Immunotherapy in HCC – When and How

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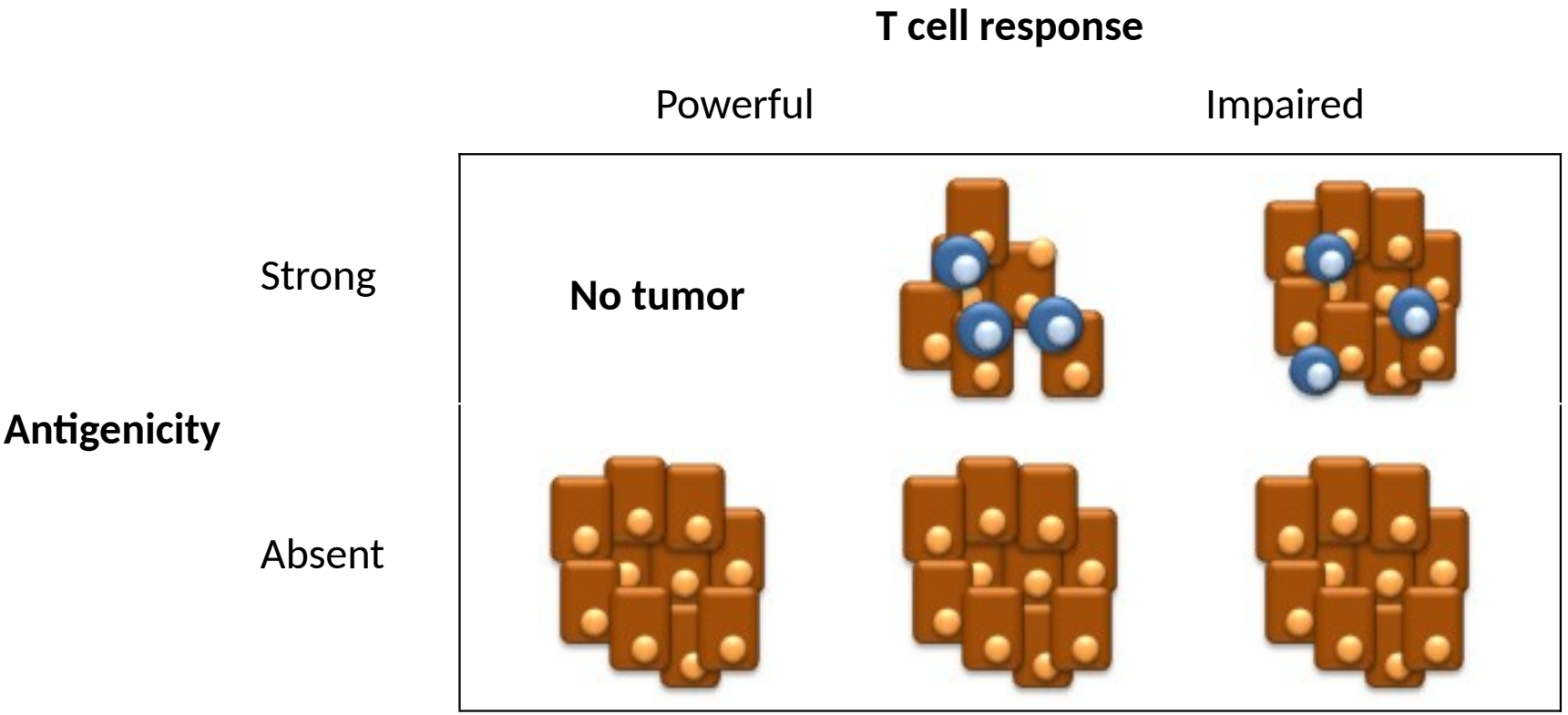
Financial Disclosures

I have received fees from the following companies and concepts over the last five years

- *Consultancy*: Adaptimmune, Astra Zeneca, Bayer, BMS, BTG, Eisai, Eli-Lilly, Ipsen, Medimmune, Merck, Onxeo, Roche, Sirtex, and Terumo.
- *Lectures*: Bayer, BMS, Ipsen, Medscape, Sirtex.
- *Research*: BMS and Sirtex.

Immune Rejection of Cancer

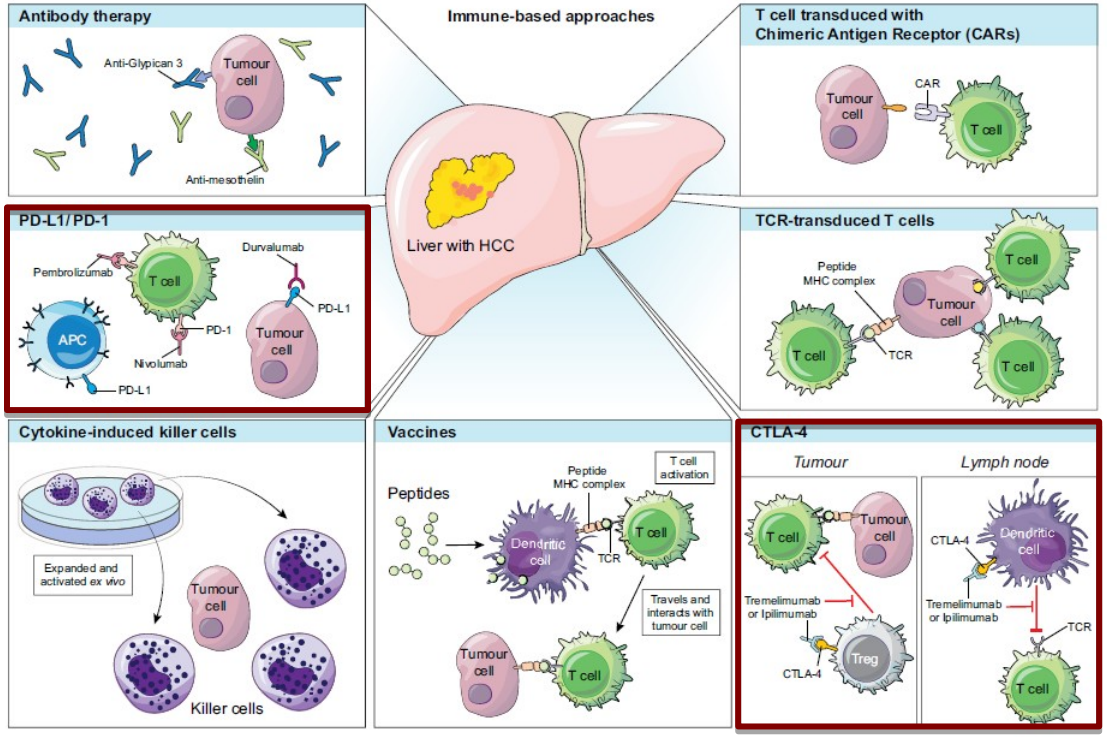


Immune-Based Therapies for HCC

Codrituzumab
(anti-GP3)

