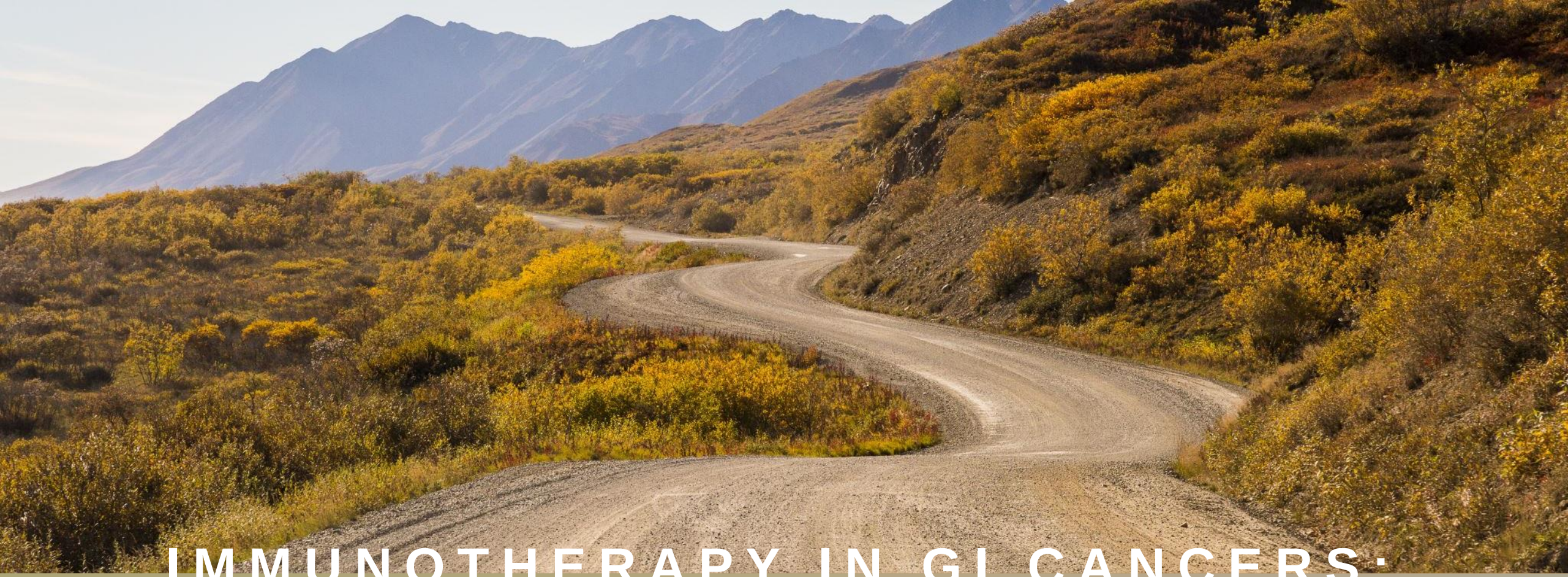

IMMUNOTHERAPY IN GI CANCERS: A WINDY ROAD TO SUCCESS IN HCC

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10/31/2020

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DISCLOSURES

- Consulting Fees: Exelixis, QED therapeutics
- Contracted Research: FivePrime, Genentech, Merck, Exelixis, Incyte

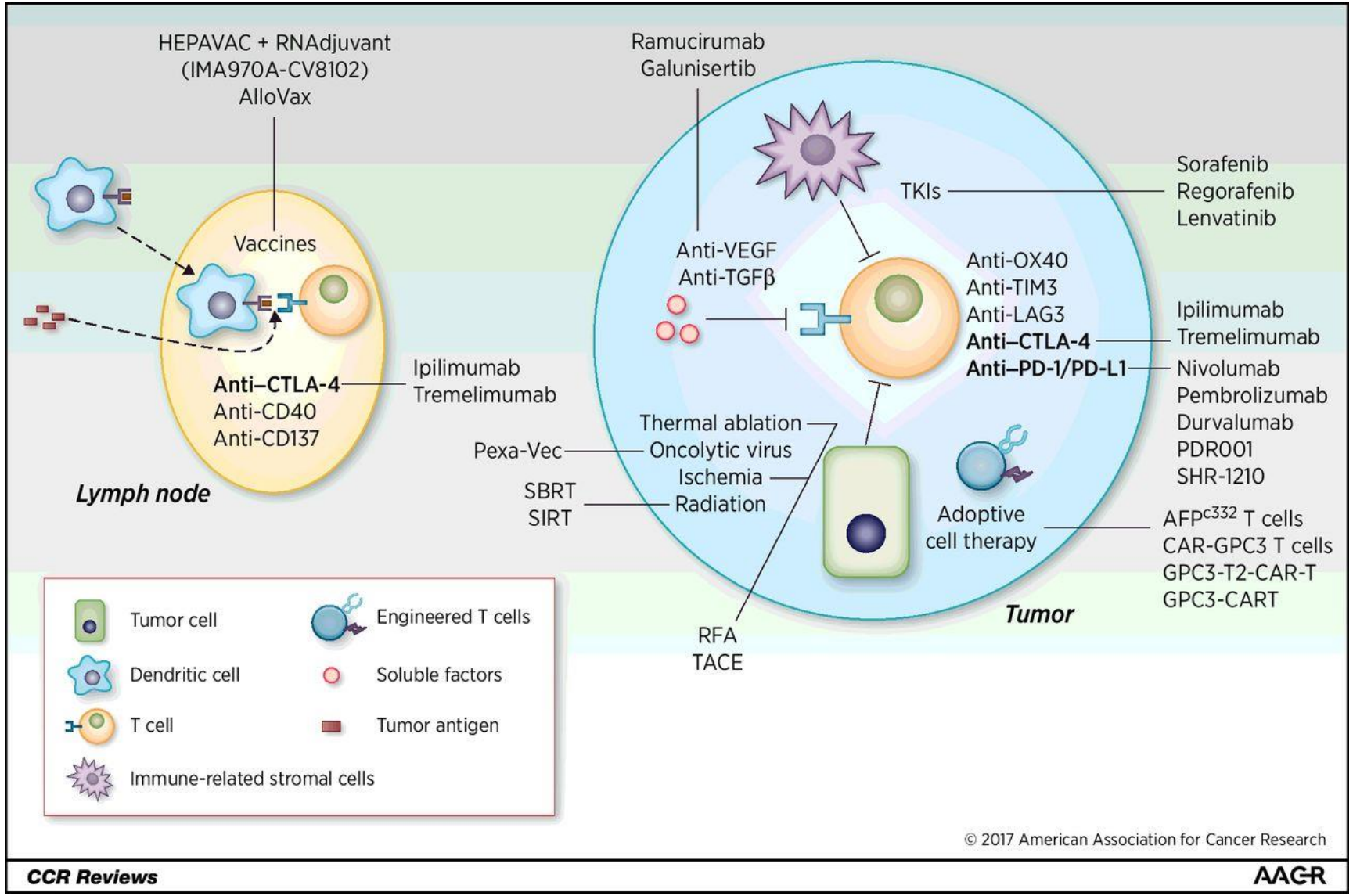
“When nothing seems to help, I go and look at a stonecutter hammering away at his rock perhaps a hundred times without as much as a crack showing in it. Yet at the hundred and first blow it will split in two, and I know it was not that blow that did it – but all that had gone before.”

