Immunotherapy in MSI-High Colorectal & Gastric Cancers

Winter Cancer Symposium
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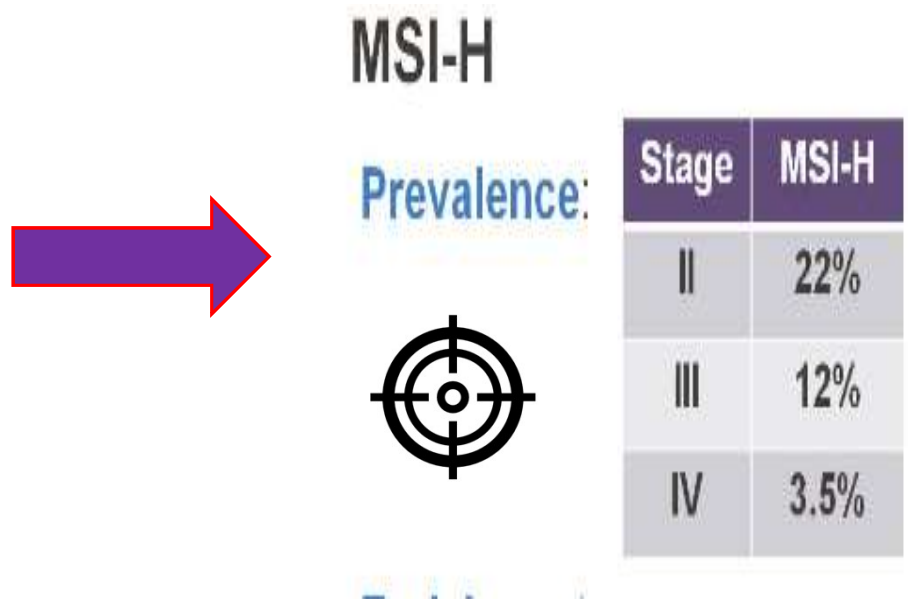
MMR-Deficiency and Immune Microenvironment

- Mismatch repair deficiency (MMR-D) referred to a deficiency in proteins responsible for DNA repair such as MSH2, MSH6, MLH1, PMS2
- MMR deficiency leads to MSI-High phenotype
- MMR deficient /MSI-H cancers usually Harbor at thousands of mutations:
  - leading to high mutational burden also known as hypermutated phenotype
- DNA Mutations generate Protein Neoantigens that are recognized by T-Cells

Tumor Location with likelihood MSI-High

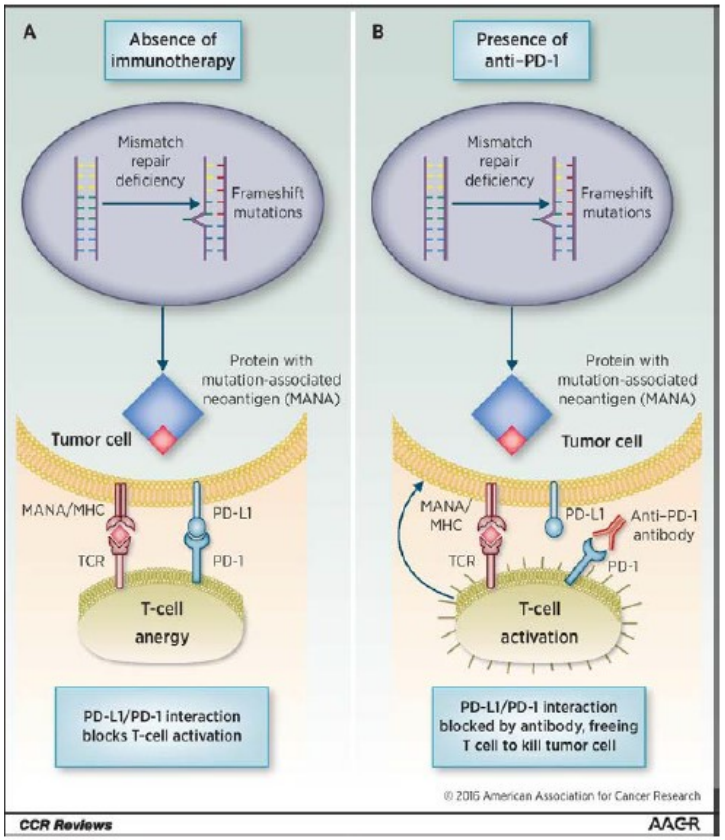
- Small bowel tumors → 25%
- Endometrial cancers → 16%
- Colorectal cancers all stages 14%
- Gastric cancers 6%
- Cholangiocarcinoma 3-8%



Stadler et al ASCO 2018 MSK-IMPACT an NGS platform

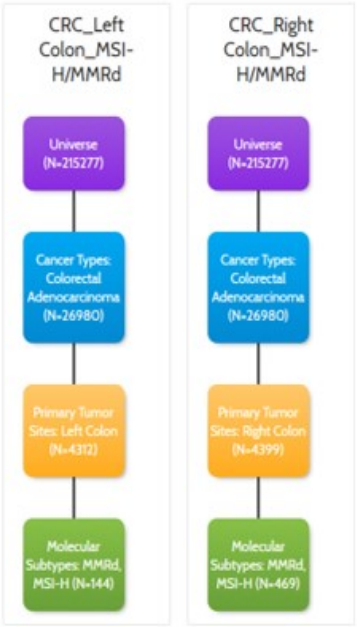
Rationale of Immunotherapy in MMR-D Cancers

- MSI-H Malignancies regardless of the tumor histology is associated with high mutational burden : hyper mutated phenotype
- High mutational burden leads to High Neoantigen expression
- High Neoantigen expression by itself→ autologous immune recognition of cancer cell
- Therefore PD-1 inhibition on tumor Neoantigen specific T-cells can activate anti tumor immune response

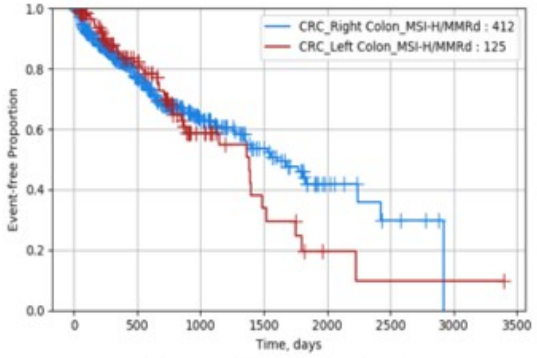


Jonathan C. Dudley et al. Clin Cancer Res 2016;22:813-820

CODEai - Tumor Location in CRC: Right Colon vs. Left Colon

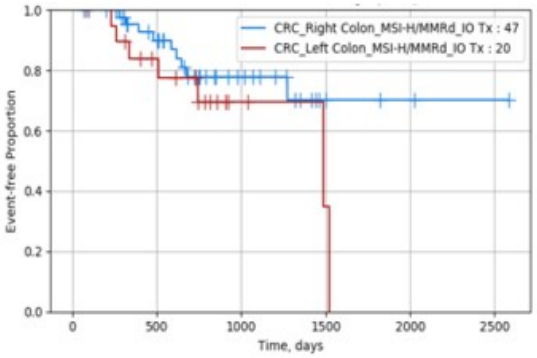


MSI-H or MMRd: Left vs. Right



Performance : Collection -> Last Contact
HR = 0.886 (95% CI: 0.626 - 1.253) p = 0.491
CRC_Left Colon_MSI-H/MMRd Median = 1387.0 days
CRC_Right Colon_MSI-H/MMRd Median = 1604.0 days
Median Difference = 217.0 days (15.6%)

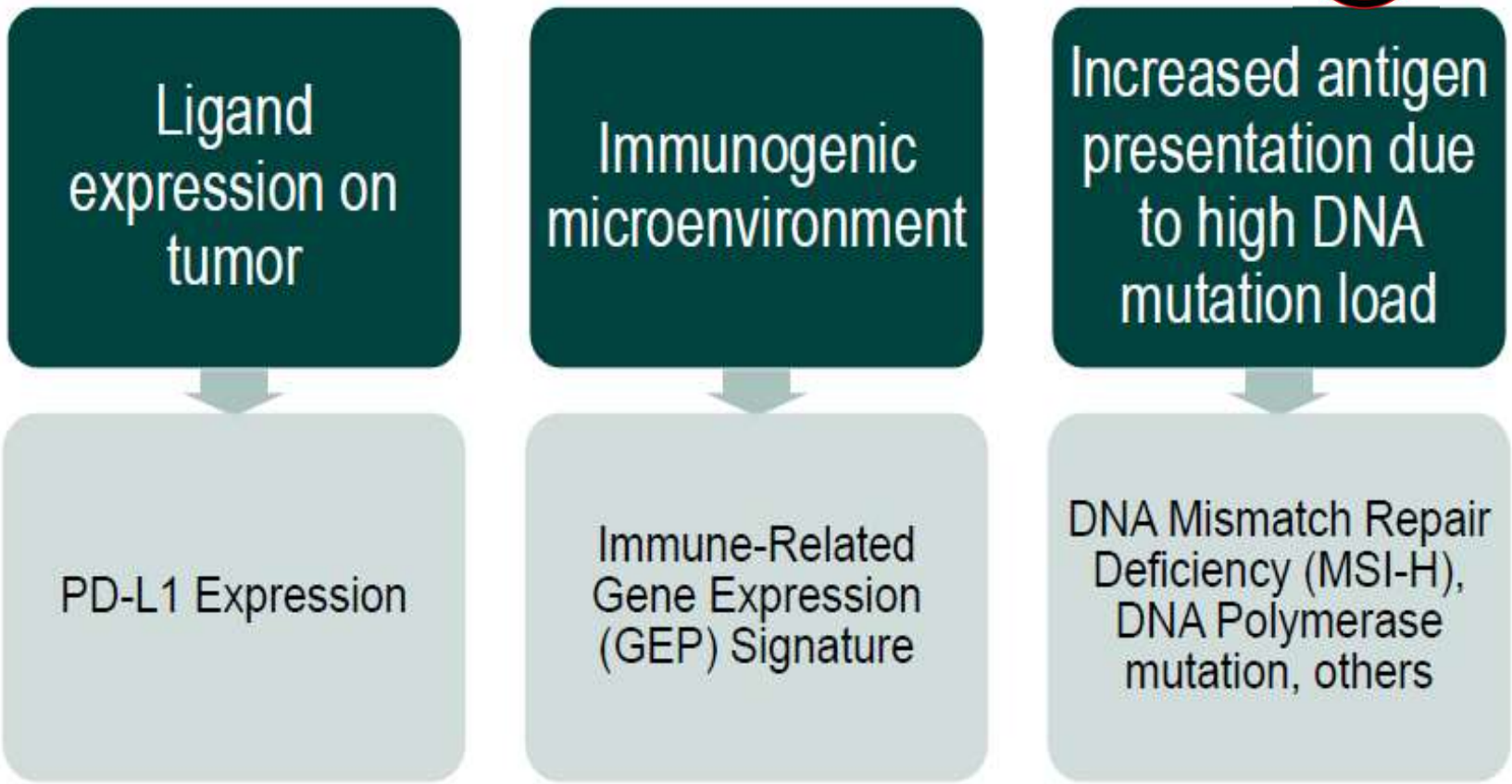
IO Therapy* Response
MSI-H or MMRd: Right vs. Left



Performance : Collection -> Last Contact
HR = 0.503 (95% CI: 0.187 - 1.357) p = 0.167
CRC_Left Colon_MSI-H/MMRd_IO Tx Median = 1487.0 days
CRC_Right Colon_MSI-H/MMRd_IO Tx Median = inf days
Median Difference = inf days (inf%)

* IO Therapy: ipilimumab, nivolumab, pembrolizumab

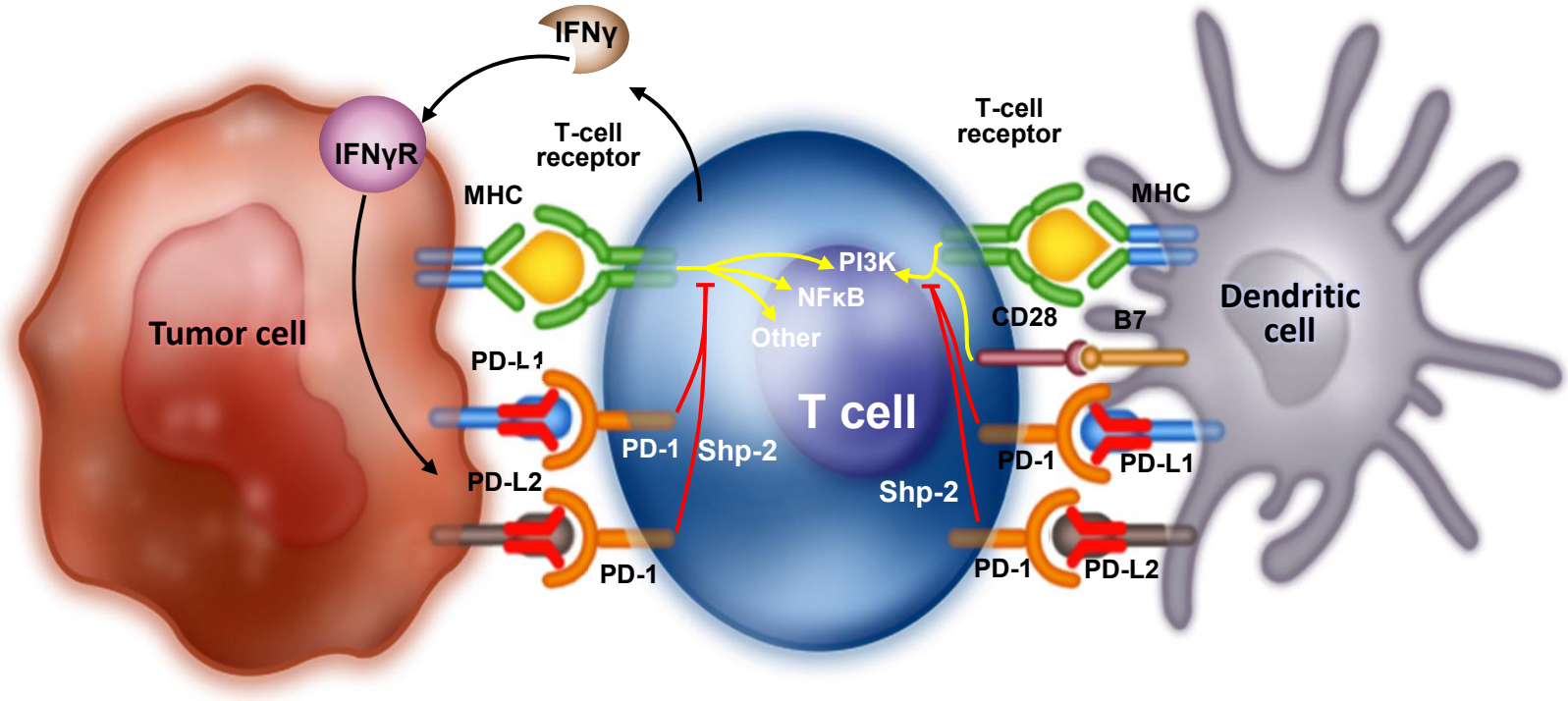
Biomarkers Identification



Mechanism of Action of Immunotherapy

PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function[11]

Binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function[12–14]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring,

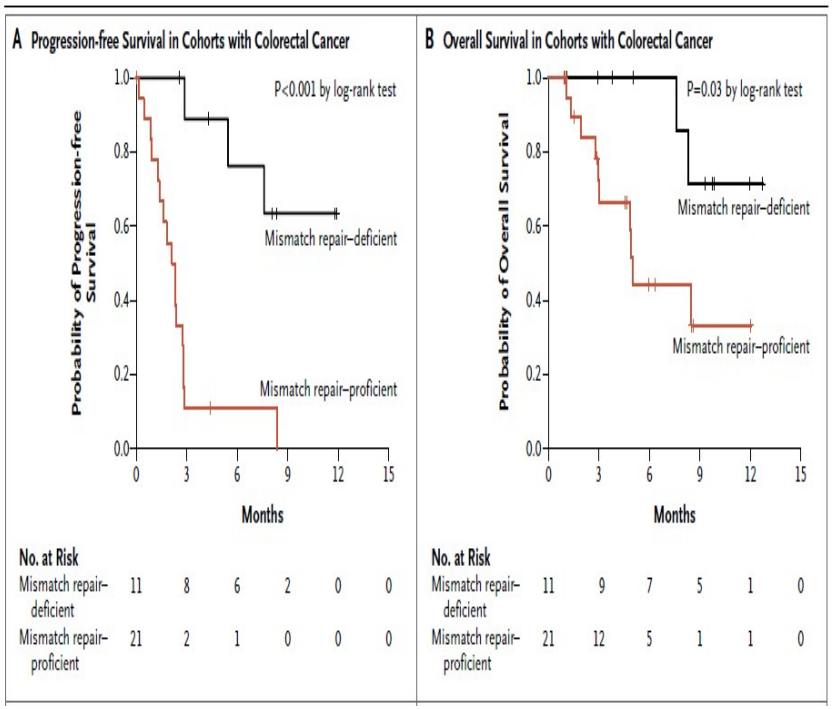
Le et al NEJM 2015:

- Phase II Trial for patients with MMR-D utilizing Pembrolizumab.
- 41 Patients with Metastatic Carcinoma with and Without MMR deficiency with Pembrolizumab between 2013-15
- Primary End Point: Immune Related ORR and PFS
- Pembrolizumab was administered intravenously at a dose of 10 mg per kilogram of body weight every 14 days
- The immune-related OR, PFS rate were :
  - 40% (4 of 10 patients) and 78% (7 of 9 patients), for MMR- deficient CRC
  - 0% (0 of 18 patients) and 11% (2 of 18 patients) for MMR-Proficient CRC .
- The median PFS and overall survival:
  - Not reached in the cohort with MMR-Deficient CRC
  - 2.2 and 5.0 months for MMR-Proficient (MSS) CRC

PD-1 Blockade in Cancer with MMR- Deficiency

(NEJM 2015)

PD-1 BLOCKADE IN MISMATCH-REPAIR DEFICIENCY



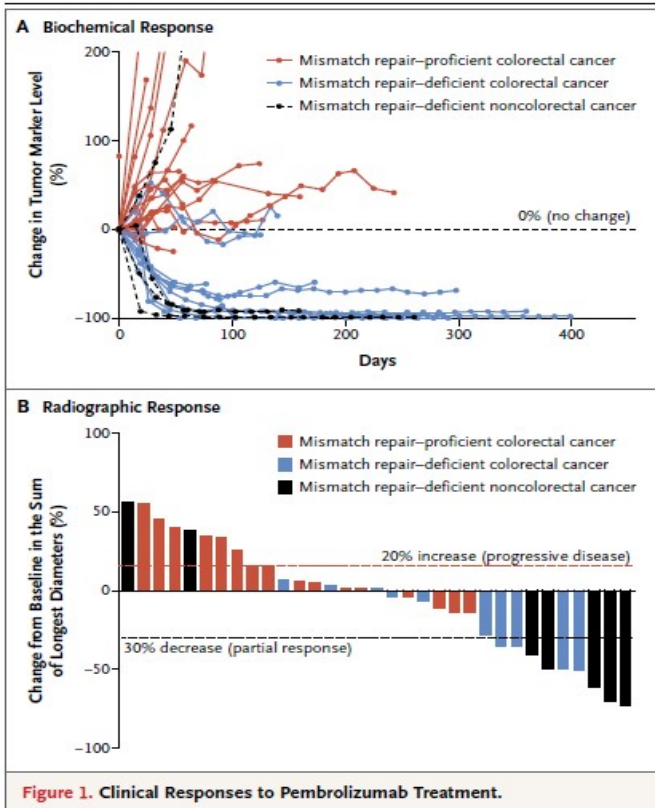
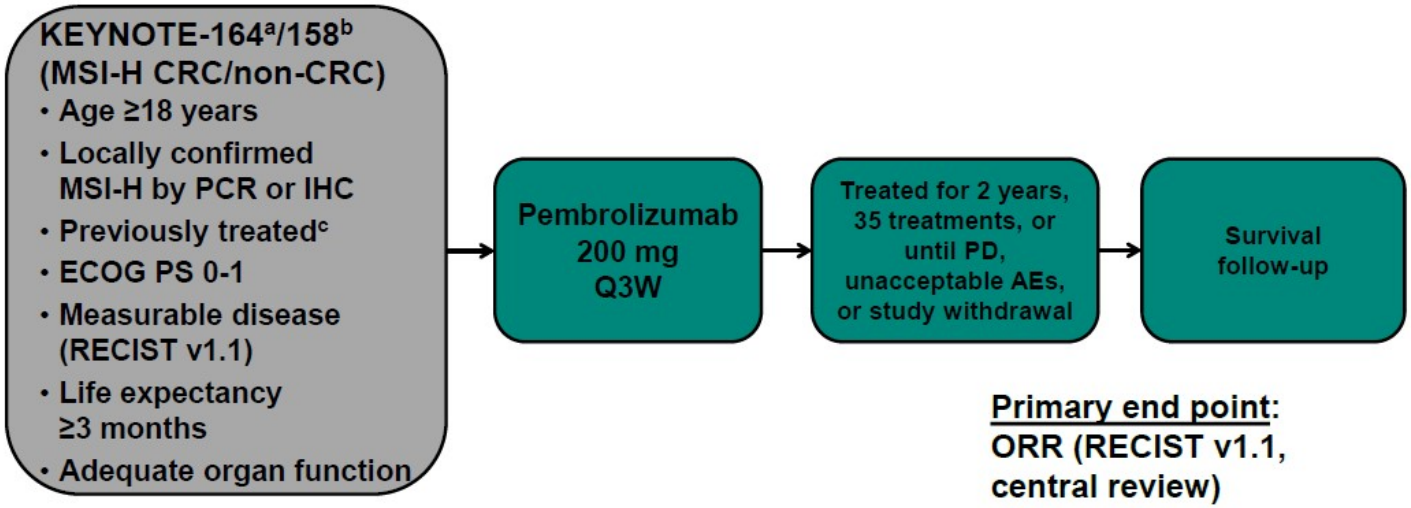


Figure 1. Clinical Responses to Pembrolizumab Treatment.

PD-1 Blockade in Cancer with MMR- Deficiency

Global Phase 2 Studies KEYNOTE-164 and KEYNOTE-158: Study Design



Primary end point:
ORR (RECIST v1.1, central review)

Secondary end points:
DOR, PFS, OS, safety

[a]Histologically confirmed, advanced, unresectable or metastatic CRC; previous treatment with approved therapies including fluoropyrimidine, oxaliplatin, and irinotecan.
[b]Histologically or cytologically confirmed, advanced, incurable non-CRC solid tumor; patients must have progressed on or be intolerant to standard therapies.
[c]≥2 prior therapies and ≥1 prior therapy for MSI-H CRC and non-CRC, respectively.
Clinicaltrials.gov: NCT02460198 and NCT02628067

Public

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Colon Cancer

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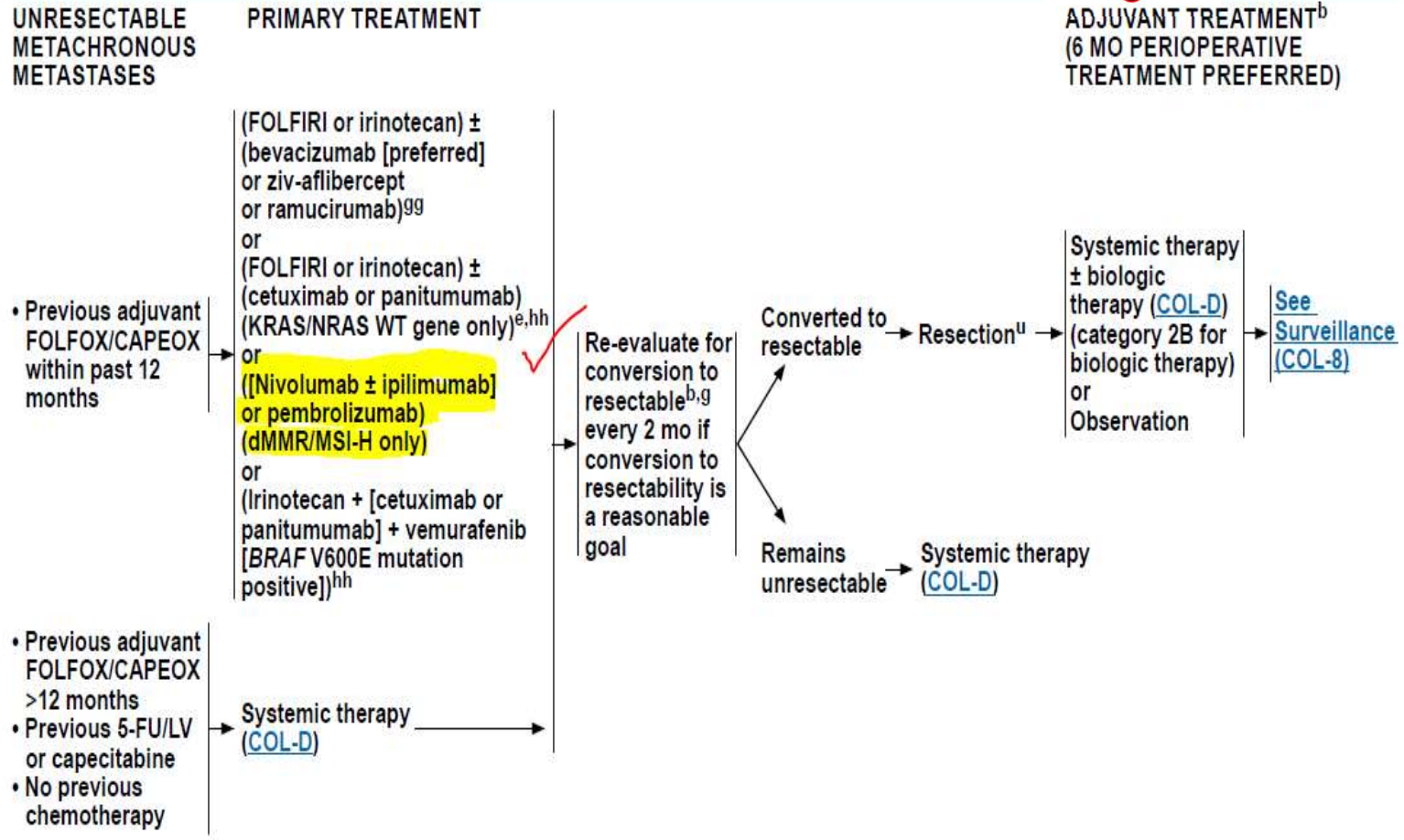
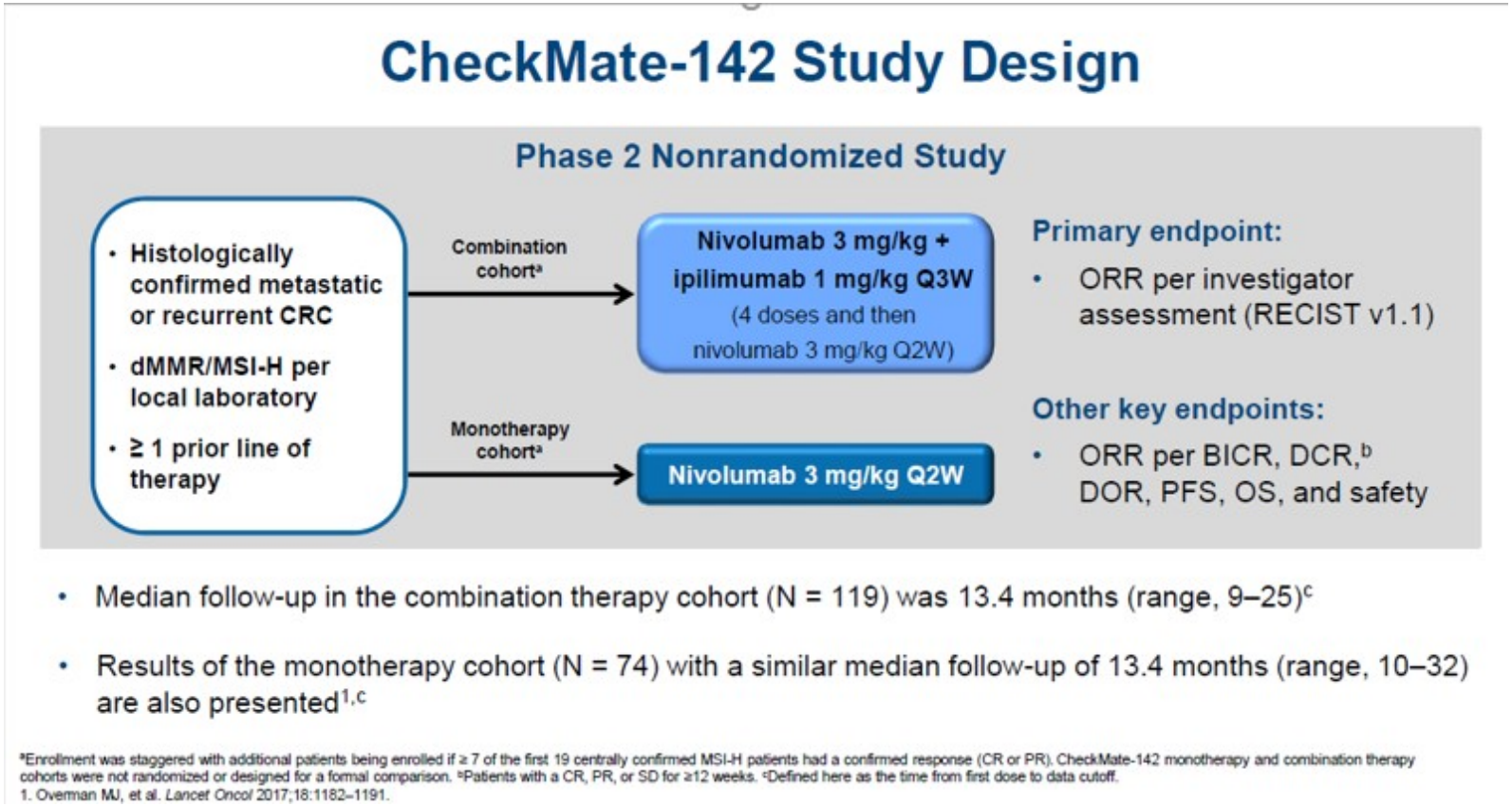


Nivolumab + Ipilimumab Combination in Patients With DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer: First Report of the Full Cohort From CheckMate-142

Thierry André,[1] Sara Lonardi,[2] Ka Yeung Mark Wong,[3] Heinz-Josef Lenz,[4] Fabio Gelsomino,[5] Massimo Aglietta,[6] Michael Morse,[7] Eric Van Cutsem,[8] Ray McDermott,[9] Andrew Graham Hill,[10] Michael B. Sawyer,[11] Alain Hendlisz,[12] Bart Neyns,[13] Magali Svrcek,[1] Rebecca A. Moss,[14] Jean-Marie Ledeine,[15] Z. Alexander Cao,[14] Shital Kamble,[14] Scott Kopetz,[16] Michael J. Overman[16]

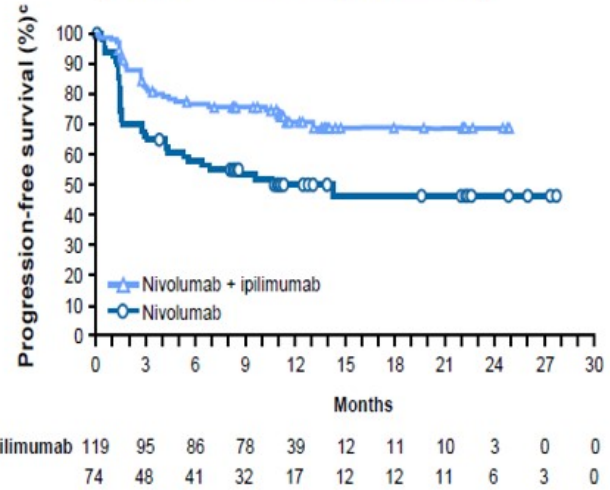
[1]Hôpital Saint Antoine and Sorbonne Universités, UMPC Paris 06, Paris, France; [2]Istituto Oncologico Veneto IOV-IRCSS, Padova, Italy; [3]The University of Sydney, Sydney Medical School, Sydney, Australia; [4]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; [5]University Hospital of Modena, Italy; [6]University of Torino, Turin, Italy; [7]Duke University Office of Research Administration, Durham, NC; [8]University Hospitals Gasthuisberg - Leuven, Leuven, Belgium; [9]St Vincent's University Hospital, Dublin, Ireland; [10]Tasman Oncology Research Pty Ltd, Southport, Queensland, Australia; [11]Cross Cancer Institute, Edmonton, AB, Canada; [12]Institut Jules Bordet, Brussels, Belgium; [13]Universitair Ziekenhuis Brussel, Brussels, Belgium; [14]Bristol-Myers Squibb, Princeton, NJ; [15]Bristol-Myers Squibb, Braine-l'Alleud, Belgium;[16]MD Anderson Cancer Center, Houston, TX