Nivolumab
Pembrolizumab
Durvalumab
Atezolizumab

CIK cells



CAR-GPC3 T cells

AFP SPEAR T cells

Tremelimumab
Ipilimumab

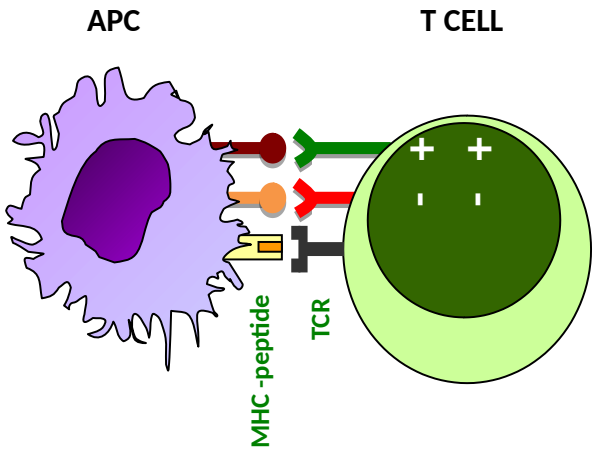
IMA970A + CV8102
(multipeptide + RNAadj)

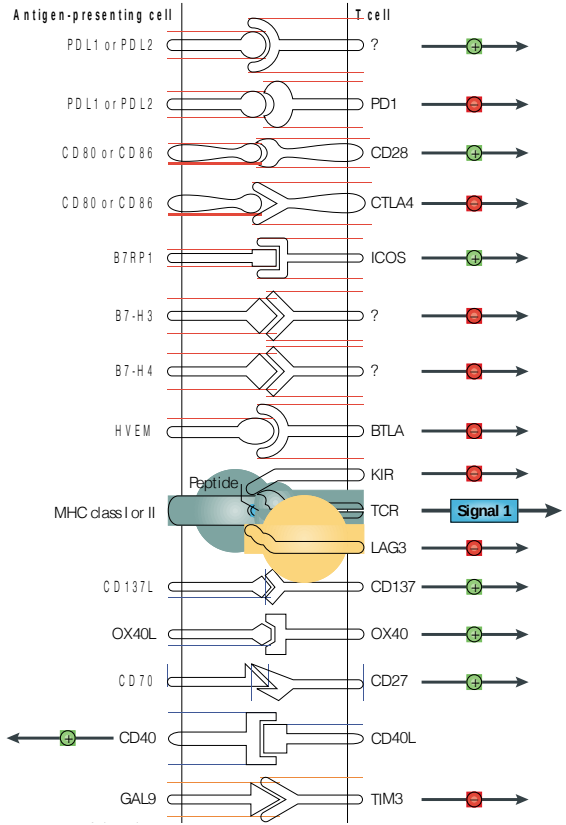
Greten and Sangro. J Hepatol 2017

Immune Checkpoint Inhibitors

Durvalumab
Atezolizumab

BLOCKADE





BLOCKADE

Nivolumab
Pembrolizumab
Tislelizumab

BLOCKADE

Tremelimumab
Ipilimumab

BLOCKADE

Lirelumab

STIMULATION

Urelumab

Checkpoint Inhibitors as 2L Therapy in HCC

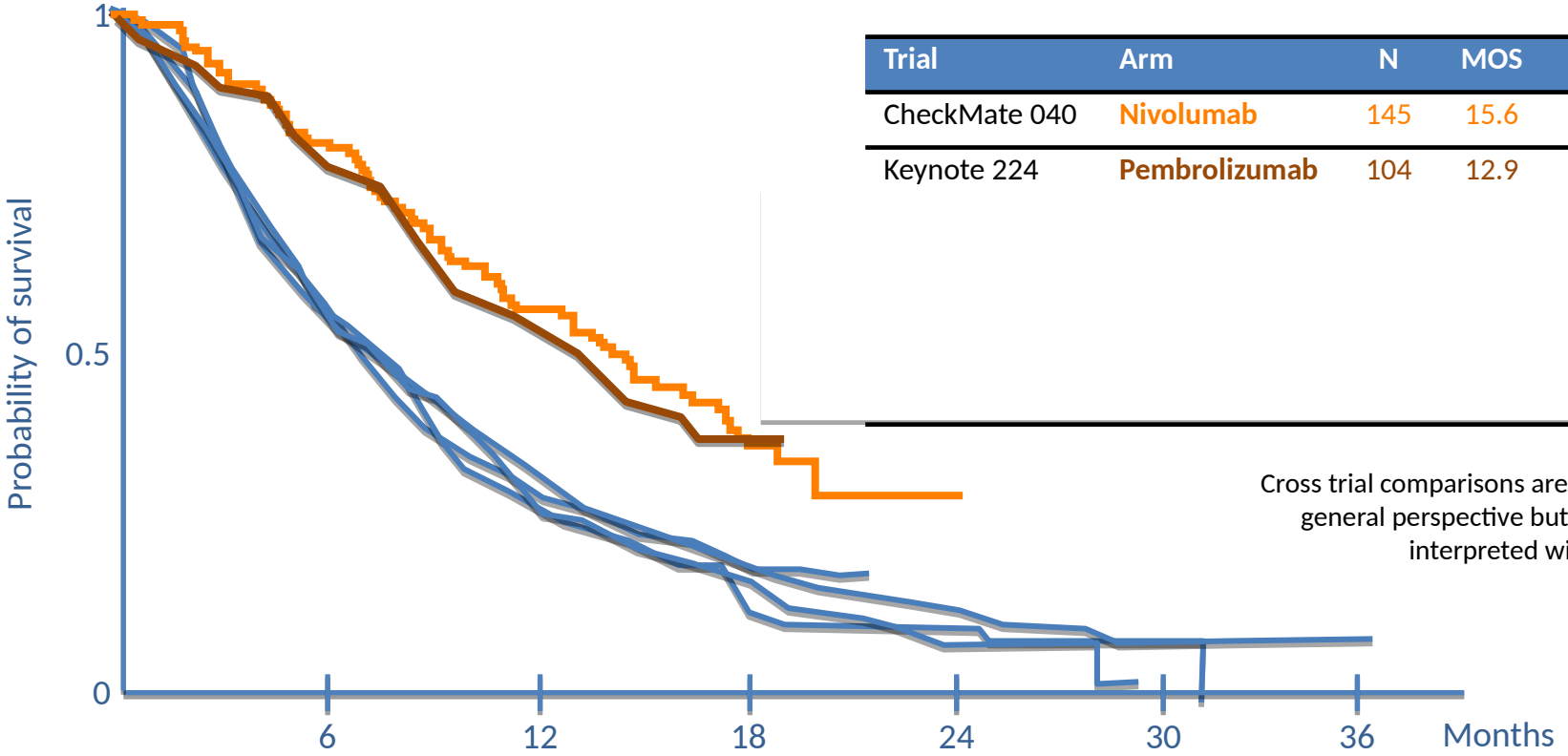
	Nivolumab	Pembrolizumab
Sample size	154 sorafenib-treated patients	104 sorafenib-treated patients
Patient features	2L or 3L Sorafenib-intolerants allowed Effective therapy for HBV+ve patients	2L Sorafenib-intolerants allowed Effective therapy for HBV+ve patients No involvement of portal vein trunk
Response rate	**14%** **regardless of etiology or AFP levels**	**17%**
Duration of response	**16.6 months in HCV patients, not reached in other etiologies**	**≥9 months in 77%**
mOS	15.1 months (95% CI 13.2–18.8)	**12.9 months (95% CI 9.7-15.5)**

