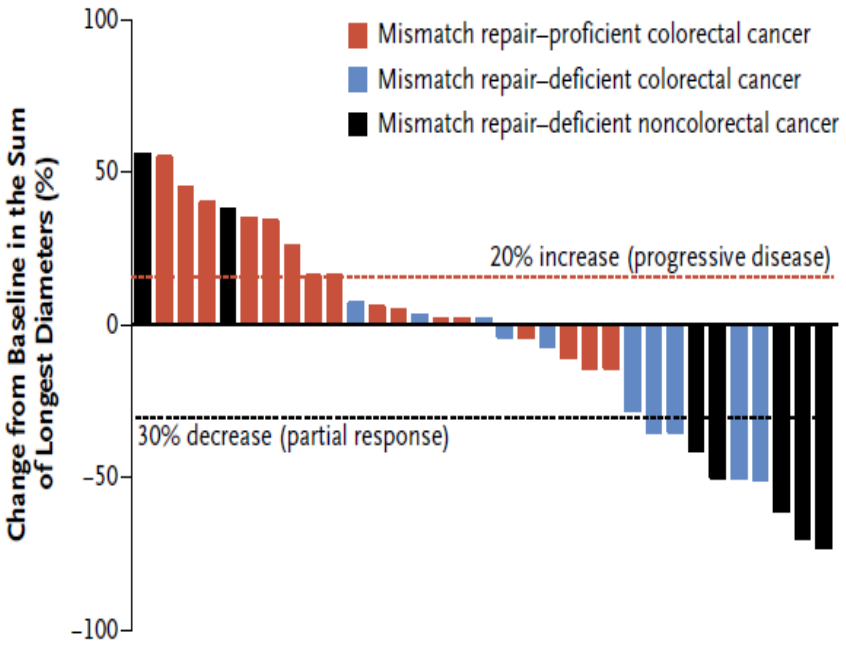
…what do we know, where do we go?

Checkpoint blockers Efficacy signal in MSI-H colorectal cancer

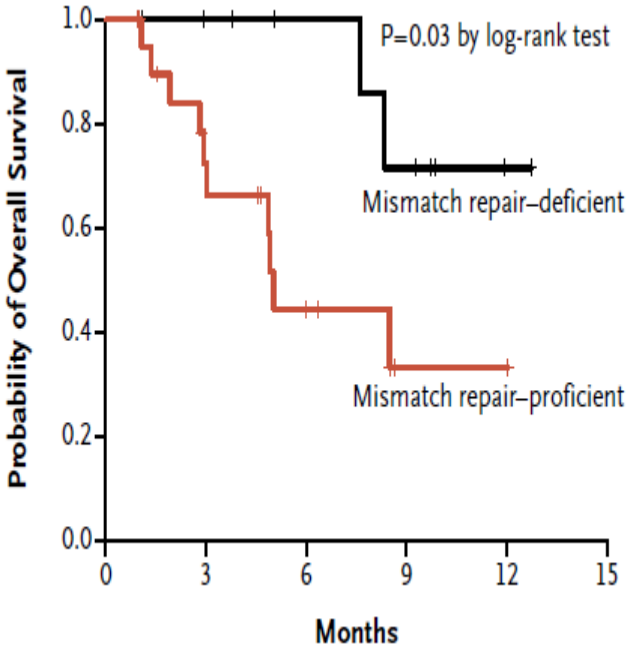
Treatment with pembrolizumab (anti-PD-1 antibody)

(n=11 mismatch repair-deficient CRC, n=21 mismatch-repair proficient CRC, n=9 mismatch-repair deficient non-CRC)

Radiographic responses*



OS in CRC



Immune-related ORR in mismatch-repair deficient vs proficient CRC: 40% vs 0%

Adjusted OS HR for mismatch-repair deficient vs proficient CRC: 0.18, *P* = .05

*RECIST-based radiographic response

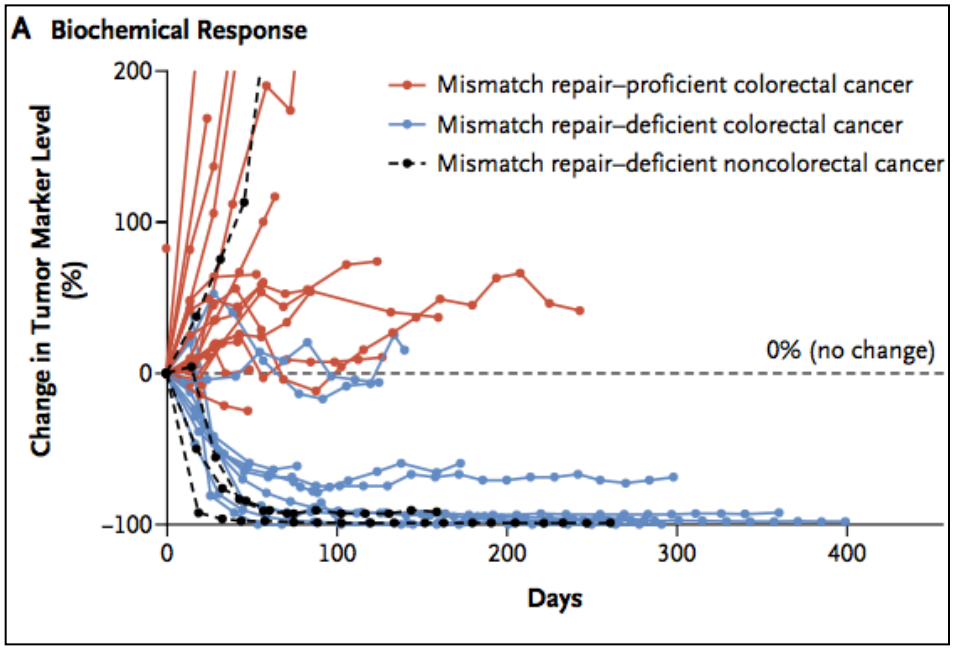
**Adjusted for elapsed time since the initial diagnosis

Le DT, et al. *N Engl J Med.* 2015;372(26):2509-2520

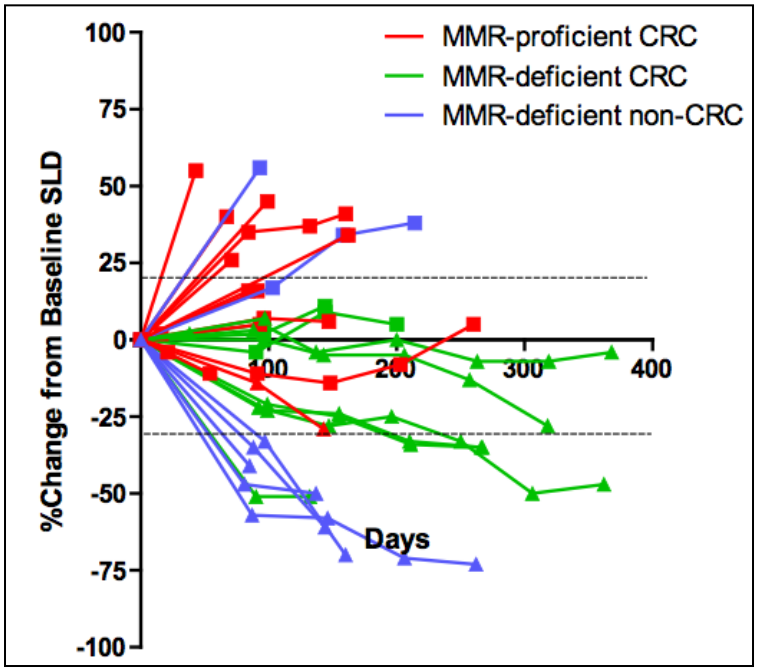
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

The NEW ENGLAND JOURNAL of MEDICINE

CEA response



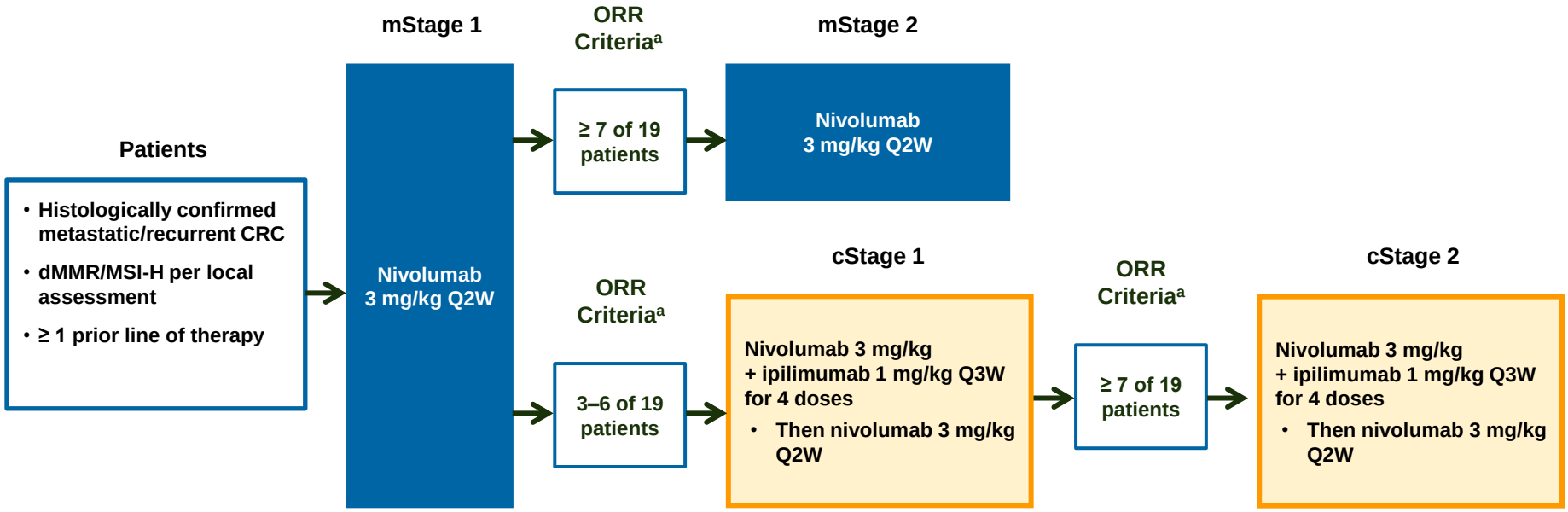
Radiographic Response



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)

Study Design and Endpoints

CheckMate 142: dMMR/MSI-H CRC



- Primary endpoint: objective response rate (ORR) per investigator assessment
- Secondary endpoint: ORR per blinded independent central review (BICR)
- Key exploratory endpoints: safety and tolerability; progression-free survival (PFS); overall survival (OS); biomarkers

cStage, combination therapy stage; mStage, monotherapy stage.
[a]ORR (complete response + partial response) in patients with centrally-confirmed MSI-H status.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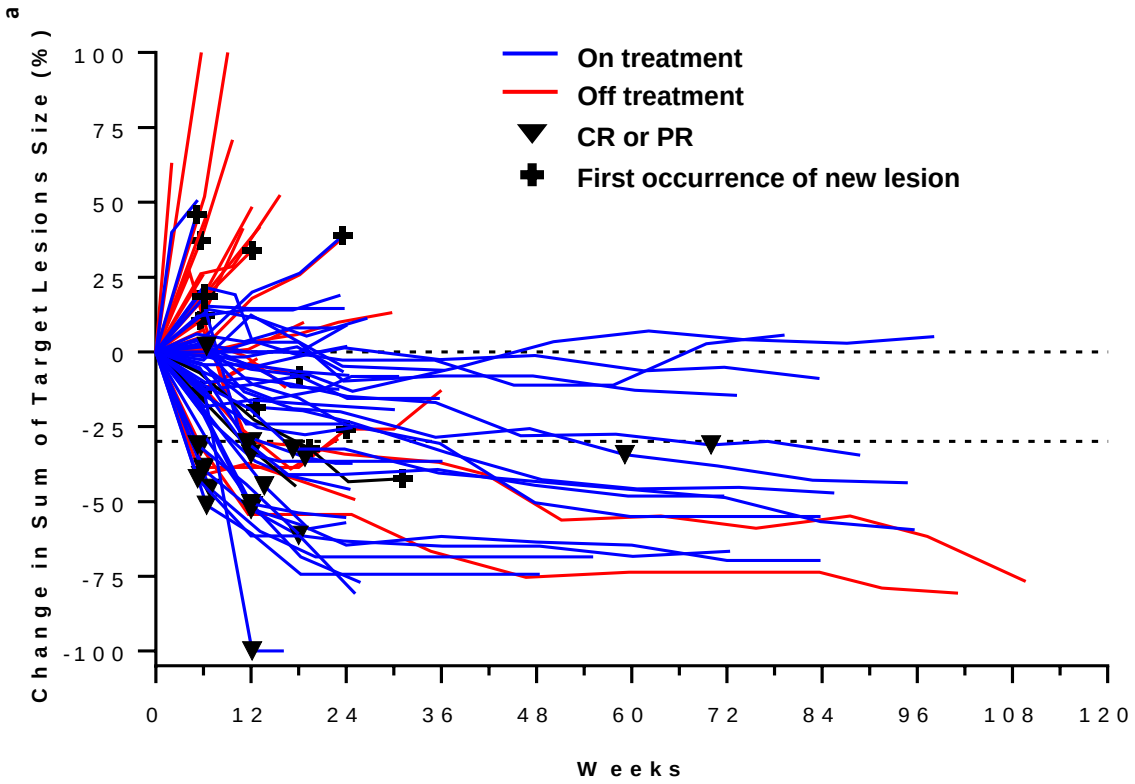
Response and Disease Control

CheckMate 142: dMMR/MSI-H CRC

	dMMR/MSI-H per Local Assessment (N = 74)[a]	
	Investigator	BICR
ORR, n (%) [95% CI]	23 (31.1) [20.8, 42.9]	20 (27.0) [17.4, 38.6]
Best overall response, n (%) Complete response Partial response Stable disease Progressive disease Not determined Not reported	 0 23 (31.1) 29 (39.2) 18 (24.3) 4 (5.4) 0	 2 (2.7) 18 (24.3) 28 (37.8) 20 (27.0) 5 (6.8) 1 (1.4)
Disease control for ≥ 12 weeks, n (%)	51 (68.9)	46 (62.2)
Median TTR (range), months	2.8 (1.2–16.1)	2.7 (1.2–17.7)
Median DOR [95% CI], months	NR [6.8, NE]	NR [NE]

DOR, duration of response; NE, not estimable; NR, not reached; TTR, time to response.
[a]Patients from monotherapy stage 1 and 2 combined.