- Jacob Riis

THE DEVELOPING STORY OF IMMUNOTHERAPY IN HCC

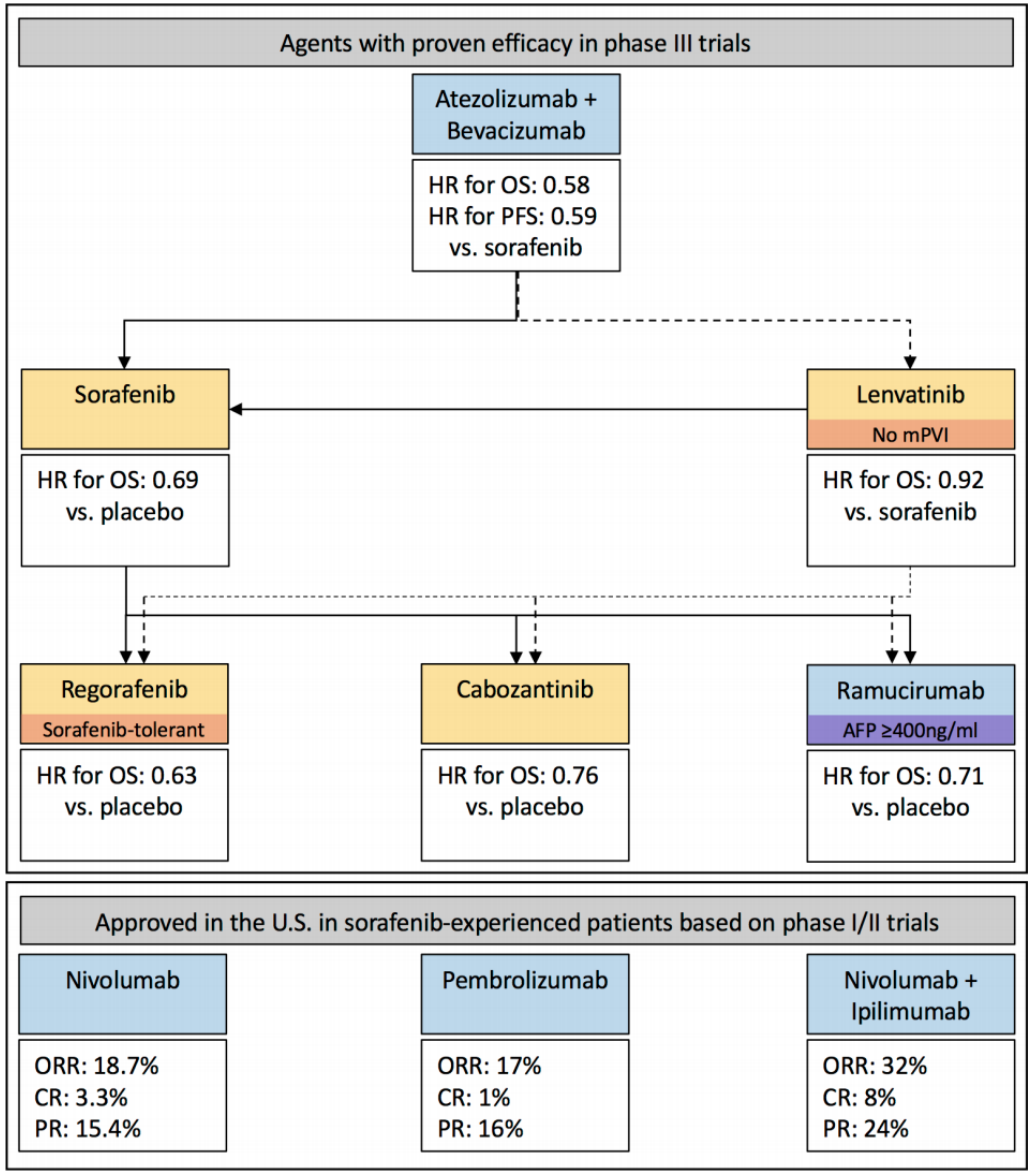
- Brief history of treatment in HCC
- Immunotherapy in HCC
- The long road ahead
- 2 cases

ONCOGENIC PATHWAYS AND TARGETS



Clin Cancer Res April 1 2018 (24) (7) 1518-1524; **DOI:** 10.1158/1078-0432.CCR-17-0289

FDA APPROVED THERAPIES FOR HCC



- 10 years between 1st disease-specific approval (sorafenib 2007) and 2nd approval (regorafenib 2017)
- Sorafenib is still the only 1st line agent approved for Childs Pugh B7
- Nivolumab and pembrolizumab approved based on non-randomized phase 2 trials (ORR)

