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Immunotherapy for the Treatment of Hepatocellular Carcinoma and Microsatellite Instability – High Cancers

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- No relevant financial relationships to disclose

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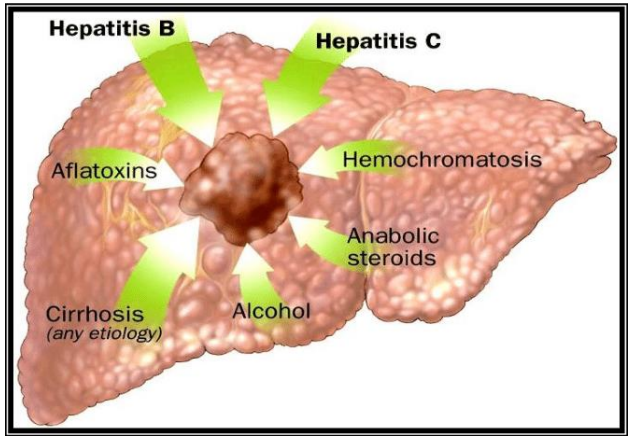
Immunotherapy for HCC

Background

- HCC is the most common type of primary liver cancer
- Often associated with cirrhosis
- 3rd leading cause of cancer death worldwide
- Treatment options:
  - Curative: orthotopic liver transplantation, surgical resection
  - Many patients are ineligible for surgery/transplant
  - Liver Directed Therapy: Chemoembolization, radiofrequency ablation, microwave ablation, radiation
  - Palliative systemic therapy: chemotherapy, targeted therapy and immunotherapy



Immunotherapeutic Strategies in HCC

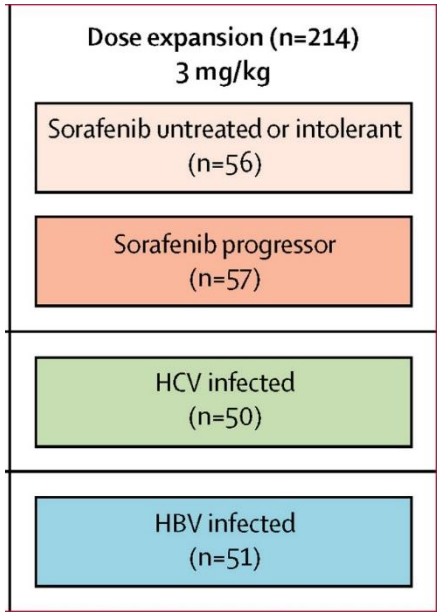
- **Checkpoint inhibition**
- Blocking inhibitory cytokines
- Vaccine therapies
- Oncolytic viruses
- Adoptive cell therapy

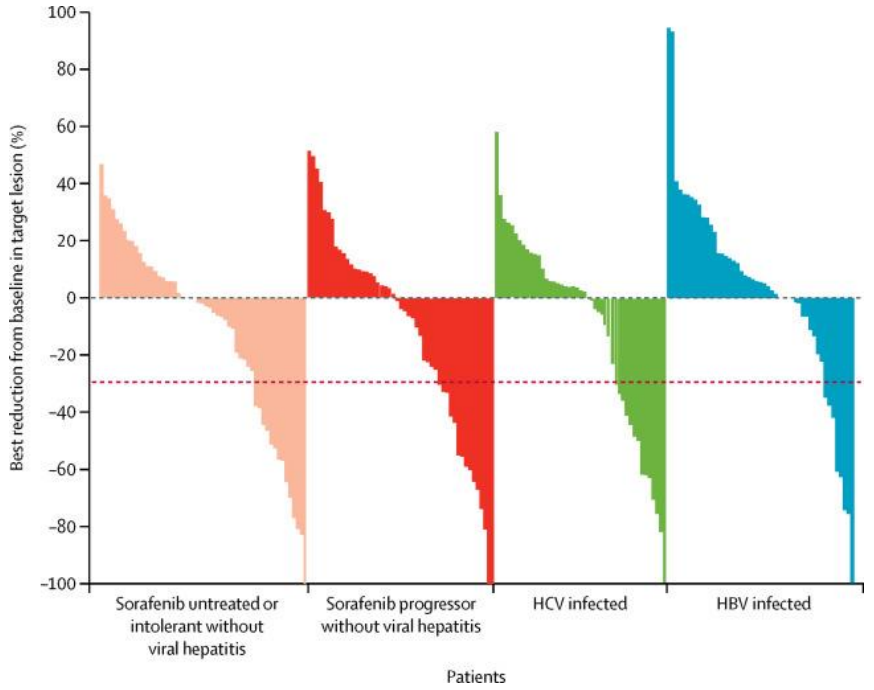
Approved checkpoint inhibitors for HCC

Drug	Approved	Study	Indication	Dose
Nivolumab	2017a	Checkmate 040 Ph I/II	Advanced HCC with previous sorafenib	240 mg Q2W or 480 mg Q4W
Pembrolizumab	2018a	Keynote 224 Ph II	Advanced HCC with previous sorafenib	200 mg Q3W
Nivolumab + Ipilimumab	2020a	Checkmate 040 Ph II/III	Advanced HCC with previous sorafenib	Nivo 1mg/kg + Ipi 3mg/kg Q3W x4, then Nivo 240mg Q2W
Atezolizumab + bevacizumab	*2020*	*IMBRAVE 150*	*Advanced HCC 1st line setting*	*Atezolizumab 1200 mg + bevacizumab 15mg/kg Q3W*

CheckMate 040: Nivolumab

- Phase I/II Advanced HCC **CPT A or B7**
- 68% prior sorafenib
- Results:
  - ORR: **20%,** 3 CR, 39 PR
  - @ 6 mo: OS = 83%, PFS = 37%
  - **@ 9 mo: OS = 74%,** PFS = 28%
- No difference if previously treated with sorafenib, No difference in AEs if HBV/HCV(+)
- Gr 3/4 TrAE: elevation of AST/ALT, elevation of bilirubin, and hepatitis
- FDA 2017: accelerated approval for RR and durability of response

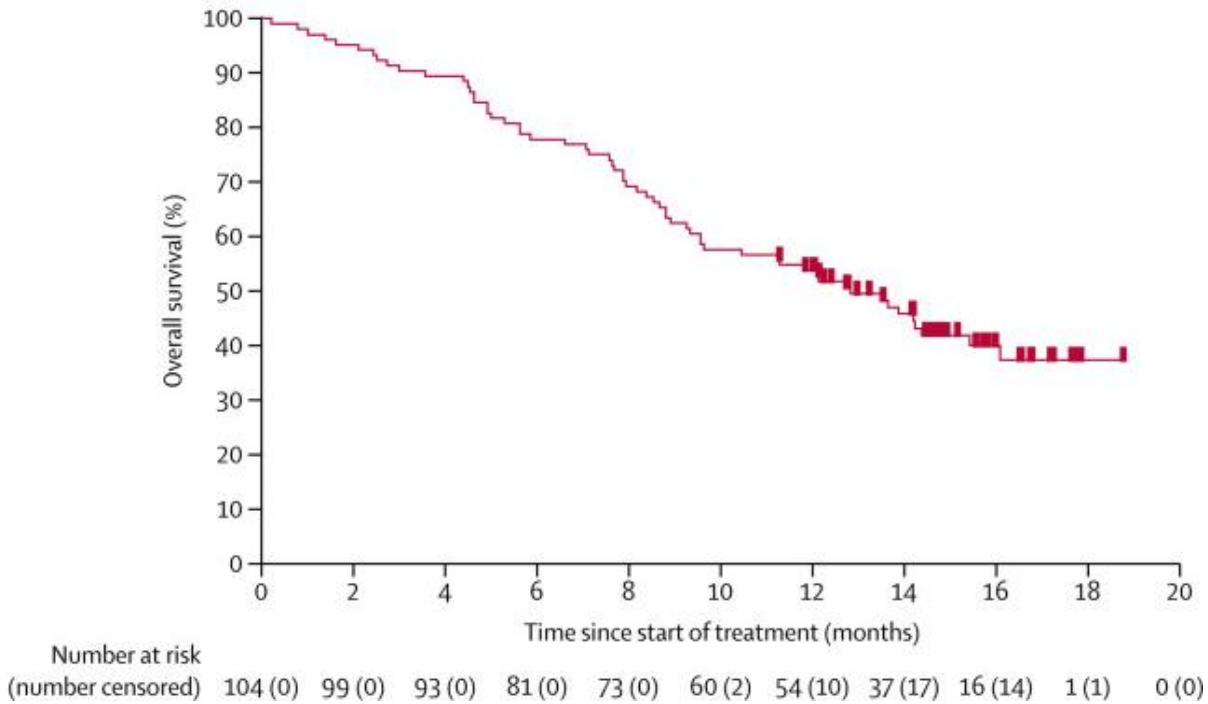




El-Khoueiry, The Lancet 2017.

KEYNOTE-224: Pembrolizumab

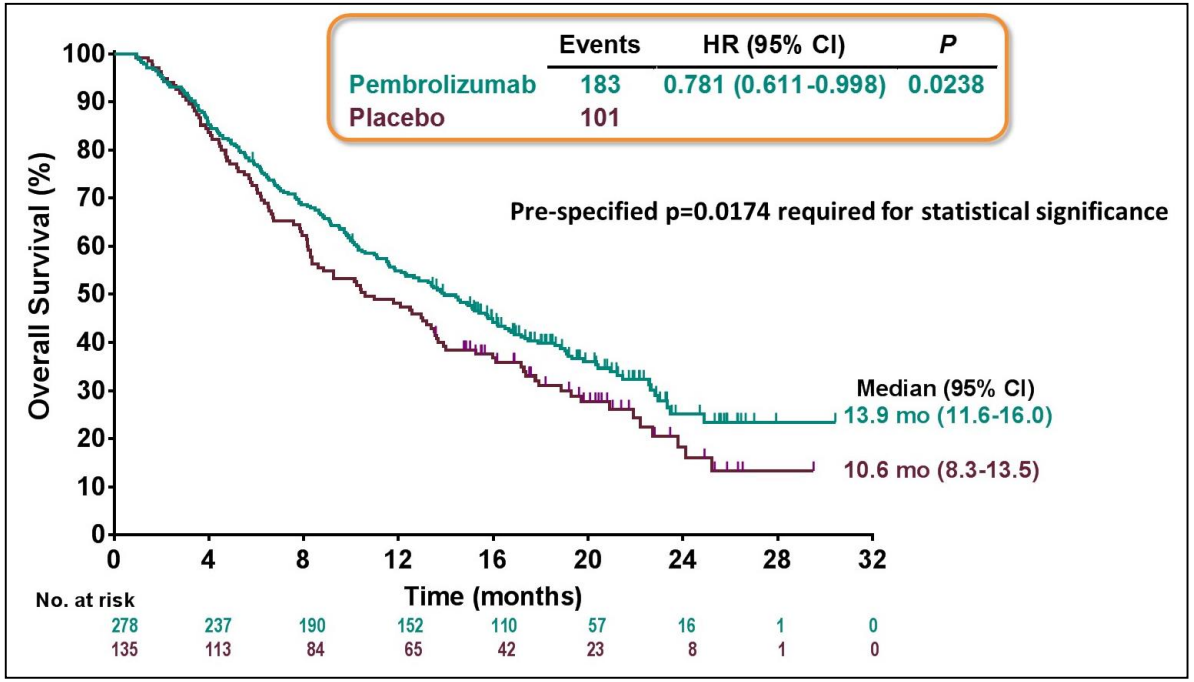
- Phase II non-randomized trial
  - Prior Sorafenib, CPT A
  - Pembrolizumab IV 200 mg Q3W
  - Primary endpoint: ORR
  - 104 patients enrolled and treated
- Results
  - ORR: **17%**, 1 CR, 17 PR
  - mPFS: 4.9 months, mOS: 12.9 months
  - 90% of responders had ≥6mo response
  - 56% of responders had ≥12mo response
- FDA 2018: accelerated approval for RR and durability of response



Zhu, Lancet Oncol 2018.