MSI-high CRC: Nivolumab Monotherapy

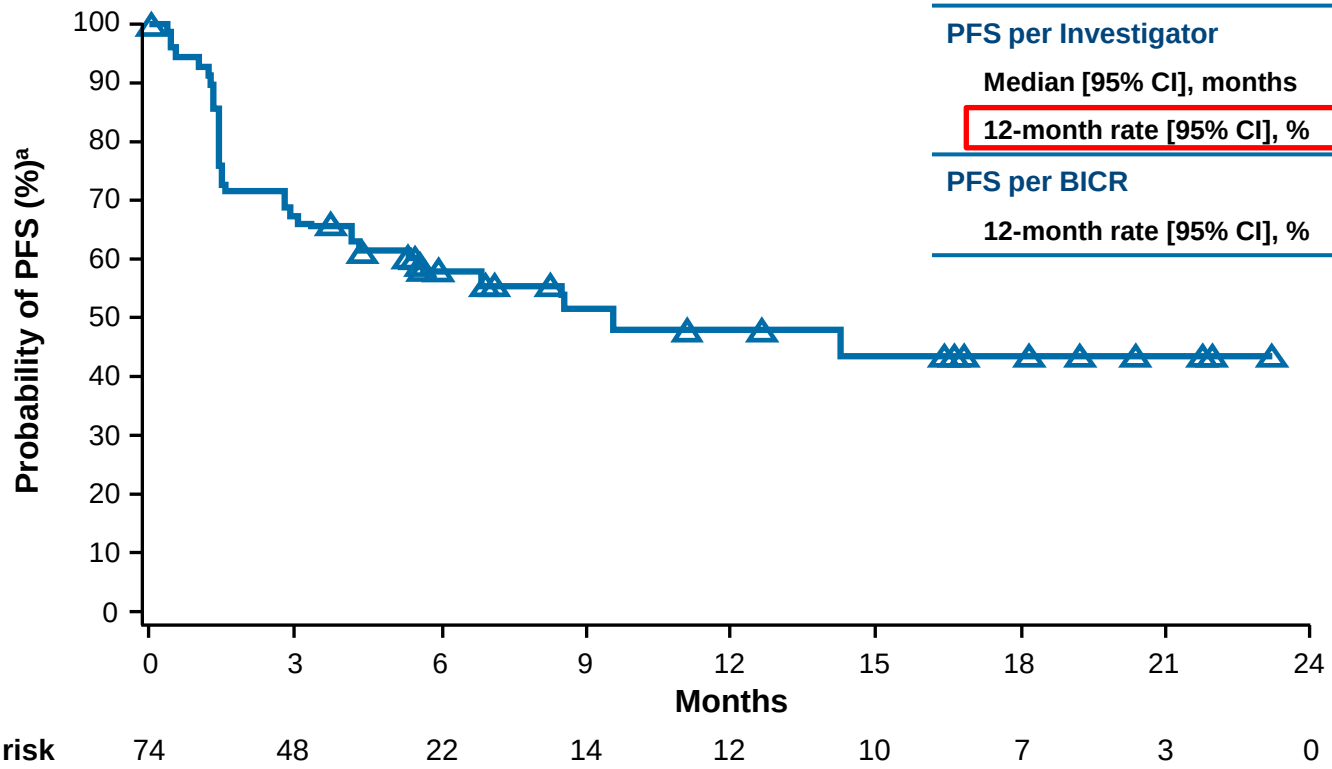


RR 31%
SD 39%
PD 24%

Disease Control ≥12weeks in 69%

Overman et al. Lancet Oncology 2017

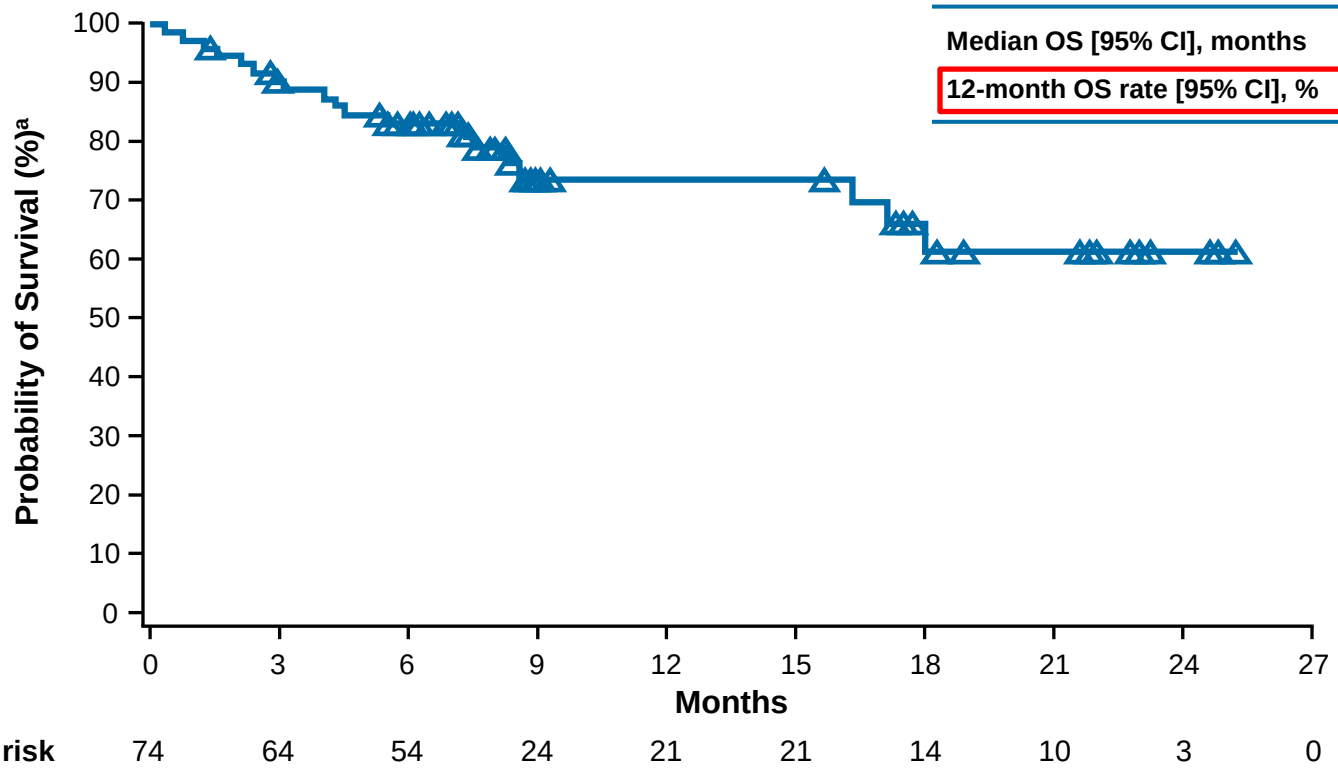
Progression-Free Survival



PFS per Investigator	
Median [95% CI], months	9.6 [4.3, NE]
12-month rate [95% CI], %	48.4 [33.6, 61.7]
PFS per BICR	
12-month rate [95% CI], %	45.6 [32.2, 58.1]

BICR, blinded independent central review; NE, not estimable. [a] Investigator assessed dMMR/MSI-H by local laboratory.

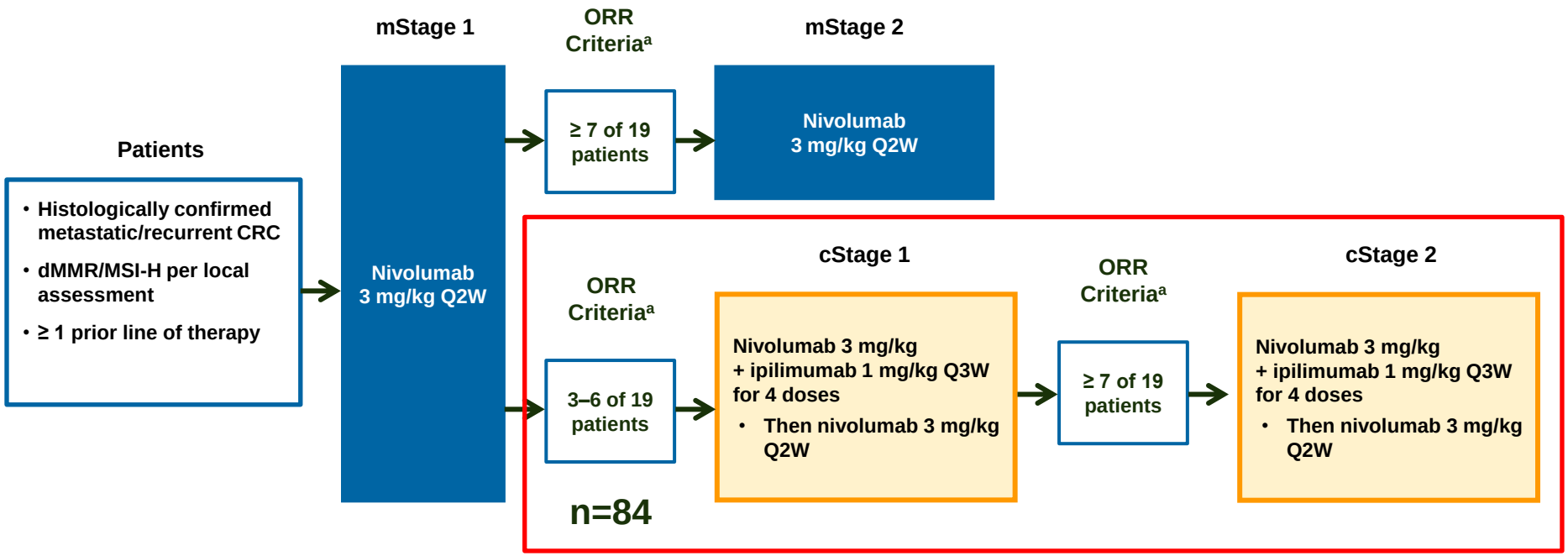
Overall Survival



NR, not reached. [a] dMMR/MSI-H assessed by local laboratory.

Study Design and Endpoints

CheckMate 142: dMMR/MSI-H CRC



- Primary endpoint: objective response rate (ORR) per investigator assessment
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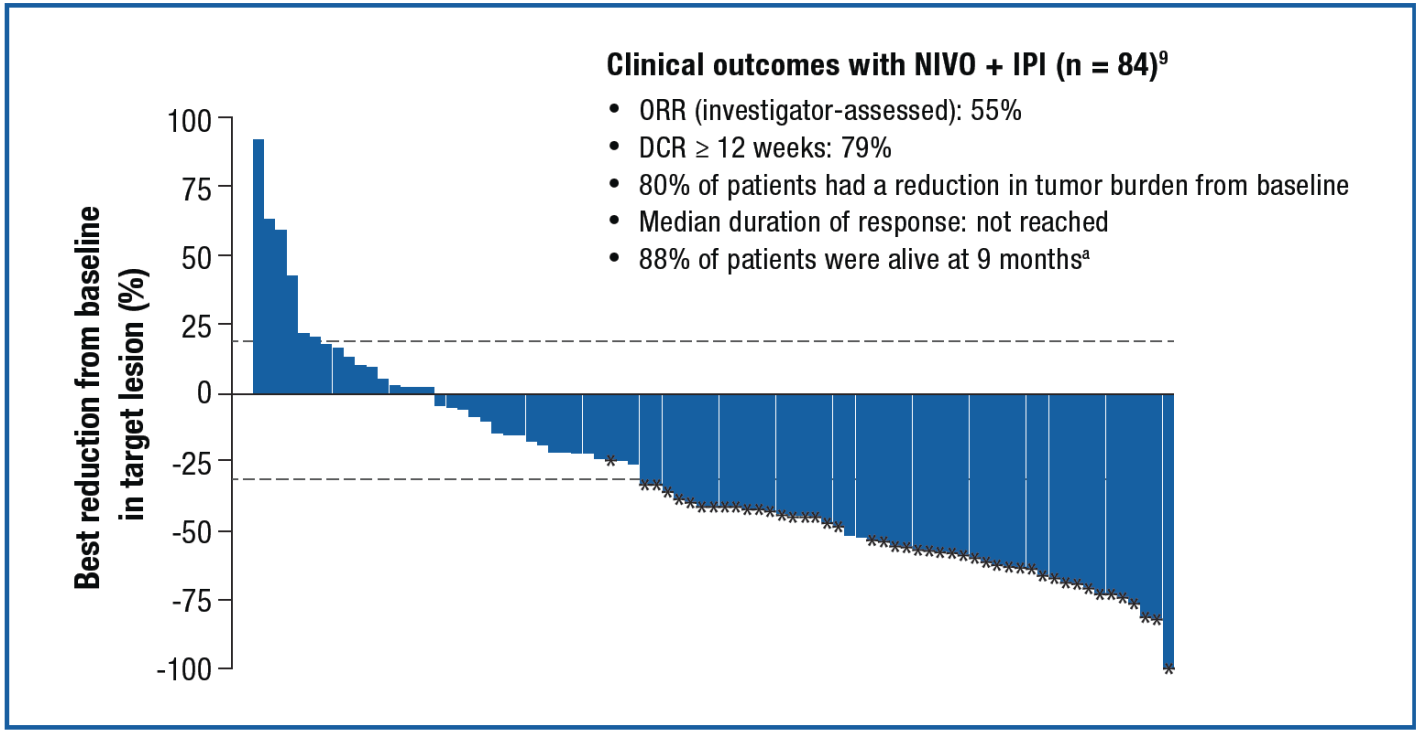
- Key exploratory endpoints: safety and tolerability; progression-free survival (PFS); overall survival (OS); biomarkers

cStage, combination therapy stage; mStage, monotherapy stage.
[a]ORR (complete response + partial response) in patients with centrally-confirmed MSI-H status.

ESMO 2017: Change in Tumor Burden by Investigator

CheckMate 142: dMMR/MSI-H CRC

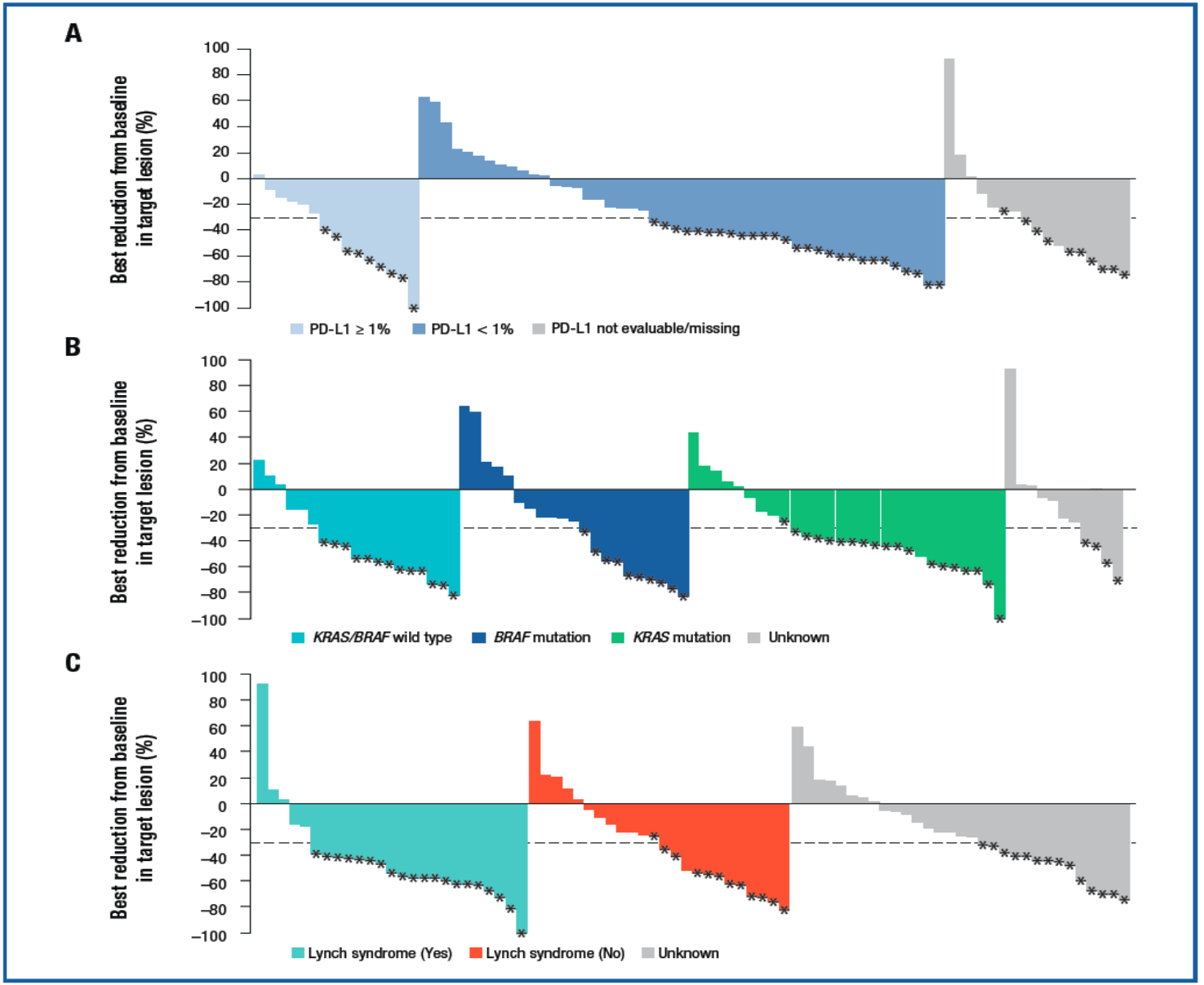


*Confirmed CR or PR per investigator

[a]Kaplan-Meier estimated

ESMO 2017: Change in Tumor Burden by Molecular Profile

CheckMate 142: dMMR/MSI-H CRC



Checkmate 142- Conclusion Biomarker

Clinical responses were observed with NIVO + IPI across all biomarker groups assessed