El-Khoueiry A, Sangro B, Yao T, et al. Lancet 2017; Zhu A, et al. Lancet 2018

Phase 2 Trials with PD-1 Inhibitors

Survival of Advanced HCC in 2L Trials

Trial	Arm	N	MOS	95%CI
CheckMate 040	**Nivolumab**	145	15.6	13.2-18
Keynote 224	**Pembrolizumab**	104	12.9	9.7-15.5

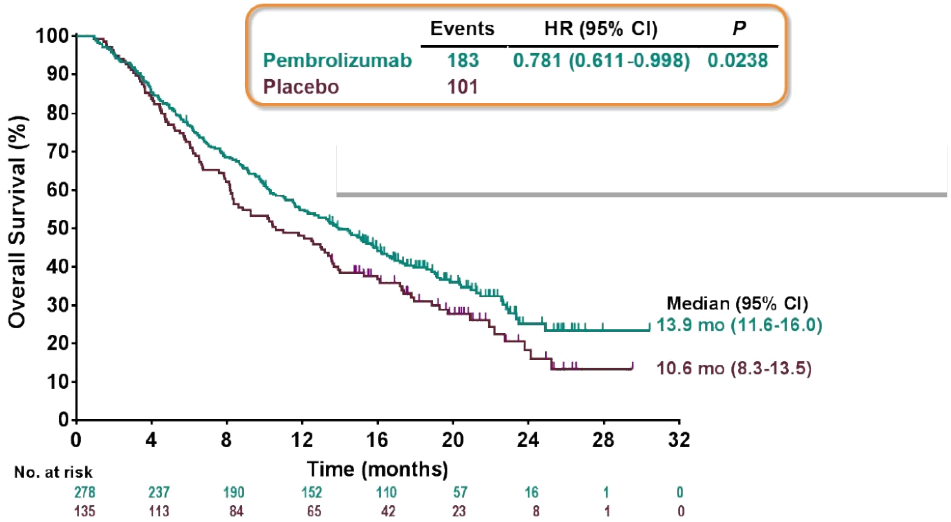


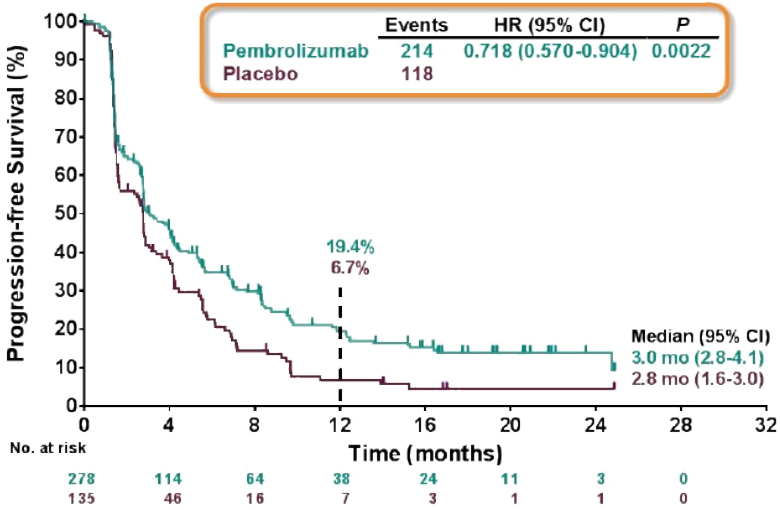
Cross trial comparisons are valid for a general perspective but should be interpreted with caution

El-Khoueiry AB et al. Presented at ASCO-GI 2018; Zhu AX et al. Presented at ASCO 2018; Llovet JM et al. J Clin Oncol 2013; Zhu AX et al. JAMA 2014; Zhu AX et al. Lancet Oncol 2015; Bruix J et al. Lancet 2017; https://www.onclive.com

Pembrolizumab as a 2L Agent in HCC (Keynote-240)

413 patients randomized to Pembrolizumab 200 mg Q3W or placebo + best supportive care