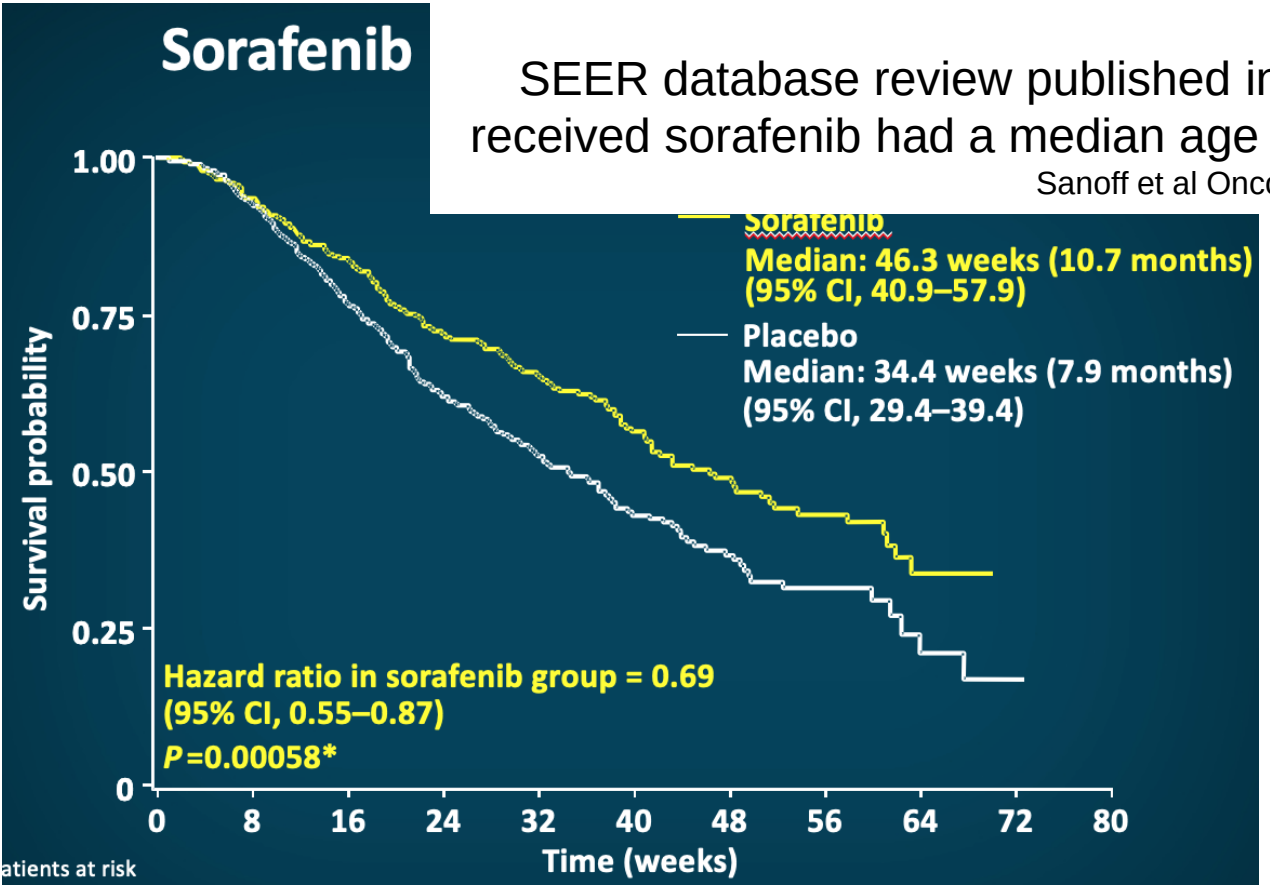
Gut Published Online First: 03 August 2020. doi: 10.1136/gutjnl-2020-321702

SORAFENIB: THE GOOD, THE BAD, AND THE UGLY

The Ugly

SEER database review published in 2017 showed that patients who received sorafenib had a median age of 70 years and mOS of 3 months.

Sanoff et al Oncologist 2016



SHARP Trial
ependent Review)

	Sorafenib n = 299 %	Placebo n = 303 %
Overall response		
Complete response	0	0
Partial response	2	1
Stable disease	71	67
Progressive disease	18	24
Progression-free rate at 4 mos.	62	42

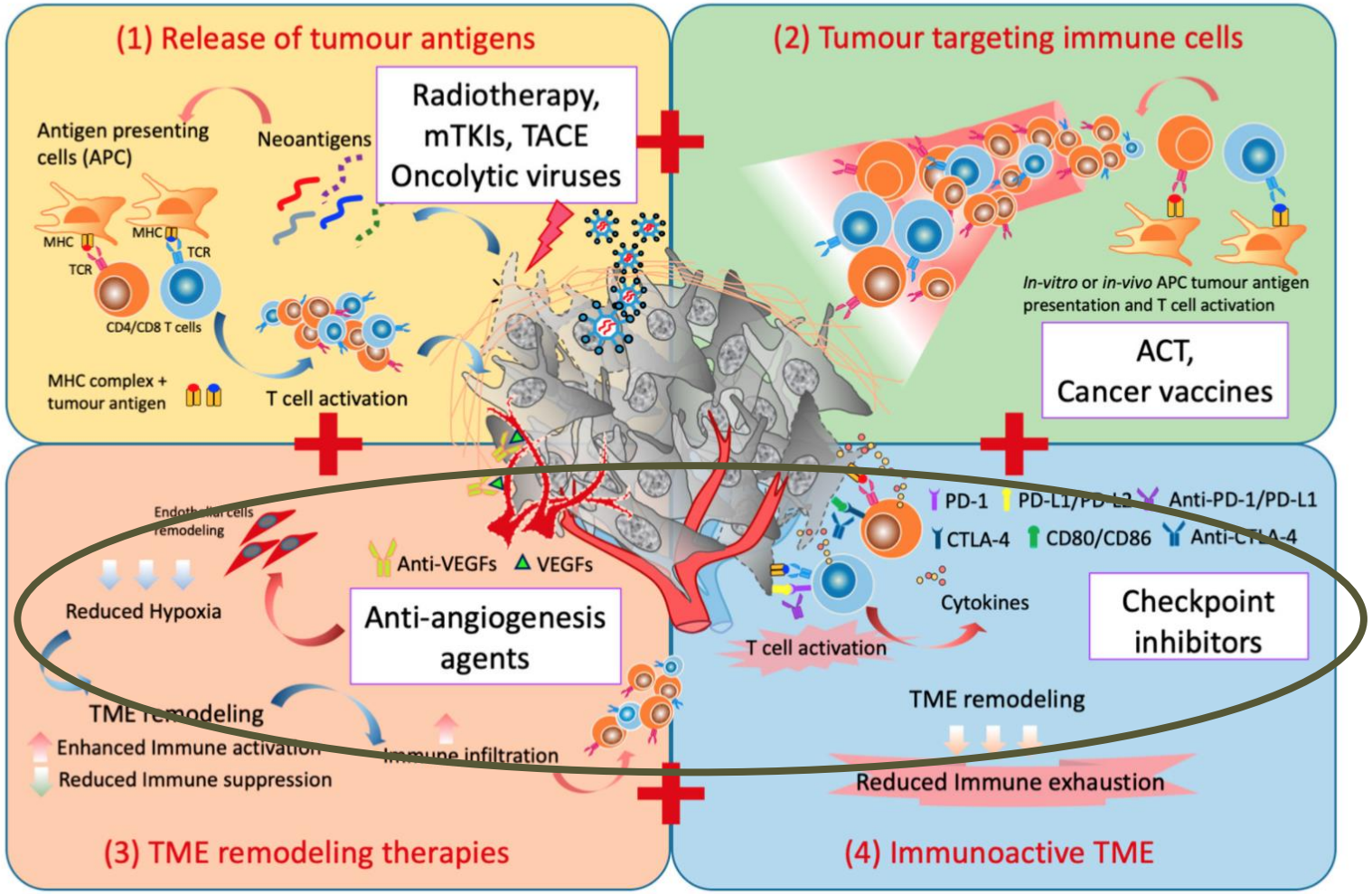
N Engl J Med 2008; 359:378-390
DOI: 10.1056/NEJMoa0708857