--Responses were observed regardless of PD-L1 tumor expression, *BRAF* or *KRAS* mutations, or a clinical history of Lynch syndrome

--Among patients with *BRAF*-mutant tumors, NIVO + IPI led to an **ORR of 48% and a DCR of 76%**

--Among patients with a clinical history of Lynch syndrome, the **ORR was 74% and the DCR was 81%**

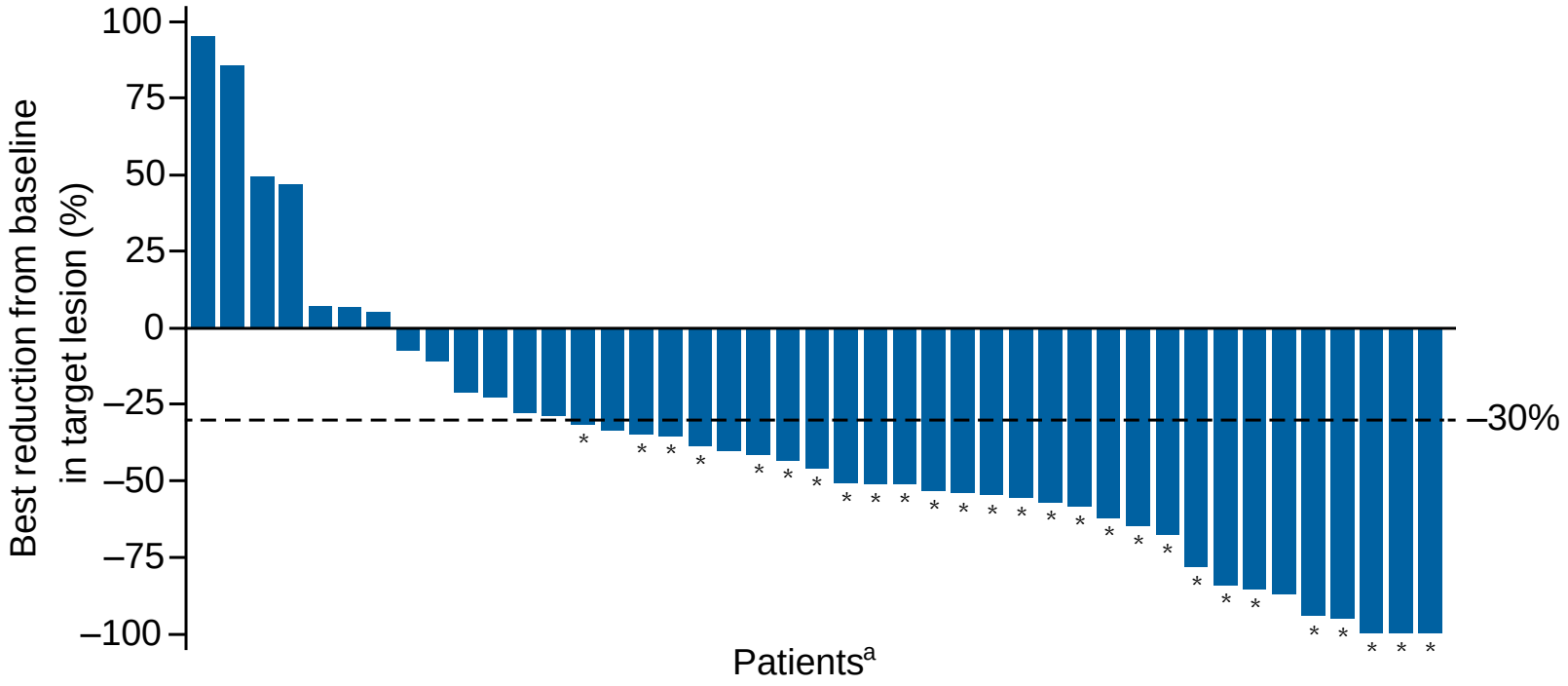
MUNICH 2018 ESMO congress

Durable Clinical Benefit With Nivolumab Plus Low-Dose Ipilimumab as First-Line Therapy in Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer

Heinz-Josef Lenz,[1] Eric Van Cutsem,[2] Maria Luisa Limon,[3] Ka Yeung Mark Wong,[4] Alain Hendlisz,[5] Massimo Aglietta,[6] Pilar García-Alfonso,[7] Bart Neyns,[8] Gabriele Luppi,[9] Dana B. Cardin,[10] Tomislav Dragovich,[11] Usman Shah,[12] Ajlan Atasoy,[13] Roelien Postema,[13] Zachary Boyd,[13] Jean-Marie Ledeine,[13] Michael James Overman,[14] Sara Lonardi[15]

[1]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [2]University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium; [3]Hospital Universitario Virgen del Rocio, Sevilla, Spain; [4]Westmead Hospital, Sydney, Australia; [5]Institut Jules Bordet, Brussels, Belgium; [6]Candiolo Cancer Institute and University of Torino Medical School, Candiolo, Italy; [7]Hospital Gral Universitario Gregorio Marañon, Madrid, Spain; [8]University Hospital Brussels, Brussels, Belgium; [9]University Hospital of Modena, Modena, Italy; [10]Vanderbilt – Ingram Cancer Center, Nashville, TN, USA; [11]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [12]Lehigh Valley Hospital, Allentown, PA, USA; [13]Bristol-Myers Squibb, Princeton, NJ, USA; [14]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [15]Istituto Oncologico Vento IOV-IRCSS, Padova, Italy

Best Reduction in Target Lesions

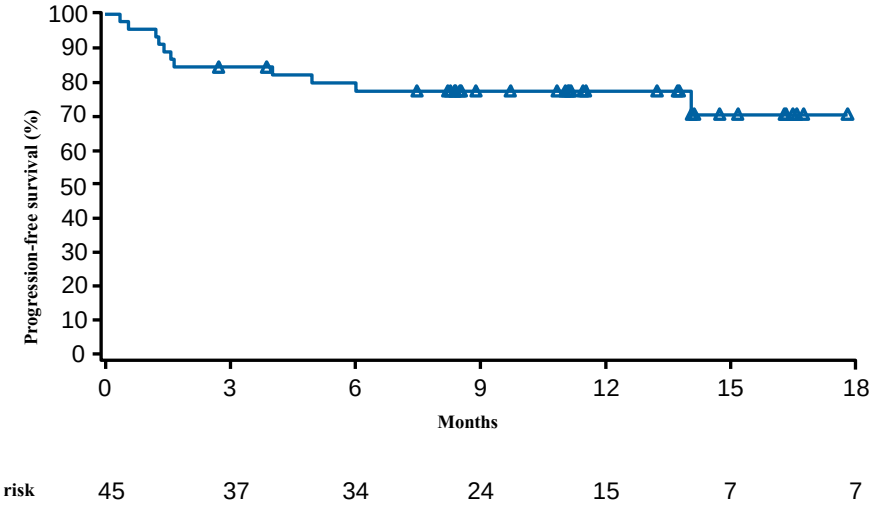


- 84% of patients had a reduction in tumor burden from baseline

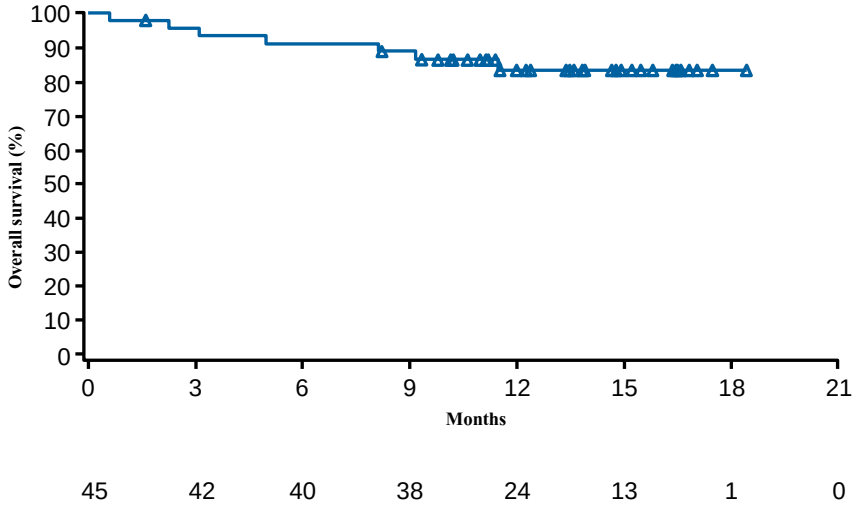
*Confirmed response per investigator assessment
[a]Evaluable patients per investigator assessment

Progression-Free and Overall Survival

PFS[a]	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median PFS, months (95% CI)	NR (14.1–NE)
9-mo rate (95% CI), %	77 (62.0–87.2)
12-mo rate (95% CI), %	77 (62.0–87.2)



OS[a]	NIVO3 (Q2W) + IPI1 (Q6W) N = 45
Median OS, months (95% CI)	NR (NE)
9-mo rate (95% CI), %	89 (74.9–95.1)
12-mo rate (95% CI), %	83 (67.6–91.7)



[a]Per investigator assessment.
mo = month; NE = not estimable; NR = not reached

Neoadjuvant Ipilimumab plus Nivolumab in Early Stage Colon Cancer

- first results of the NICHE study

Myriam Chalabi, Lorenzo Fanchi, Jose van den Berg, Geerard Beets, Arend Aalbers, Petur Snaebjornsson, Cecile Grootscholten, Marjolijn Mertz, Marta Lopez, Elvira Nuijten, Maria Kuiper, Marleen Kok, Monique van Leerdam, Ton Schumacher, Emile Voest, John Haanen

Netherlands Cancer Institute - Amsterdam

NETHERLANDS CANCER INSTITUTE
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efficacy - major response in 100% of dMMR tumors

dMMR (n=7)		
Pre-treatment clinical stage	**Pathological stage at resection**	**Residual vital tumor**
cT2N2a	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT3N0	ypT0N0	0 %
cT3N2a	ypT1N0	1 %
cT4aN2a	ypT2N0	2 %
cT4aN1a	ypT3N1	2 %

pMMR (n=8)		
Pre-treatment clinical stage	**Pathological stage at resection**	**Residual vital tumor**
cT3N1a	ypT3N2	85 %
cT3N0	ypT3N0	90 %
cT2N0	ypT3N1	90 %
cT2N0	ypT3N0	90 %
cT3N1b	ypT3N1	90 %
cT3N1b	ypT3N2	95 %
cT3N0	ypT3N0	100%
cT2N0	ypT2N0	100 %

*Major pathological response = <10% residual vital tumor
Residual vital tumor %: average of scores by two independent pathologists

Optimal treatment of mCRC in the presence of MSS


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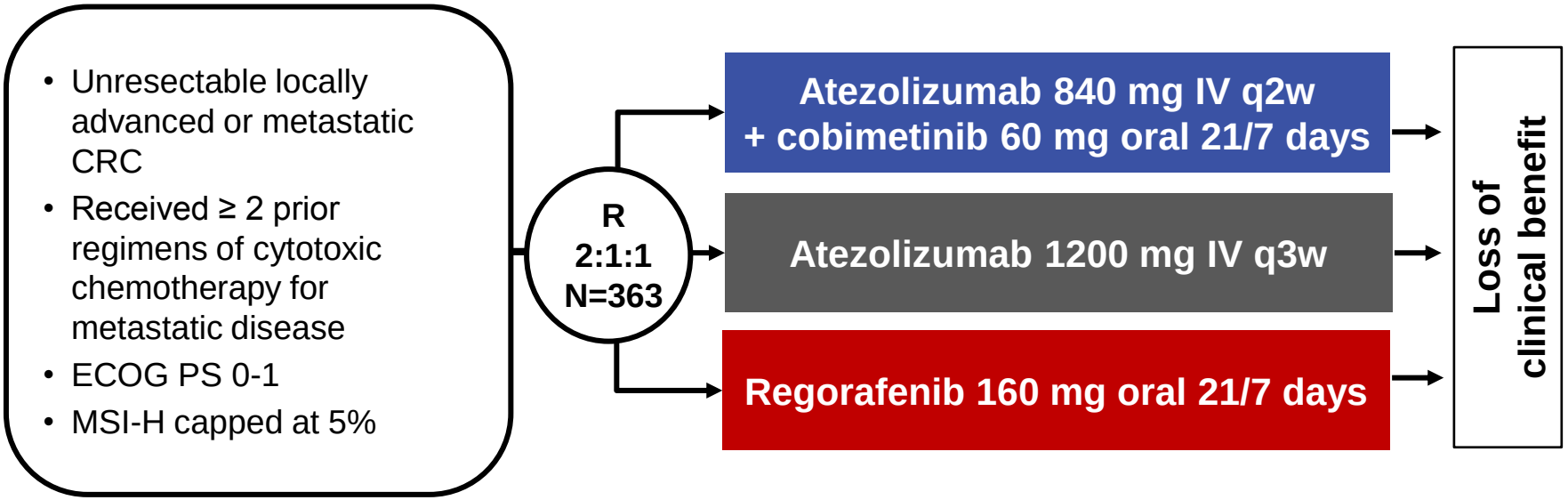
IMblaze370: randomised, Phase III, multicentre, open-label study in mCRC



Stratification

- Extended *RAS* mutation status (≥ 50% patients in each arm)
- Time since diagnosis of first metastasis (< 18 months vs ≥ 18 months)

Primary endpoint

- OS[a]
  - Atezo + cobi vs rego
  - Atezo vs rego

INV-assessed key secondary endpoints

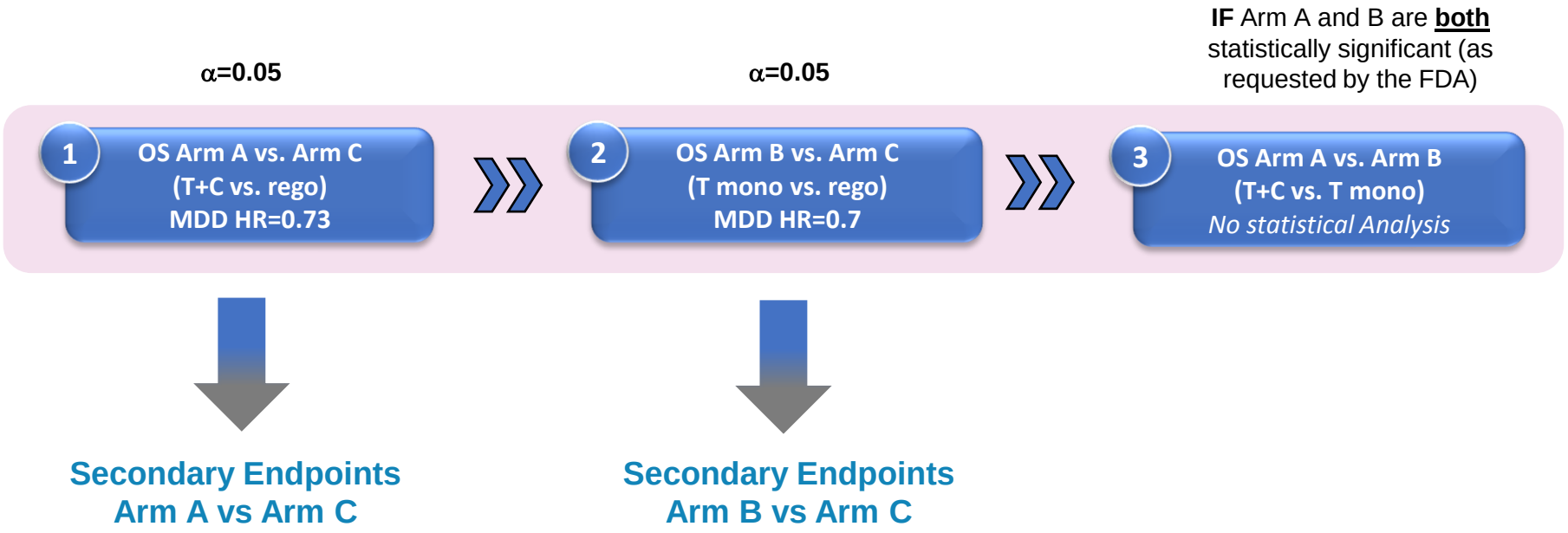
- PFS
- ORR
- DOR

- Data cutoff date: March 9, 2018

Atezo, atezolizumab; cobi, cobimetinib; INV, investigator; rego, regorafenib.