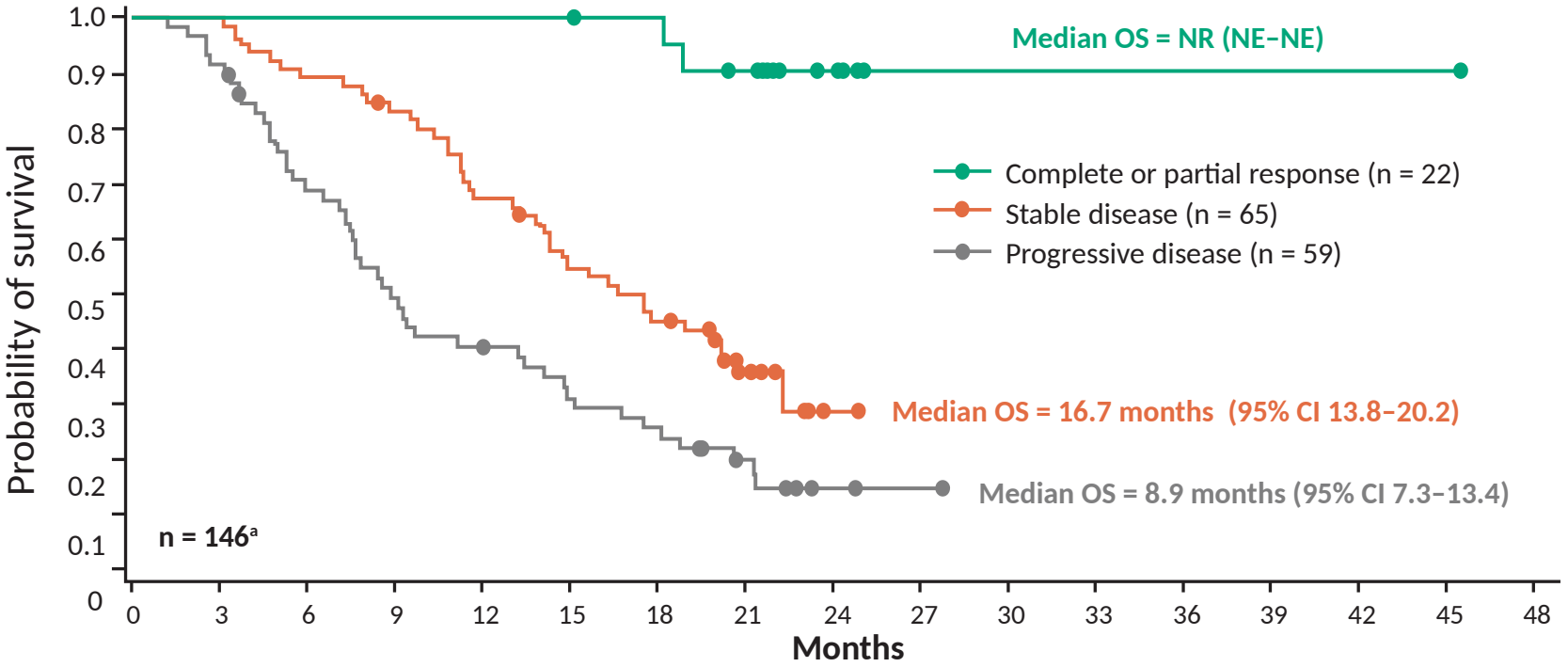




Finn R, et al. Presented at ASCO 2019

Clinical Trials with PD-1 Inhibitors (Nivolumab)

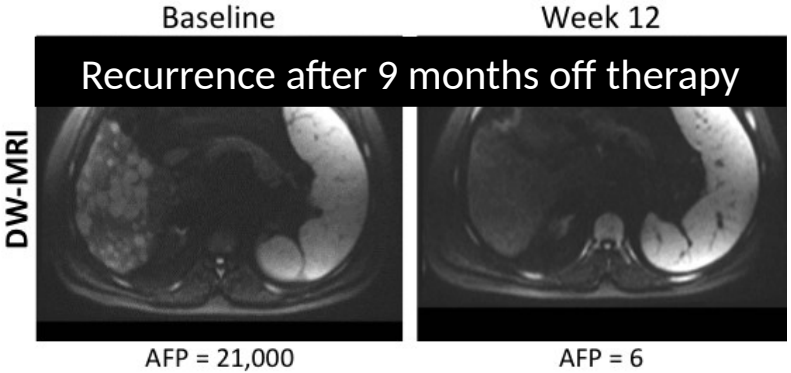
Response and Survival Among Sorafenib Experienced Patients



[a]Best overall response was not able to be determined in 8 patients.

Meyer T, et al. Presented at EASL 2018

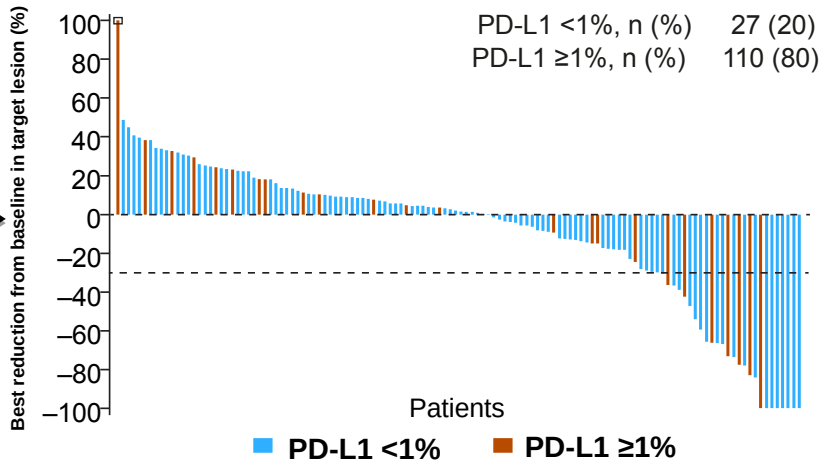
Deep Responses to Nivolumab

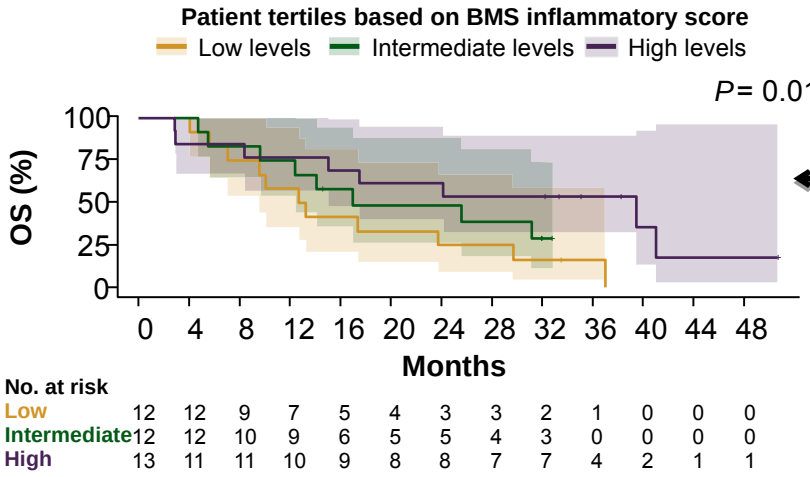


CM040 Biomarker Analysis

Sorafenib-experienced population, n = 137

- Deep responses and robust OS were observed regardless of tumor cell PD-L1 status



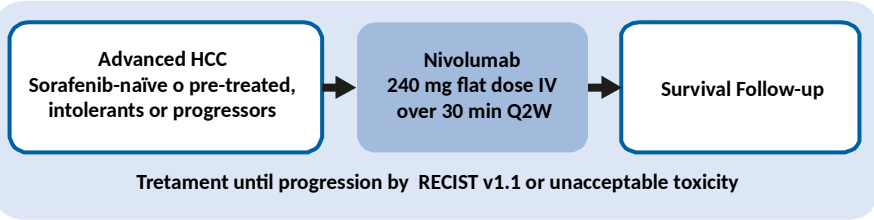


□ % change truncated to 100%.

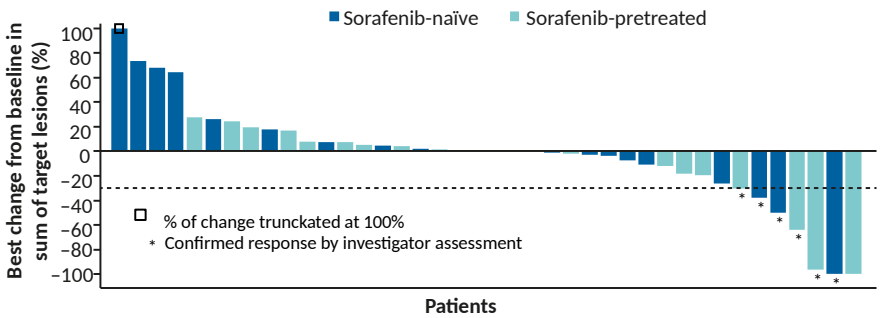
[a]Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy.