Nivolumab & Ipi MMR-D CRC
(GI-ASCO 2018)



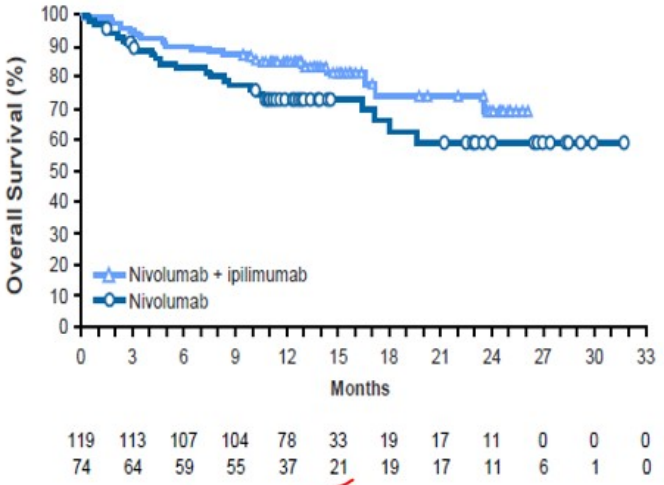
Checkmate 142
PFS and OS

	Nivolumab + ipilimumab[a,b]
9-month rate (95% CI), %	76 (67.0, 82.7)
12-month rate (95% CI), %	71 (61.4, 78.7)



No. at Risk											
Nivolumab + ipilimumab	119	95	86	78	39	12	11	10	3	0	0
Nivolumab	74	48	41	32	17	12	12	11	6	3	0

	Nivolumab + ipilimumab[a,d]
9-month rate (95% CI), %	87 (80.0, 92.2)
12-month rate (95% CI), %	85 (77.0, 90.2)



Nivolumab + ipilimumab	119	113	107	104	78	33	19	17	11	0	0	0
Nivolumab	74	64	59	55	37	21	19	17	11	6	1	0

- With similar follow-up, combination therapy provided improved PFS and OS relative to monotherapy[a,e,f]

[a]Median follow-up was 13.4 months (range, 9–25). [b]Median PFS was not reached (95% CI, not estimable). [c]PFS per investigator assessment. [d]Median OS was not reached (95% CI, 18.0, not estimable).
[e]Median follow-up was 13.4 months (range, 10–32). [f]CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison.

1. Overman MJ, et al. *Lancet Oncol* 2017;18:1182–1191.

- The changing landscape of Management of CRC continues to evolve
- Stratification of Response based on biomarkers and Identification of Mechanism Resistance is needed
- Great Need to move Immunotherapy to First Line therapy in MMR-d Metastatic CRC

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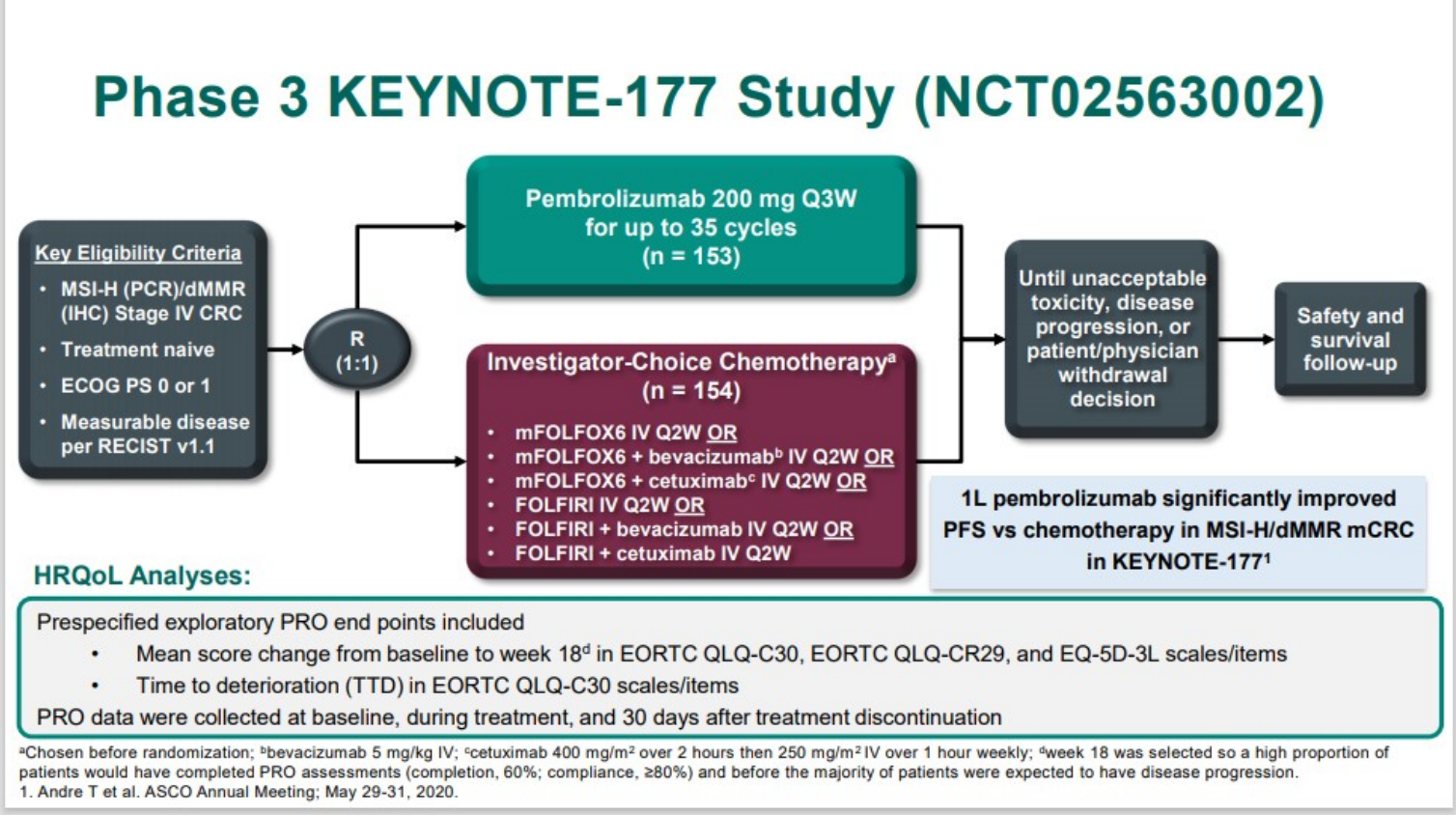
ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*

KEYNOTE 177

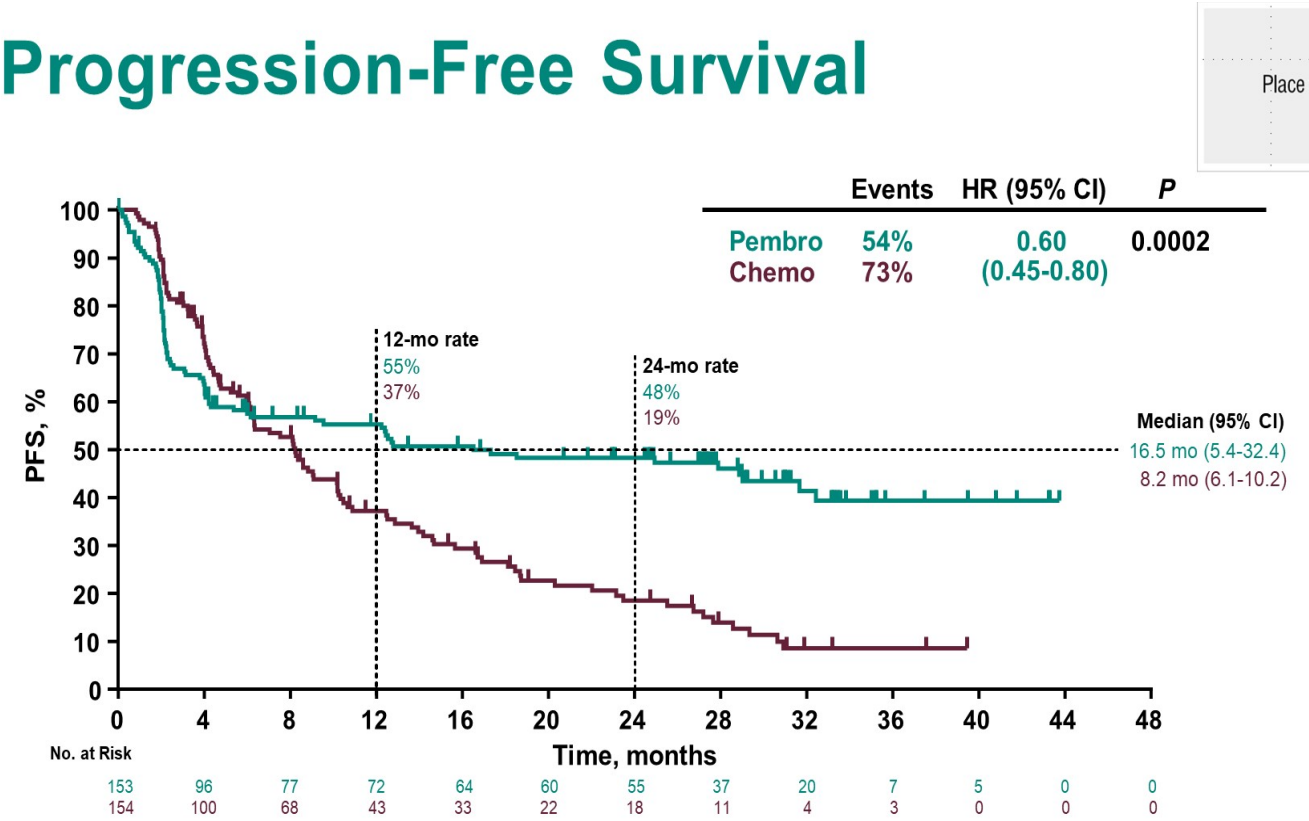
(ASCO 2020)



KEYNOTE 177

(ASCO 2020)

Progression-Free Survival



Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

KEYNOTE 177

(ASCO 2020)

Summary of Best Anti-Tumor Response

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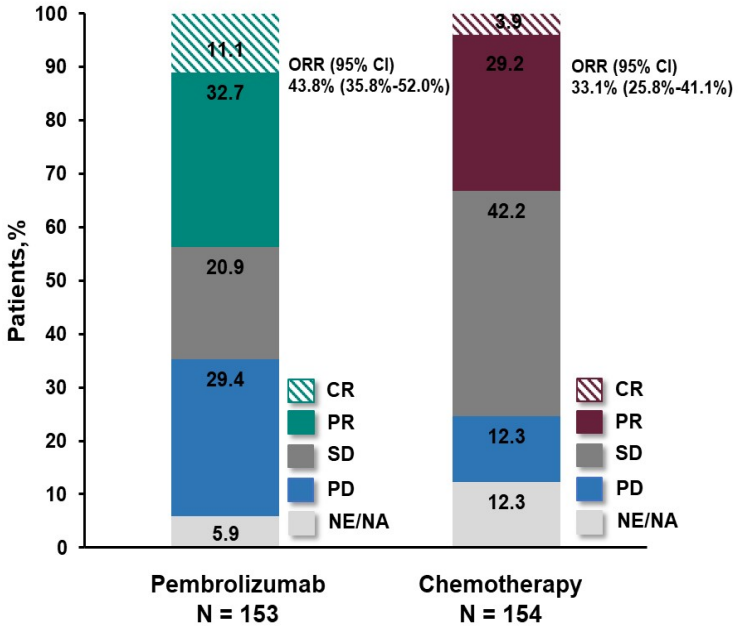
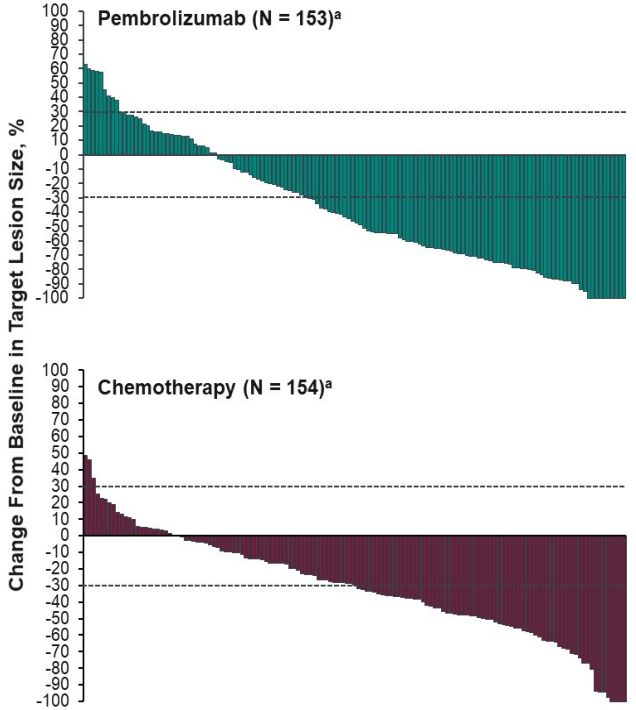




9 (6%) patients in the pembrolizumab arm and 19 (12%) in the chemotherapy arm were not evaluable (NE) or had no assessment (NA); [a]104 of 138 (75%) evaluable patients in the pembrolizumab arm and 111 of 135 (82%) evaluable patients in the chemotherapy arm had a reduction from baseline in target lesion size. Evaluable patients include those with ≥1 post-baseline target lesion imaging assessment in the intention-to-treat population; Data cut-off: 19Feb2020.

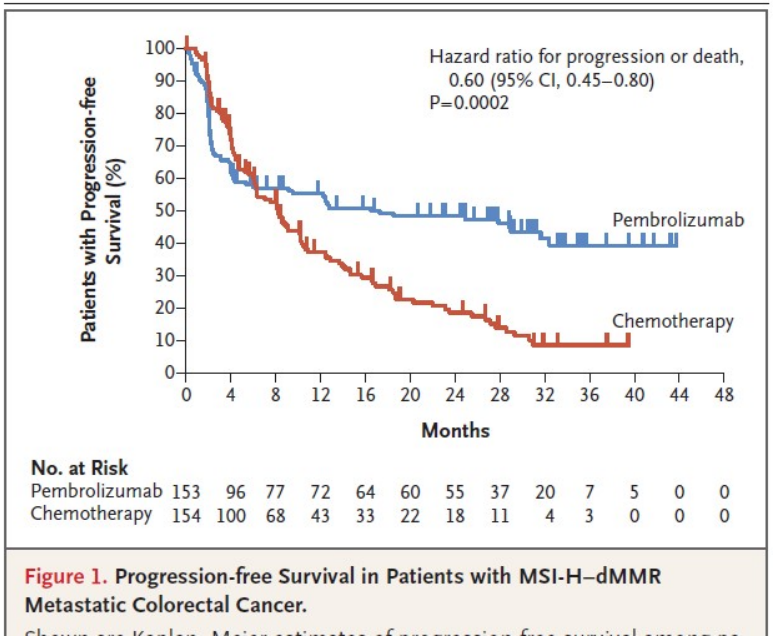
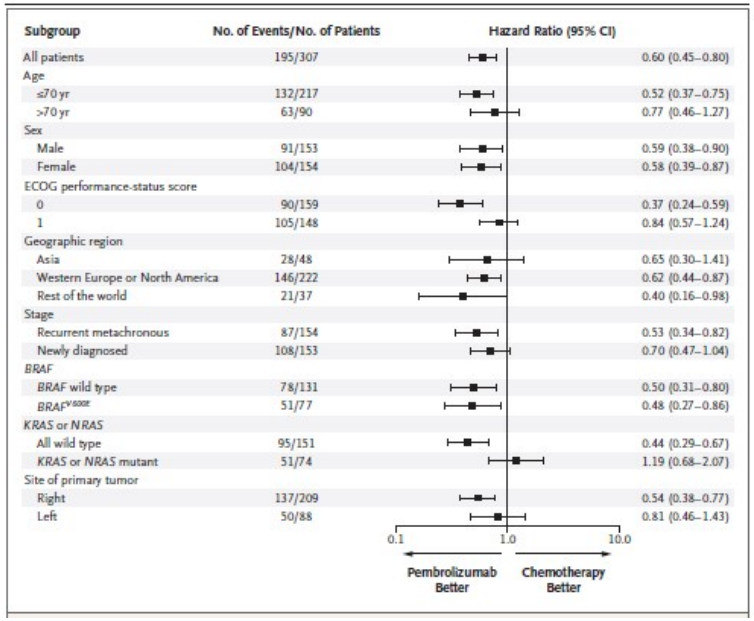


Figure 1. Progression-free Survival in Patients with MSI-H–dMMR Metastatic Colorectal Cancer.