[a] Two-sided type I error rate of 0.05 was controlled by hierarchical testing (testing atezo vs rego only if atezo + cobi vs rego was positive). NCT02788279.

Statistical testing plan for the primary endpoints of IMblaze370



*At time of PFS readout there will be an early interim analysis of OS with negligible alpha attributed to this analysis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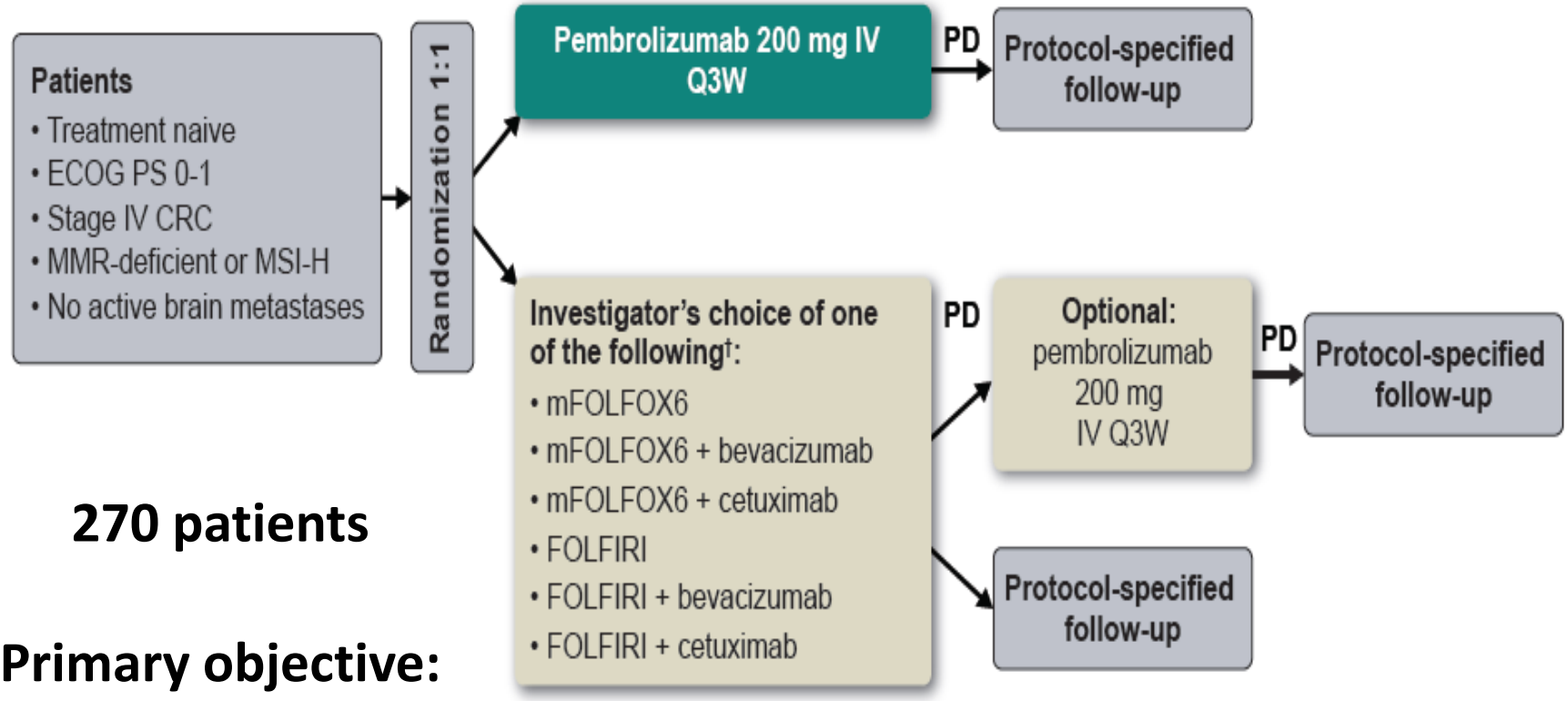
ONGOING TRIALS

Keynote 177
first line mCRC MSI-H

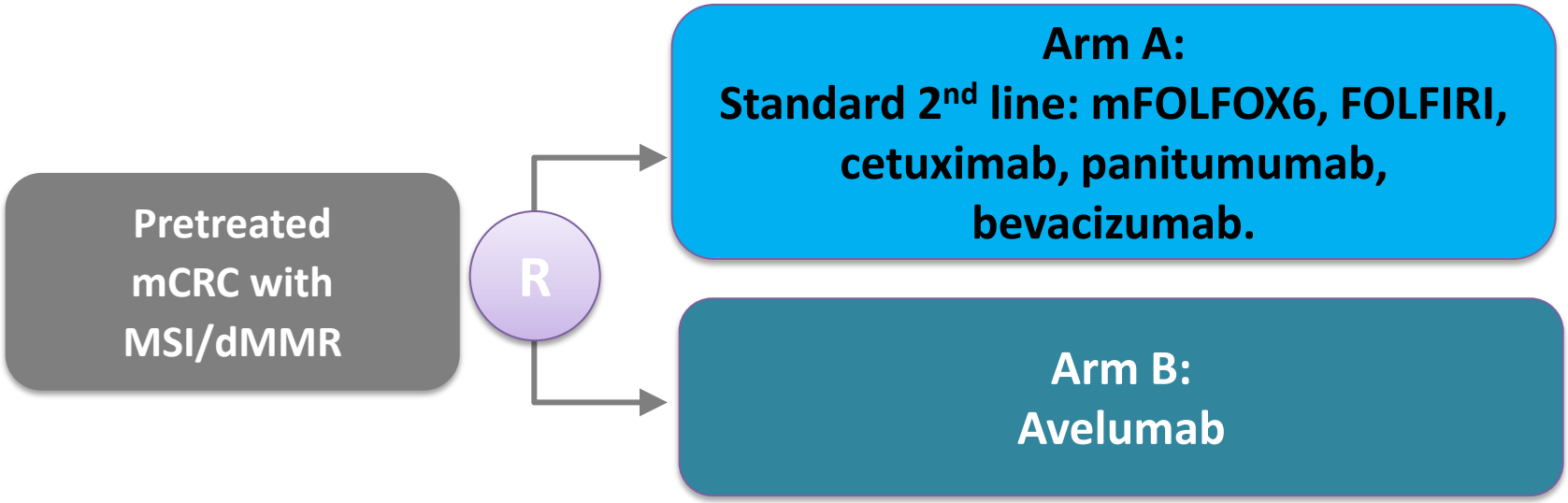


270 patients

Primary objective: PFS

J Taieb WCGIC Barcelona 2016

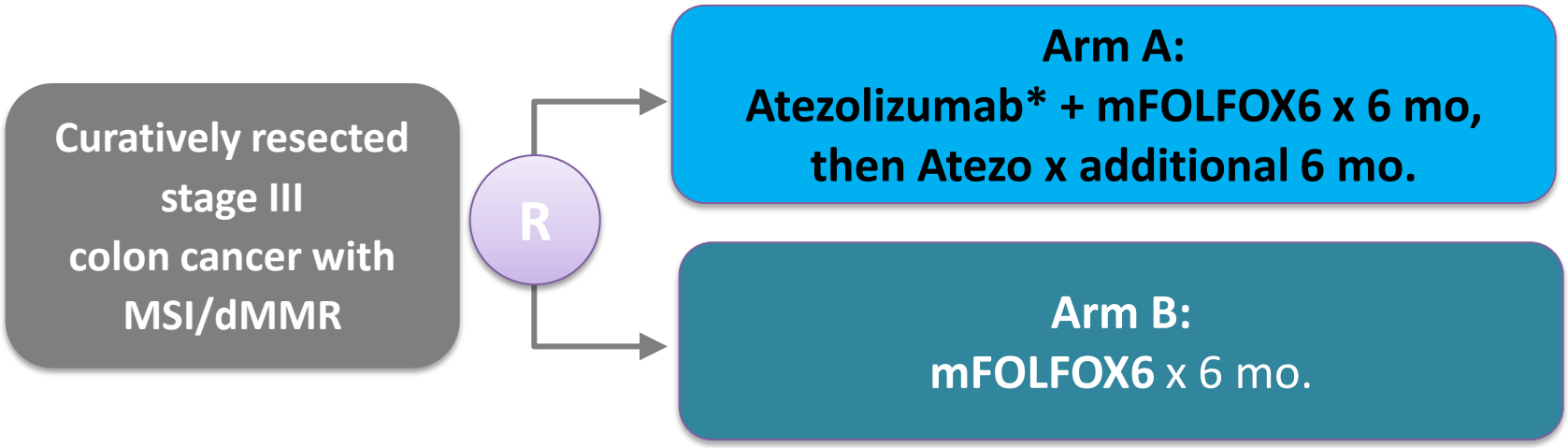
PRODIGE SAMCO TRIAL
2nd line mCRC MSI-H



- Avelumab (anti-PD-L1 Ab); dose of 10 mg/kg IV q2 wk.
- Accrual goal: N= 116; HR 0.59
- **Primary endpoint: PFS (+5 months)**

PI: J Taieb, HEGP, Paris

Alliance Trial of Atezolizumab as Adjuvant Therapy in Stage III MSI Colon Cancer



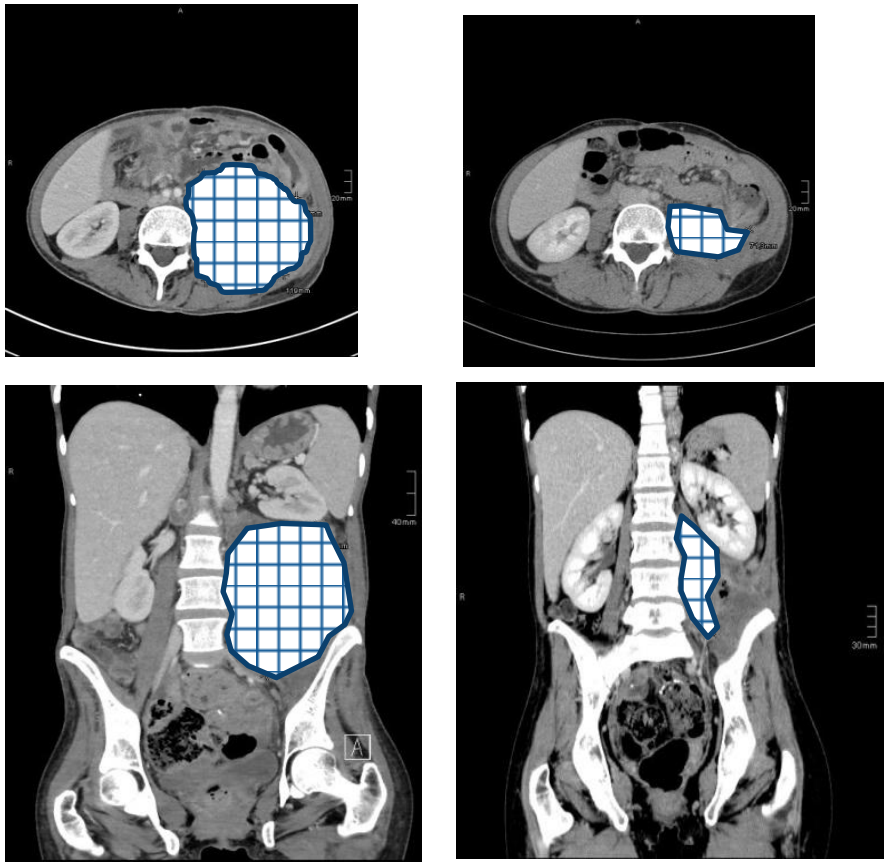
- Atezo (anti-PD-L1 Ab); dose of 800 mg IV q2 wk.
- Stratification factors: N1 vs N2, primary site and age.
- Accrual goal: N= 900; HR 0.65
- **Primary endpoint: DFS**

PI: Frank Sinicrope, Mayo Clinic

Many other trials ongoing or planned

- Phase II:
  - Atezolizumab (anti-PD-L1 Ab)+ FOLFOX+ bev (reported)
  - Durvalumab (all commers?)
  - Pembrolizumab in MSS with high immunoscore
- Phase I/II:
  - Chemotherapy plus anti-PD1
  - Ipilumumab basket study with specific mCRC cohorts
  - Tremelimumab
- Randomized phase II and III
- ….

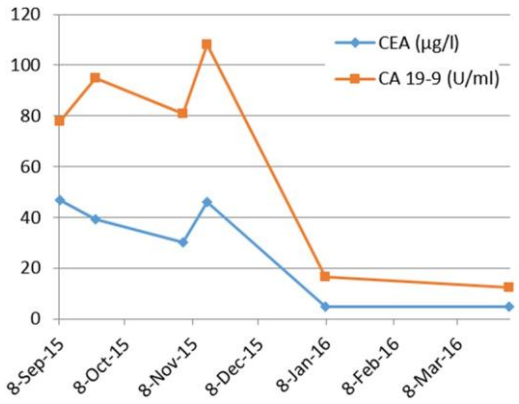
Impressive response upon anti-PD1 treatment in MMR-deficient mCRC patients



baseline

after 3 month

Impressive response: on the left showing the bulky metastasis before treatment and on the right after three months treatment with pembrolizumab



Kieler-M et al. ESMO Open. 2016 Dec 15;1(6):e000084. doi: 10.1136/esmoopen-2016-000084.

Conclusion

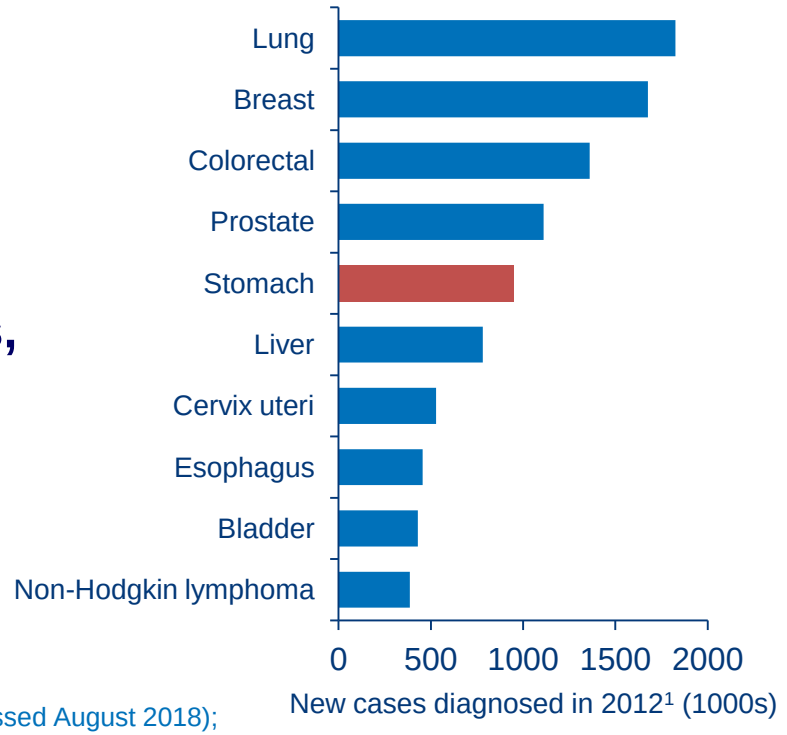
- Trials are ongoing in mCRC and in the adjuvant setting
- Colon cancer probably less easy than others
- MSI-H tumors : a good target
- Others may be: PolE, PolD, MSS with immune infiltrates…
- Combination with targeted agents:
  - + chemotherapy, sequence?
  - + radiotherapy?
  - + targeted agents: anti-angiogenics; MEK…?