Melero I, et al. Presented at AACR 2019

CM040 Child B Cohort



- Objective response rate (INV RECIST v1.1): 12.1 %
- Disease control rate (INV RECIST v1.1): 55.1 %



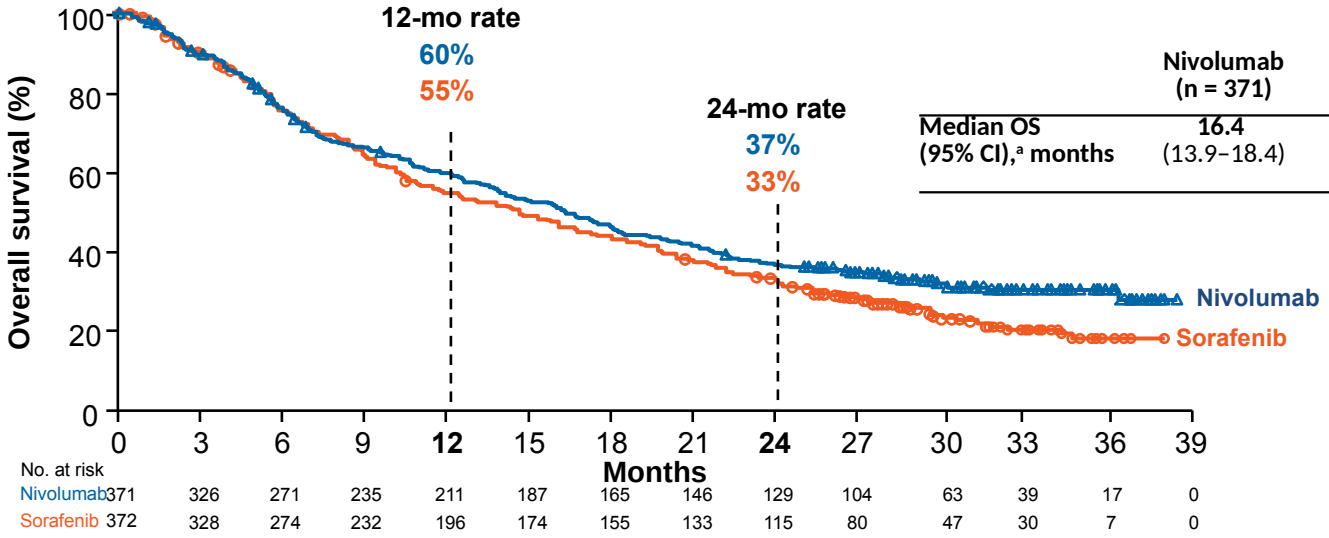
%	Child-Pugh B[a] N = 49		Child-Pugh A N = 262	
	Any Grade	G 3–4	Any Grade	G 3–4
TOTAL	51	24.5	78.6	22.5
Cutaneous disorders	22.4	24.1	39.3	2.3
General disorders	14.3	0	32.1	1.5
Hematologic disorders	10.2	2.0	8.8	2.3
Gastrointestinal disorders	10.2	4.1	34.7	2.7
Metabolic disorders	8.2	2.0	14.9	2.7
Nervous system disorders	6.1	0	8.4	0
Infections and infestations	4.1	0	1.9	0
Muscleskeletal disorders	4.1	0	11.5	0.4
Endocrine disorders	2.0	0	6.5	0.4
Hepatic TRAEs [b]				
Blood tests	12.2	8.2	28.2	14.1
Increased AST	4.1	4.1	10.3	5.7
Increased ALT	2.0	0	9.9	3.8
Increased liver tests	2.0	0	0.4	0.4
Hepatobiliary disorders	6.1	6.1	2.7	0.4
Hypertransaminasemia	4.1	4.1	0.8	0
Altered liver function	2.0	2.0	NR	NR
Hyperbilirubinemia	2.0	0	1.1	0

- Database lock: November 8, 2018
- Data from cohorts 1 and 2 of CheckMate 040 are presented for indirect comparison

Matilla A, et al. Presented at AEEH 2019

Nivolumab as a 1L Agent in HCC (CheckMate-459)

743 patients randomized to Nivolumab 240 mg Q2W or Sorafenib 800 mg/d



	Nivolumab (n = 371)	Sorafenib (n = 372)	HR (95% CI)[b]	P value[c]
Median OS (95% CI),[a] months	16.4 (13.9–18.4)	14.7 (11.9–17.2)	0.85 (0.72–1.02)	0.0752

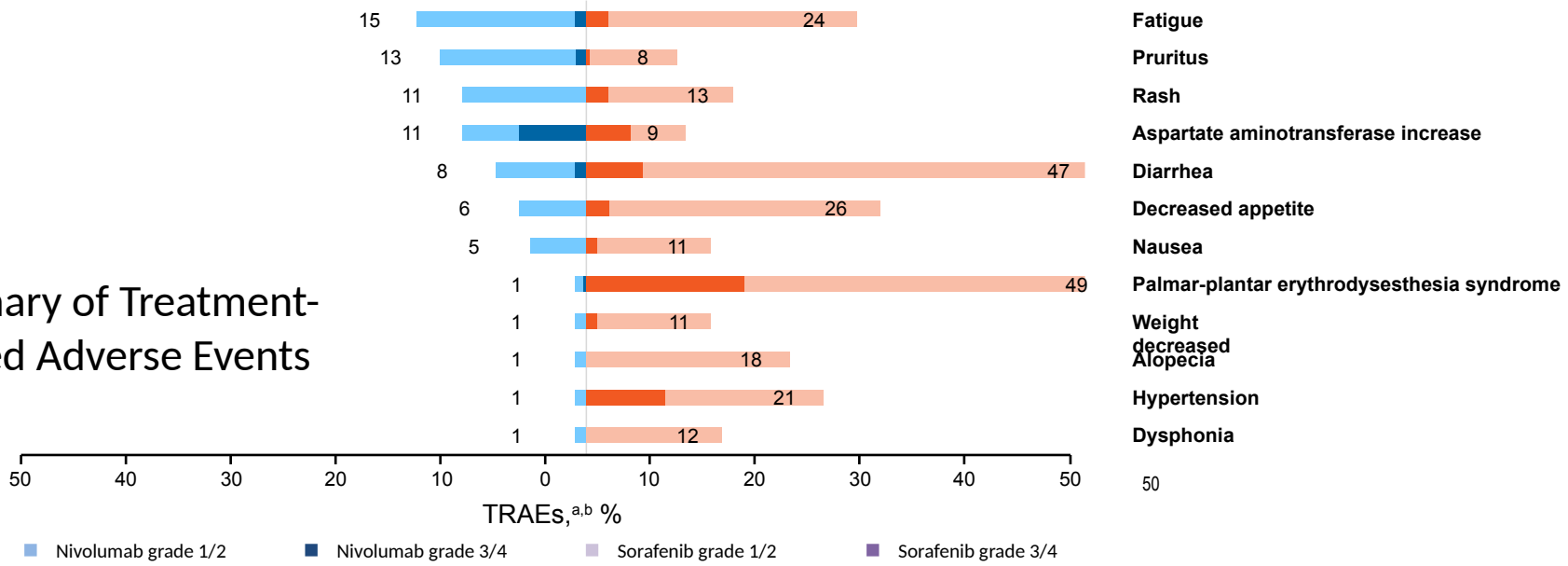
- **The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit.**
- **140 patients (38%) in the nivolumab arm and 170 patients (46%) in the sorafenib arm received subsequent systemic therapy**

[a]Based on Kaplan–Meier estimates; [b]Stratified Cox proportional hazards model. HR is nivolumab over sorafenib; [c]*P* value from log-rank test; final OS boundary: 0.0419 for a 2-sided nominal *P* value. HR, hazard ratio.