IMMUNOTHERAPY BREAKS THROUGH IN HCC

Study name	Year	Therapy	Setting	Design	Outcomes
CheckMate-040	2017	Nivolumab	Unresectable/metastatic	Phase I/II (n=262)	ORR 20%, CR 1%, mPFS 4.0 mos Grade 3-5 TRAEs 19%
KEYNOTE-224	2018	Pembrolizumab	Unresectable/metastatic	Phase II (n=104)	ORR 17%, CR 1%, mPFS 7.0 mos, Grade 3-5 TRAEs 26%

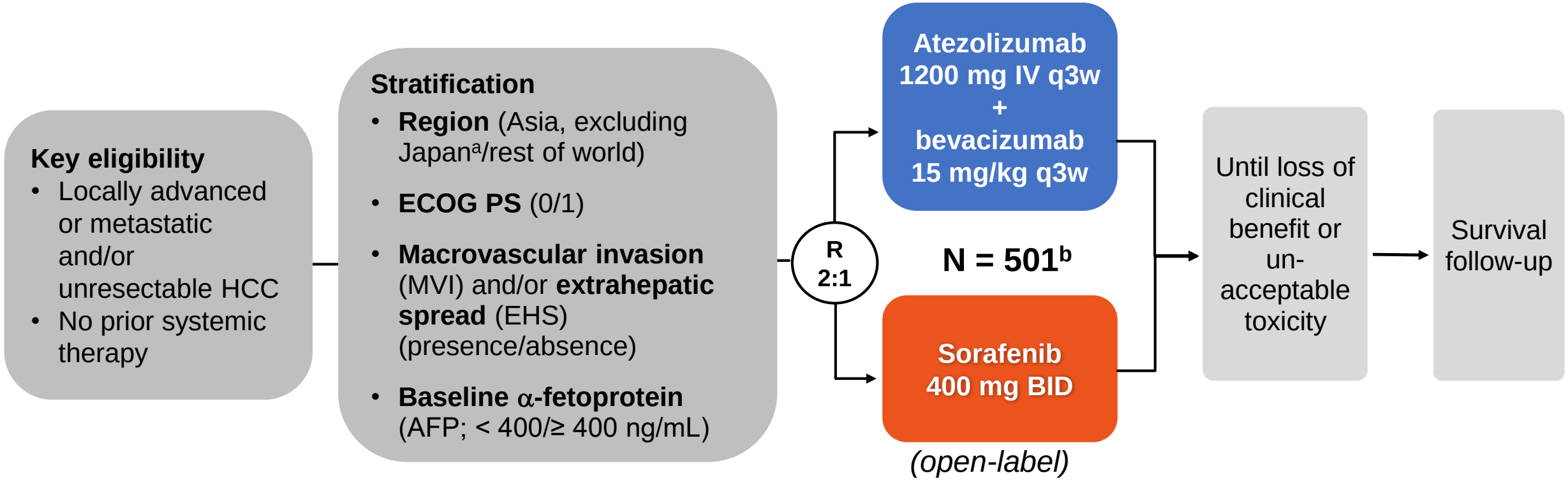
Approvals of the above agents made in part based on surrogate endpoints (ORR).
Since these approvals, the phase 3 CheckMate-459 investigating nivolumab vs sorafenib in the first line setting did not meet statistical significance for an OS benefit.

HOW TO IMPROVE ON MODEST BENEFIT OF SINGLE AGENTS?