KEYNOTE-240: Pembrolizumab

- Phase III RPCT, 2nd line
- Primary endpoints: OS, PFS
- Results: primary endpoints did not meet statistical significance.
  - OS: HR = 0.78, p = 0.0238
  - PFS: HR = 0.78, p = 0.0209
  - ORR **16.9**% (95% CI 12.7-21.8) vs 2.2% (95% CI 0.5-6.4%), p = 0.00001



Finn, ASCO 2019

Checkmate 459: Nivo vs Sora 1st line

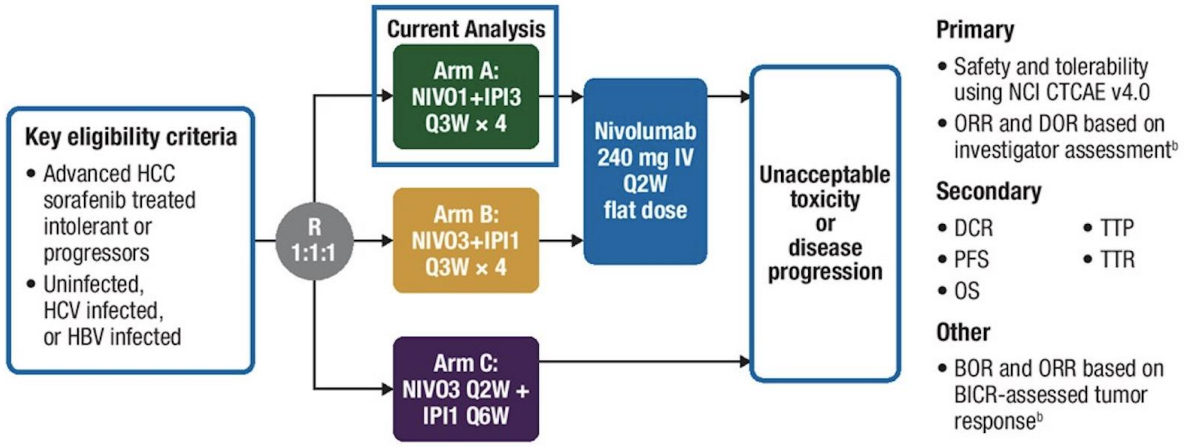
- Randomized Phase III
  - 743 patients
  - 1:1 to NIVO (240 mg IV Q2W) or SOR (400 mg oral BID)
- Primary Endpoint: OS
  - Not met
  - mOS 16.4 mo for NIVO
  - mOS 14.7 mo for SOR
  - (HR 0.85 [95% CI: 0.72–1.02]; P = 0.0752)
- ORR: 15 NIVO vs 7 SOR

Table: LBA38_PR Efficacy results

	NIVO n = 371	SOR n = 372
Median OS (95% CI), mo	16.4 (13.9–18.4)	14.7 (11.9–17.2)
12-mo OS rate, % (95% CI)	59.7 (54.4–64.6)	55.1 (49.8–60.1)
24-mo OS rate, % (95% CI)	36.8 (31.8–41.8)	33.1 (28.3–38.0)
Median PFS, mo (95% CI)	3.7 (3.1–3.9)	3.8 (3.7–4.5)
ORR, n (%)	57 (15)	26 (7)
BOR, n (%)		
Complete response	14 (4)	5 (1)
Partial response	43 (12)	21 (6)
ORR by baseline tumor PD-L1 expression, n/n (%)		
PD-L1 ≥1%	20/71 (28)	6/64 (9)
PD-L1 <1%	36/295 (12)	20/300 (7)

Yau et al. LABR V874-875. Vol 30 Suppl 5. Annals of Oncol, 2019.

CheckMate 040, Cohort 4: Nivo + Ipi



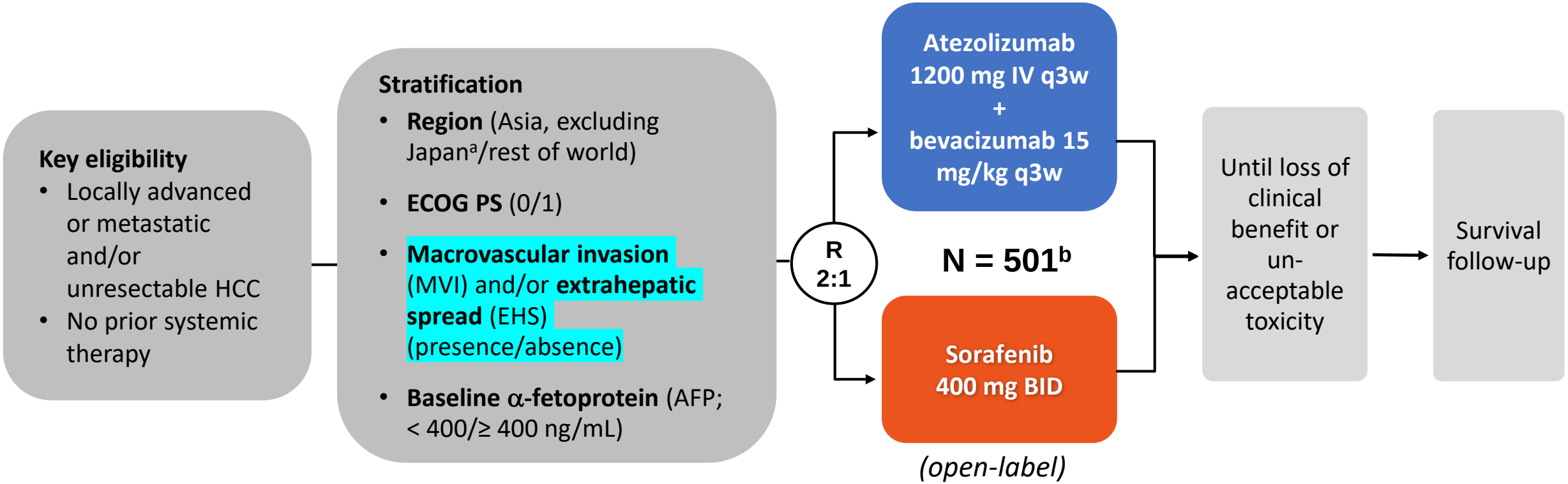
	NIVO1+IPI3 Q3W[a]		
	Sorafenib ≤ 6 months n = 28	Sorafenib > 6 months n = 22	Total n = 50
ORR by BICR using RECIST v1.1,[b] n (% [95% CI])	8 (28.6 [13.2–48.7])	8 (36.4 [17.2–59.3])	16 (32.0 [19.5–46.7])
Best overall response, n (%)			
CR	2 (7)	2 (9)	4 (8)
PR	6 (21)	6 (27)	12 (24)
SD	4 (14)	5 (23)	9 (18)
PD	13 (46)	7 (32)	20 (40)
DCR,[c] % (95% CI)	46.4 (27.5–66.1)	63.6 (40.7–82.8)	54.0 (39.3–68.2)
DCR with SD ≥ 6 months, % (95% CI)	35.7 (18.6–55.9)	45.5 (24.4–67.8)	40.0 (26.4–54.8)
Median time to response (range),[d] months	1.35 (1.1–2.7)	2.6 (1.2–12.8)	2.0 (1.1–12.8)
Median duration of response (range),[d] months	16.0 (4.6+ to 29.0+)	NR (4.6–30.5+)	17.5 (4.6–30.5+)

[a]Four doses, followed by NIVO 240 mg IV Q2W flat dose; [b]Defined as CR + PR; [c]Defined as CR + PR + SD + non-CR/non-PD; [d]Patients with CR or PR.

- Nivo 1mg/kg + Ipi 3mg/kg Q3W X4 -> Nivo 240mg Q4W
- 28 mo follow up
- ORR was 33%, CR 8%
- ***Gr 3 and 4 Any AEs: 53%***
- ***Gr 3 and 4 hepatobiliary AEs: 33%***
- FDA 2020: accelerated approval for RR and durability of response

He, Yau et al. ASCO GI 2020 .

IMbrave150: AtezoBev vs Sora 1st line



Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

Cheng et al. IMBRAVE150 ESMO ASIA 2019.

IMbrave150 baseline characteristics

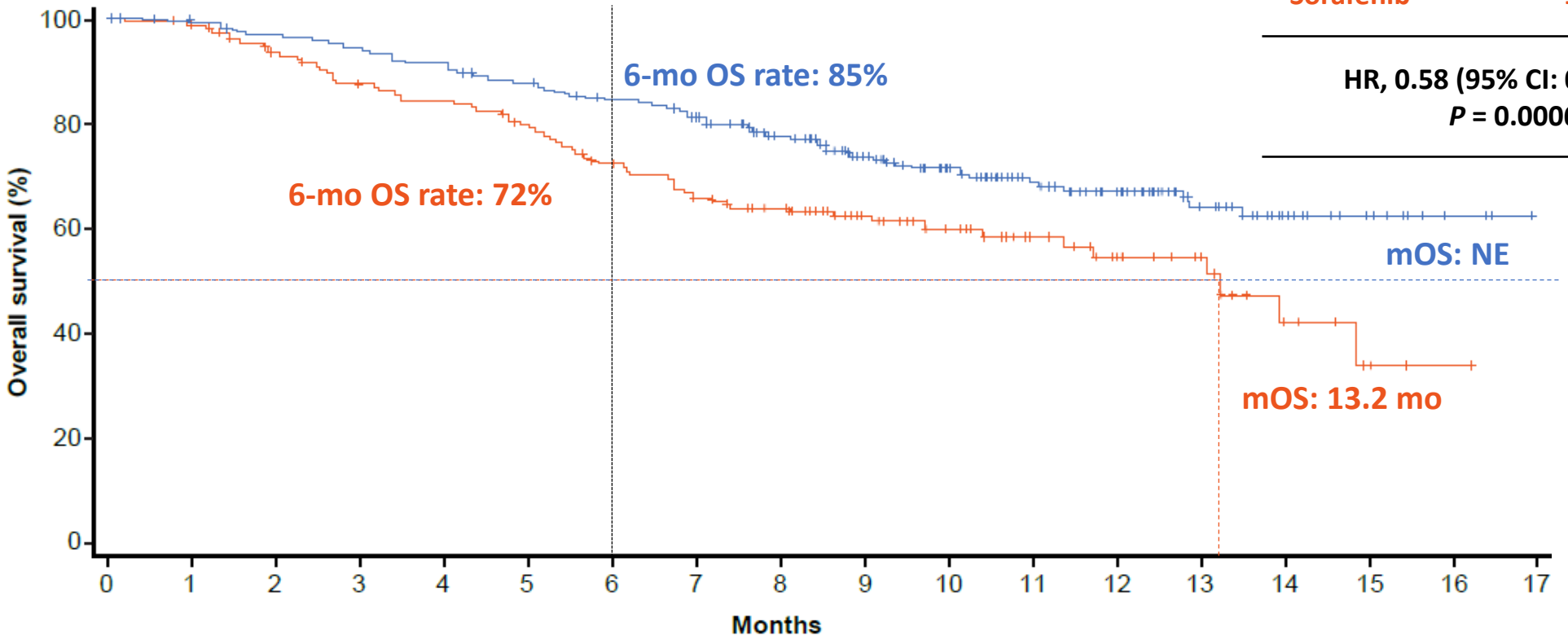
Characteristic	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median age (range), years	64 (26-88)	66 (33-87)
Sex, male, n (%)	277 (82)	137 (83)
Region, n (%)		
Asia (excluding Japan[a])	133 (40)	68 (41)
Rest of world	203 (60)	97 (59)
ECOG PS 1, n (%)	127 (38)	62 (38)
Child-Pugh class, n (%)		
A | B	333 (99) | 1 (< 1)	165 (100) | 0
BCLC staging at study entry, n (%)		
A | B | C	8 (2) | 52 (15) | 276 (82)	6 (4) | 26 (16) | 133 (81)
Aetiology of HCC, n (%)		
HBV | HCV | Non-viral	164 (49) | 72 (21) | 100 (30)	76 (46) | 36 (22) | 53 (32)
AFP ≥ 400 ng/mL, n (%)	126 (38)	61 (37)
EHS, n (%)	212 (63)	93 (56)
MVI, n (%)	***129 (38)***	***71 (43)***
EHS and/or MVI, n (%)	258 (77)	120 (73)
Prior TACE, n (%)	130 (39)	70 (42)
Prior radiotherapy, n (%)	34 (10)	17 (10)

Cheng et al. IMBRAVE150 ESMO ASIA 2019.