Yau T, et al. Presented at ESMO 2019

Nivolumab as a 1L Agent in HCC (CheckMate-459)

Summary of Treatment-Related Adverse Events

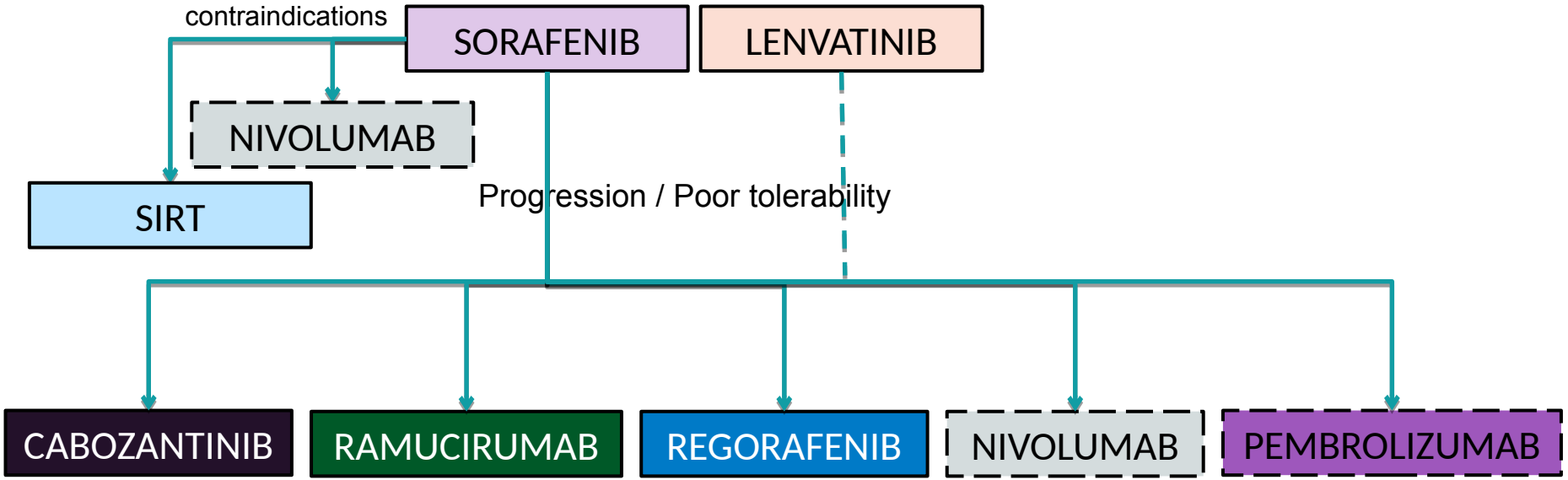


- Nivolumab demonstrated an improved safety profile compared with sorafenib, with fewer grade 3/4 TRAEs and TRAEs leading to discontinuation versus sorafenib
  - Grade 3/4 TRAEs were reported in 81 patients (22%) in the nivolumab arm and 179 patients (49%) in the sorafenib arm

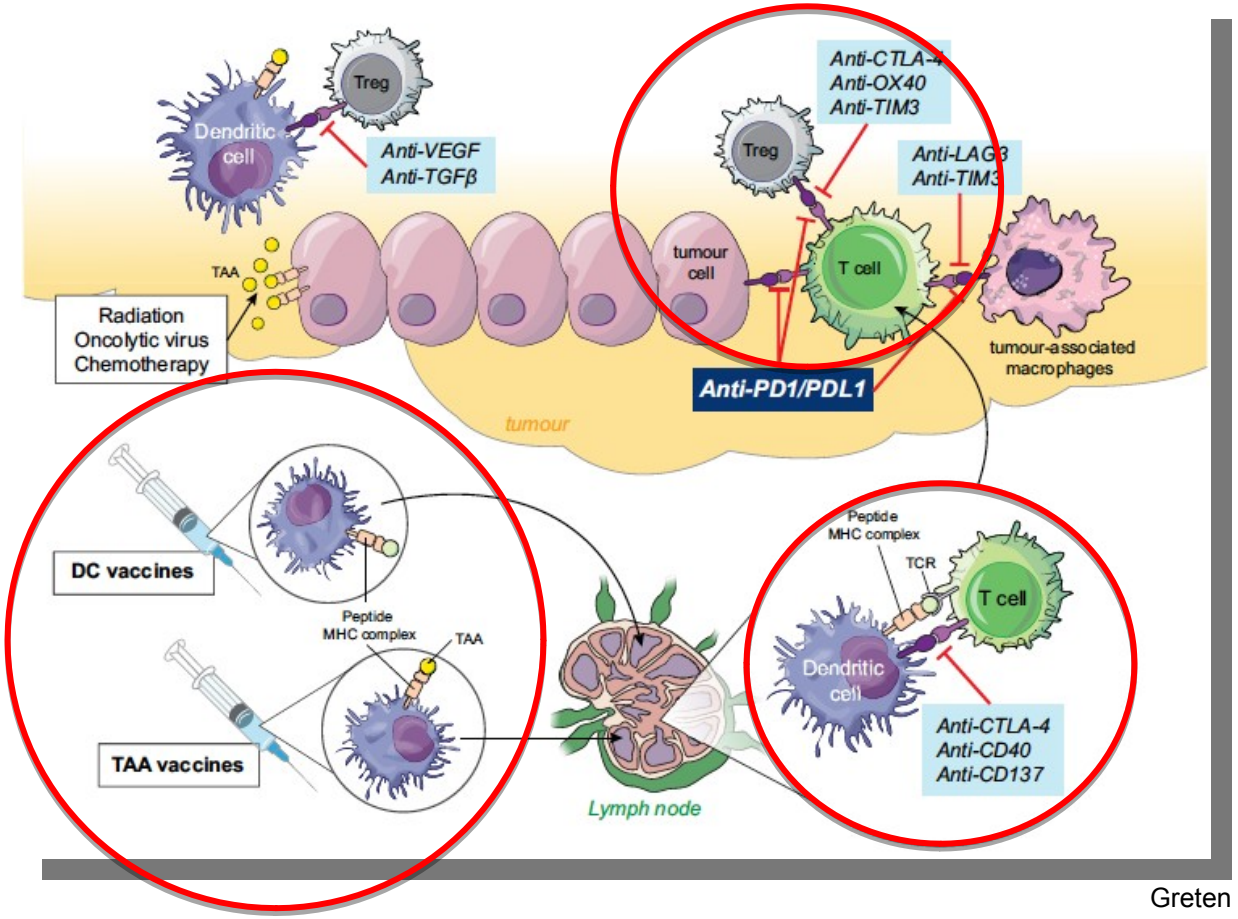
[a]Events occurring in > 10% of patients in either treatment arm. data labels represent rates of any-grade events; [b]One grade 5 event was reported in the nivolumab arm (cerebrovascular event), and 1 was reported in the sorafenib arm (hepatic failure). TRAE, treatment-related adverse event.