Shown are Kaplan–Meier estimates of progression-free survival among pa



Keynote 177

(ASC0 2020)

Duration of Response

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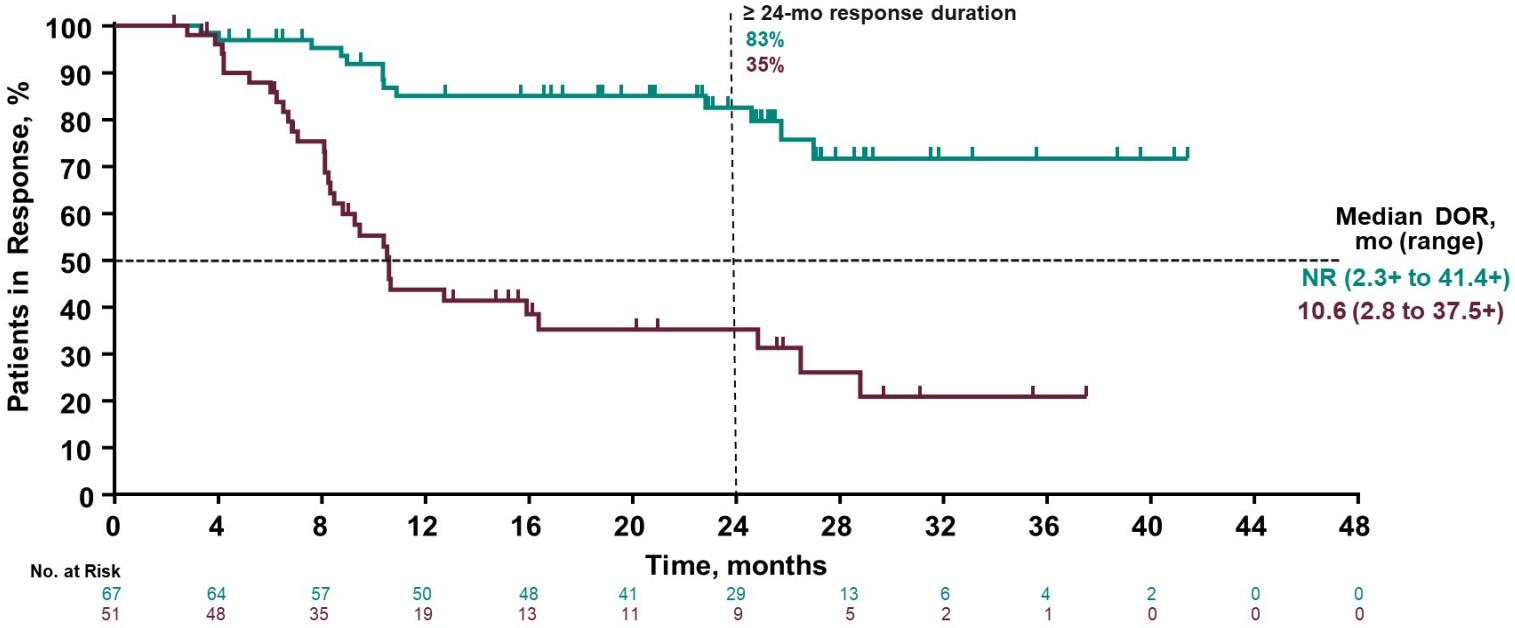

- Median time to response (range) was 2.2 mo (1.8-18.8) and 2.1 (1.7-24.9) for patients in the pembrolizumab and chemotherapy arms

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

Progression-Free Survival
WITH CROSS OVER

Progression-Free Survival 2

Time from randomization to progression on next line therapy or any cause death

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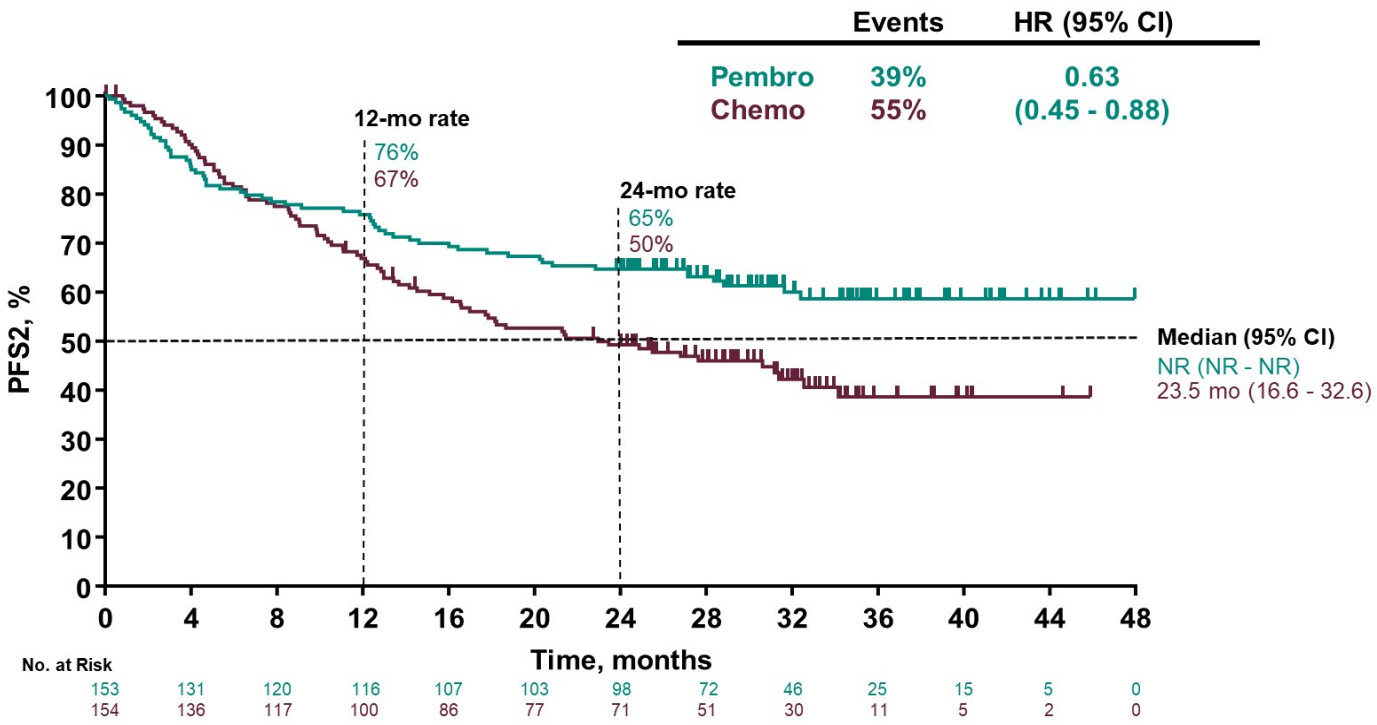

Data cut-off: 19Feb2020; PFS2 assessed per RECIST v1.1 by investigator.

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

INITIAL THERAPY[c]

Patient appropriate for intensive therapy

- FOLFOX ± bevacizumab[d] → Progression → See COL-D (2 of 13)
- or CAPEOX ± bevacizumab[d] → Progression → See COL-D (2 of 13)
- or FOLFOX + (cetuximab or panitumumab)[e,f] (*KRAS/NRAS/BRAF* WT and left-sided tumors only) → Progression → See COL-D (2 of 13)
- or FOLFIRI[g] ± bevacizumab[d] → Progression → See COL-D (3 of 13)
- or FOLFIRI[g] + (cetuximab or panitumumab)[e,f] (*KRAS/NRAS/BRAF* WT and left-sided tumors only) → Progression → See COL-D (3 of 13)
- or FOLFOXIRI[g,h] ± bevacizumab[d] → Progression → See COL-D (4 of 13)
- or ([Nivolumab ± ipilimumab] or pembrolizumab [preferred]*)[i,j,k,l] (dMMR/MSI-H only)[e] → Progression → See COL-D (5 of 13)

Patient not appropriate for intensive therapy

- 5-FU ± leucovorin ± bevacizumab[d]
- or Capecitabine ± bevacizumab[d]
- or (Cetuximab or panitumumab)[e,f] (category 2B) (*KRAS/NRAS/BRAF* WT and left-sided tumors only)
- or (Nivolumab or pembrolizumab [preferred])[i,j,k,l] (dMMR/MSI-H only)[e]
- or Nivolumab + ipilimumab[i,j,k,l] (dMMR/MSI-H only)[e] (category 2B)
- or (Trastuzumab[m] + [pertuzumab or lapatinib])[n] or fam-trastuzumab deruxtecan-nxki[o] (HER2-amplified and *RAS and* BRAF WT)[e]

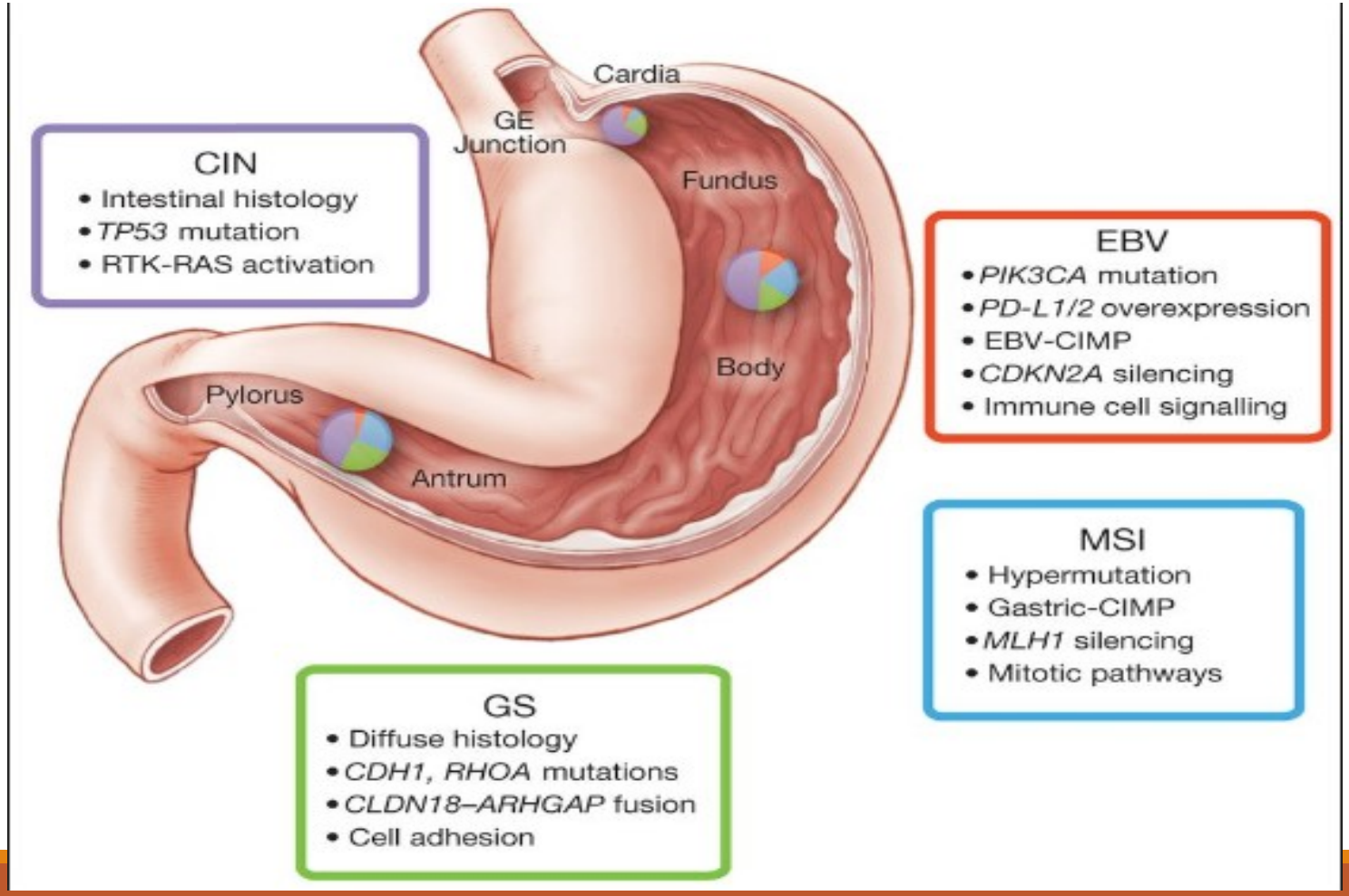
→ Progression

- Improvement in functional status → Consider initial therapy as above[p] or If previous fluoropyrimidine, see COL-D (5 of 13)
- No improvement in functional status → Best supportive care See NCCN Guidelines for Palliative Care

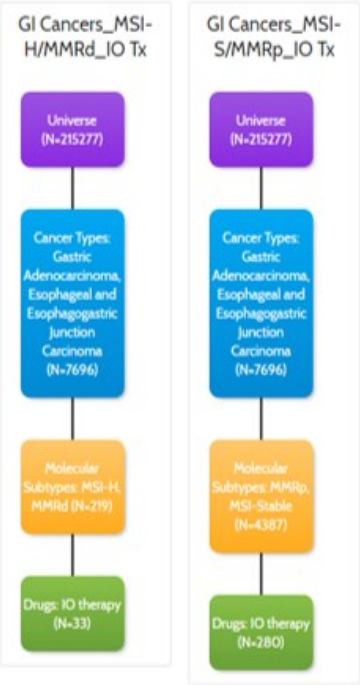
* Patients should be followed closely for 10 weeks to assess for response.