OS: co-primary endpoint

Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)

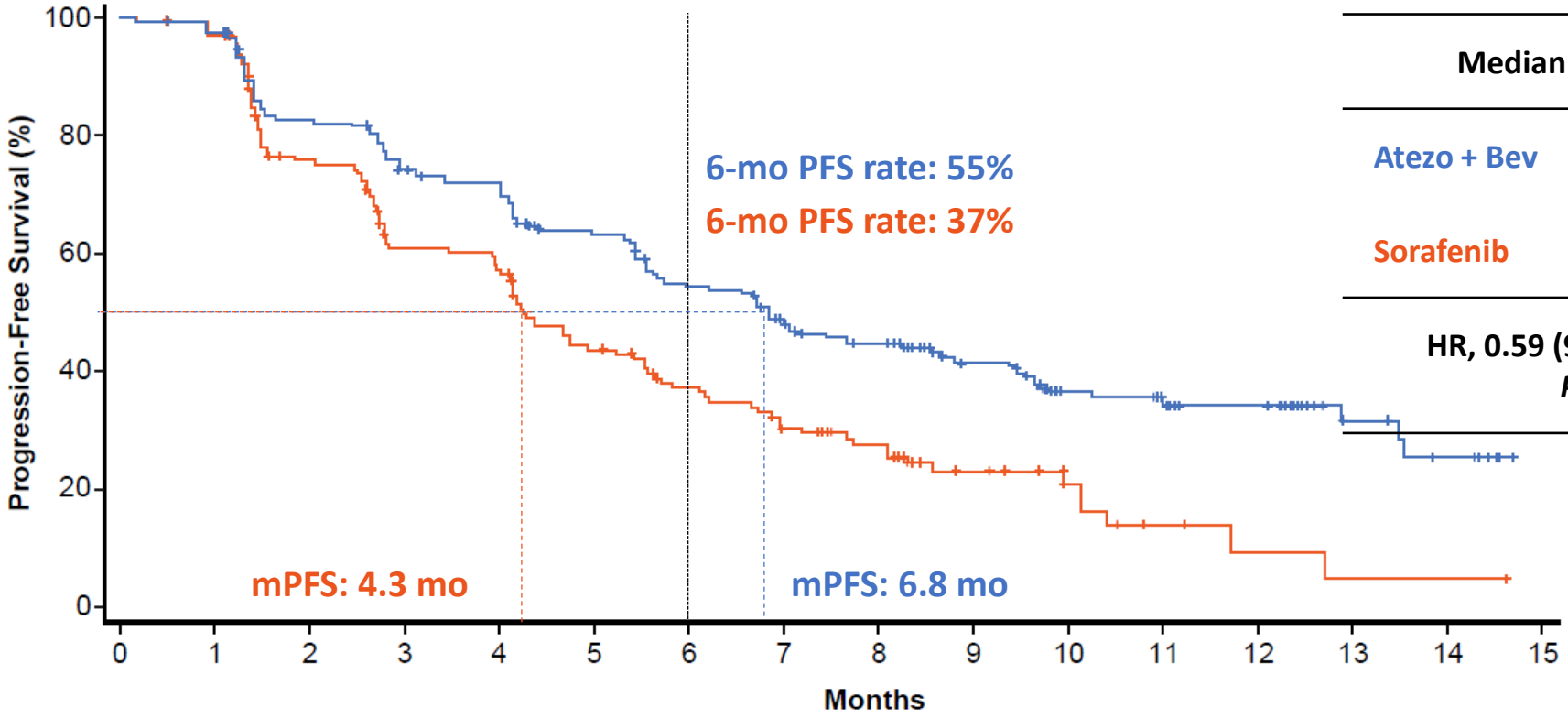
HR, 0.58 (95% CI: 0.42, 0.79)[b]
P = 0.0006[b,c]



No. at risk																	
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

Cheng et al. IMBRAVE150 ESMO ASIA 2019.

Confirmed PFS[a]: co-primary endpoint



Median PFS (95% CI), mo[b]	
Atezo + Bev	6.8 (5.7, 8.3)
Sorafenib	4.3 (4.0, 5.6)

HR, 0.59 (95% CI: 0.47, 0.76)[c,d]
P < 0.0001[d]

No. at risk															
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE

Cheng et al. IMBRAVE150 ESMO ASIA 2019.

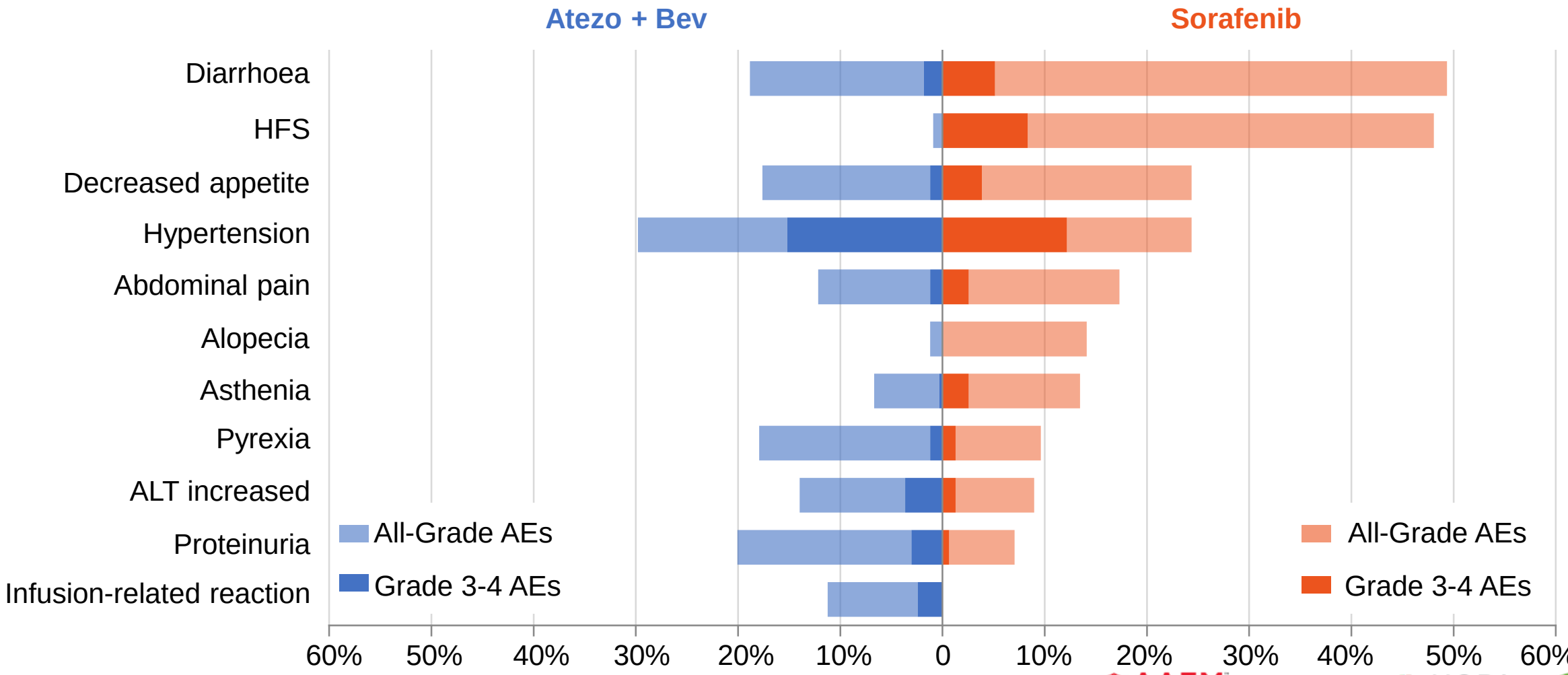
RRs and Duration of Response

	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)[a]	Sorafenib (n = 158)
Confirmed ORR, n **(%)** (95% CI)	89 **(27)** (23, 33)	19 **(12)** (7, 18)	108 **(33)** (28, 39)	21 **(13)** (8, 20)
CR	18 (6)	0	33 (10)	3 (2)
PR	71 (22)	19 (12)	75 (23)	18 (11)
Stratified *P* value[b]	**< 0.0001**		**< 0.0001**	
SD, n (%)	151 (46)	69 (43)	127 (39)	66 (42)
PD, n (%)	64 (20)	39 (25)	66 (20)	40 (25)
DCR, n (%)	240 (74)	88 (55)	235 (72)	87 (55)
Median DOR, months (95% CI)	NE	6.3 (4.7, NE)	NE	6.3 (4.9, NE)
Event-free rate at 6 months, n (%)	88	59	82	63

Cheng et al. IMBRAVE150 ESMO ASIA 2019.

Safety

≥ 10% frequency of AEs in either arm and > 5% difference between arms

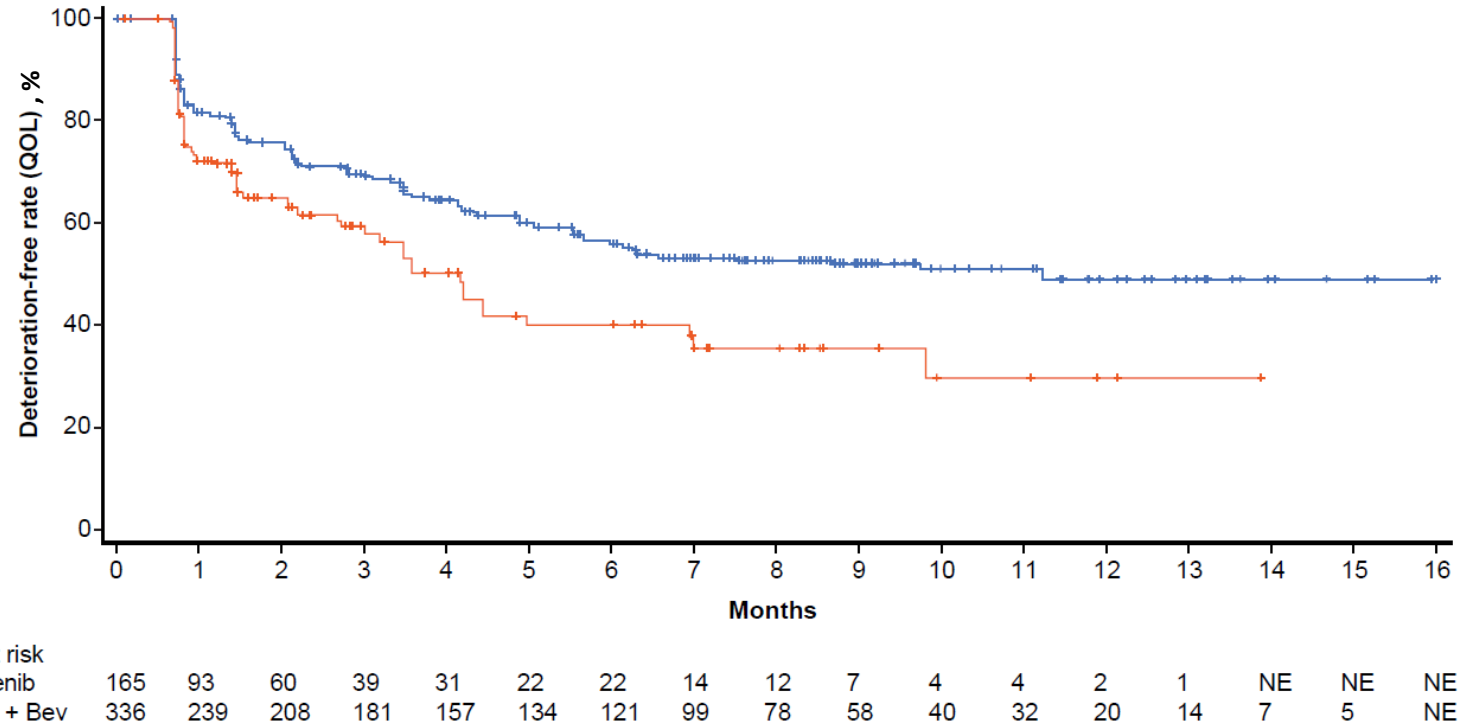


Cheng et al. IMBRAVE150 ESMO ASIA 2019.