Cancers **2019**, *11*(12), 1926; https://doi.org/10.3390/cancers11121926

IMBRAVE150 STUDY DESIGN



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

[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

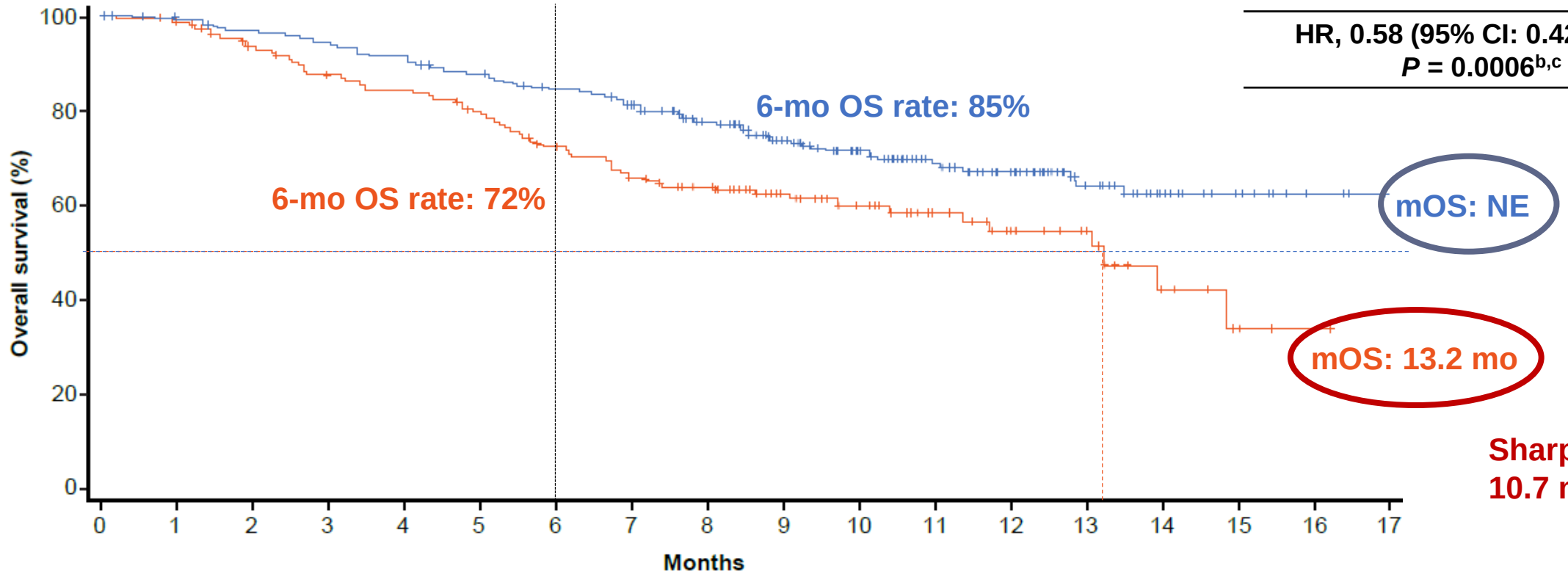
IMBRAVE150 BASELINE CHARACTERISTICS (ITT)

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)

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]