Yau T, et al. Presented at ESMO 2019

Systemic Therapy of HCC 2019



Improving the Effect of PD-1/PD-L1 Blockade



Greten and Sangro. J Hepatol 2017.

Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C☆

Bruno Sangro[1,2,*], Carlos Gomez-Martin[3], Manuel de la Mata[4,2,5], Mercedes Iñarrairaegui[1,2], Elena Garralda[3], Pilar Barrera[4,2], Jose Ignacio Riezu-Boj[6], Esther Larrea[6], Carlos Alfaro[7], Pablo Sarobe[6], Juan José Lasarte[6], Jose L. Pérez-Gracia[7], Ignacio Melero[6,7,†], Jesús Prieto[1,2,6,†]

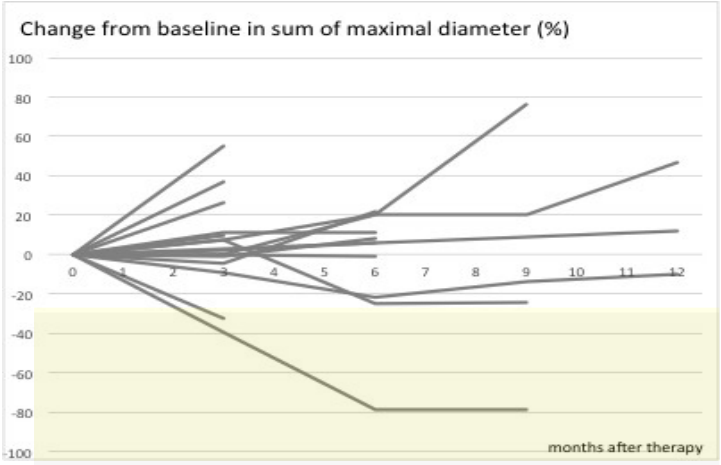
Editorial

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Facing the dawn of immunotherapy for hepatocellular carcinoma

Martin F. Sprinzl, Peter R. Galle*

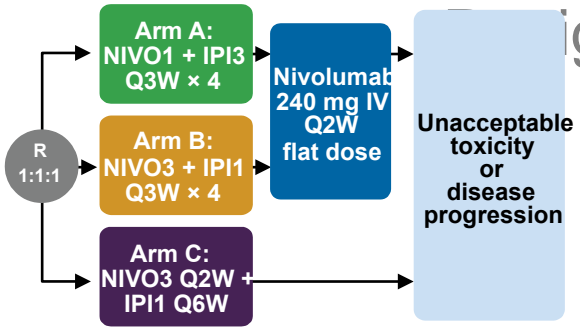
- Single agent **Tremelimumab**
- 17 (21) patients evaluable
- 100% HCV infected
- **18 % response rate** (Inv RECIST 1.0)
- **76 % disease control rate**
- 6.4 months median TTP



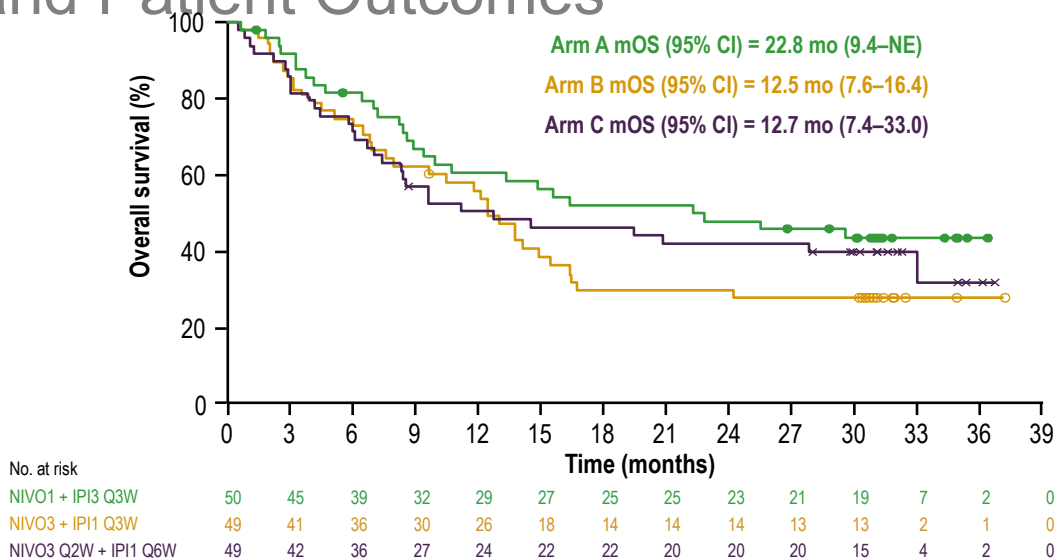
Sangro B, et al. J Hepatol 2013, 59:81

CM040 Nivolumab Plus Ipilimumab Combination Cohort

ign and Patient Outcomes



	Arm A n = 50	Arm B n = 49	Arm C n = 49
ORR by BICR,[a]	32%	31%	31%
24-month OS rate (95% CI), %	48 (34–61)	30 (18–44)	42 (28–56)