Patient-reported outcomes

- Atezolizumab + bevacizumab delayed the time to deterioration of patient-reported quality of life compared with sorafenib

Quality of life Median TTD (95% CI), mo[b]	
Atezo + Bev	11.2 (6.0, NE)
Sorafenib	3.6 (3.0, 7.0)
HR, 0.63 (95% CI: 0.46, 0.85)	



Cheng et al. IMBRAVE150 ESMO ASIA 2019.

The Fine Print, Patient Selection

- CPT A patients only
- Endoscopy within 6 months prior to enrolment
- Excluded: incompletely treated EV or high risk for bleeding
- Bleeding AEs
  - *Bleeding of any grade: Atezo Bev 25.2% vs Sorafenib 17.3%*
  - *Fatal Bleeding: Atezo Bev: 6 vs Sorafenib: 1*

Finn et al. NEJM 2020
Kelly R. NEJM 2020

Treatment Paradigm Shift in HCC

- Immunotherapy may take a larger share of first-line treatment
  - Current 1st line: Sorafenib, Levnatinib, Atezo + Bev
  - Promising pivotal trials in the 1st line all contain IO agents

ICI + Multi-TKI	ICI + ICI
Lenvatinib + Pembrolizumab (LEAP-002)	Durvalumab + Tremelimumab (HIMALYA)
Cabozantinib + Atezolizumab (COSMIC-312)	Nivolumab + Ipilimumab (CheckMate 9dw)

Post-Sorafenib Second line TKI options in HCC

	ORR	mPFS	mOS	Gr 3/4 AE rate, Tox
Second line vs placebo, post-sorafenib trials				
Cabozantinib (CELESTIAL)	4% vs 1%	5.2 mos	10.2 vs 8 mos	68% of patients
Regorafenib (RESORCE)	11% vs 4% (modified RECIST)	3.1 mos	10.6 vs 7.8 mos	50% of patients, 70% dose reduced
Ramucirumab (REACH2)	5% vs 1%	2.8 mos	8.5 VS 7.3 mos	35%, no HFS
First line Trials vs sorafenib, NCCN suggested options in 2nd line				
Lenvatinib (REFLECT 1st line data)	24% vs 9%	7.4 mos	13.6 mos vs 12.3 mos	57%

Conclusions

- Since many patients are ineligible for surgical resection/transplant, there is a great need for systemic therapies in HCC
- Immune Checkpoint inhibitors are the only approved immunotherapeutic strategies for HCC (Nivolumab, Nivo-Ipi, Pembrolizumab and Atezolizumab and Bevacizumab)
- Combination strategies produce higher RRs, need to balance vs toxicity
- Atezolizumab and Bevacizumab is the new standard 1st line treatment in eligible patients
- Ongoing 1st line trials looking at various IO combination strategies (TKI, anti-CTLA-4)

Immunotherapy in MSI-H Cancers

Tissue Agnostic and mCRC

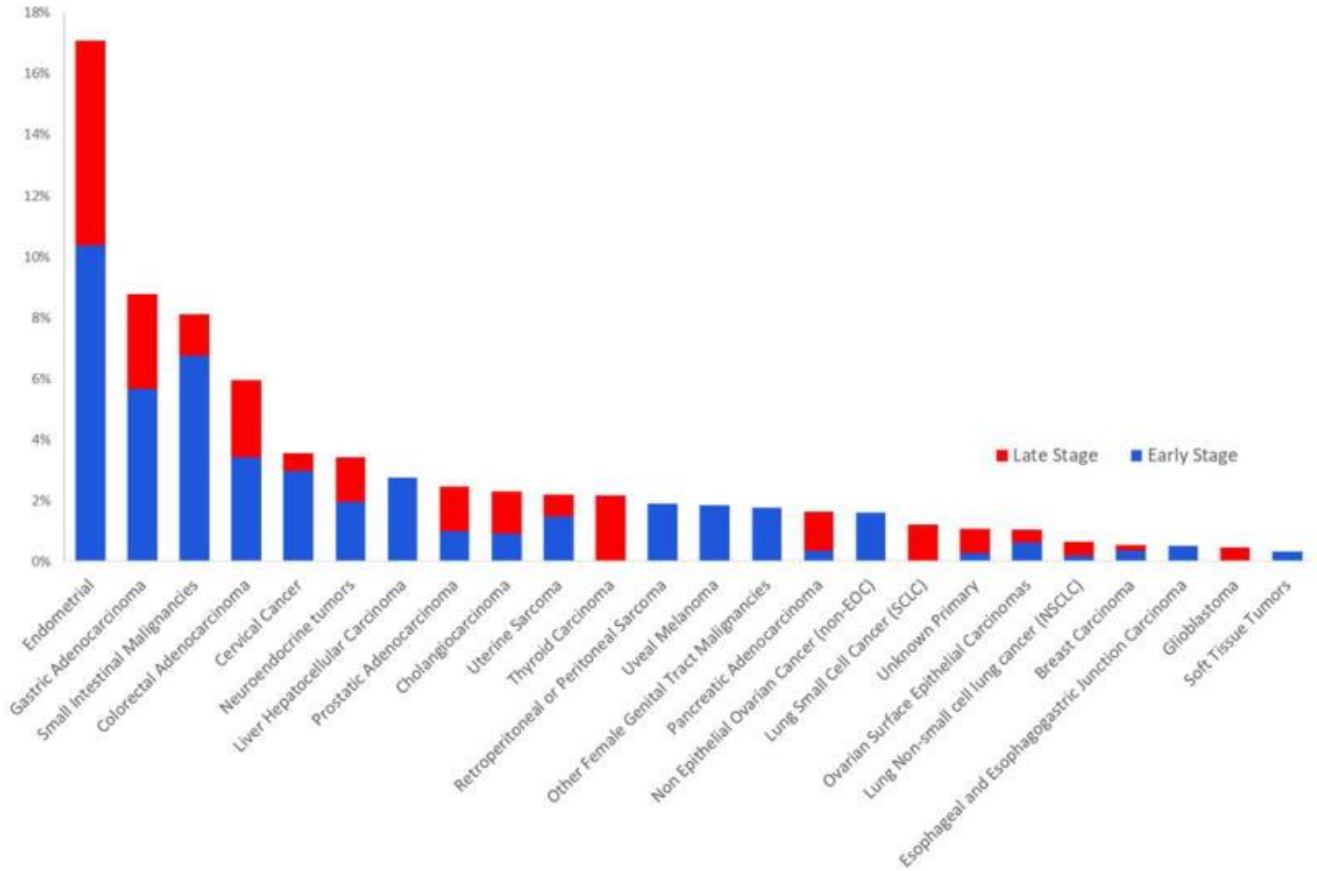
Biology of Mismatch Repair Deficiency and Tumor Mutation Burden

- MMR is a repair mechanism for single base insertions and deletions when slippage occurs during DNA replication by DNA polymerase.
- These errors often occur in areas of short, repetitive DNA sequences, termed microsatellites
- There are four MMR proteins: MLH1, MSH2, MSH6, PMS2
  - A deficiency in one or more of these proteins results in inability to repair errors, resulting in increased frequency/burden of mutations (TMB high) and increased variability in microsatellite regions (MSI-H)

MSI-H vs dMMR, sporadic vs Lynch

- The presence of MSI represents phenotypic evidence of MMR deficiency/dysfunction
- Testing:
  - dMMR: IHC demonstrates loss of one of the 4 proteins
  - MSI-H: via PCR or NGS showing increased length/variability of microsatellites
- Mutations in MMR proteins can result from:
    - Germline deficiency / Hereditary causes (Lynch syndrome)
    - Somatic mutations
    - Silencing through promoter methylation (BRAF V600e)

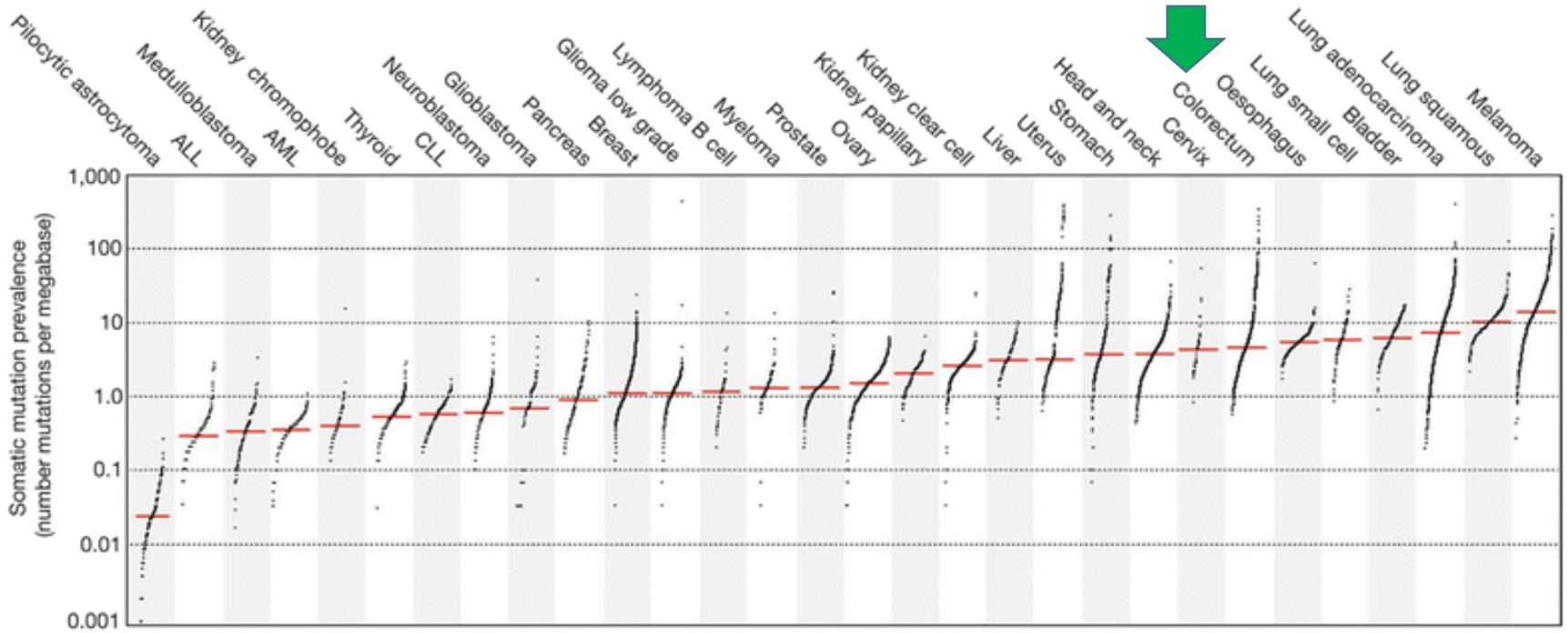
Many tumors are MSI-H or dMMR



Le, Science 2017.