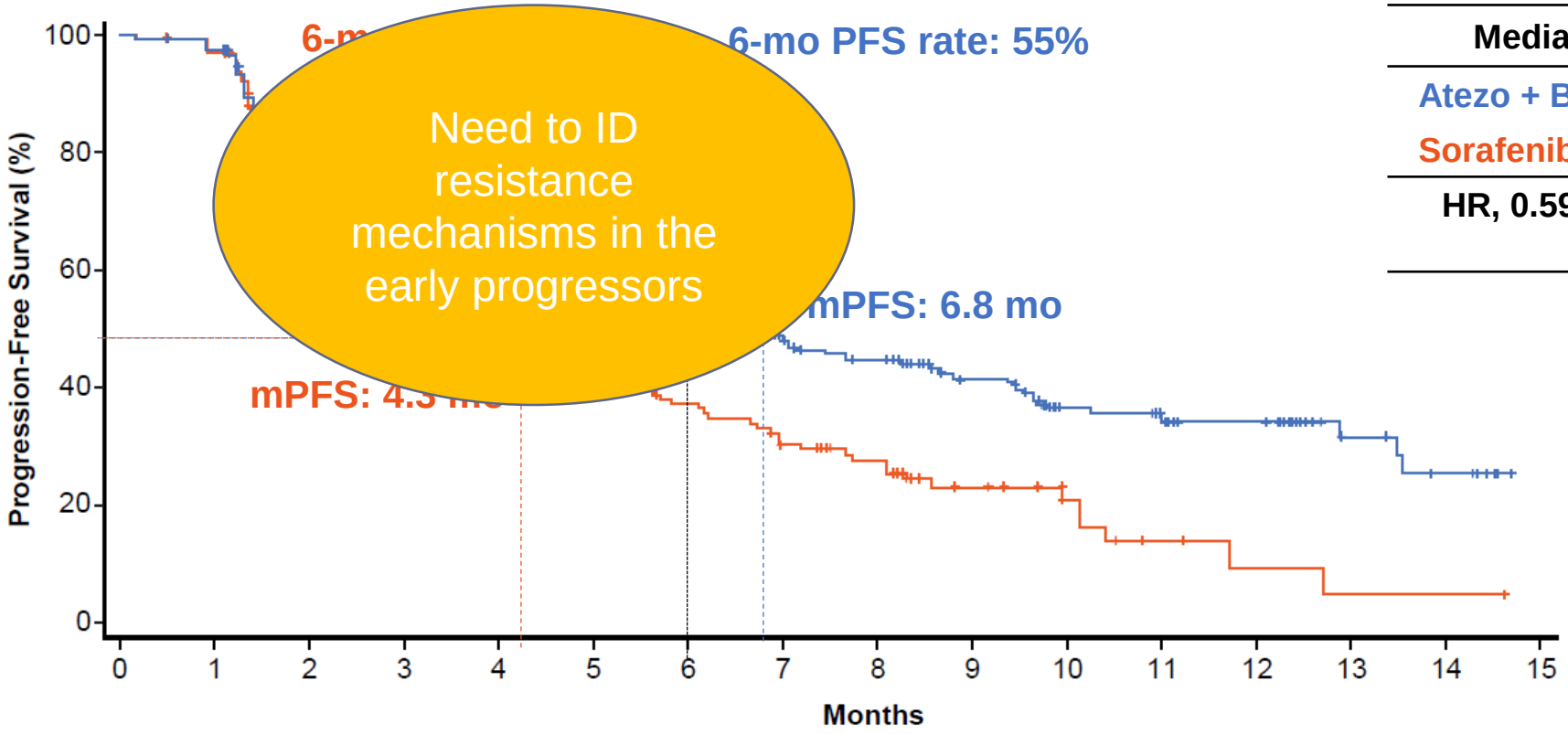


Sharp trial: mOS 10.7 mos

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

NE, not estimable. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

CONFIRMED PFS[A]: CO-PRIMARY ENDPOINT



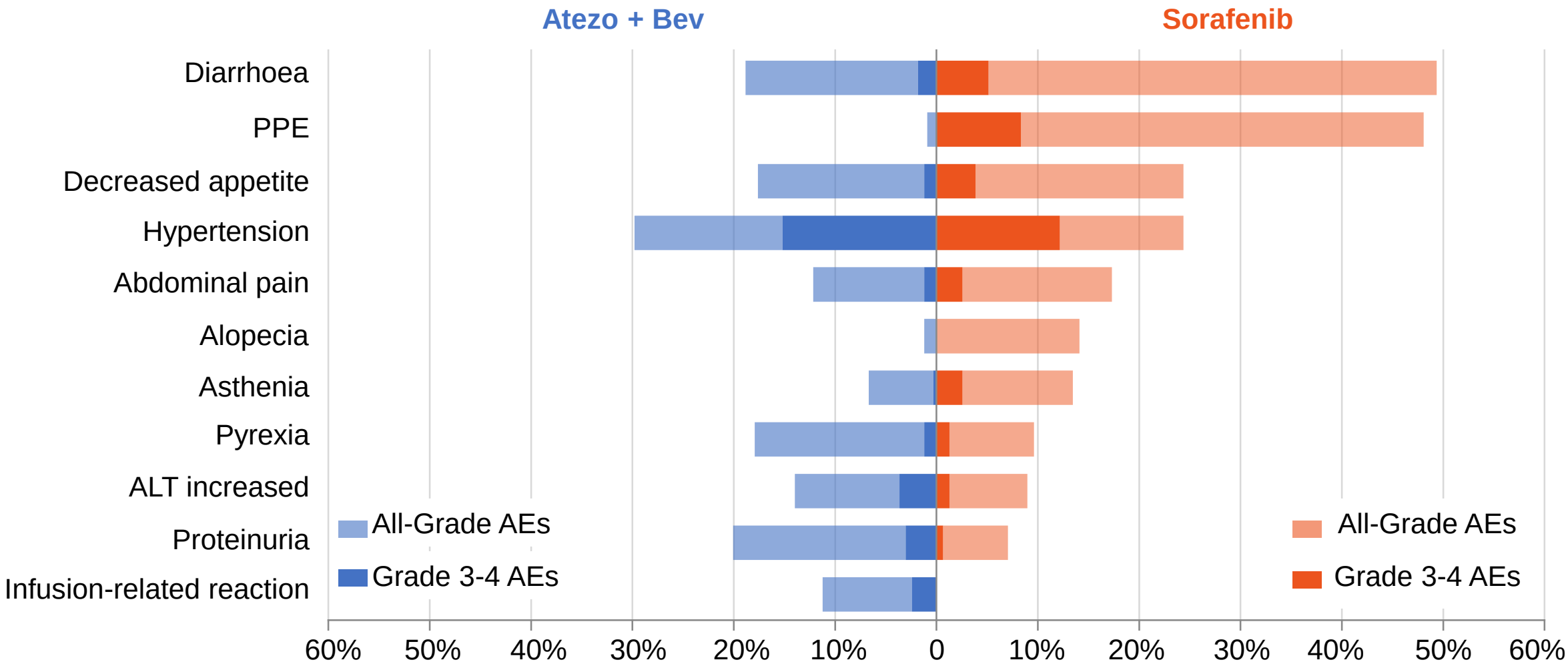
Median PFS (95% CI), mo[b]	
Atezo + Bev	6.8 (5.7, 8.3)
Sorafenib	4.3 (4.0, 5.6)
HR, 0.59 (95% CI: 0.47, 0.76)[c,d] *P* < 0.0001[d]	

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

[a] Assessed by IRF per RECIST 1.1. [b] 197 patients (59%) in the Atezo + Bev arm vs 109 (66%) in the sorafenib arm had an event. [c] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [d] The 2-sided *P* value boundary is 0.002. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

SAFETY

≥ 10% FREQUENCY OF AES IN EITHER ARM AND > 5% DIFFERENCE BETWEEN ARMS[A]



PPE, palmar-plantar erythrodysaesthesia.
[a] Safety-evaluable population.

IMBRAVE150 CONCLUSIONS

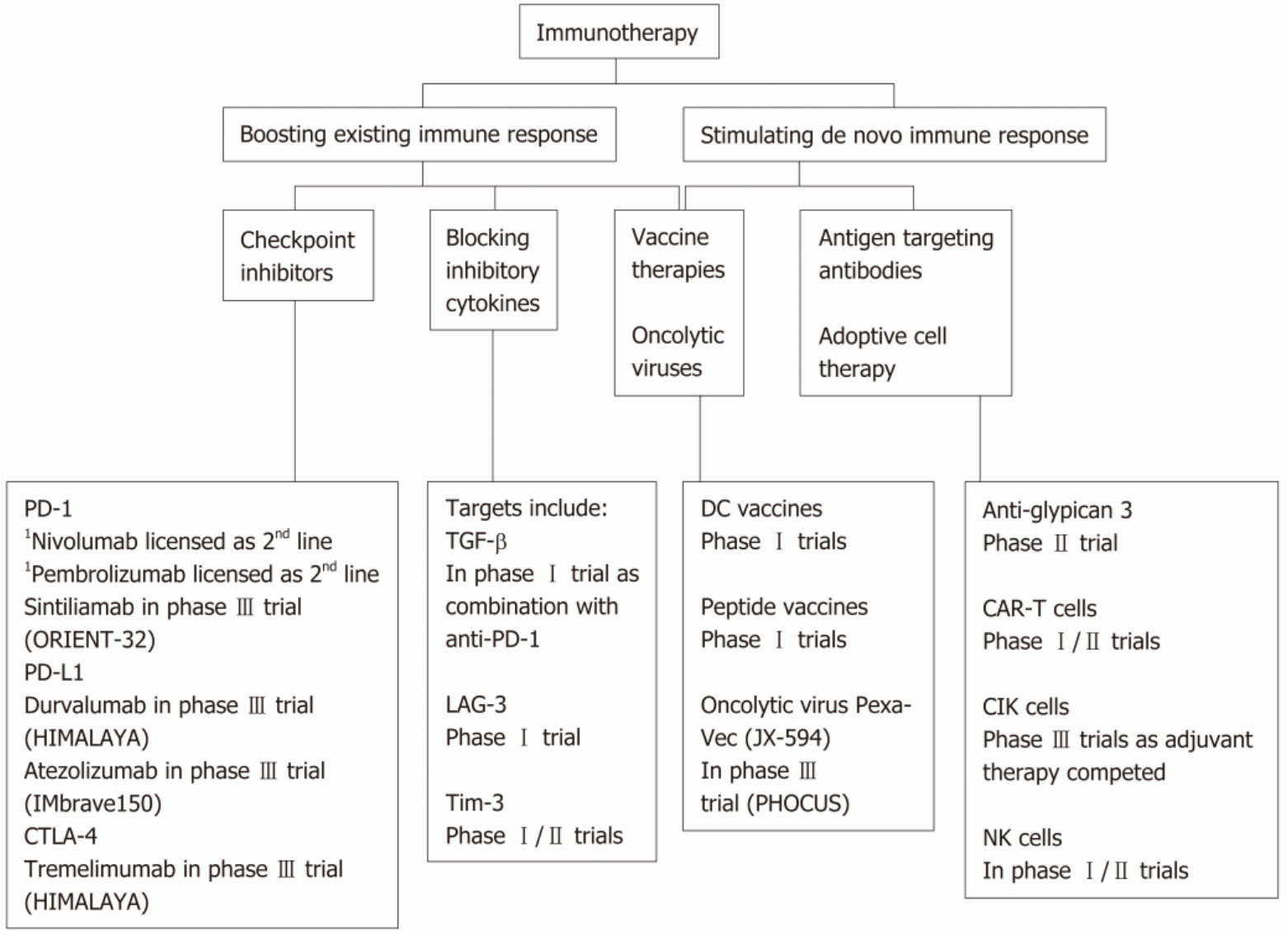
- IMbrave150 demonstrated statistically significant and clinically meaningful improvement with atezolizumab + bevacizumab over sorafenib for OS and IRF-assessed PFS per RECIST 1.1
  - OS HR, 0.58 (95% CI: 0.42, 0.79); *P* = 0.0006
  - IRF-PFS HR, 0.59 (95% CI: 0.47, 0.76); *P* < 0.0001