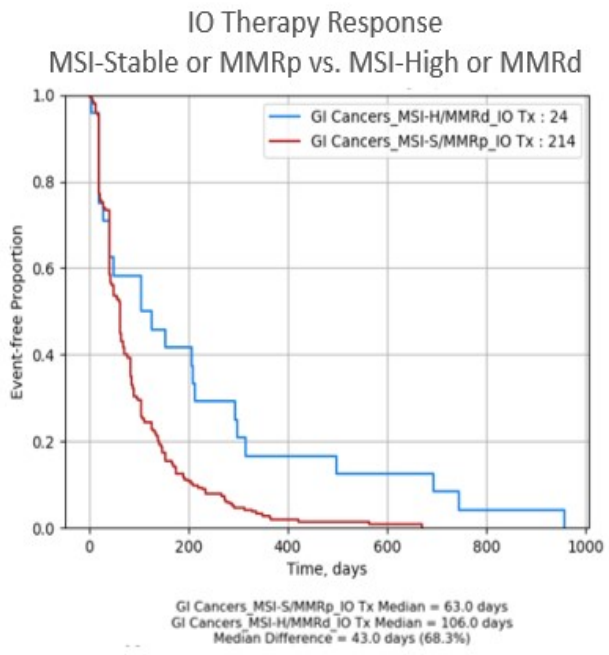
See footnotes on COL-D (7 of 13)

Gastroesophageal & Gastric Cancers



CODEai – IO Therapy in Gastric Adenocarcinoma, Esophageal and Esophagogastric Junction Carcinoma





VIRTUAL 2020 ESMO congress

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiation therapy: first results of the CheckMate 577 study

Ronan J. Kelly,[1] Jaffer A. Ajani,[2] Jaroslaw Kuzdzal,[3] Thomas Zander,[4] Eric Van Cutsem,[5] Guillaume Piessen,[6] Guillermo Mendez,[7] Josephine Feliciano,[8] Satoru Motoyama,[9] Astrid Lièvre,[10] Hope Uronis,[11] Elena Elimova,[12] Cecile Grootscholten,[13] Karen Geboes,[14] Jenny Zhang,[15] Lili Zhu,[15] Ming Lei,[15] Kaoru Kondo,[15] James M. Cleary,[16] Markus Moehler[17]

[1]The Charles A. Sammons Cancer Center at Baylor University Medical Center, Dallas, TX, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Jagiellonian University, John Paul II Hospital, Cracow, Poland; [4]University Hospital of Cologne, Cologne, Germany; [5]University Hospitals Gasthuisberg, Leuven and KULeuven, Leuven, Belgium; [6]University of Lille, Claude Huriez University Hospital, Lille, France; [7]Fundacion Favaloro, Buenos Aires, Argentina; [8]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [9]Akita University Hospital, Akita, Japan; [10]CHU Pontchaillou, Rennes 1 University, Rennes, France; [11]Duke Cancer Institute, Durham, NC, USA; [12]Princess Margaret Cancer Centre, Toronto, ON, Canada; [13]Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [14]UZ Gent, Gent, Belgium; [15]Bristol Myers Squibb, Princeton, NJ, USA; [16]Dana Farber Cancer Institute, Boston, MA, USA; [17]Johannes-Gutenberg University Clinic, Mainz, Germany

Presentation number LBA9

CheckMate 577 study design

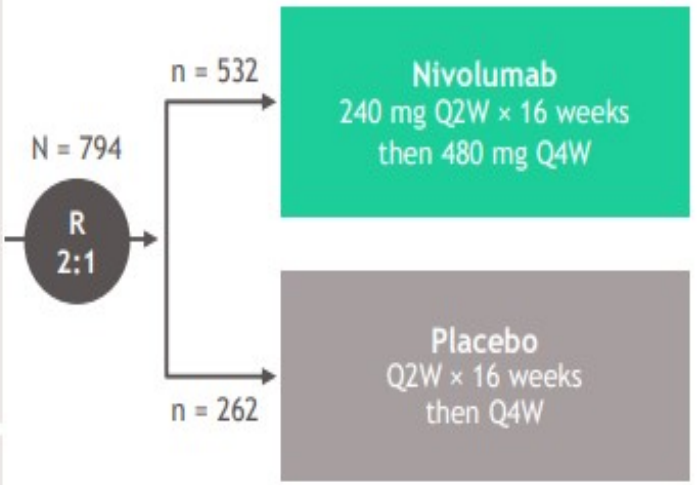
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria

- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors

- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Primary endpoint:

- DFS[e]

Secondary endpoints:

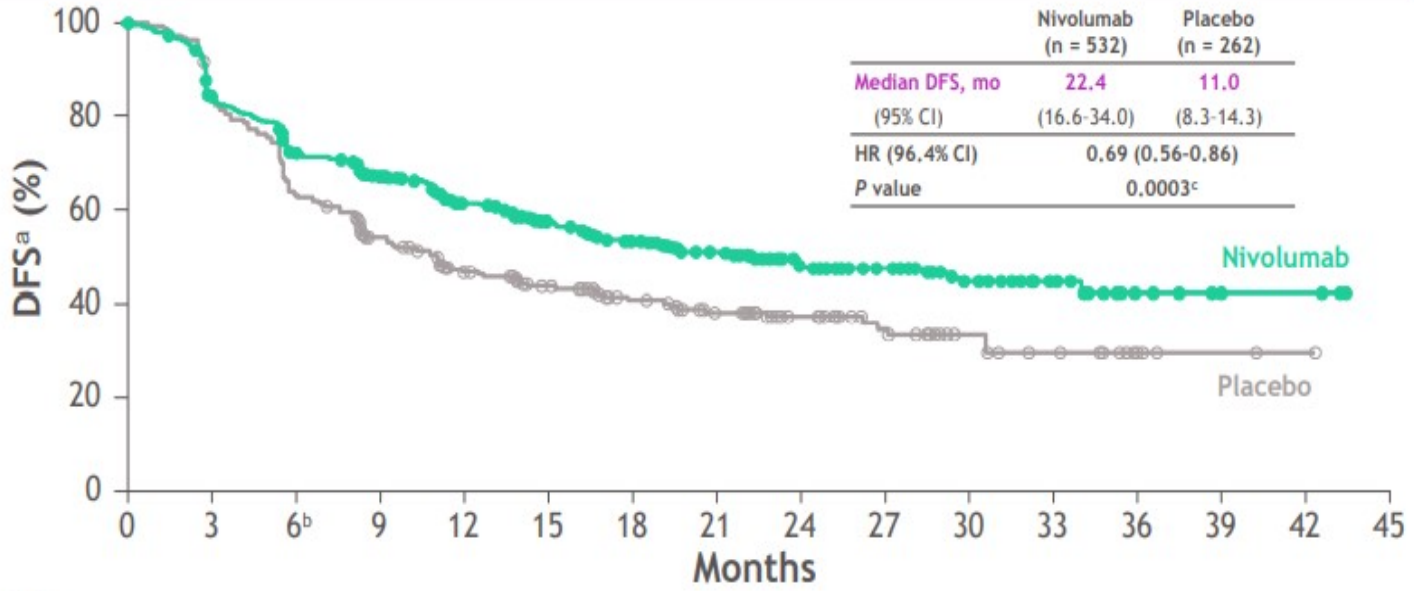
- OS[f]
- OS rate at 1, 2, and 3 years

- Median follow-up was 24.4 months (range, 6.2-44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

CHECKMATE 577
(ESMO 2020)

Disease-free survival



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6-34.0)	(8.3-14.3)
HR (96.4% CI)	0.69 (0.56-0.86)	
P value	0.0003[c]	

No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

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

[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the pre-specified interim analysis required the *P* value to be less than 0.036.

CHECKMATE 577

(ESMO 2020)

Summary

- Nivolumab is the first adjuvant therapy to provide a statistically significant and clinically meaningful improvement in DFS versus placebo in resected EC/GEJC following neoadjuvant CRT
  - 31% reduction in the risk of recurrence or death and a doubling in median DFS
  - DFS benefit across multiple pre-specified subgroups
- Nivolumab was well tolerated with an acceptable safety profile
  - Incidence of serious TRAEs and TRAEs leading to discontinuation were ≤ 9% with nivolumab and 3% with placebo
- These results represent the first advance in years for this group of patients, potentially establishing adjuvant nivolumab as a new standard of care

CheckMate 649 study design

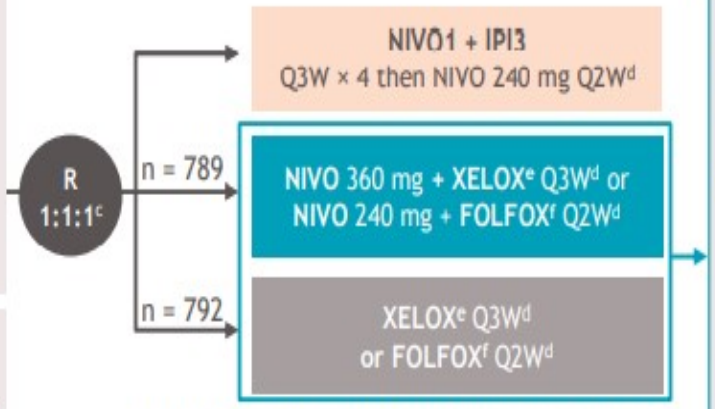
- CheckMate 649 is a randomized, open-label, phase 3 study[a]

Key eligibility criteria

- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors

- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



N = 1581, including 955 patients (60%) with PD-L1 CPS ≥ 5

Dual primary endpoints:

- OS and PFS[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:

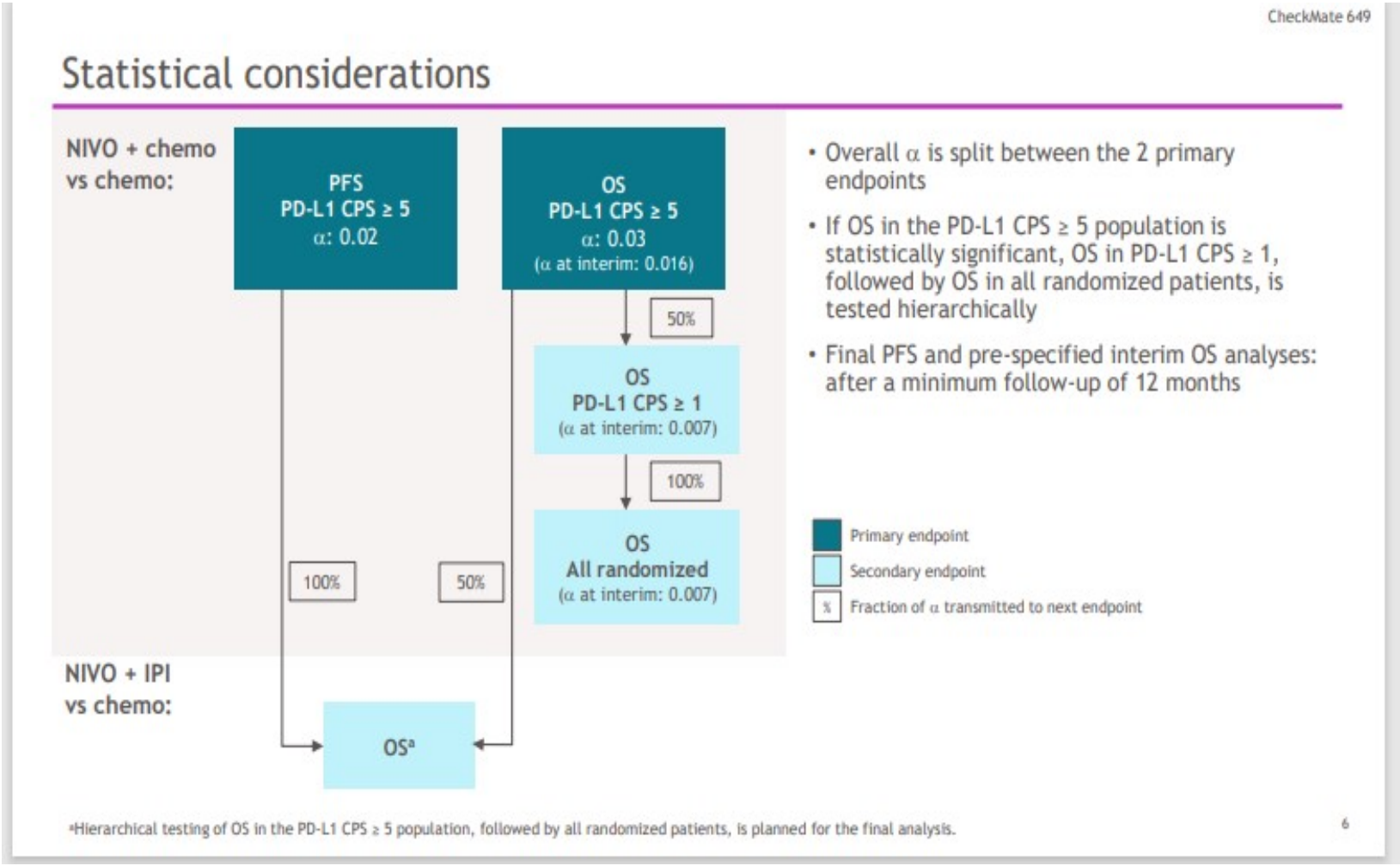
- OS (PD-L1 CPS ≥ 1 or all randomized)
- OS (PD-L1 CPS ≥ 10)
- PFS[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- ORR[g]

- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

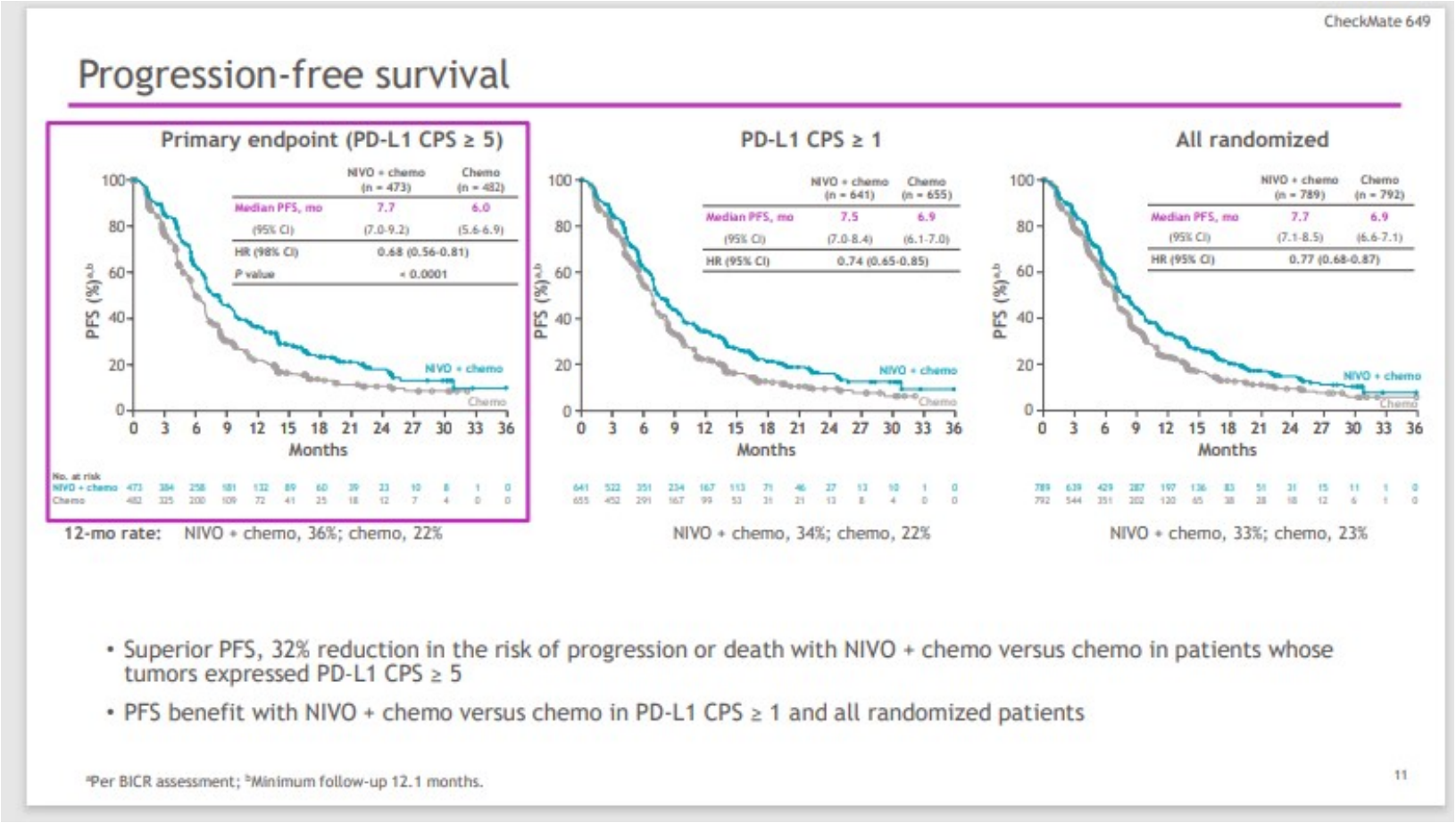
[a]ClinicalTrials.gov number, NCT02872116; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1-14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1-2); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

CHECKMATE 649

(ESMO 2020)



CHECKMATE 649
(ESMO 2020)

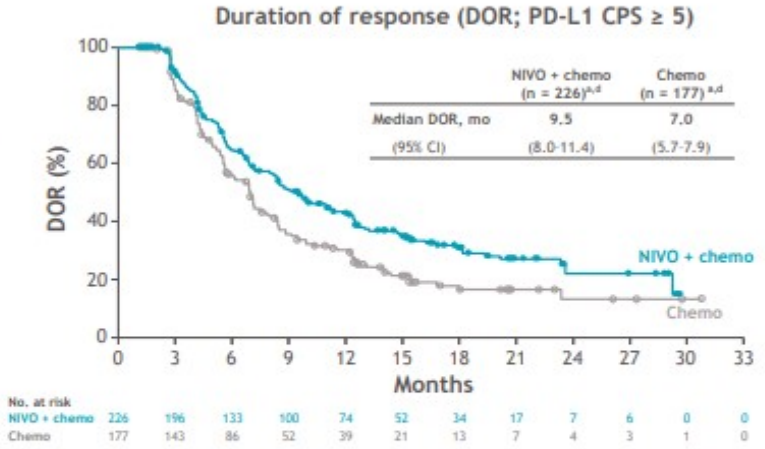


CHECKMATE 649

(ESMO 2020)

Response and duration of response

	PD-L1 CPS ≥ 5	
	NIVO + chemo (n = 378)[a]	Chemo (n = 391)[a]
ORR, %	60	45
95% CI	55-65	40-50
P value[b]	< 0.0001	
Best overall response,[c] %		
Complete response	12	7
Partial response	48	38
Stable disease	28	34
Progressive disease	7	11
Not evaluable	6	10
Median TTR (range), months	1.5 (0.8-10.2)	1.5 (1.0-7.1)



- ORR was higher with NIVO + chemo versus chemo, and responses were more durable

[a]Randomized patients who had target lesion measurements at baseline per BICR assessment; [b]ORR was not formally tested, the pre-specified *P* value is descriptive; [c]Percentages may not add up to 100% due to rounding; [d]Number of responders.