Somatic mutations by cancer type

A consequence of hypermutability due to mismatch repair deficiency is increase in the TMB and the potential production of a ***neoantigen*** that can be recognized by the immune system, offering the opportunity for ICI therapy



Alexandrov, Nature 2013.

Anti-PD-1 ICI phase 1: MSI-H CRC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

- Initial phase 1 study of Nivo
- Expansion in melanoma, non–small-cell lung cancer, renal-cell cancer, castration-resistant prostate cancer, and colorectal cancer
- ***Only 1 out of 33 CRC patients had a response -> MSI-H***

Anti-PD-1 MSI-H Refractory Cancers

JHU IIT with Pembro. Three cohorts, A: MSI-H CRC, B MSS CRC, D MSI-H non-CRC
41 patients, (9 nonCRC)

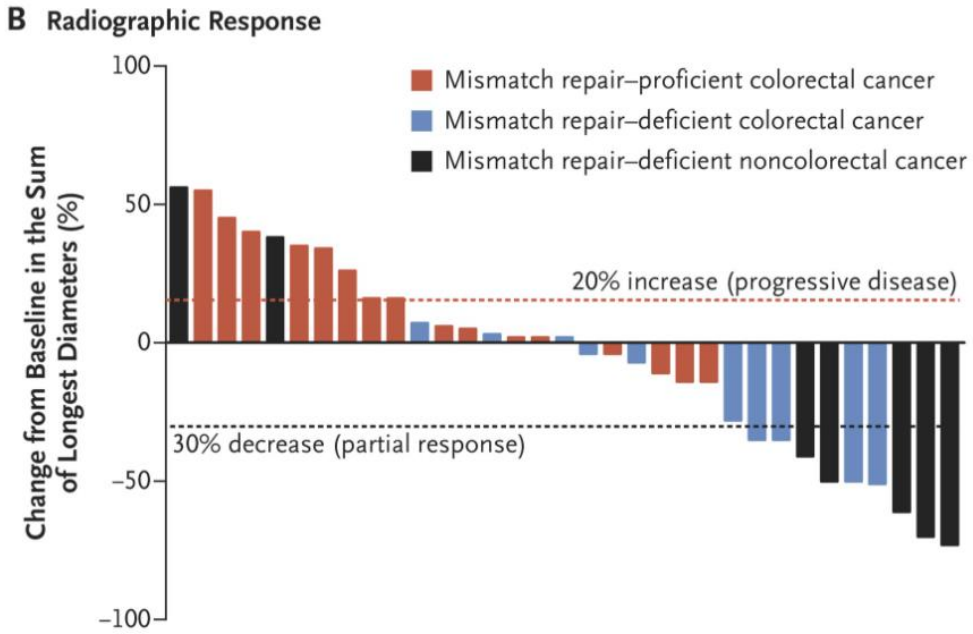


Table 2. Objective Responses According to RECIST Criteria.

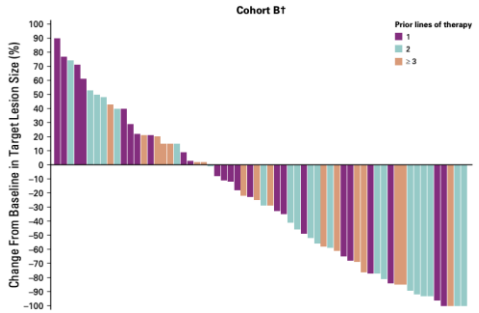
Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2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

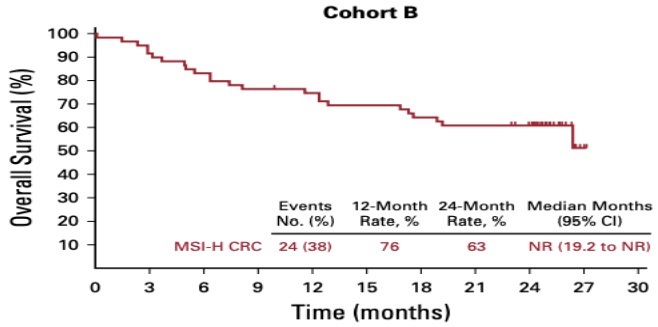
Le et al, NEJM 2015.

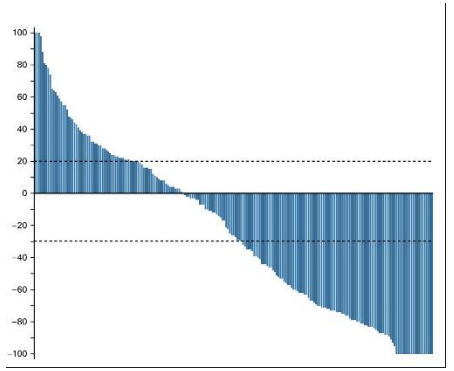
Clinical Data – KEYNOTE-164 and 158

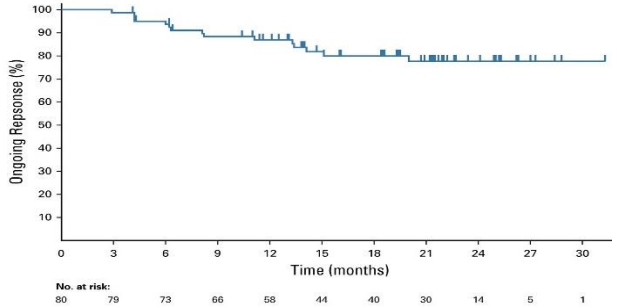
pembrolizumab monotherapy MSI-H refractory cancers

- KEYNOTE-164
  - 124 pts with MSI-H CRC (90% with ≥2 prior therapies)
  - ORR: 33%
  - mOS 31.4 mos
  - Gr 3-4 TRAE 16%
- KEYNOTE-158
  - 233 patients, 27 tumor types
  - ORR 34.3%
  - mOS 23.5 mos
  - Gr 3-5 TRAE 14.6%