  Co-primary endpoints in ITT population
- PFS and OS benefits were generally consistent across subgroups
- Statistically significant and clinically meaningful improvements were seen in ORR and responses were durable with atezolizumab + bevacizumab
- The safety and tolerability profile of atezolizumab + bevacizumab was in line with the known safety profiles of each individual component and the underlying disease
- Treatment with atezolizumab + bevacizumab resulted in a clinically meaningful delay in deterioration of patient-reported quality of life vs sorafenib
- FDA approval of atezolizumab plus bevacizumab May 2020

THE LONG ROAD AHEAD: FDA APPROVAL OF IO AGENTS IN GI CANCERS(SEPT 2020)

	1st Line	2nd Line	3rd Line	Comments
Esophageal SCC		Pembro for PD-L1 CPS ≥10		
Gastroesophageal ACA			Pembro for PD-L1 CPS ≥1	Nivo approved in Asia based on ATTRACTION-2
Pancreas Ca				
Hepatocellular Ca	Atezolizumab+ BEV	Pembrolizumab Nivolumab		Pembro and Nivo approval based on non-randomized studies
Biliary Ca				
Colorectal Ca	Pembro for MSI-H/ MMR-D		Nivo +/- Ipi and Pembro for MSI-H/ MMR-D	
Anal SCC				
MSI-H/ MMR-D Ca			Pembrolizumab	Tumor-entity independent approval
TMB 10+ (Foundation)			Pembrolizumab	Tumor-entity independent approval

ONGOING DEVELOPMENTS WITH IMMUNOTHERAPY IN HCC



World J Gastroenterol. 2019 Jun 28; 25(24): 2977–2989

UOFA HCC CLINICAL TRIALS

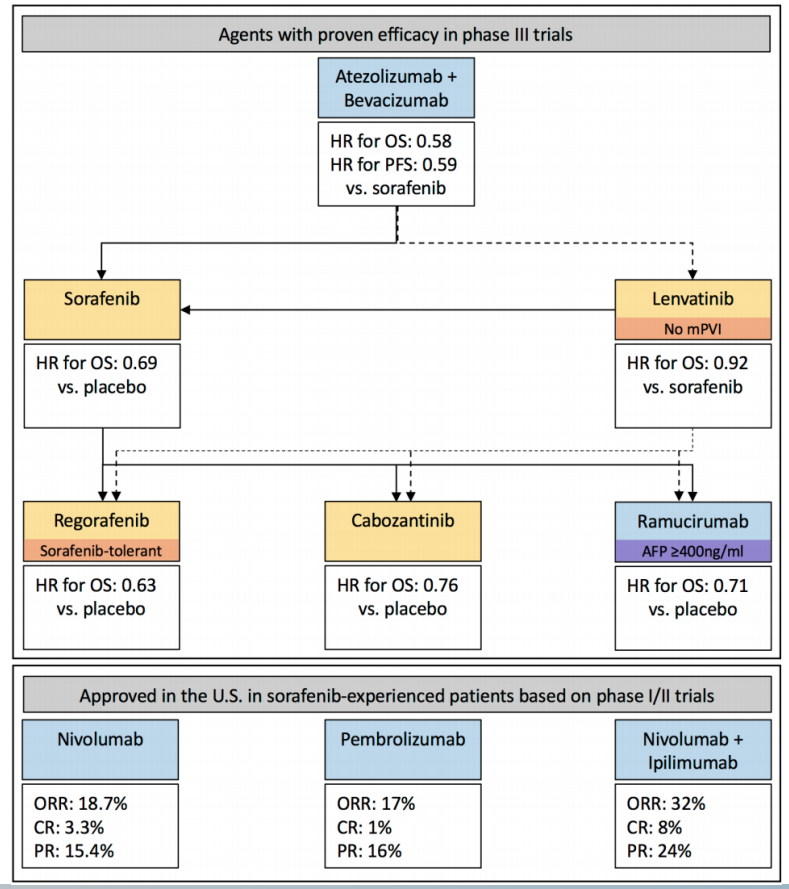
- **Merck MK-3475-937:** A Phase 3 Double-blinded, Two-arm Study to Evaluate the Safety and Efficacy of **Pembrolizumab (MK-3475)** versus Placebo as Adjuvant Therapy in Participants with Hepatocellular Carcinoma and Complete Radiological Response after Surgical Resection or Local Ablation (KEYNOTE-937)
- **AstraZeneca D933GC00001:** A Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Study of Transarterial Chemoembolization (TACE) in Combination with either **Durvalumab** Monotherapy or **Durvalumab plus Bevacizumab** Therapy in Patients with Locoregional Hepatocellular Carcinoma
- **Merck MK-7902-002 (Currently closed to accrual):** A Phase 3 Multicenter, Randomized, Double-blinded, Active-controlled, Clinical Study to Evaluate the Safety and Efficacy of Lenvatinib (E7080/MK-7902) in Combination with **Pembrolizumab (MK-3475)** Versus Lenvatinib in First-line Therapy of Participants with Advanced Hepatocellular Carcinoma (LEAP-002)

CASE 1

55 yo woman with history of etoh-related cirrhosis who is seeking a second opinion regarding treatment of her HCC. She has a history of Child Pugh A liver disease, and she is in good condition with mild nonbleeding gastric varices. She was previously treated with sorafenib, and restaging CT after 12 weeks of treatment demonstrates progression in 3 liver masses, a sternal mass, and 2 lung nodules.