13

CHECKMATE 649

(ESMO 2020)

Summary

- NIVO is the first PD-1–inhibitor to demonstrate superior OS and PFS in combination with chemo versus chemo alone in previously untreated patients with advanced GC/GEJC/EAC
  - Statistically significant and clinically meaningful OS benefit in patients whose tumors expressed PD-L1 CPS ≥ 5 and ≥ 1 and in all randomized patients
  - Survival benefit across multiple pre-specified subgroups (assessed in primary population)
  - PFS benefit in PD-L1 CPS ≥ 5 (statistically significant), PD-L1 CPS ≥ 1, and all randomized patients
- No new safety signals were identified with NIVO + chemo
- **NIVO + chemo represents a new potential standard 1L treatment for patients with advanced GC/GEJC/EAC**

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Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/ gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study

N. Boku[1], M.H. Ryu[2], D.-Y. Oh[3], S.C. Oh[4], H.C. Chung[5], K.-W. Lee[6], T. Omori[7], K. Shitara[8], S. Sakuramoto[9], I.J. Chung[10], K. Yamaguchi[11], K. Kato[1], S.J. Sym[12], S. Kadowaki[13], K. Tsuji[14], J.-S. Chen[15], L.-Y. Bai[16], L.-T. Chen[17], Y.-K. Kang[2]

[1]Division of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea, [3]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [4]Division of Hematology and Oncology, Department of Internal Medicine, College of Medicine, Korea University, Seoul, South Korea, [5]Division of Medical Oncology, Yonsei Cancer Center, Song-Dang Institute for Cancer Research, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea, [6]Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea, [7]Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan, [8]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [9]Department of Gastroenterological Surgery, Saitama Medical University International Medical Center, Hidaka, Japan, [10]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Chonnam National University College of Medicine, Hwasun, South Korea, [11]Department of Gastroenterological Chemotherapy, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan, [12]Department of Internal Medicine, Division of Medical Oncology, School of Medicine, Gachon University Gil Medical Center, Incheon, South Korea, [13]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, [14]Department of Medical Oncology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan, [15]Division of Hematology and Oncology, Department of Internal Medicine, Linkou Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan, [16]Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, and China Medical University, Taichung, Taiwan, [17]National Institute of Cancer Research, National Health Research Institutes, and National Cheng Kung University Hospital, National Cheng Kung University, Tainan, and Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

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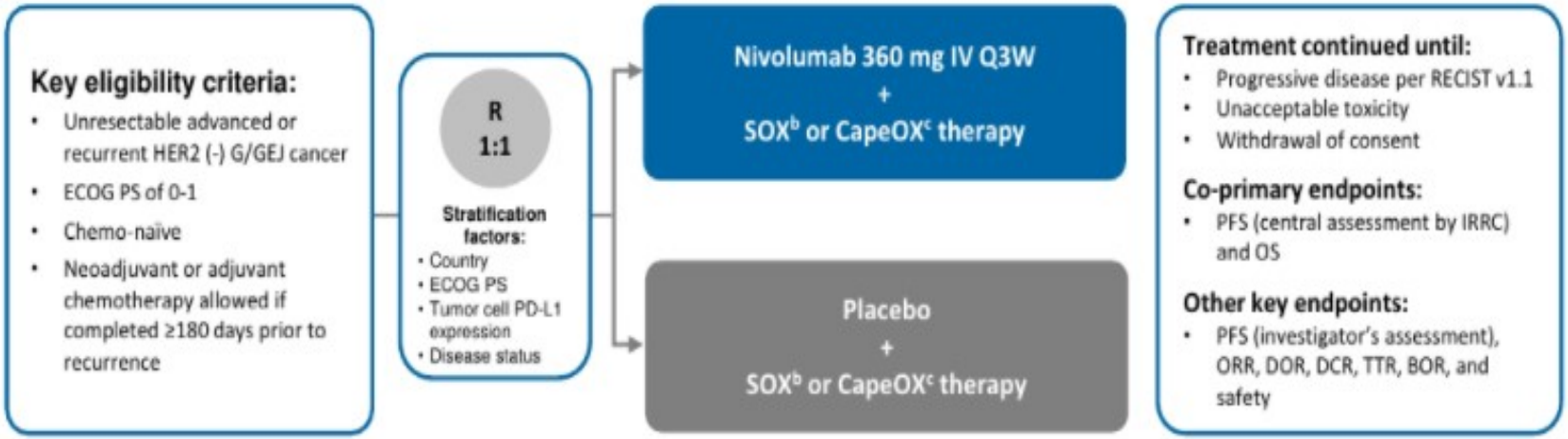
Phase 3 part of ATTRACTION-4: Study Design

- 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

[a]ClinicalTrials.gov Identifier: NCT02746796,
[b]SOX : S-1 (tegafur-gimeracil-oteracil potassium) 40 mg/m^2 orally twice daily (days 1–14) and Oxaliplatin 130 mg/m^2 IV (day 1), q3w
[c]CapeOX : Capecitabine 1000 mg/m^2 orally twice daily (days 1–14) and Oxaliplatin 130 mg/m^2 IV (day 1), q3w

ATTRACTION 4 TRIAL
(ESMO 2020)

ATTRACTION-4

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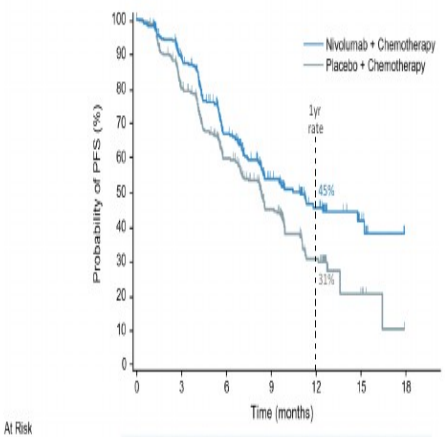
Progression-Free Survival (Interim Analysis)



	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

At Risk							
Nivolumab + Chemotherapy	362	274	168	94	46	13	0
Placebo + Chemotherapy	362	259	160	80	30	5	0

Data cut off : 31 Oct 2018 at interim analysis

9

ATTRACTION-4

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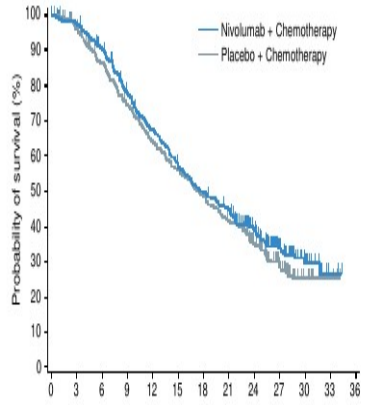
Overall Survival (Final Analysis)



	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	

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

Data cut off : 31 Jan 2020 at final analysis

- NIVO + Chemo demonstrated a statistically significant improvement in PFS, but not in OS
  - Higher overall response rates and more durable responses

- The pre-specified objective of the phase 3 part of ATTRACTION-4 was achieved, showing clinically meaningful efficacy

- NIVO + Chemo demonstrated a manageable safety profile

- NIVO + Chemo could be considered a new first-line treatment option in unresectable advanced or recurrent G/GEJ cancer

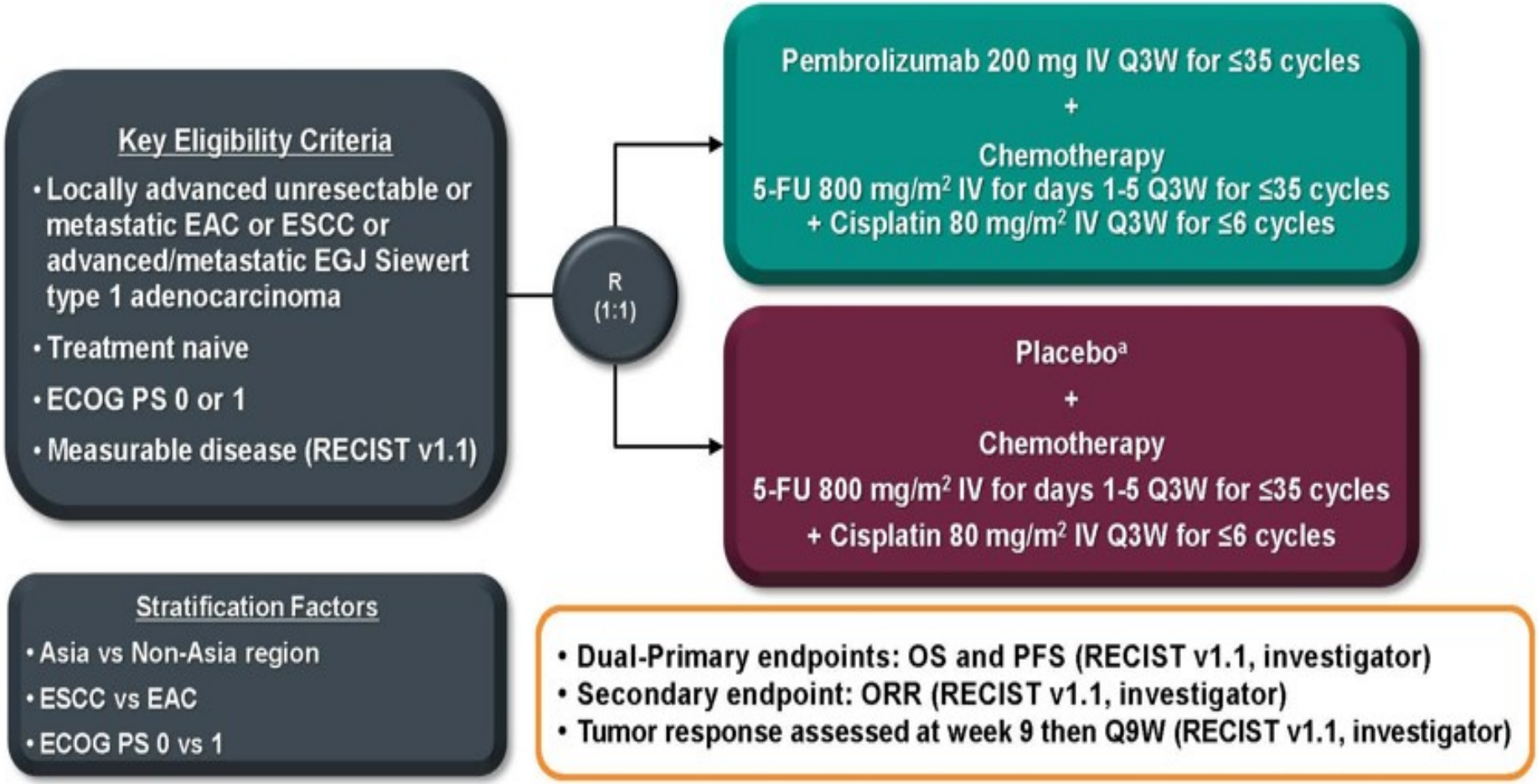
Pembrolizumab Plus Chemotherapy Versus Chemotherapy as First-Line Therapy in Patients With Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study

Ken Kato,[1] Jong-Mu Sun,[2] Manish A. Shah,[3] Peter Enzinger,[4] Antoine Adenis,[5] Toshihiko Doi,[6] Takashi Kojima,[6] Jean-Philippe Metges,[7] Zhigang Li,[8] Sung-Bae Kim,[9] Byoung Chul Cho,[10] Wasat Mansoor,[11] Shau-Hsuan Li,[12] Patrapim Sunpaweravong,[13] Maria Alsina Maqueda,[14] Eray Goekkurt,[15] Qi Liu,[16] Sukrut Shah,[16] Pooja Bhagia,[16] Lin Shen[17]

[1]National Cancer Center Hospital, Tokyo, Japan; [2]Samsung Medical Center, Sungkyunkwan University Seoul, Republic of Korea, [3]Weill Cornell Medical College, New York, NY, USA; [4]Dana Farber Cancer Institute, Boston, MA, USA; [5]IRCM, Inserm, Université Montpellier, ICM, Montpellier, France; [6]National Cancer Center Hospital East, Kashiwa, Japan;[7]CHU Brest – Institut de Cancerologie et d'Hematologie ARPEGO Network, Brest, France; [8]Shanghai Chest Hospital Esophageal Disease Center, Shanghai, China; [9]Asan Medical Center, Seoul, Republic of Korea; [10]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; [11]Christie Hospital NHS Trust, Manchester, United Kingdom; [12]Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan;[13]Prince of Songkla University Hospital, Songkhla, Thailand; [14]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [15]Hematology Oncology Practice Eppendorf, and University Cancer Center Hamburg, Hamburg, Germany; [16]Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; [17]Peking University Cancer Hospital & Institute; Beijing, China

Kato KN590 ESMO 2020

KEYNOTE-590 Study Design (NCT03189719)

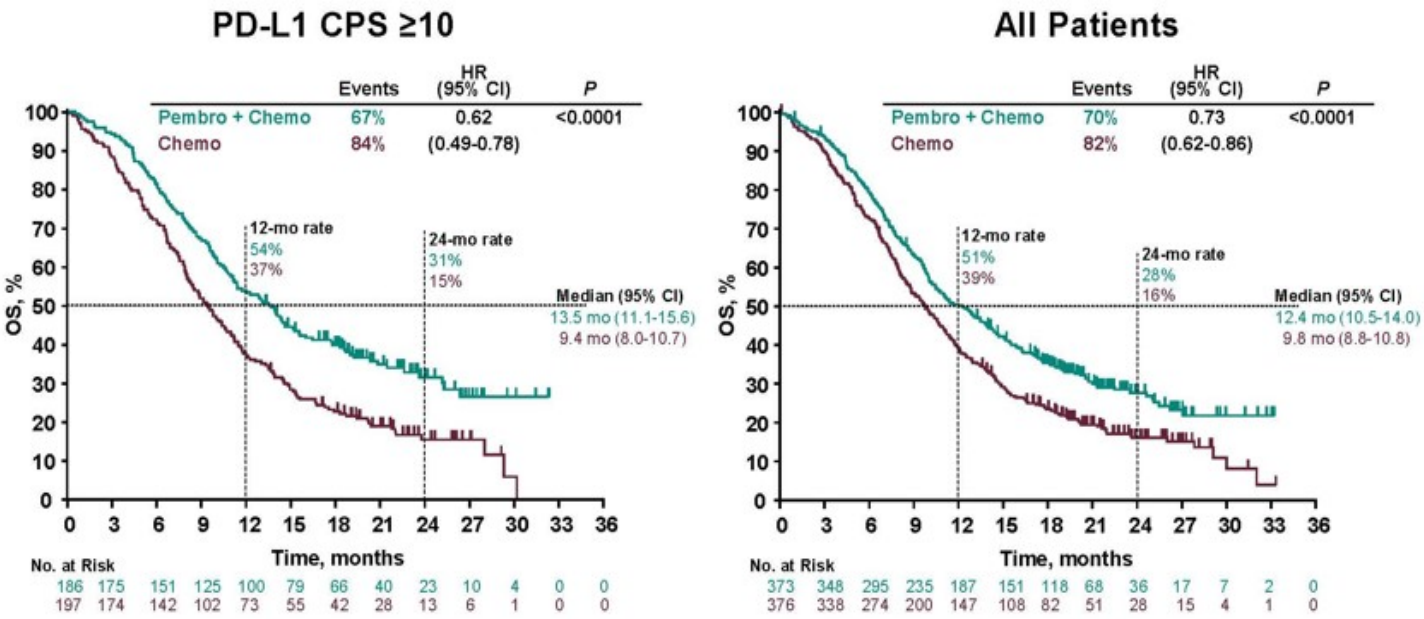


[a]Saline IV Q3W for ≤35 cycles. All treatments were continued for the specified number of cycles or until disease progression, intolerable toxicity, withdrawal of consent, or physician decision; EAC, esophageal adenocarcinoma; EGJ, esophagogastric junction, ESCC, esophageal squamous cell carcinoma.