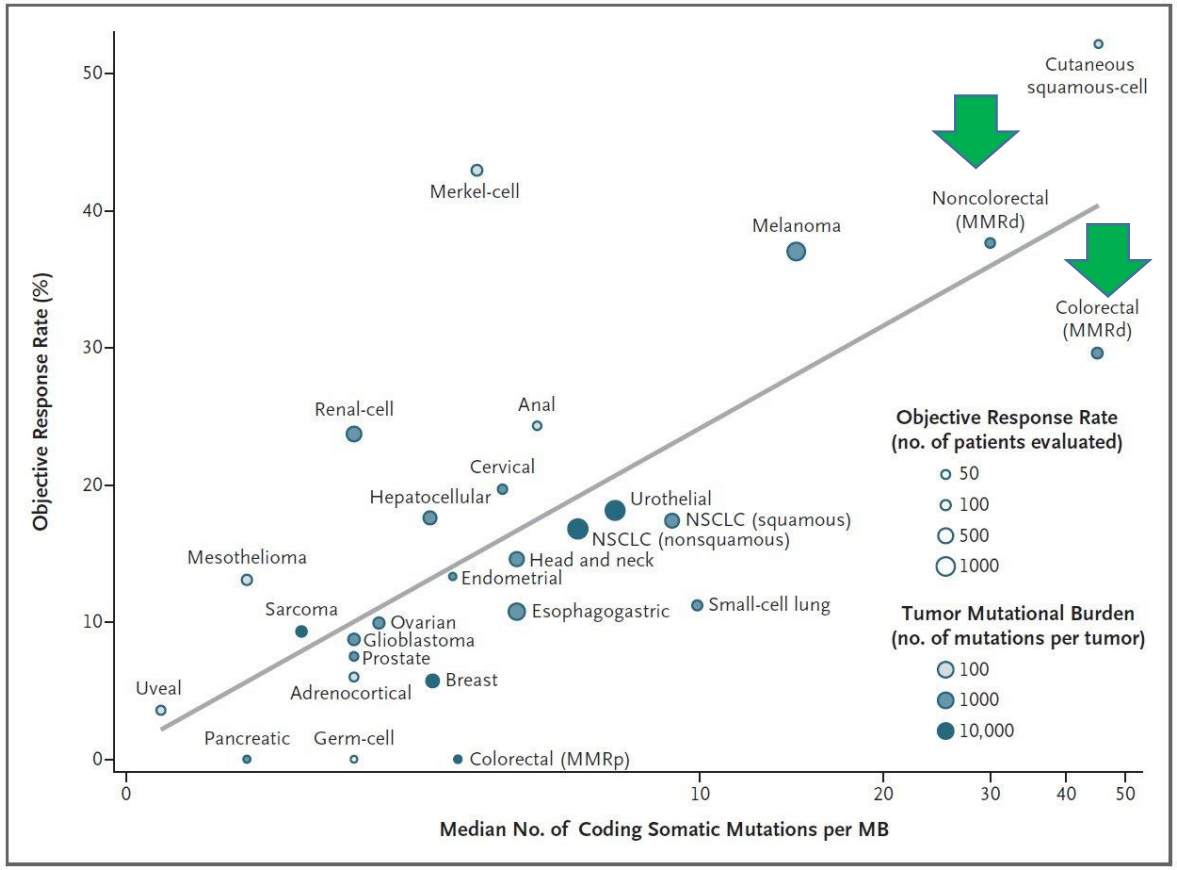


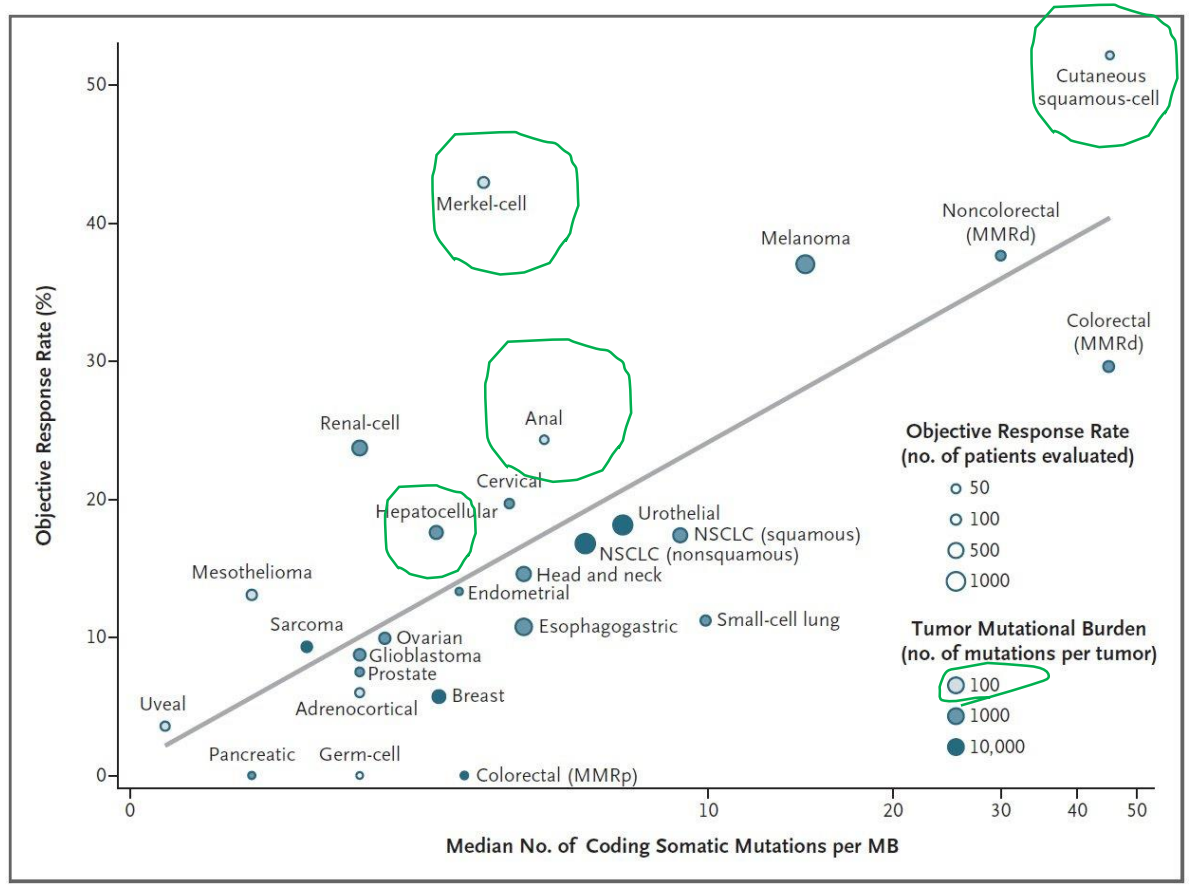




Le et al. JCO 2020.
Marabelle et al. JCO 2020

TMB, MSI status, Antigen Quality



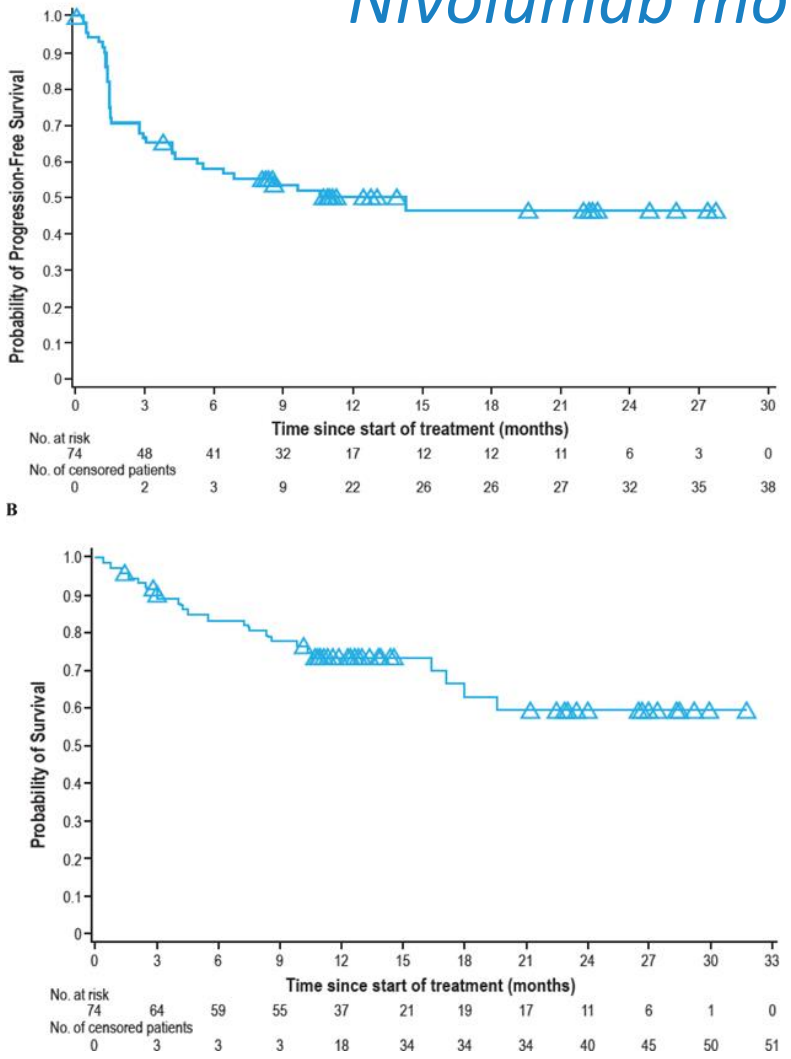


Le et al, NEJM 2015.

Le et al. NEJM 2015; 372:2509-20.

Clinical Data – CheckMate 142

Nivolumab monotherapy CRC 2nd line and beyond



- mCRC with MSI-H, progressed after ≥1 therapy
- Nivolumab 3 mg/kg Q2W
- At 12 months: 31% ORR
- 68.9% disease control >12 weeks
- Median DOR not reached

Overman, Lancet Oncol 2017.

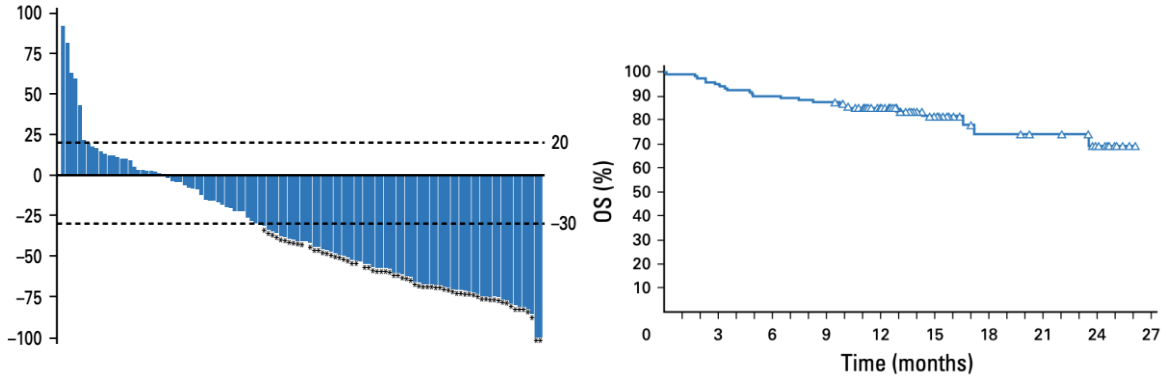
Clinical Data – CheckMate 142
Nivolumab + Ipilimumab MSI-H/dMMR CRC

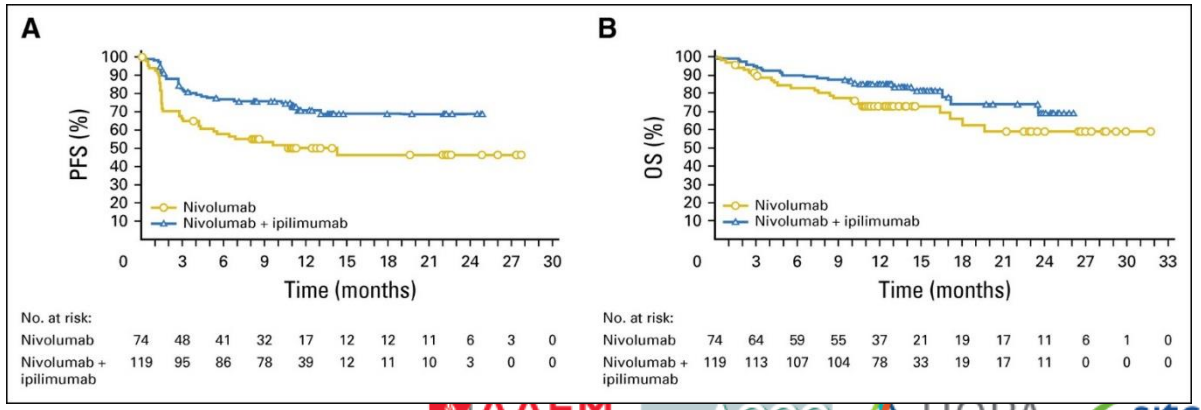
- 199 pt MSI-H/dMMR mCRC

- 76% with ≥2 prior lines of chemo
- Nivolumab 3mg/kg + ipilimumab 1 mg/kg Q3W (4 doses), then nivolumab 3 mg/kg Q2W

- At 13.4 months: ***55% ORR***
- PFS:
  - 76% (9 months)
  - 71% (12 months)

- **Gr3-4 TRAE: 33%**





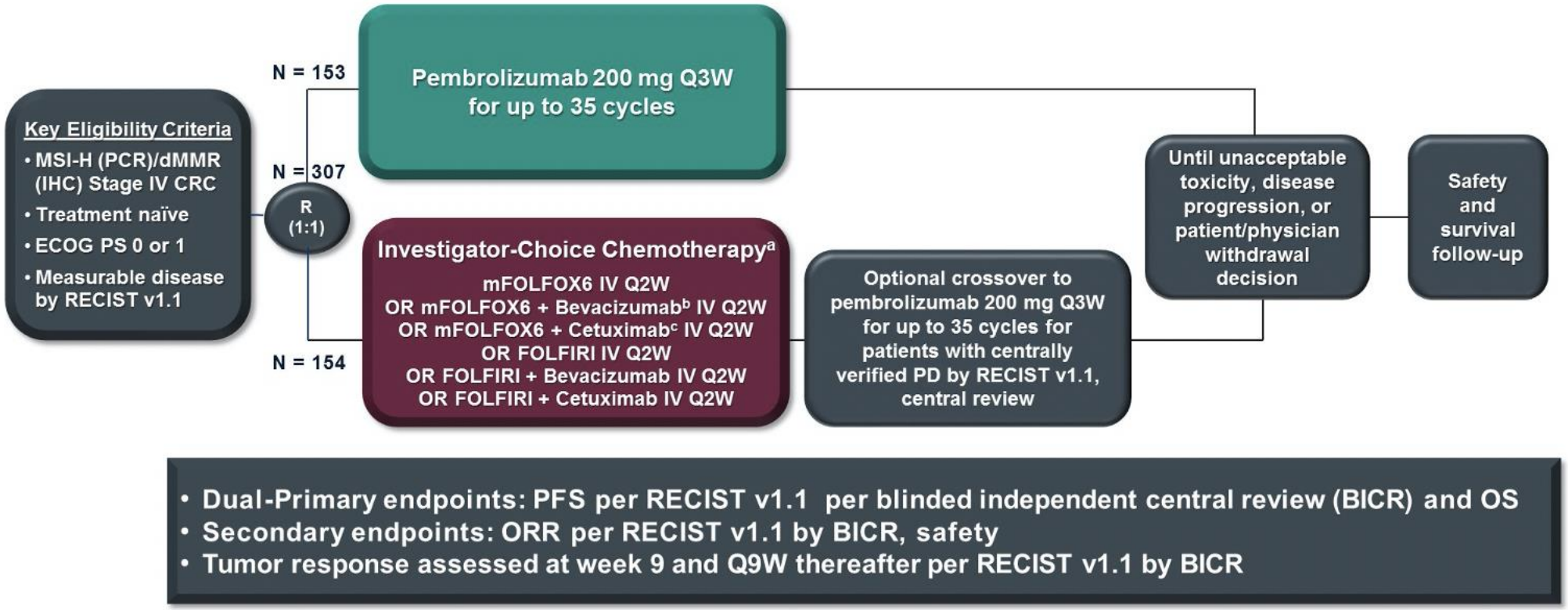
Overman, J Clin Oncol 2018.