Gastric-Cancer

…what do we know, where do we go?

The burden of gastric cancer

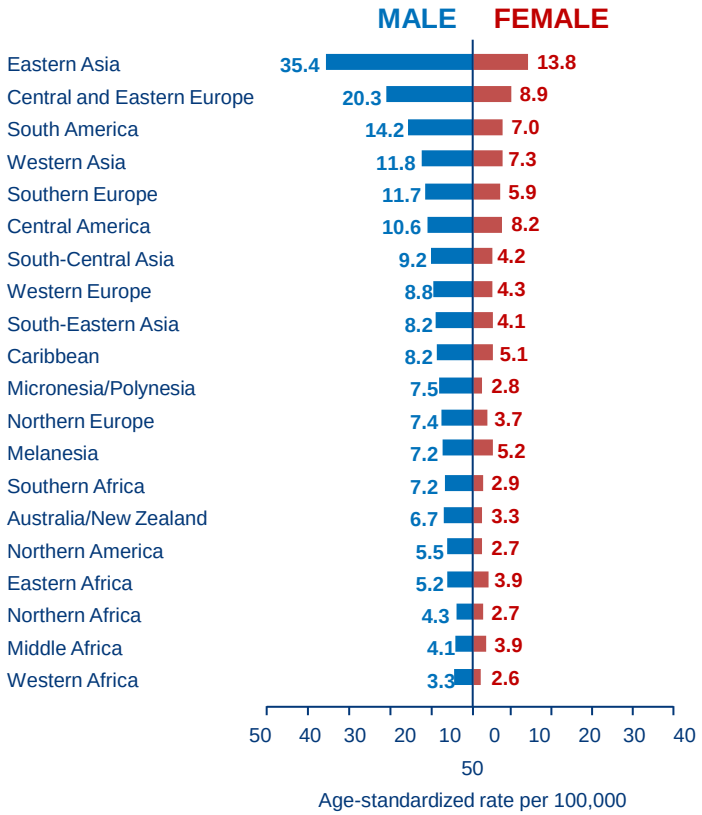
- **Fifth most common malignancy worldwide with 952,000 new cases in 2012[1]**
- **It is the third leading cause of cancer death in both sexes[2]**
- **Due to its asymptomatic early features, gastric cancer is diagnosed in many patients at an advanced stage[3,4]**
- **Despite a falling global incidence and significant progress in treatment, further efforts are necessary to improve prognosis[4]**



1. WCRF. http://www.wcrf.org/int/cancer-facts-figures/worldwide-data (date last accessed August 2018);
2. GLOBOCAN Stomach Cancer Fact Sheet. http://globocan.iarc.fr/old/FactSheets/cancers/stomach-new.asp (date last accessed August 2018);
3. Jou E, et al. World J Gastroenterol 2016;22:4812–23; 4. Pasechnikov V, et al. World J Gastroenterol 2014;20:13842–62

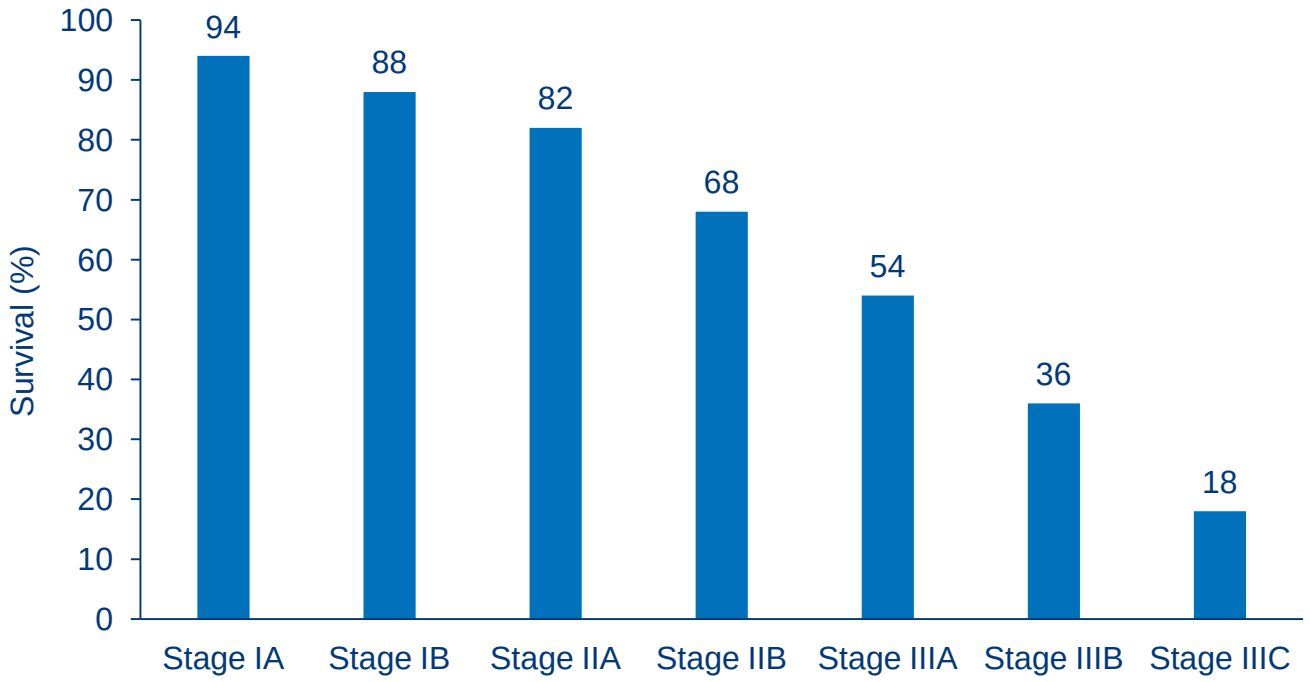
Global variability in gastric cancer: Incidence

- **The incidence of gastric cancer is highest in Eastern Asia, Central and Eastern Europe, and South America[1]**
- **Over 70% of gastric cancer cases occur in developing countries[2]**
- **Globally, rates were twice as high in men than women[1] in 2012**



1. Torre LA, et al. CA Cancer J Clin 2015;65:87; 2. GLOBOCAN Stomach Cancer Fact Sheet. http://globocan.iarc.fr/old/FactSheets/cancers/stomach-new.asp (date last accessed August 2018)

Gastric cancer: 5-year survival by stage*

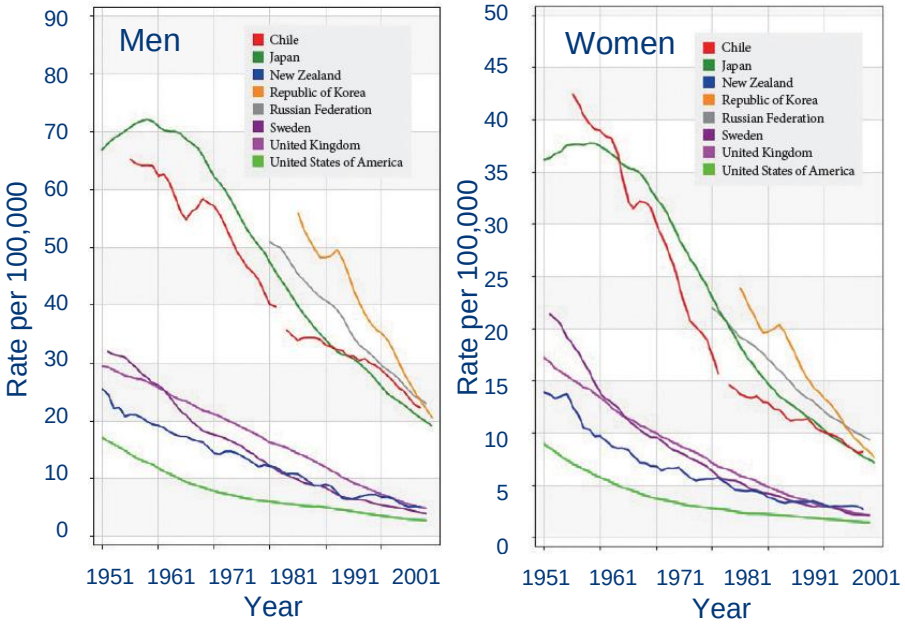


*For stomach cancer treated with surgery

ACS. Survival Rates for Stomach Cancer by Stage. https://www.cancer.org/cancer/stomach-cancer/detection-diagnosis-staging/survival-rates.html
(date last date last accessed August 2018)

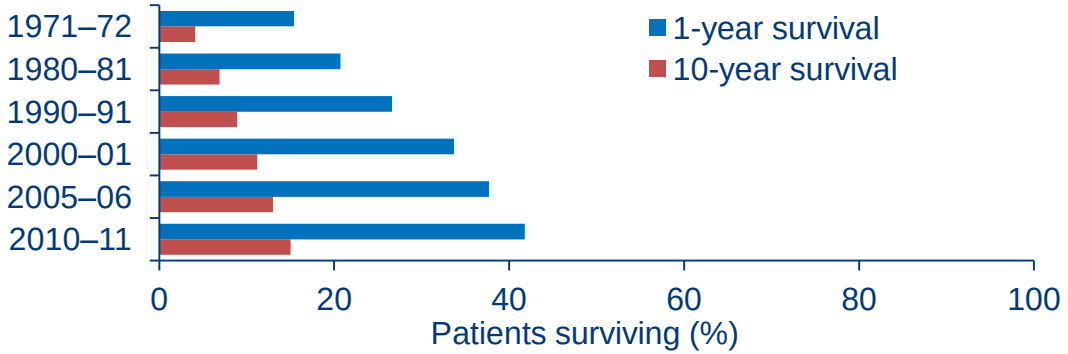
Global variability in gastric cancer survival

- **5-year survival rates are <30% in most countries**
  - **Exception: 5-year survival rates are ~70% in South Korea and Japan due to screening programs**



Survival in patients with gastric cancer

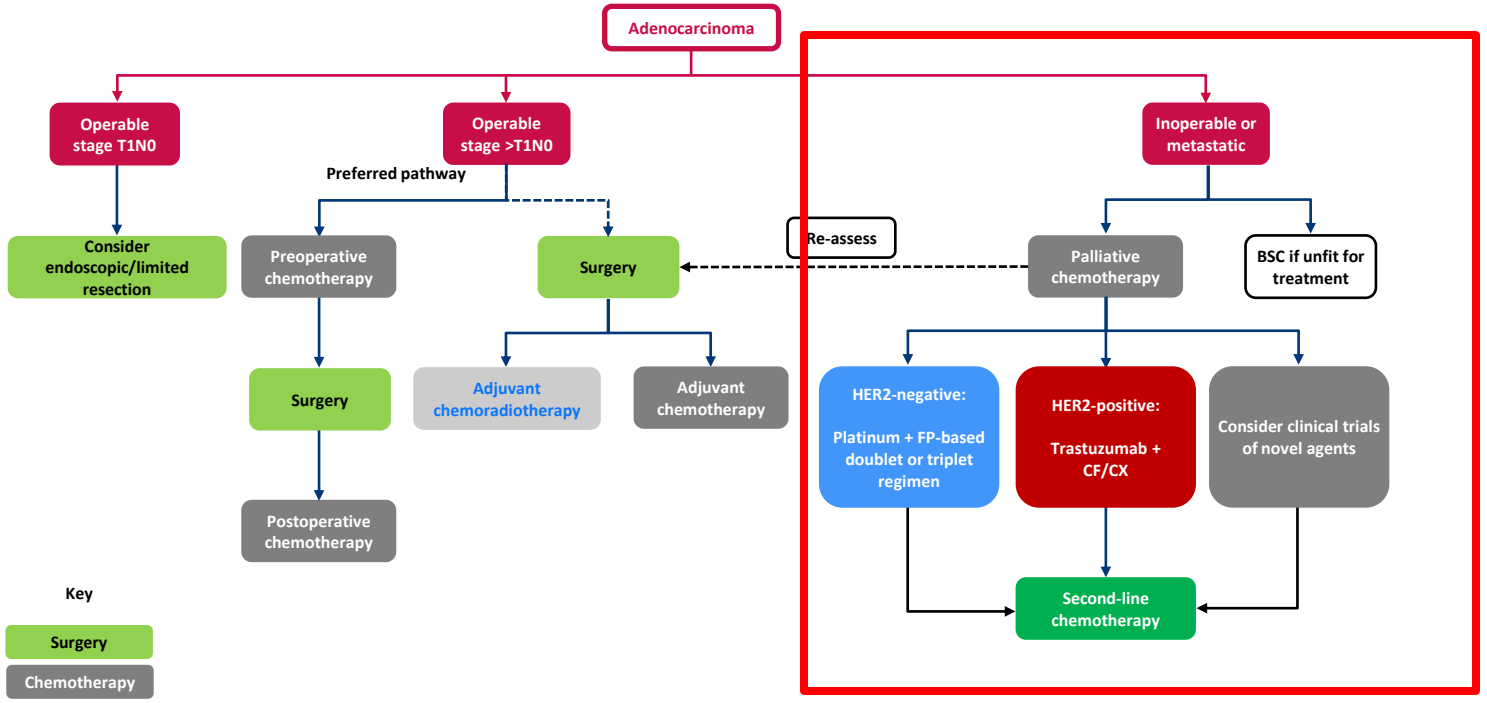
- **In most regions, survival from gastric cancer continues to be poor: in Western countries including Europe and the US, 5-year survival does not exceed 25%[1]**
- **Five-year survival rate is relatively good only in Japan, reaching 90% due to screening by endoscopic examination and early tumor resection[2]**



US, United States

1. Pasechnikov V, et al. World J Gastroenterol 2014;20:13842–62; 2. Parkin DM, et al CA Cancer J Clin 2005;55(2):74–108; 3. Cancer Research UK. www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/survival (date last accessed August 2018)

Current ESMO recommendations for treatment of gastric cancer



BSC, best supportive care; CF, cisplatin and 5-fluorouracil; CX, cisplatin and capecitabine; ESMO, European Society for Medical Oncology; FP, fluoropyrimidine; HER2, human epidermal growth factor receptor 2

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

Second-line treatment of advanced gastric cancer

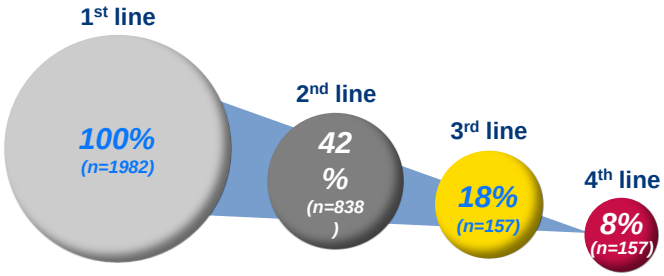
- **Second-line treatment options include irinotecan, docetaxel, or paclitaxel if not used before[1]**
- **Ramucirumab (anti-VEGFR-2 monoclonal antibody) has shown a survival benefit vs cytotoxic chemotherapy[2]**
  - **Ramucirumab added to paclitaxel has shown a survival advantage compared with paclitaxel alone[2]**
  - ***As a single agent as well vs placebo[3]***
- ***Second-line chemotherapy with a taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as single agent or in combination with paclitaxel, is recommended for patients who are of PS 0–1***
- **Re-challenge may be appropriate in patients with disease progression >3 months after first-line chemotherapy[1]**

PS, performance status; VEGFR, vascular endothelial growth factor receptor

1. Smyth EC, et al. Ann Oncol 2016;27 (suppl 5):v38–49; 2. Wilke H, et al. Lancet Oncol 2014;15:1224–35; 3. Fuchs CS, et al. Lancet 2014;383:31–9