KEYNOTE 590
(ESMO 2020)

Kato KN590 ESMO 2020

Overall Survival

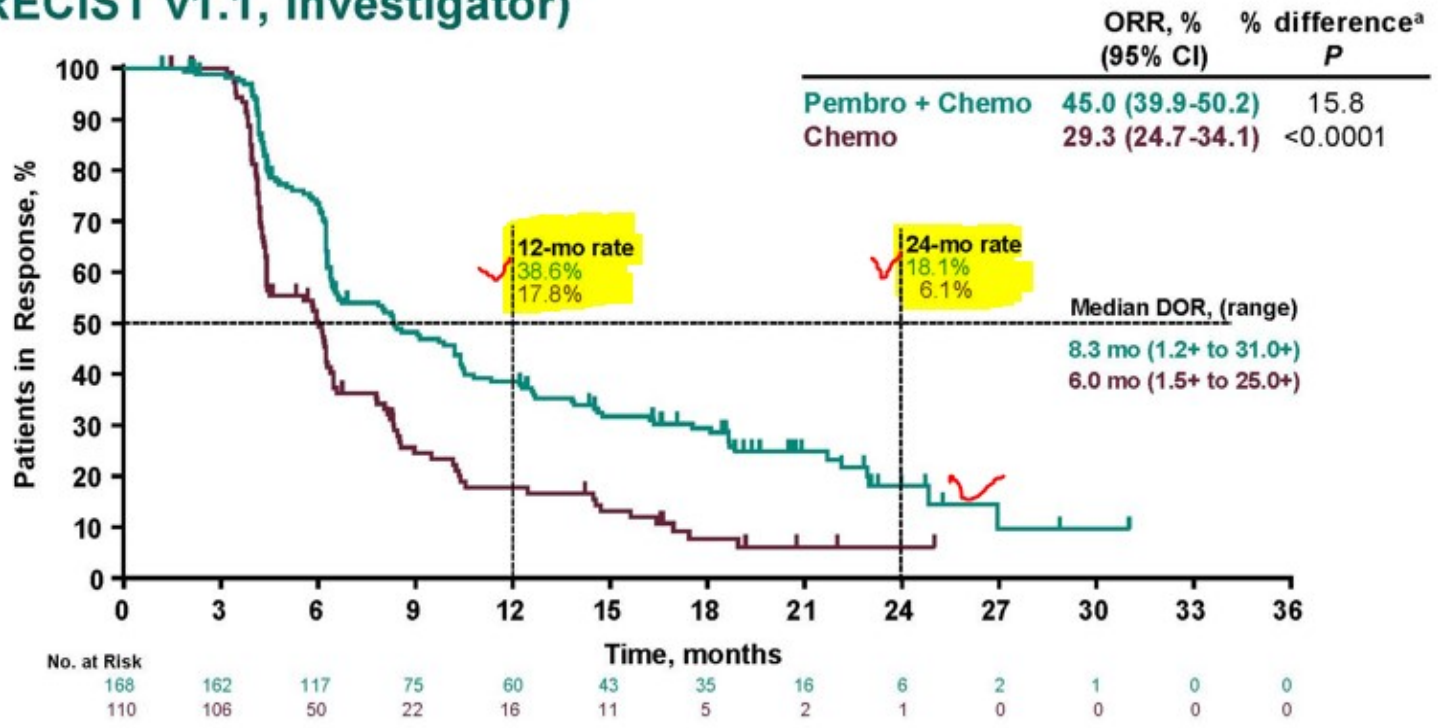


Data cut-off: July 2, 2020.

KEYNOTE 590
(ESMO 2020)

Kato KN590 ESMO 2020

Response Rate and Duration: All Patients
(RECIST v1.1, investigator)



[a]Estimate based on Miettinen & Nurminen method stratified by geographic region, histology, and ECOG performance status; Data cut-off: July 2, 2020.

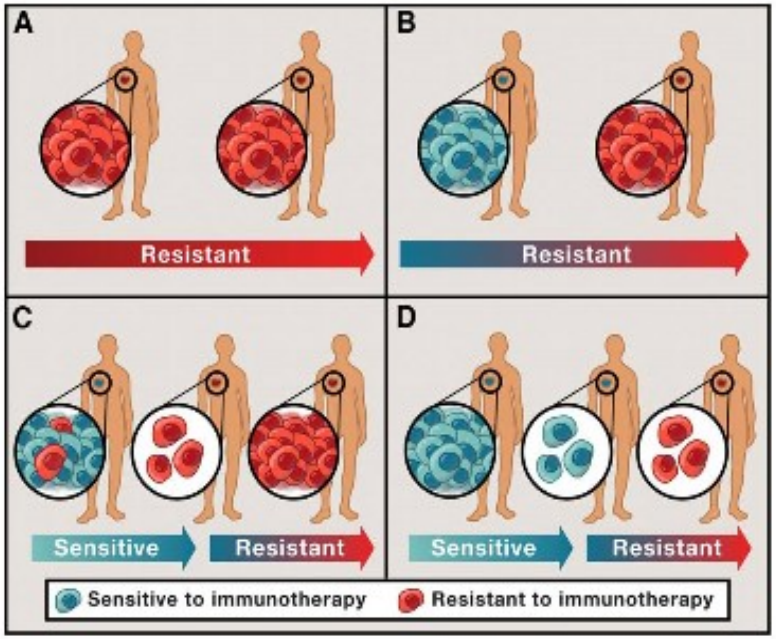
KEYNOTE 590 ESMO 2020

- First-line pembrolizumab plus chemotherapy vs chemotherapy plus placebo provided a statistically significant and clinically meaningful improvement in OS, PFS, and ORR in patients with locally advanced and metastatic esophageal cancer including EGJ adenocarcinoma
  - Superior OS: ESCC CPS ≥10 (HR 0.57, *P*<0.001), ESCC (HR 0.72, *P*=0.006), CPS ≥10 (HR 0.62, *P*<0.001), all patients (HR 0.73, *P*<0.001)
  - Superior PFS: ESCC (HR 0.65), CPS ≥10 (HR 0.51), all patients (HR 0.65), all *P*<0.001
  - Superior ORR: all patients (45.0% vs 29.3%, Δ15.8%, *P*<0.001)
- Comparable safety profile between the two treatment groups
  - No new safety signals detected
- Pembrolizumab plus chemotherapy should be a new standard-of-care as first-line therapy in patients with locally advanced and metastatic esophageal cancer including EGJ adenocarcinoma

Resistance Mechanism of Immunotherapy

Intrinsic Resistance Mechanisms to Immunotherapy

Scenarios that intrinsic resistance can be developed

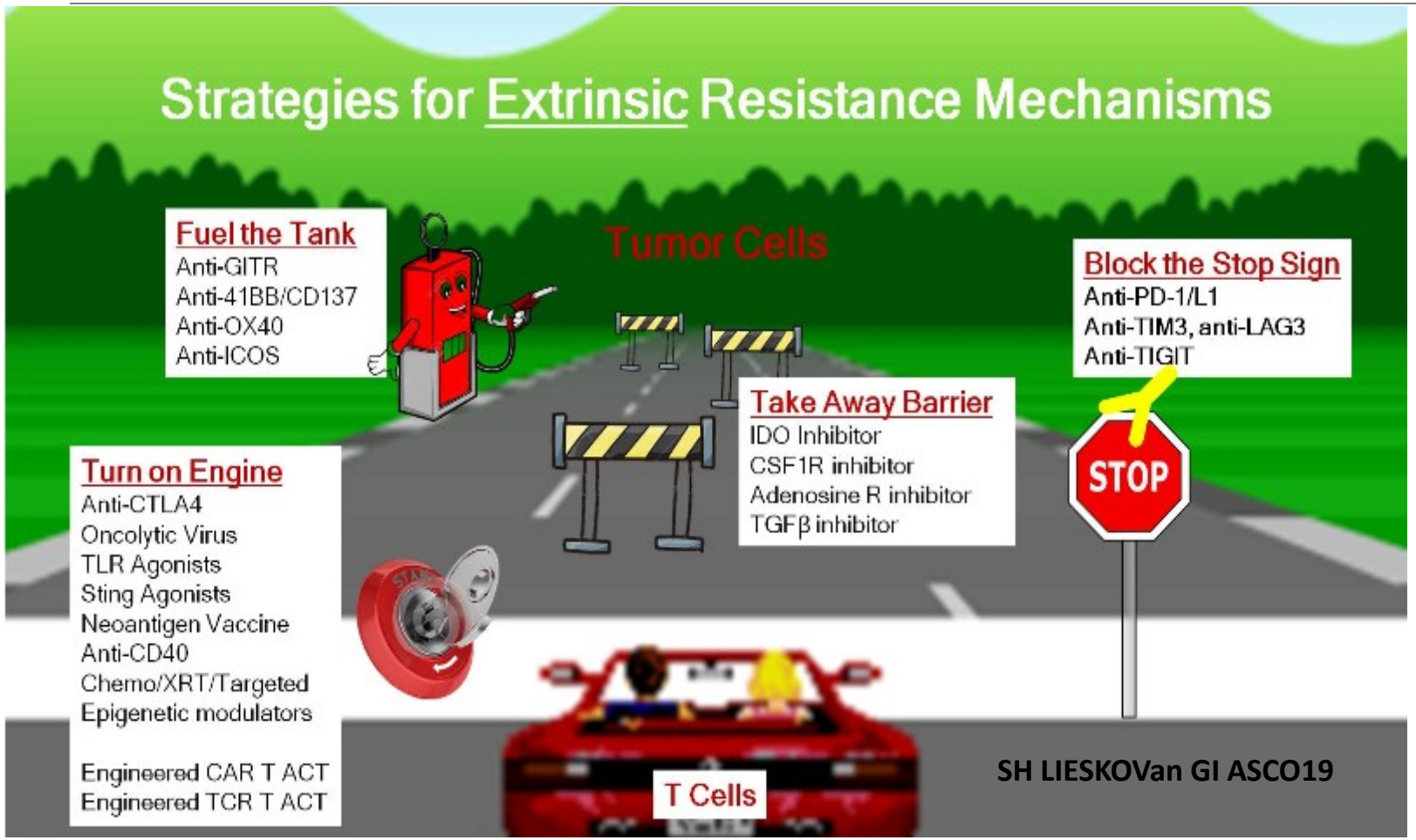


Primary resistance:
Immune escape mechanisms that exist in the non-responding patients

Acquired resistance:
Immune escape mechanisms that developed after an initial response

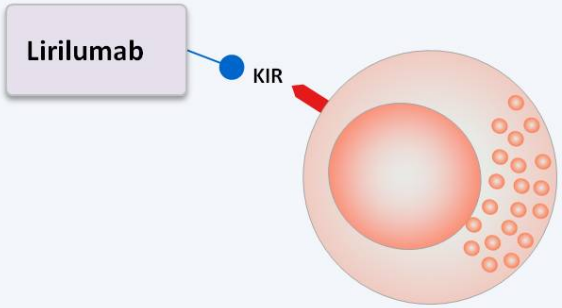
Sharma, Hu-Lieskovan, Wargo, Ribas. Cell, 2017
Hu-Lieskovan and Ribas. Cancer Journal. 2017

Mechanism of Resistance of Immunotherapy



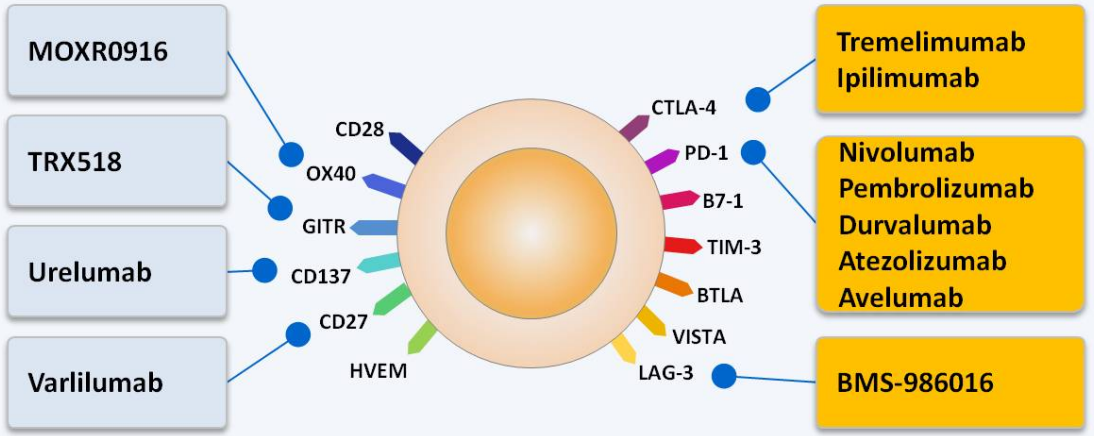
Targeting Checkpoints as an Approach to Cancer Therapy

Select Agents Targeting NK Cells (Innate Immunity)



Adapted from Pardoll et al.[1]

Select Agents Targeting T Cells (Adaptive Immunity)



Adapted from Mellman et al and Pardoll et al.[1,2]

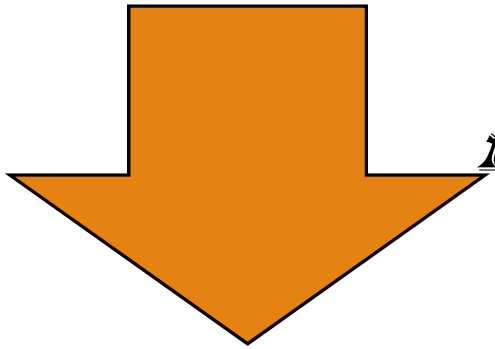
Blocking agents | **Stimulating agents**

*

CTLA-4=cytotoxic T-lymphocyte antigen-4; GITR=glucocorticoid-induced TNFR family related gene; KIR=killer-cell immunoglobulin-like receptor; LAG-3=lymphocyte-activation gene-3; NK=natural killer; PD-1=programmed death-1; PD-L1=programmed death ligand-1.

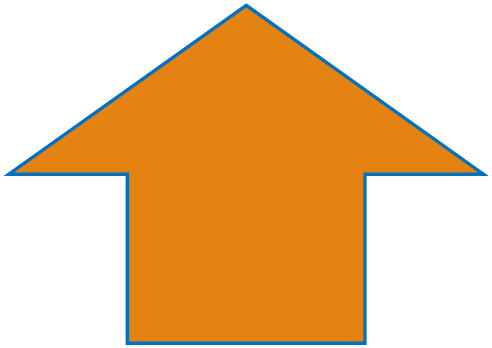
1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264. 2. Mellman I et al. *Nature*. 2011;480(7378):480-489. 3. Clinicaltrials.gov.