FDA-approved immunotherapies for refractory MSI-high populations

Drug	Approved	Indication	Dose
Pembrolizumab	2017	Adult/pediatric patients with unresectable/metastatic **MSI-H or dMMR solid tumors** with progression on other treatment **MSI-H or dMMR colorectal cancer** with progression after a fluoropyrimidine, oxaplatin, and irinotecan	Adults: 200 mg Q3W Pediatric: 2 mg/kg (up to 200 mg) Q3W
Nivolumab	2017	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaplatin, and irinotecan	≥40 kg: 240 mg Q2W or 480 mg Q4W <40 kg: 3 mg/kg Q2W
Ipilimumab + nivolumab	2018	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaplatin, and irinotecan	≥40 kg: 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W for 4 doses, Then nivolumab 240 mg Q2W or 480 mg Q4W

KEYNOTE-177: Pembro vs SOC Chemo

1st line treatment of MSI-H stage IV CRC

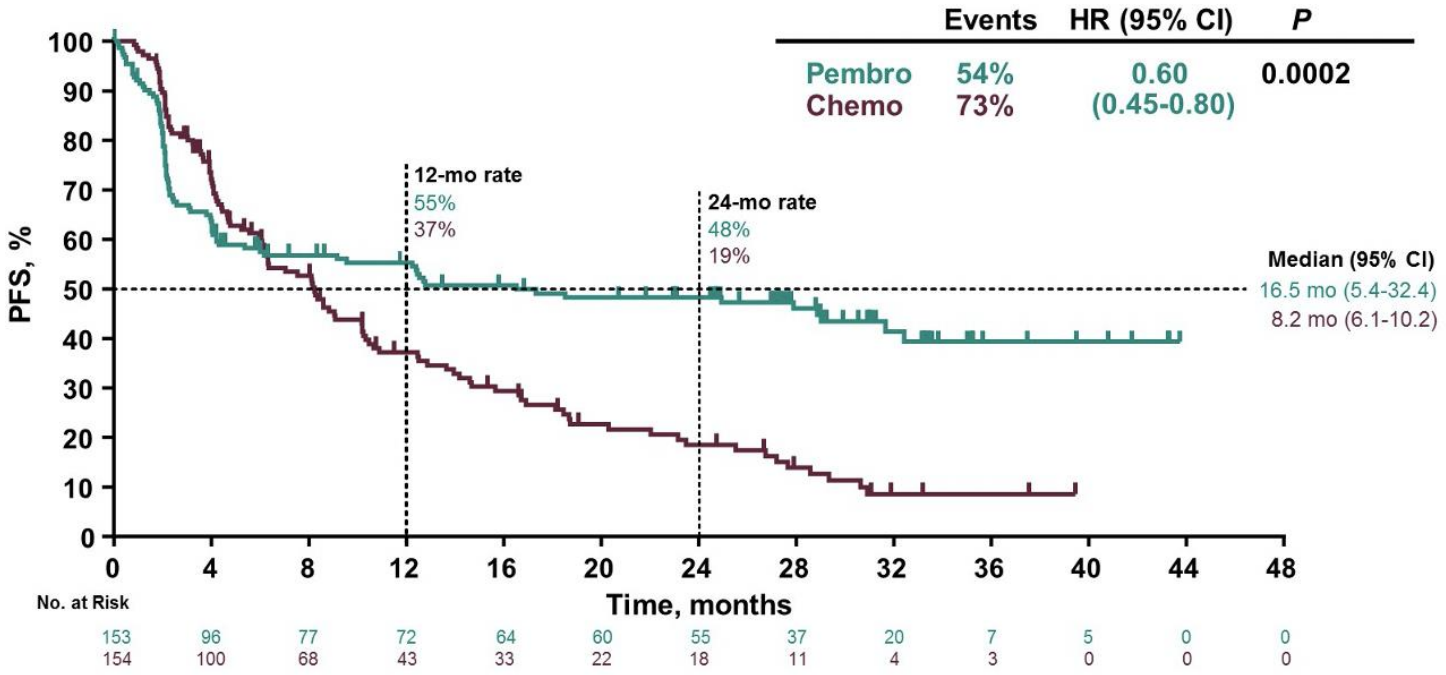


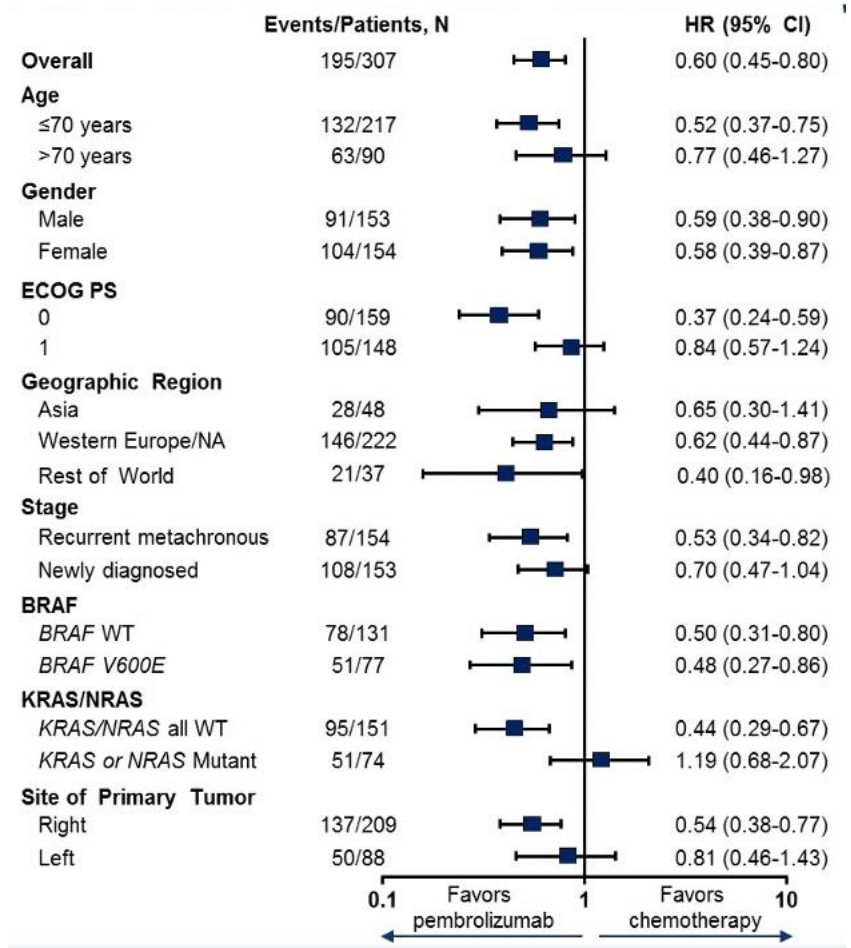
Andre et al. Presented at ASCO 2020.

KEYNOTE-177: Pembro vs SOC Chemo

1st line treatment of MSI-H stage IV CRC

Primary Endpoint: PFS – met, positive study
mPFS: 16.5 vs 8.2 (P vs Chemo)
24mo PFS: 48% vs 19%





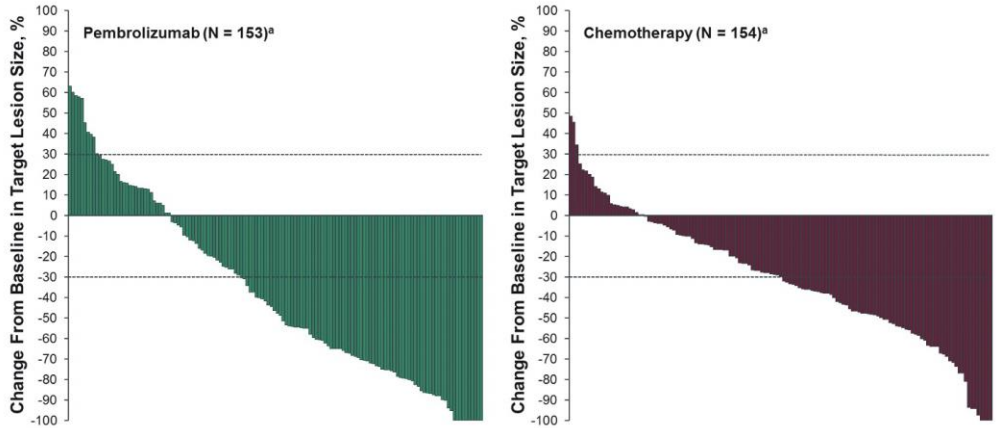
Andre et al. Presented at ASCO 2020.

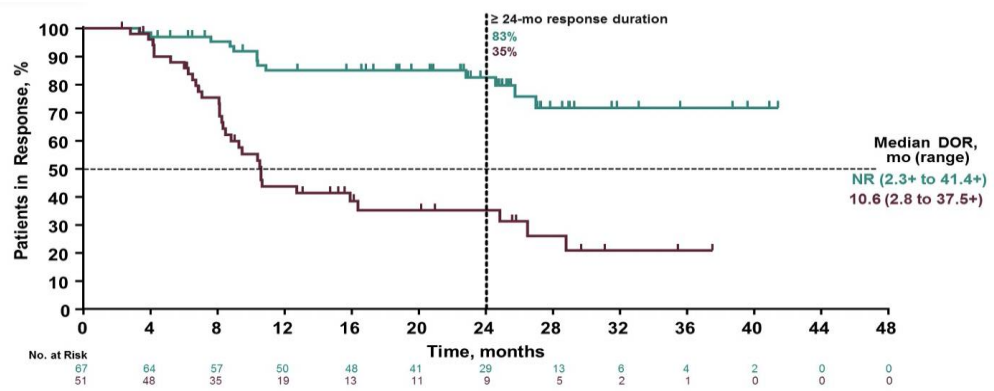
KEYNOTE-177: Pembro vs SOC Chemo

1st line treatment of MSI-H stage IV CRC

Primary Endpoint: ORR met, positive study: 43.8 vs 33.1
mDOR: Not met vs 10.6mo

	Pembrolizumab N = 153	Chemotherapy N = 154
ORR, n (%)	**67 (43.8)**	**51 (33.1)**
Difference, estimate (95% CI)	10.7 (-0.2-21.3)	
P-value	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)





Andre et al. Presented at ASCO 2020.

Case Studies

Case Study 1

- 56 yr old male with active hepatitis C cirrhosis and multifocal HCC on both lobes with multiple mediastinal and abdominal adenopathy. There is invasion of the portal vein with small tumor thrombus. He is CPT A. Portal hypertension controlled on nadolol, furosemide and spironolactone. No ascites. No encephalopathy. He has no prior autoimmune disease. BP is well controlled at 120/80. You recommend atezolizumab and bevacizumab.
- What is recommended prior to starting therapy?
  a) PD-L1 staining of tumor tissue
  b) Endoscopy to rule out esophageal varices
  c) Treatment and cure of Hepatitis C
  d) MRI of the Brain to rule out intracranial metastases

Case Study 1

- What is recommended prior to starting therapy?
  a) PD-L1 staining of tumor tissue
  b) Endoscopy to rule out esophageal varices
  c) Treatment and cure of Hepatitis C
  d) MRI of the Brain to rule out intracranial metastases

All of the patients included in the IMBRAVE 150 study of atezolizumab and bevacizumab had to have had an endoscopy for EV screening and treatment within 6mo of enrollment. Bevacizumab poses a risk for significant bleeding.