What are her next options?

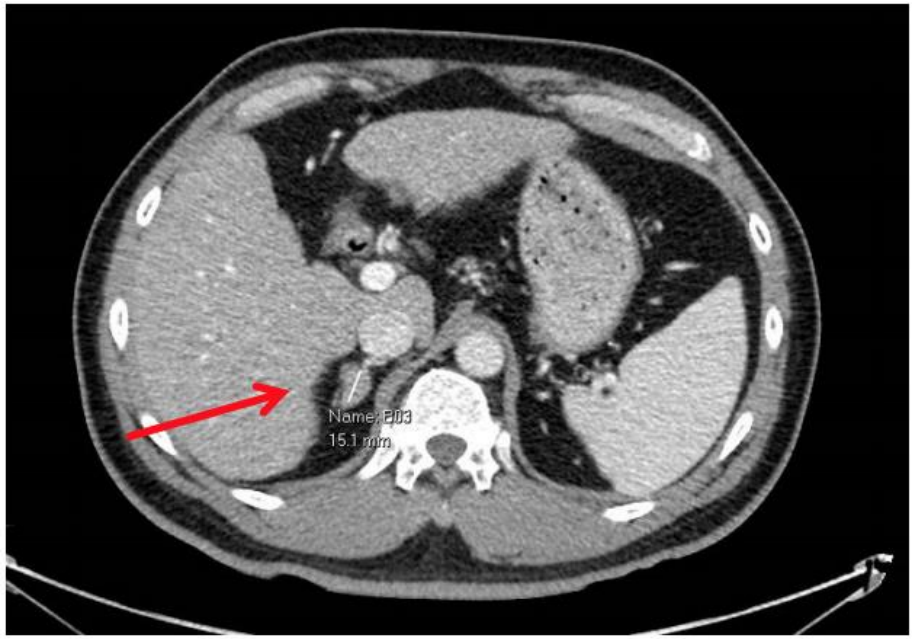
1. Lenvatinib
2. Atezolizumab/bevacizumab
3. Nivolumab
4. Cabozantinib
5. Ramucirumab
6. Pembrolizumab
7. Clinical trial

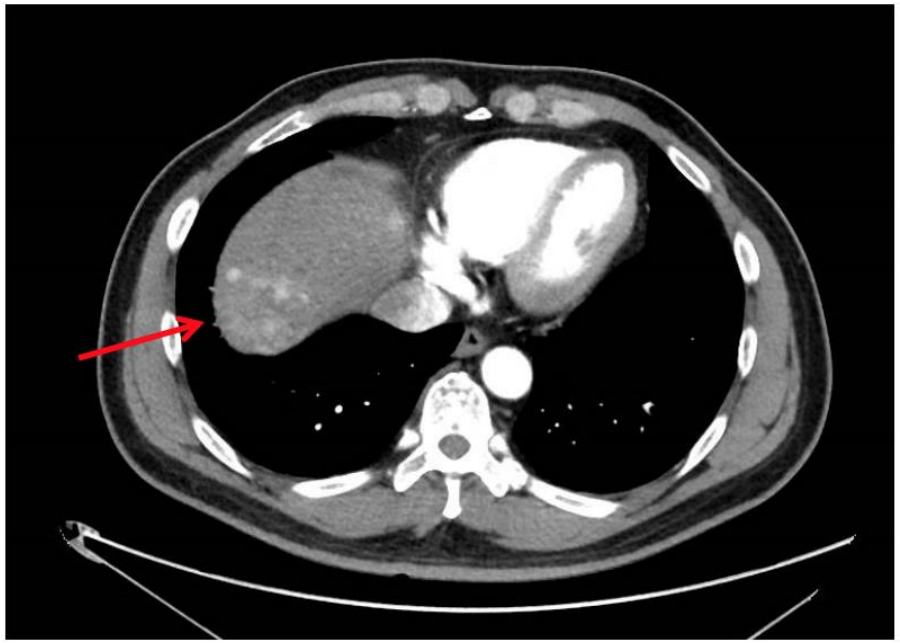


Gut Published Online First: 03 August 2020. doi: 10.1136/gutjnl-2020-321702

CASE 2

62 yo man with history of HCV cirrhosis presents to the ED with RUQ abdominal pain rated a 7-8 out of 10, and AST/ALT elevation in the 200s. He states this pain is especially noticeable when he takes a deep breath. He notes decreased appetite and weight loss of 10 lbs over 4 weeks. CT chest/abd reveals a RLL nodule and a 5.4cm liver mass.





CASE 2

What next?

1. Admission for pain control and further workup
2. Discuss with pt need for urgent followup with PCP for further workup
3. Obtain a PET/CT scan
4. Consult heme/onc
5. Biopsy

CASE 2

Pt was admitted to medicine with a heme/onc consult who recommended pt obtain PET/CT scan and biopsy of the liver mass. PET/CT reveals a solitary liver 5.4 cm liver lesion and RLL lung lesion that are both FDG avid positive (SUV 15). Biopsy is positive for HCC. Pt noted to have Child Pugh score of B7. Pt is interested in pursuing treatment.

In addition to optimal supportive care and pain control, what next?

1. Refer to transplant clinic
2. Refer to IR for consideration of locoregional treatment
3. Refer pt to outpatient heme/onc clinic for discussion regarding treatment

CASE 2

Upon review of options in OP heme/onc clinic, which treatment recommendation would you make?

1. Atezolizumab/bevacizumab
2. Sorafenib
3. Lenvatinib
4. Single agent Nivolumab
5. Single agent Pembrolizumab

THANK YOU!

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