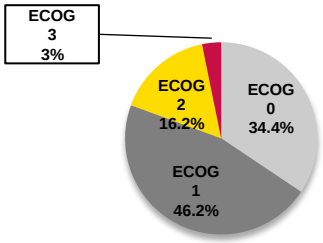
Post-second-line treatment in patients with advanced gastric cancer

- **Many patients with advanced/metastatic gastric cancer are motivated to receive post–second-line treatment and have adequate performance status to do so[1]**
  - **In an EMR database study, 26% of patients received third- or fourth-line therapy[2]**
- **There is a lack of standard treatment options particularly following first-line therapy**
- **There is no established third-line therapy for advanced gastric cancer[1]**
- **Many patients progressing beyond second-line treatment remain fit for further therapy[1]**
- **There is a need for effective and well-tolerated therapies[1,3]**

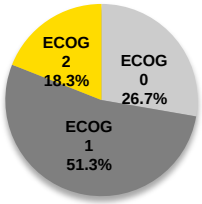


N=1982 patients with gastric cancer and EMR data who received chemotherapy between January 2004 and January 2012 in oncology practices subscribing to the US-wide IMS Health Oncology Database[2]

ECOG PS (%) of patients at start of 1st-line treatment[3]



ECOG PS (%) of patients at start of 3rd line treatment[4]



ECOG PS, Eastern Cooperative Oncology Group performance status; EMR, electronic medical record; US, United States

1. Kim SM, et al. World J Gastroenterol 2015;21:8811–6; 2. Hess LM, et al. Gastric Cancer 2016;19:607–15;
3. Jou E, et al. World J Gastroenterol 2016;22:4812–23; 4. Fanotto V, et al. Oncologist 2017;22:1–7

Post-second-line treatment in patients with advanced gastric cancer

ESMO guidelines:[1]

- **Treatment options may be used sequentially in second and third line, but there is no clear evidence for a benefit beyond second-line treatment**

- **Further options are needed for both second-line and post-second-line chemotherapy[1,2]**
- **Findings of systematic reviews:**
  - **Compared with BSC, everolimus or regorafenib in the second- or third-line setting had no benefit in terms of OS, but provided a median PFS gain of Δ0.3 and Δ1.6 months, respectively[3]**
  - **Compared with BSC, apatinib in the third- or later-line setting showed increased OS (Δ1.8 to Δ2.3 months) and PFS (Δ0.8 to Δ2.3 months)[3]**
  - **Compared with placebo or BSC, third-line chemotherapy showed superior OS and PFS[4]**

BSC, best supportive care; ESMO, European Society for Medical Oncology; OS, overall survival; PFS, progression-free survival

1. Smyth EC, et al. Ann Oncol 2016;27 (suppl 5):v38–49; 2. Takahari D. Gastric Cancer 2017;20:395–406; 3. ter Veer E, et al. Cancer Metastasis Rev 2016;35:439–56; 4. Zheng Y, et al. Medicine 2017;96(24):e6884

Cancer treatment beyond second line

ATTRACTION-2

Nivolumab (ONO-4538/BMS-936558) as Salvage Treatment After Second- or Later-Line Chemotherapy for Advanced Gastric or Gastroesophageal Junction Cancer (AGC): A Double-Blinded, Randomized, Phase 3 Trial

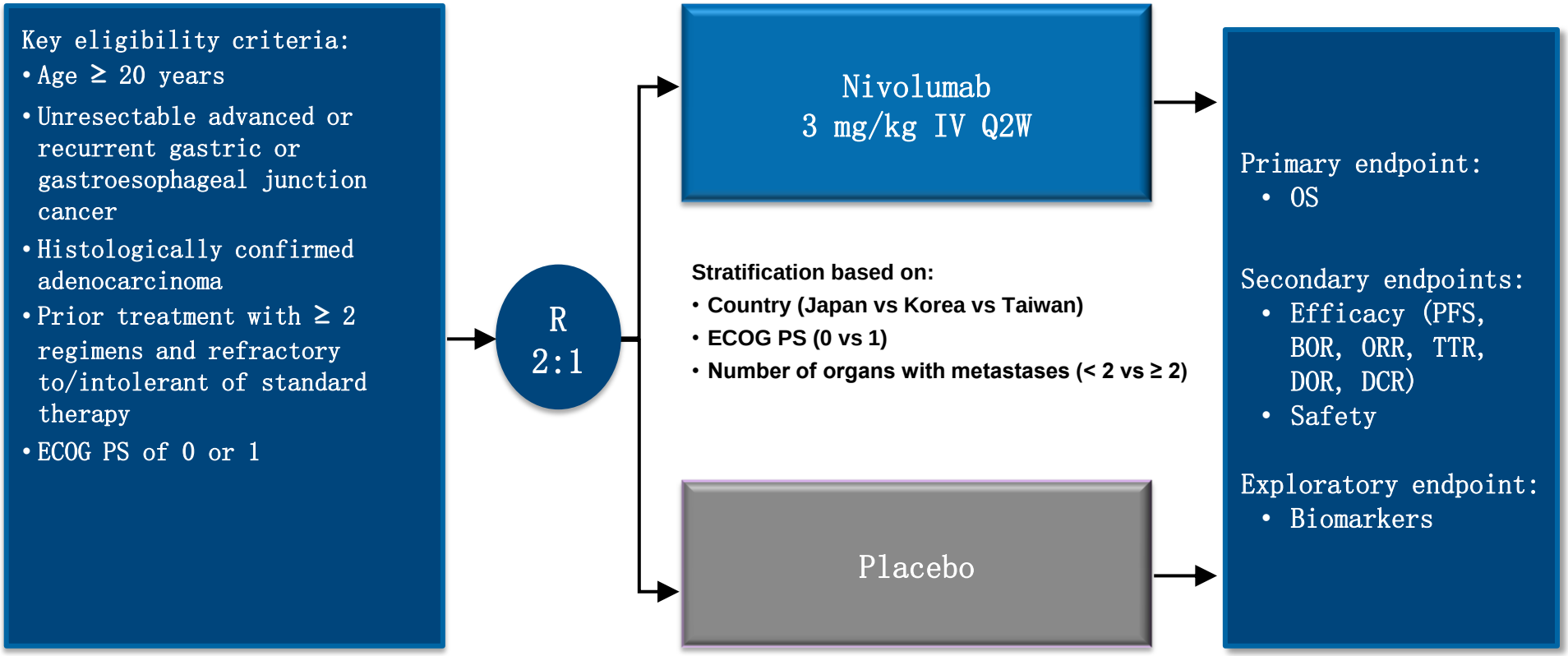
Yoon-Koo Kang,[1] Taroh Satoh,[2] Min-Hee Ryu,[1] Yee Chao,[3] Ken Kato,[4] Hyun Cheol Chung,[5] Jen-Shi Chen,[6] Kei Muro,[7] Won Ki Kang,[8] Takaki Yoshikawa,[9] Sang Cheul Oh,[10] Takao Tamura,[11] Keun-Wook Lee,[12] Narikazu Boku,[4] Li-Tzong Chen[13]

[1]Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; [2]Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan; [3]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan; [4]Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [5]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Song Dang Institute for Cancer Research, Yonsei University College of Medicine, Yonsei University Health System, Seoul, Korea; [6]Division of Hematology/Oncology, Department of Internal Medicine, Linkou Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [7]Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [8]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [9]Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan; [10]Division of Hematology/Oncology, Internal Medicine Department, College of Medicine, Korea University, Seoul, Korea; [11]Medical Oncology, Kindai University, Faculty of Medicine, Osakasayama, Japan; [12]Division of Hematology/Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea; [13]National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan

Nivolumab is not approved in Europe for the treatment of gastric cancer

Nivolumab is not approved in Europe for the treatment of gastric cancer

Study Design and Endpoints



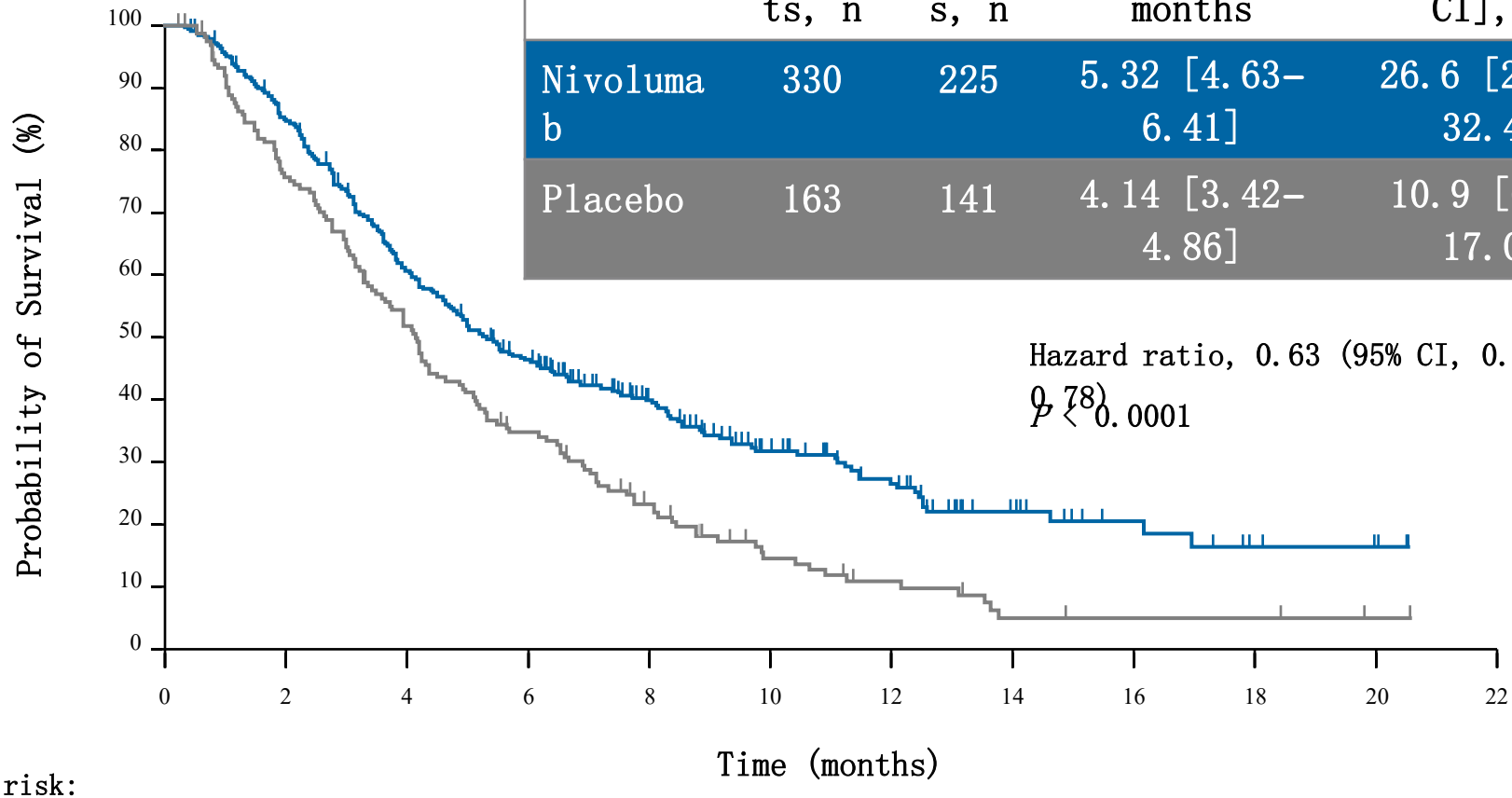
- Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug

Nivolumab is not approved in Europe for the treatment of gastric cancer

BOR, best overall response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV; intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to tumor response.

Overall Survival

	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]



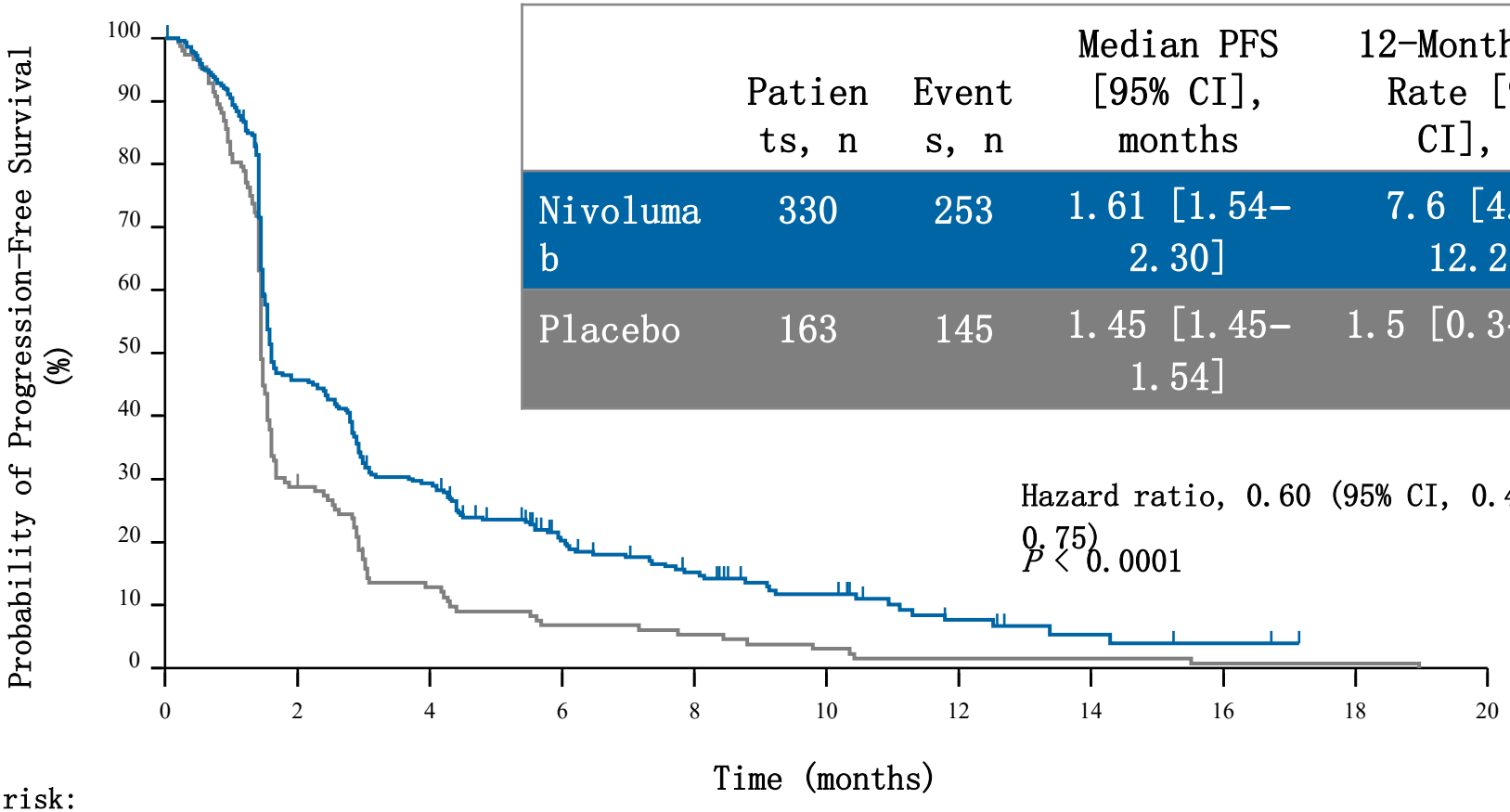
At risk:

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

Nivolumab is not approved in Europe for the treatment of gastric cancer

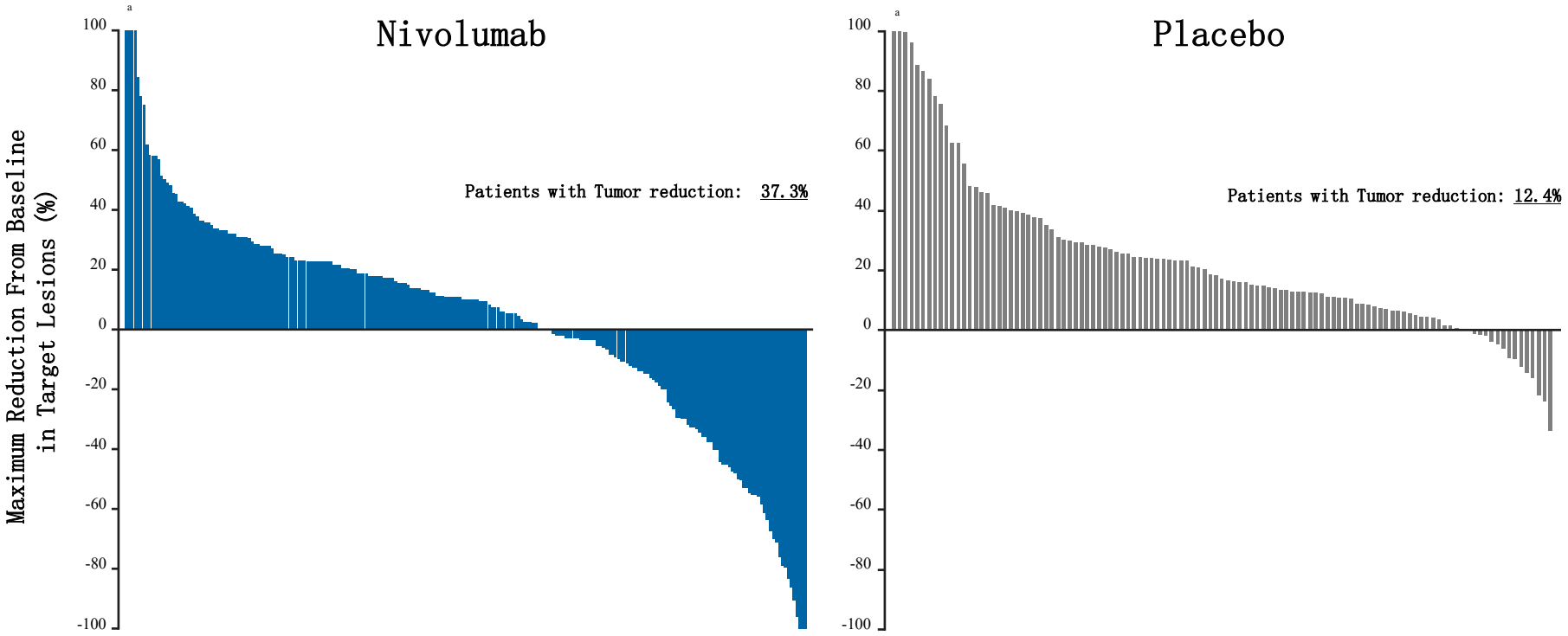
Progression-Free Survival

	Patients, n	Events, n	Median PFS [95% CI], months	12-Month PFS Rate [95% CI], %
Nivolumab	330	253	1.61 [1.54-2.30]	7.6 [4.2-12.2]
Placebo	163	145	1.45 [1.45-1.54]	1.5 [0.3-4.8]



Nivolumab is not approved in Europe for the treatment of gastric cancer

Maximum Reduction in Tumor Burden From Baseline



[a] Patients with a change in tumor burden that exceeds 100%.

Nivolumab is not approved in Europe for the treatment of gastric cancer

MADRID 2017 ESMO congress

KEYNOTE-059: Efficacy and Safety of Pembrolizumab Alone or in Combination With Chemotherapy in Patients With Advanced Gastric or Gastroesophageal Cancer

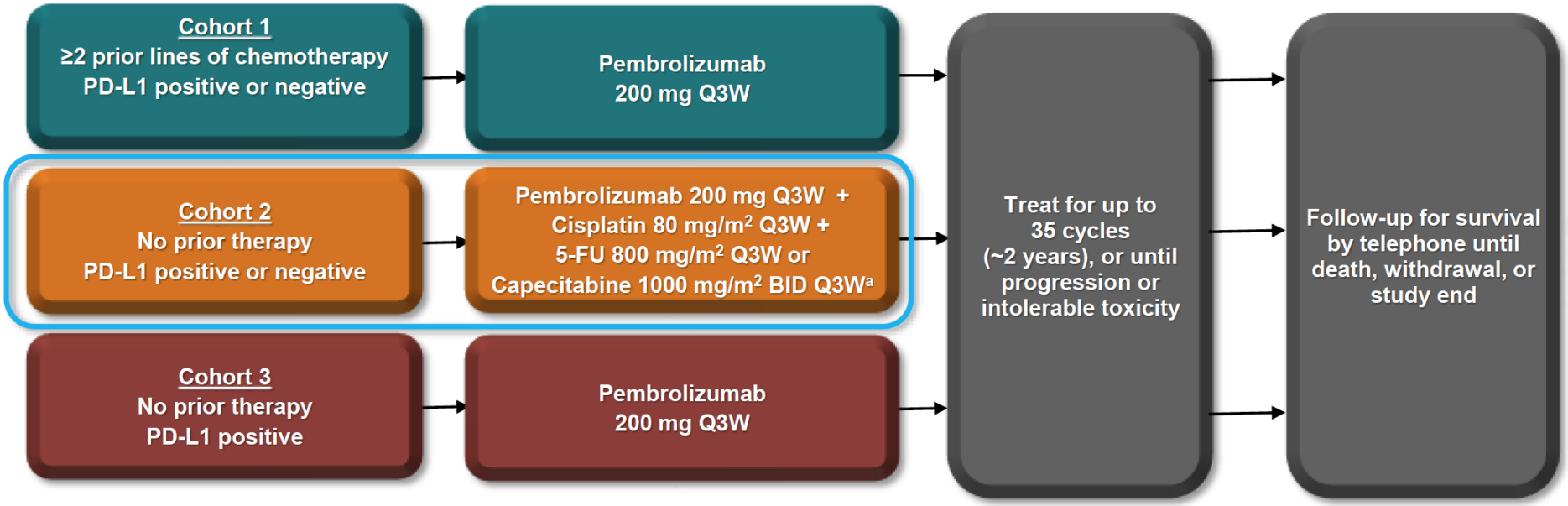
Zev A. Wainberg,[1] Shadia I. Jalal,[2] Kei Muro,[3] Harry H. Yoon,[4] Marcelo Garrido,[5] Talia Golan,[6] Toshihiko Doi,[7] Daniel V. Catenacci,[8] Ravit Geva,[9] Geoffrey Ku,[10] Jonathan Bleeker,[11] Yung-Jue Bang,[12] Hiroki Hara,[13] Hyun Cheol Chung,[14] Mary J. Savage,[15] Jiangdian Wang,[15] Minori Koshiji,[15] Rita P. Dalal,[15] Charles S. Fuchs[16]

[1]David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA, USA; [2]Indiana University School of Medicine, Indianapolis, IN, USA; [3]Aichi Cancer Center Hospital, Nagoya, Aichi, Japan; [4]Mayo Clinic, Rochester, MN, USA; [5]Pontificia Universidad Católica de Chile, Santiago, Chile; [6]Sheba Medical Center and the Sackler School of Medicine, Tel Aviv, Israel; [7]National Cancer Center East, Chiba, Japan; [8]University of Chicago Medicine, Chicago, IL, USA; [9]Tel Aviv-Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel; [10]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [11]Sanford Health, Sioux Falls, SD, USA; [12]Seoul National University Hospital, Seoul, Republic of Korea; [13]Saitama Cancer Center, Saitama, Japan; [14]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [15]Merck & Co., Inc., Kenilworth, NJ, USA; [16]Yale Cancer Center, New Haven, CT, USA

PRESENTED AT: ASCO ANNUAL MEETING '16

Pembrolizumab is not approved in Europe for the treatment of gastric cancer

KEYNOTE-059 Study Design



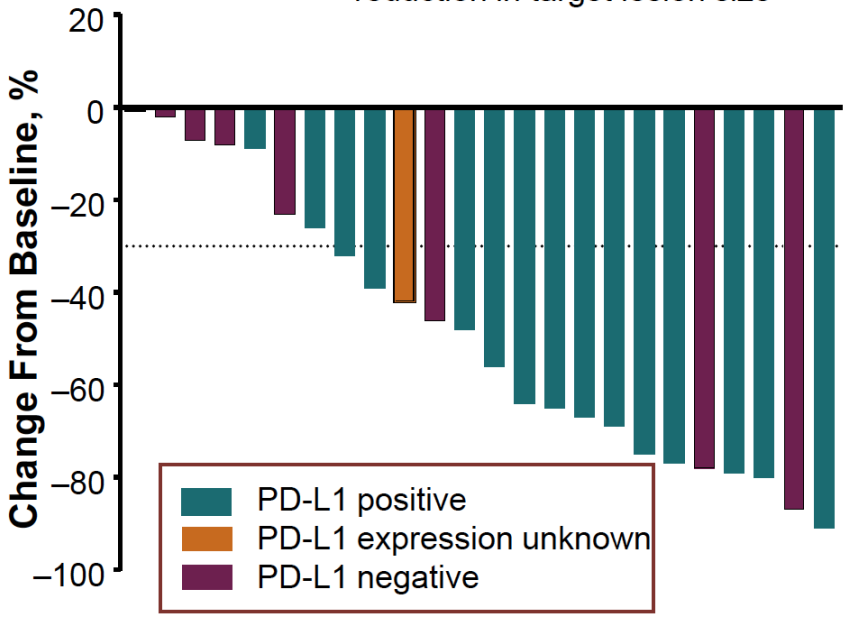
[a]Capecitabine was administered only in Japan.

Pembrolizumab is not approved in Europe for the treatment of gastric cancer

Cohort 2: Best Percentage Change and Longitudinal Change in Target Lesion Size

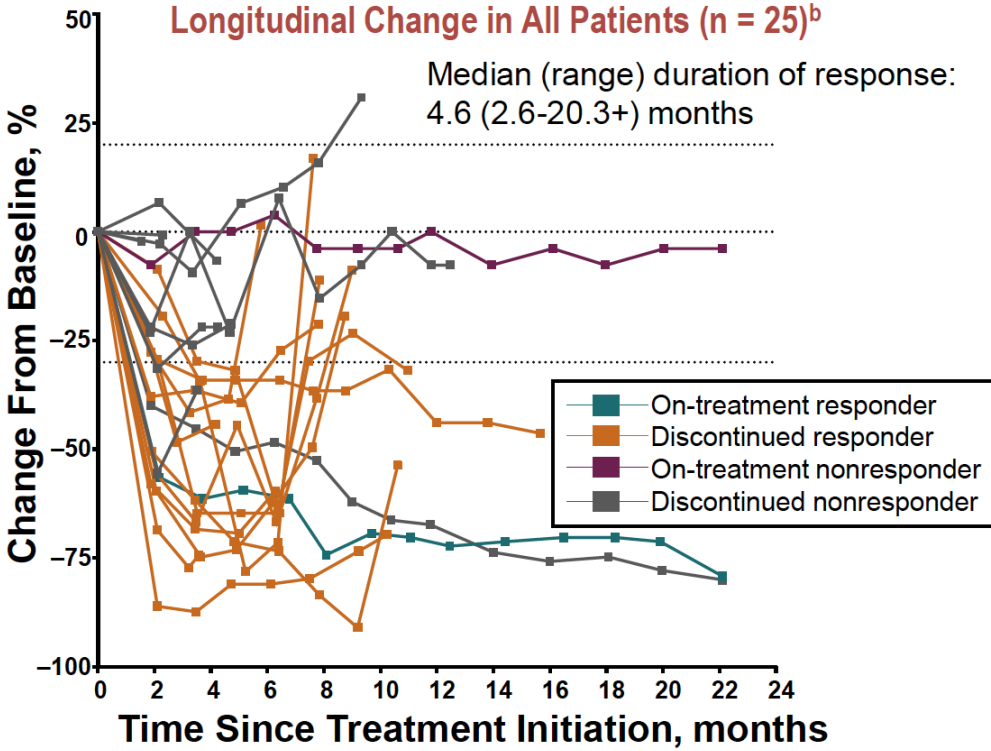
Best Percentage Change in All Patients (n = 24)[a]

24 patients (96%) experienced a reduction in target lesion size



Longitudinal Change in All Patients (n = 25)[b]

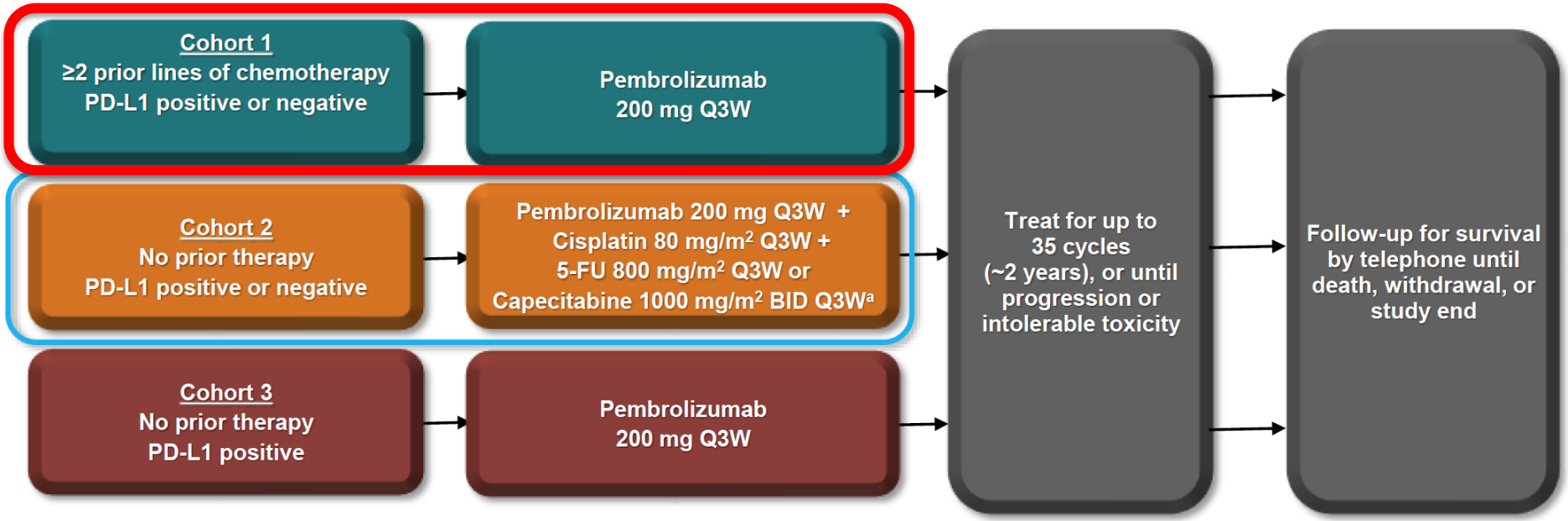
Median (range) duration of response: 4.6 (2.6-20.3+) months



[a]Only patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 postbaseline assessment were included (n = 25); assessment was nonevaluable for 1 patient.
[b]Longitudinal change in the sum of the longest target lesion diameters from baseline in patients with ≥1 postbaseline assessment (n = 25).
+No progressive disease at last disease assessment.
Data cutoff: April 21, 2017.

Pembrolizumab is not approved in Europe for the treatment of gastric cancer

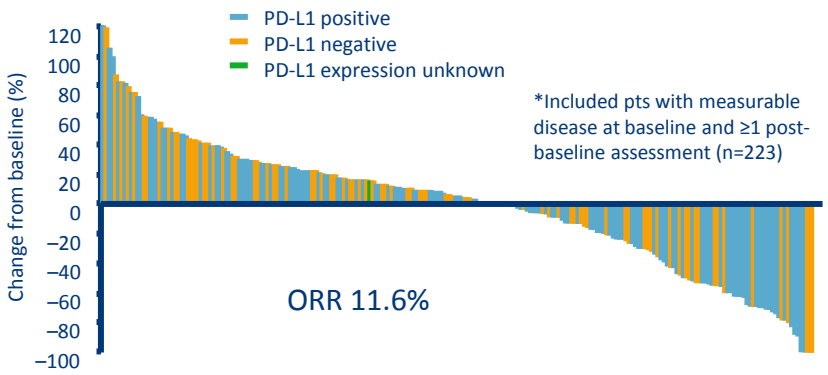
KEYNOTE-059 Study Design



[a]Capecitabine was administered only in Japan.