Case Study 2

- 29 yr old female comes for consultation for newly diagnosed stage IV ascending colon cancer with multiple liver and peritoneal metastases. Molecular testing shows MSI-H by PCR and BRAF V600E activating mutation. What will you recommend as first line therapy?

a) Encorafenib + binimetinib + cetuximab
b) Encorafenib + cetuximab
c) Pembrolizumab
d) Regorafenib

Case Study 2

- What will you recommend as first line therapy?
  a) FOLFIRI + Cetuximab
  b) Encorafenib + cetuximab
  c) Pembrolizumab
  d) Regorafenib

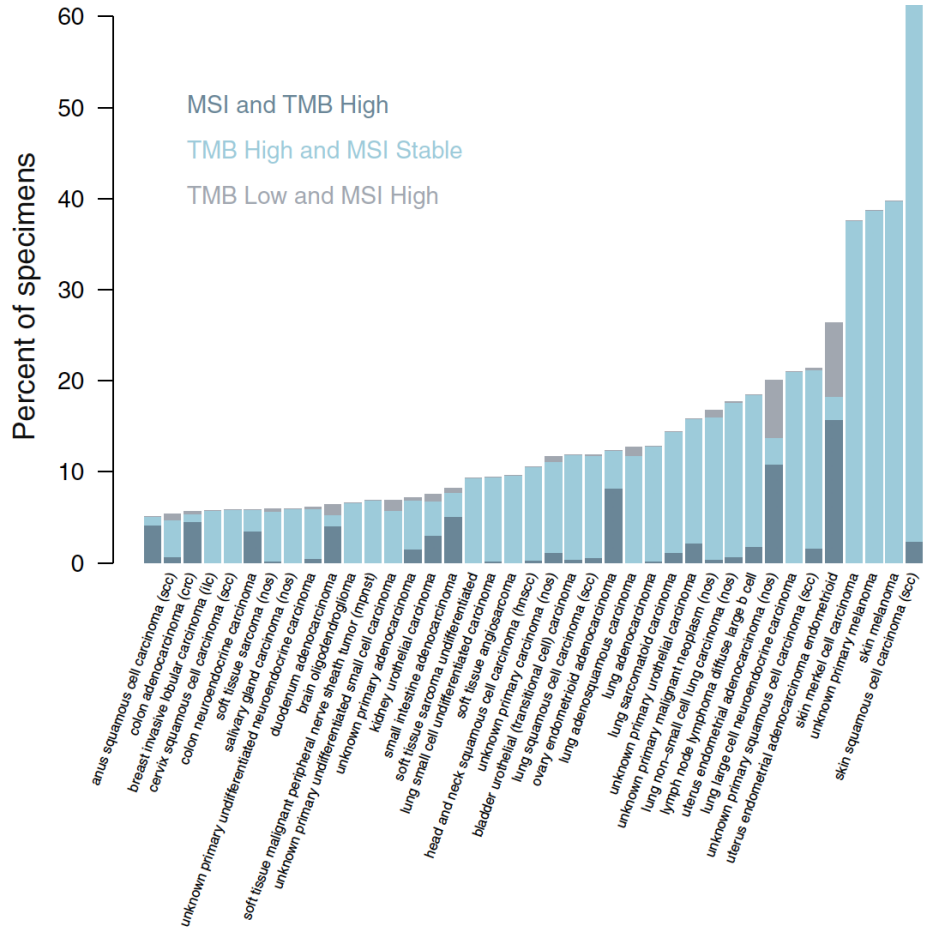
The Keynote-177 trial showed superiority (PFS and ORR) of pembrolizumab vs SOC doublet chemotherapy in the 1st line treatment of metastatic MSI-H CRC, including BRAFV600E mutant patients. All other choices are second line or higher. Chemotherapy with either doublet or triplet such as FOLFOXIRI can be considered, but cetuximab is not recommended in patients harboring RAS or RAF mutations, in this case, BRAFV600E

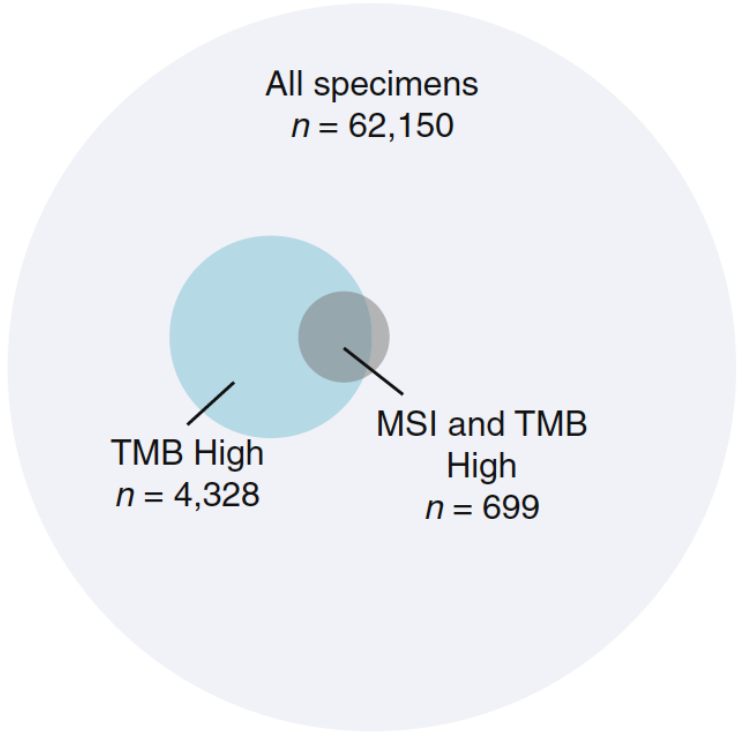
The End

Questions?

Extra slides

Tissue Agnostic Immunotherapy Indications: High-TMB, MSI-H



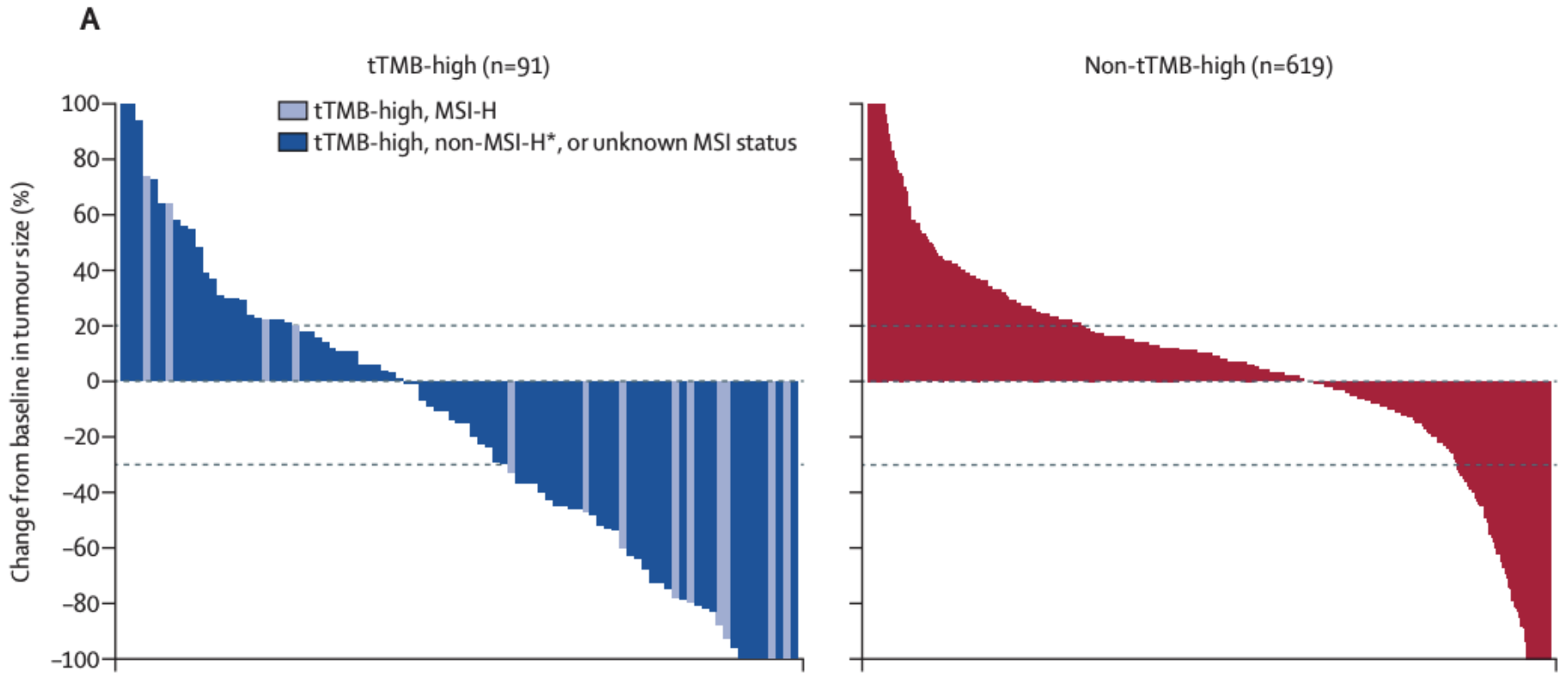


Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 2017; 9:34

Keynote-158, TMB analysis

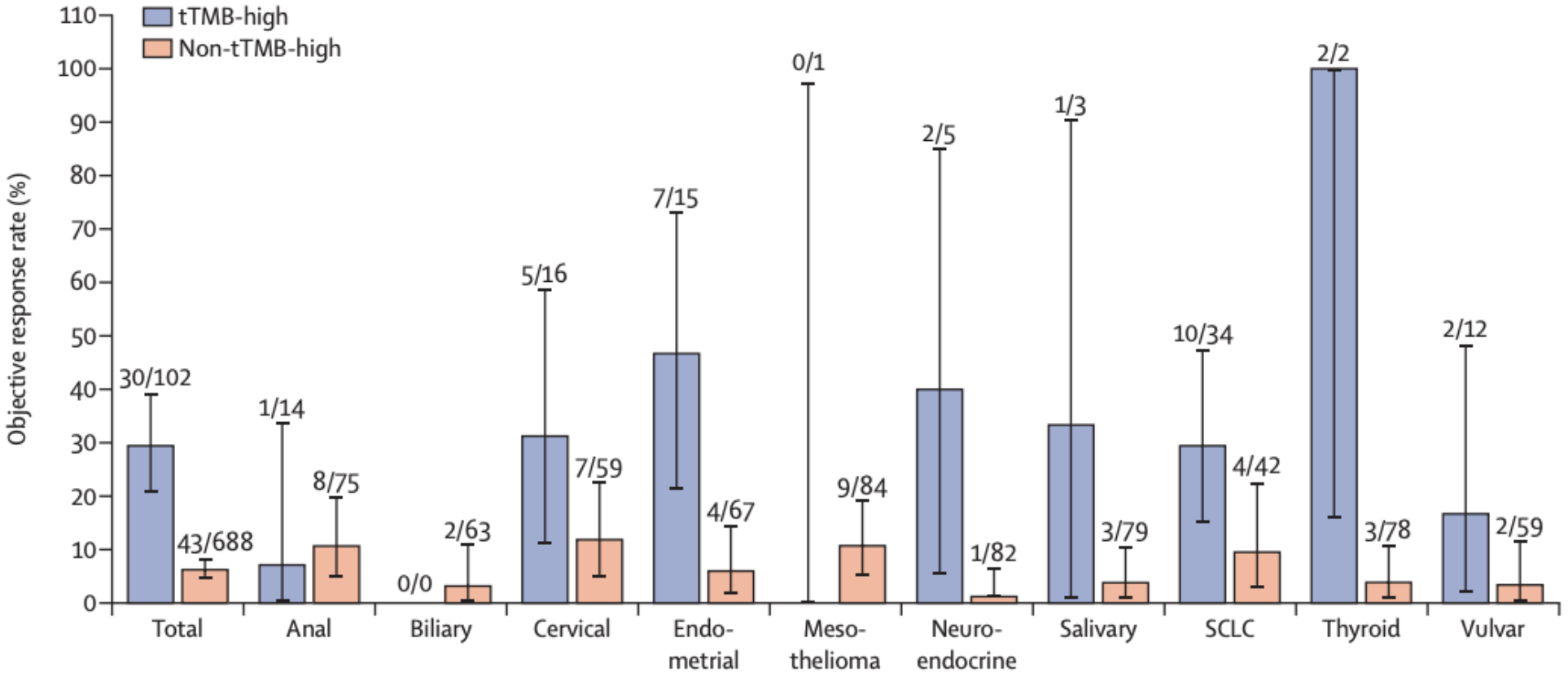
prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study

tTMB-high status (≥10 mut/M non-tTMB-high status (<10)



Marabelle et al. Lancet Oncol, 2020.

Keynote-158, TMB analysis



Marabelle et al. Lancet Oncol, 2020.