Treatment Decision-Making

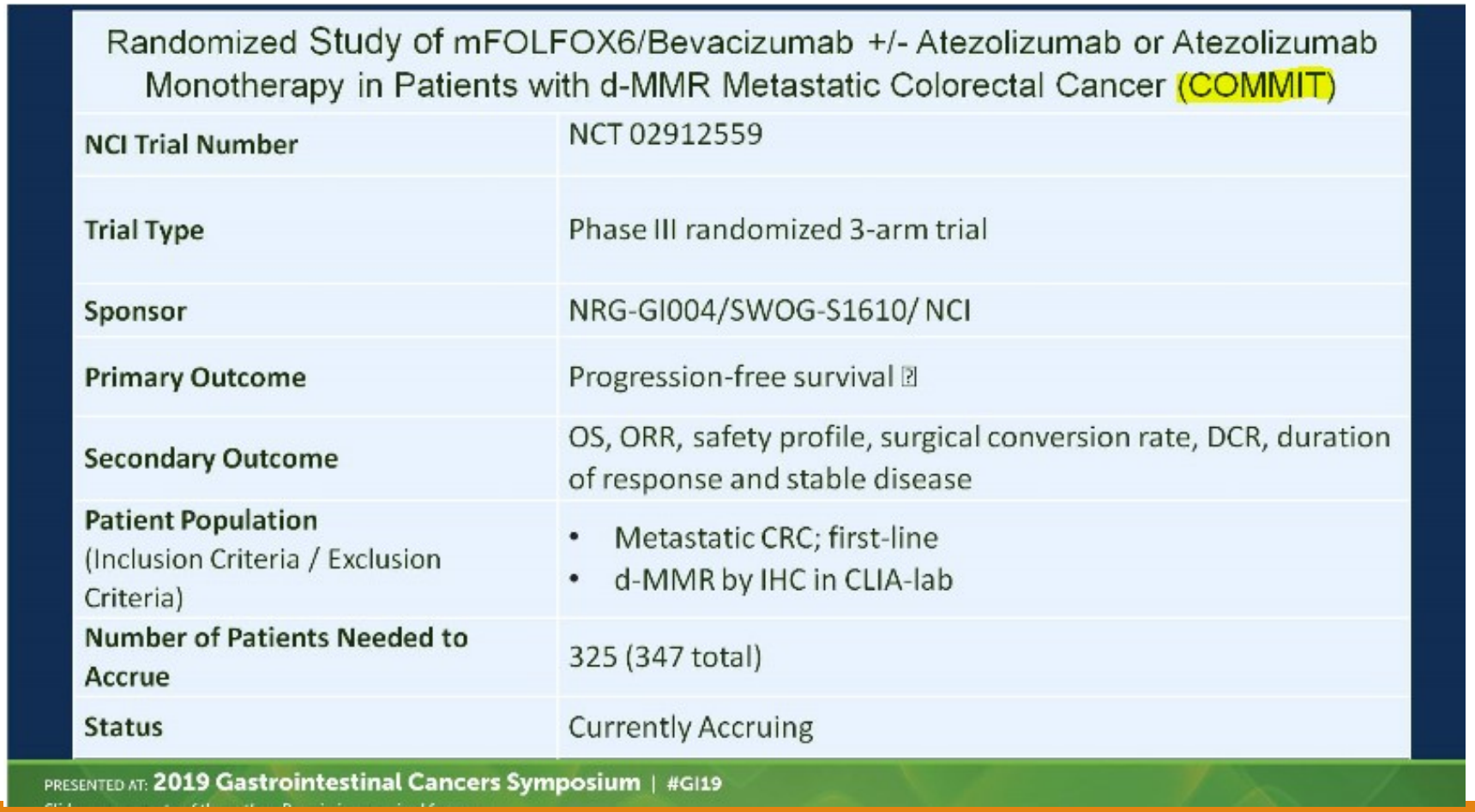


RECURRENCE RISK
ABSOLUTE TREATMENT BENEFIT

TOXICITY
COST



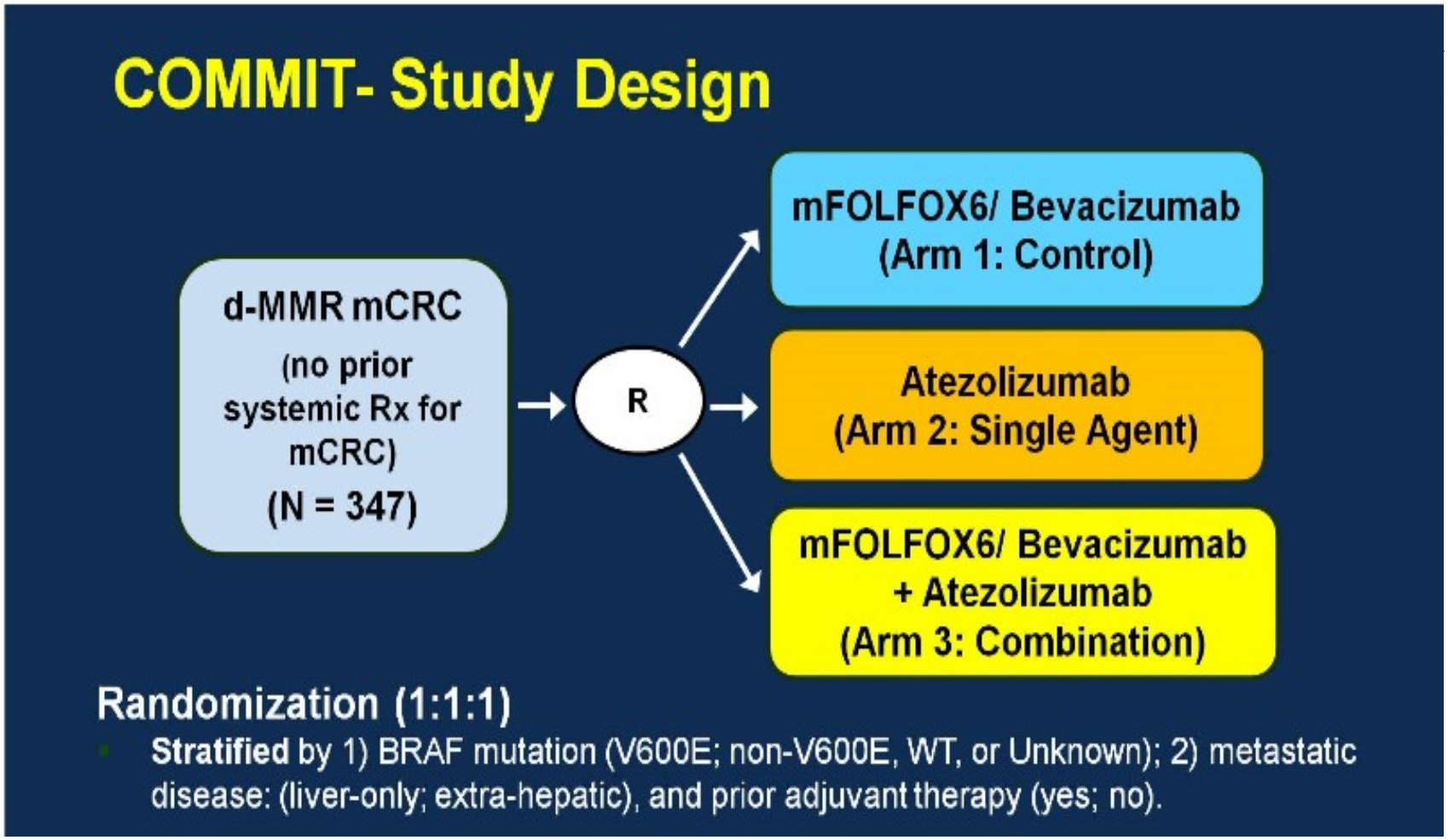
The COMMIT Trial Stage IV CRC MMRd



Randomized Study of mFOLFOX6/Bevacizumab +/- Atezolizumab or Atezolizumab Monotherapy in Patients with d-MMR Metastatic Colorectal Cancer (COMMIT)	
NCI Trial Number	NCT 02912559
Trial Type	Phase III randomized 3-arm trial
Sponsor	NRG-GI004/SWOG-S1610/ NCI
Primary Outcome	Progression-free survival
Secondary Outcome	OS, ORR, safety profile, surgical conversion rate, DCR, duration of response and stable disease
Patient Population (Inclusion Criteria / Exclusion Criteria)	• Metastatic CRC; first-line • d-MMR by IHC in CLIA-lab
Number of Patients Needed to Accrue	325 (347 total)
Status	Currently Accruing

PRESENTED AT: **2019 Gastrointestinal Cancers Symposium** | #GI19

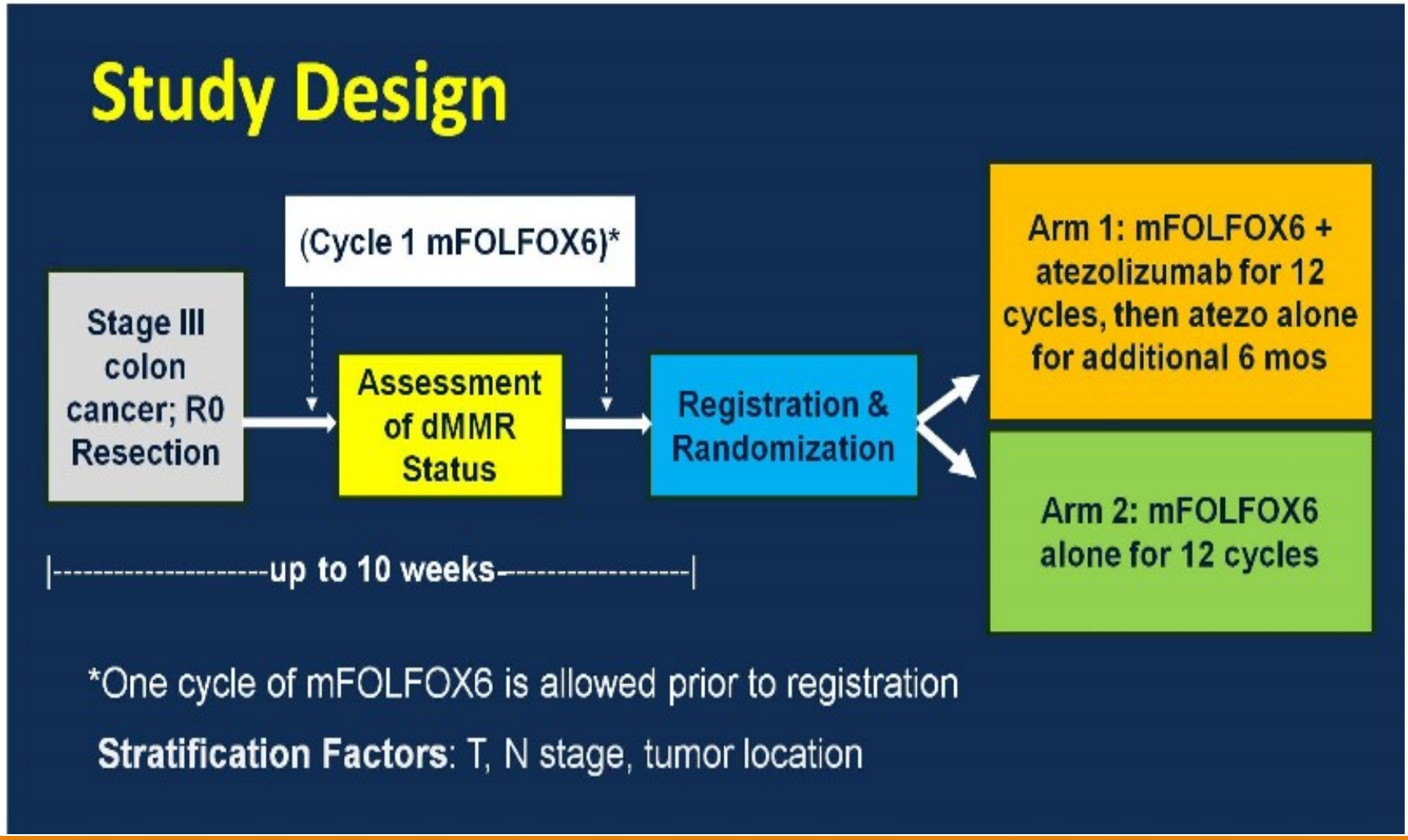
The COMMIT Trial Stage IV CRC MMRd



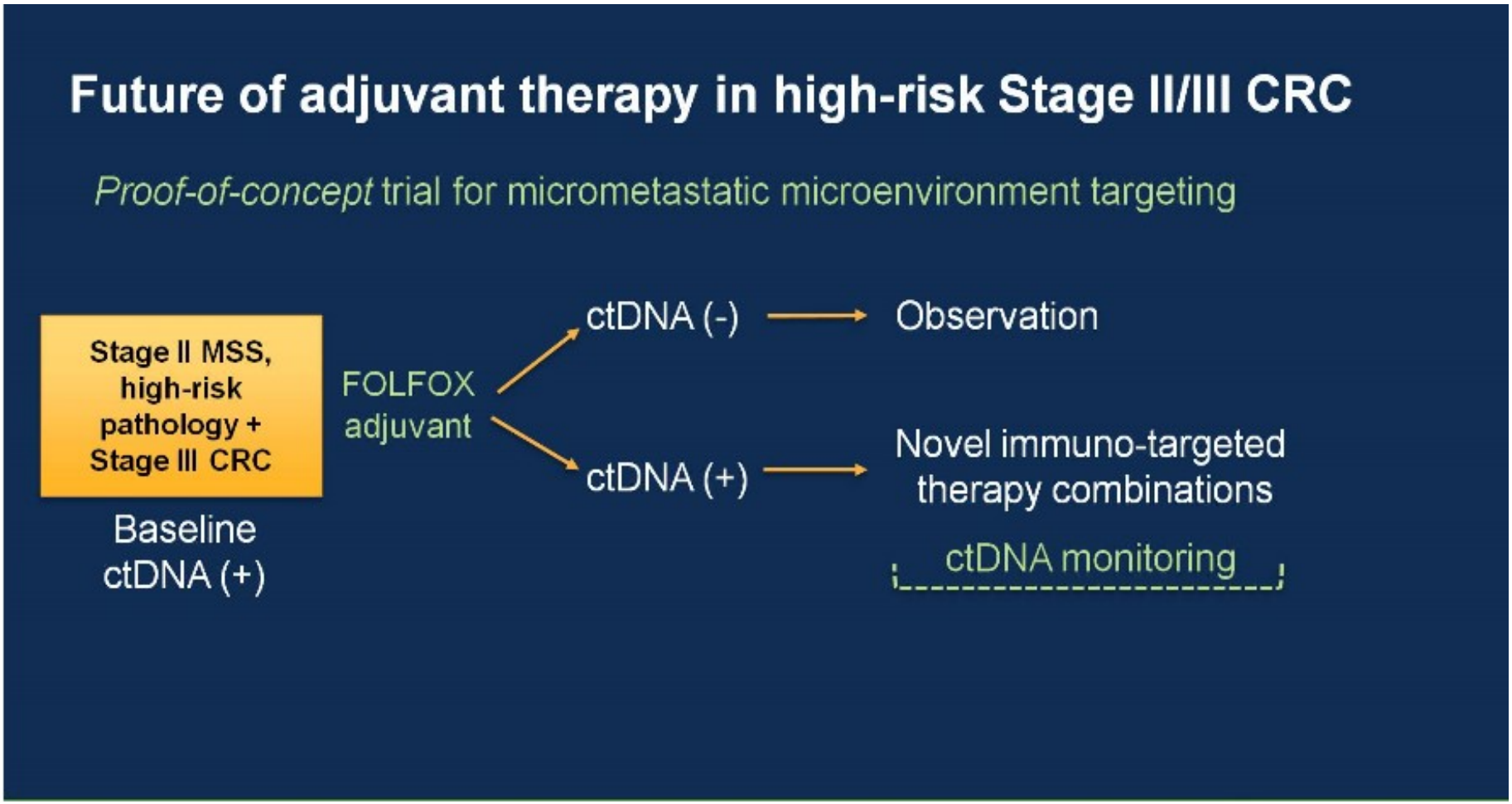
The ATOMIC Trial stage III CRC MMRd

mFOLFOX6 with or without Atezolizumab in Patients with Stage III Colon Cancer and Deficient DNA Mismatch Repair (ATOMIC)	
NCI Trial Number	NCT02912559
Trial Type	Phase III Adjuvant Trial
Sponsor	Alliance A021502/ NCI
Primary Outcome	Disease-free survival
Secondary Outcome	OS, adverse event profile
Patient Population (Inclusion Criteria / Exclusion Criteria)	• Resected stage III adenocarcinoma (any T, $N_{1-2}M_0$). • d-MMR by IHC (local or reference lab)
Number of Patients Needed to Accrue	557 (700 total)
Status	Currently Accruing

The ATOMIC Trial stage III CRC MMRd



Future of Immunotherapy in CRC MMR-Deficient



In CONLCUSION

- Immunotherapy is new standard Now for Metastatic CRC MMRd
- The Treatment Paradigm of Gastric /GE junction carcinoma is an evolving process
- The addition of Nivolumab in the adjuvant after Preopertaive Chemo- radiotherapy followed by Surgery of Esophageal/ GE carcinoma led to a significant improvement in DFS
  - (22 months Vs 11 months) with P= 0.003 (Checkmate 577)
  - Awaiting for FDA Approval
- Nivo + Chemotherapy will represent a new standard of care for metastatic Gastric adenocarcinoma / Esophageal/ GE
  - In the Asian Population improvement of PFS 11.45 Vs (Attraction4)
- Pembro + Chemotherapy should also be new standard for metastatic Esophageal Carcinoma Including GE junction adeno