Pembrolizumab is not approved in Europe for the treatment of gastric cancer

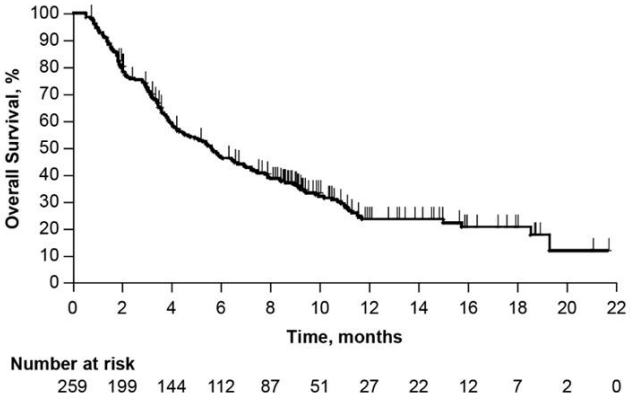
KEYNOTE-059: Pembrolizumab in chemorefractory mGC (2)



RECIST response rates are modest
(identical to nivolumab in ATTRACTION-02)

Responses in PD-L1-positive and -negative patients

	PD-L1 status		Line of Treatment	
	Positive (n = 148)	Negative (n = 109)	3rd (n = 134)	≥ 4th (n = 125)
ORR (%)	15.5 (10.1-22.4)	6.4 (2.6-12.8)	16.4 (10.6-23.8)	6.4 (2.8-12.2)



mGC, metastatic gastric cancer;
ORR, overall response rate; PD-L1, programmed death ligand 1;
RECIST, Response Evaluation Criteria In Solid Tumors
Fuchs CS, et al. JAMA Oncol 2018;4(5):e180013

Combination-IOs: Checkmate 032 EG Cohort

Western patients with advanced/metastatic EG cancer with progression on ≥1 prior chemotherapy
N = 160

Nivolumab 3 mg/kg IV Q2W (NIVO 3)	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV Q3W* (NIVO 1 + IPI 3)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV Q3W* (NIVO 3 + IPI 1)
Median (range) follow-up, mo†: 28 (17 to 35)	24 (21 to 33)	22 (19 to 25)

Primary endpoint:

- ORR per RECIST v1.1

Secondary endpoints:

- OS, PFS, TTR, DOR
- Safety

Exploratory endpoint:

- PD-L1 tumor expression (Dako 28-8 pharmDx assay)

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.

Nivolumab as well as ipilimumab are not approved in Europe for the treatment of gastric cancer

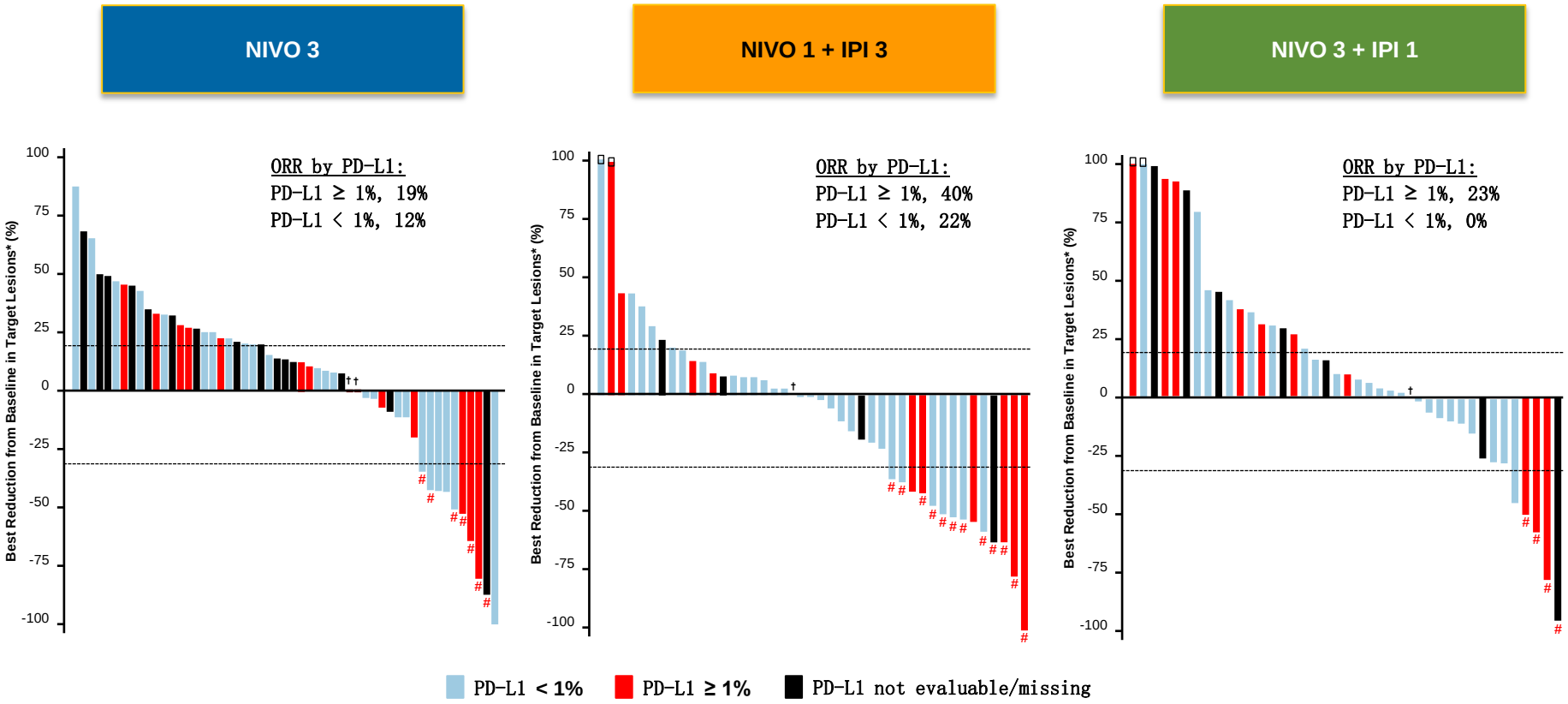
Objective Response

	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
ORR, n (%)*	**7 (12)**	**12 (24)**	**4 (8)**
[95% CI]	[5, 23]	[13, 39]	[2, 19]
BOR, n (%)*			
Complete response	1 (2)	1 (2)	0
Partial response	6 (10)	11 (22)	4 (8)
Stable disease	12 (20)	8 (16)	15 (29)
Progressive disease	34 (58)	23 (47)	24 (46)
Not evaluable	6 (10)	6 (12)	9 (17)
DCR, n (%)†	19 (32)	20 (41)	19 (37)
Median TTR (range), months	1.6 (1.2 to 4.0)	2.7 (1.2 to 14.5)	2.6 (1.3 to 2.8)
Median DOR (95% CI), months	7.1 (3.0, 13.2)	7.9 (2.8, NE)	NR (2.5, NE)

BOR, best objective response; DCR, disease control rate; NR, not reached, NE, not estimable.
* Investigator review.
† Patients with a BOR of complete response, partial response, or stable disease.

Nivolumab as well as ipilimumab are not approved in Europe for the treatment of gastric cancer

Best Reduction in Target Lesions



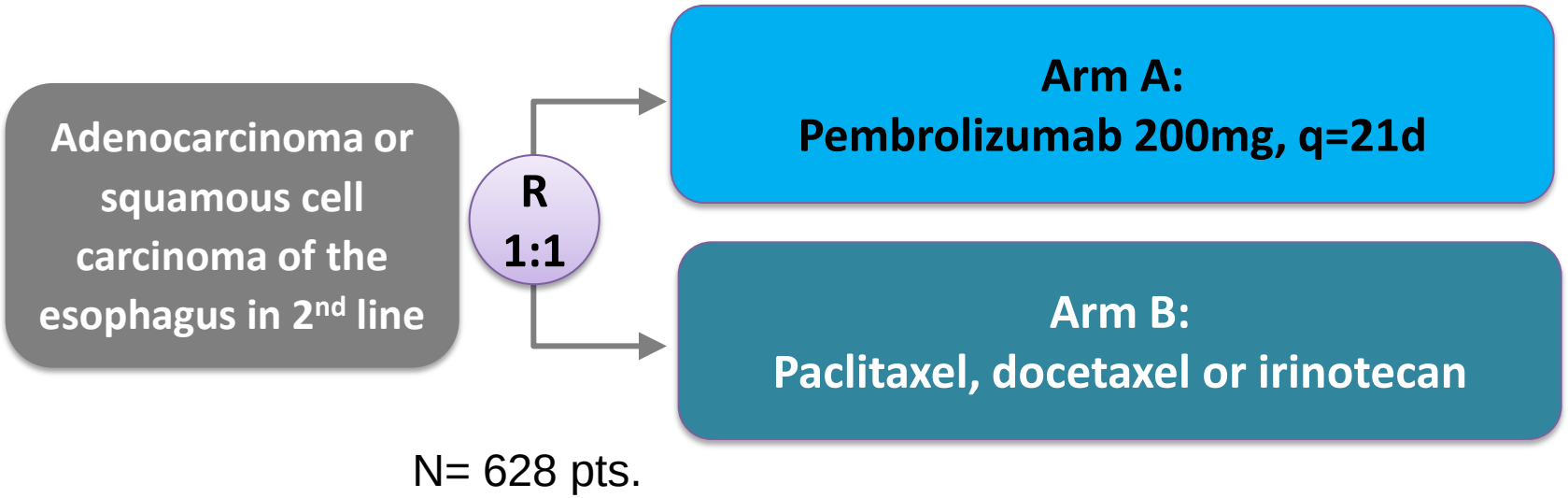
- Responses were observed regardless of PD-L1 expression

* 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).

Nivolumab as well as ipilimumab are not approved in Europe for the treatment of gastric cancer

Esophageal Cancer

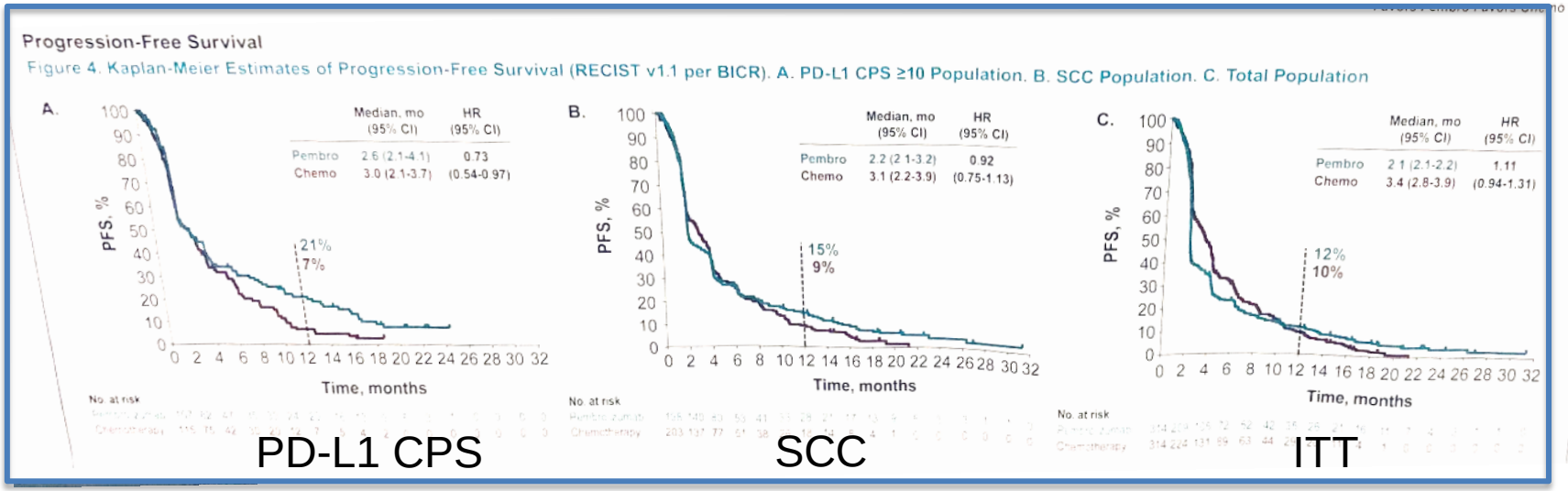
Keynote-181
in Stage IV Esophageal Cancer



N= 628 pts.

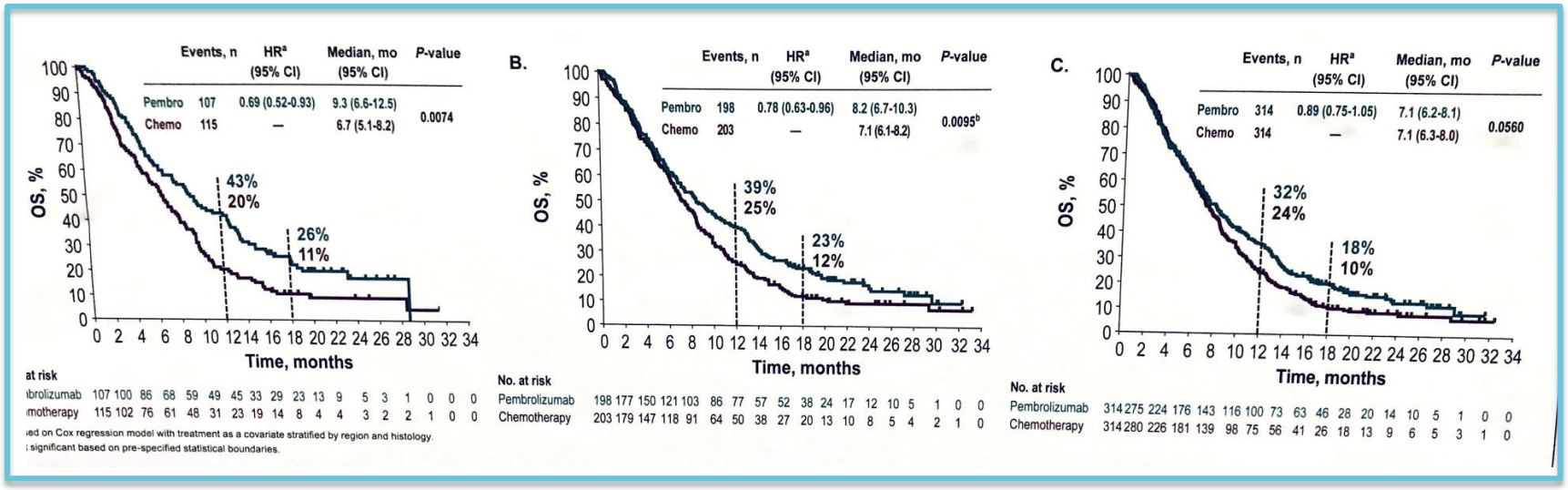
- Primary efficacy end points are PFS (per RECIST v1.1, blinded central imaging vendor review) and OS.
- Secondary end points include ORR (per RECIST v1.1, blinded central imaging vendor review).

Progession Free Survival



PD-L1 CPS SCC ITT

Overall Survival



PD-L1 CPS SCC ITT

Conclusion

- Trials are ongoing in GC in the palliative and adjuvant setting
- Colon cancer probably less easy than others
- MSI-H tumors : a good target
- Others may be: PD-L1 expression in upper GI
- Combination with targeted agents:
  - + chemotherapy
  - + radiotherapy
  - + other IOs


Thank You !
Unfallstation
Mensa