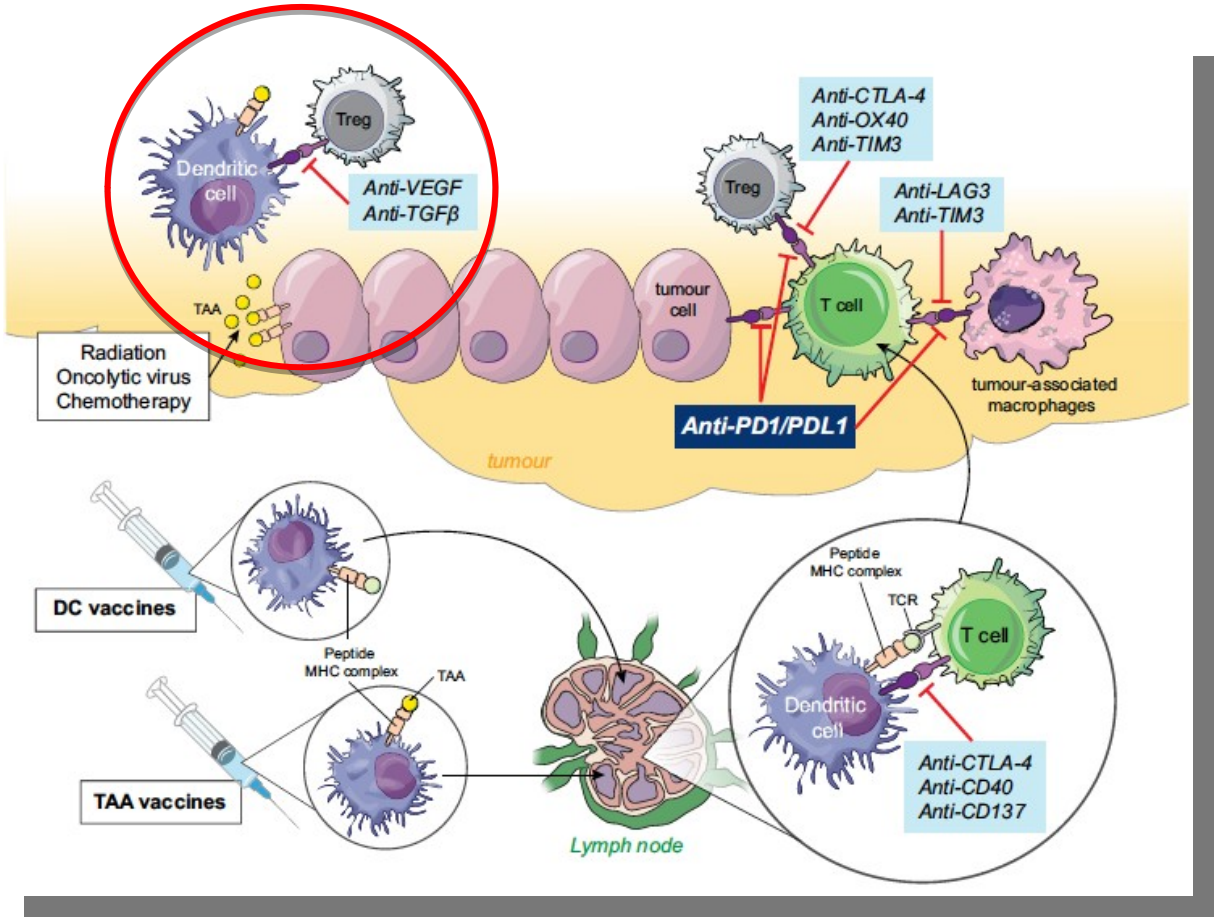


- Similar ORR, DCR, and DOR were observed across arms, with consistently high ORR (> 30%)
- Patients in arm A had the highest CR rate (8%) and most promising mOS of 22.8 months

[a]By BICR using RECIST v1.1. Defined as complete response + partial response.
NE, not estimable.

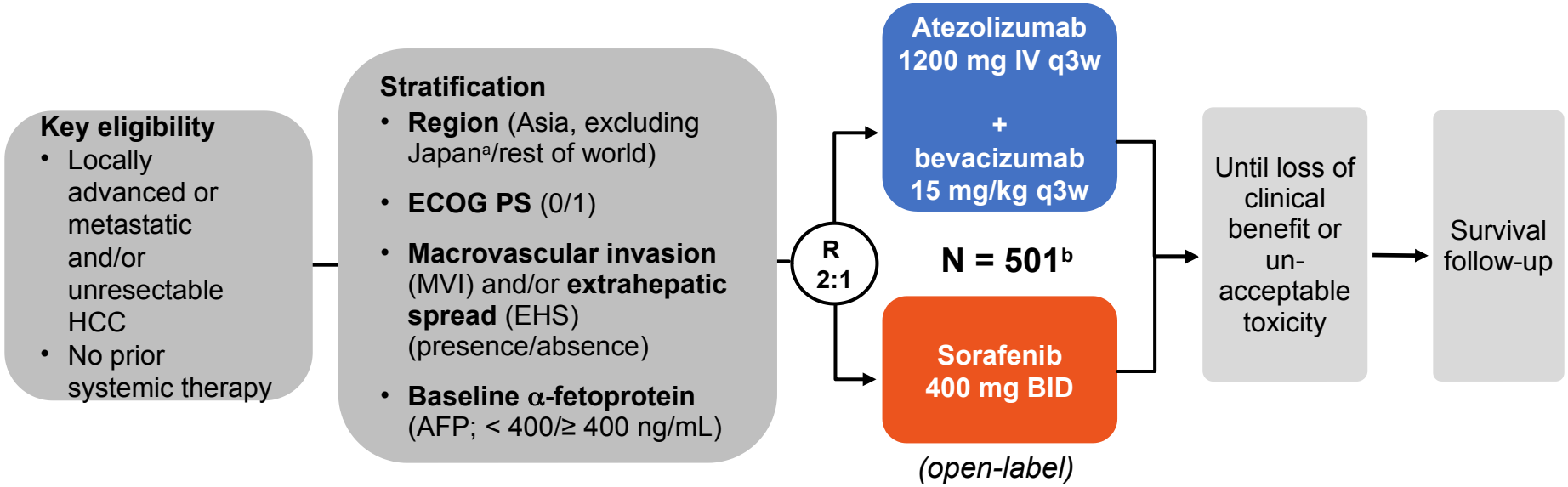
Sangro B, et al. Presented at AASLD 2019

Improving the Effect of PD-1/PD-L1 Blockade



Greten and Sangro. J Hepatol 2017.

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

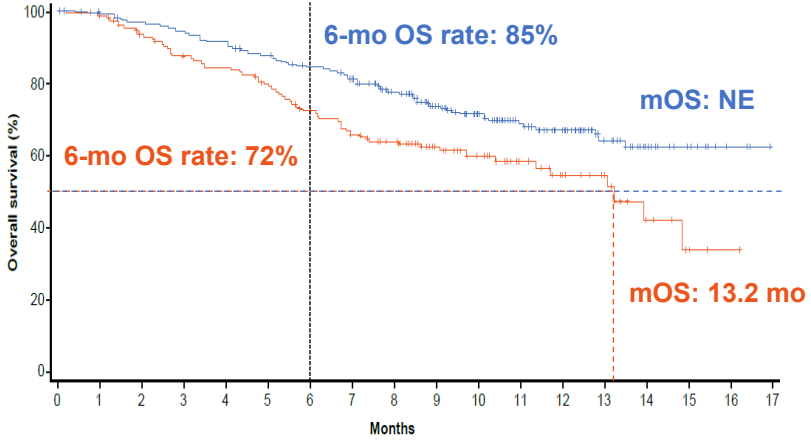
[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

Cheng AL, et al. Presented at ESMO Asia 2019

Imbrave 150 Atezolizumab + Bevacizumab vs. Sorafenib

Overall Survival and Confirmed PFS

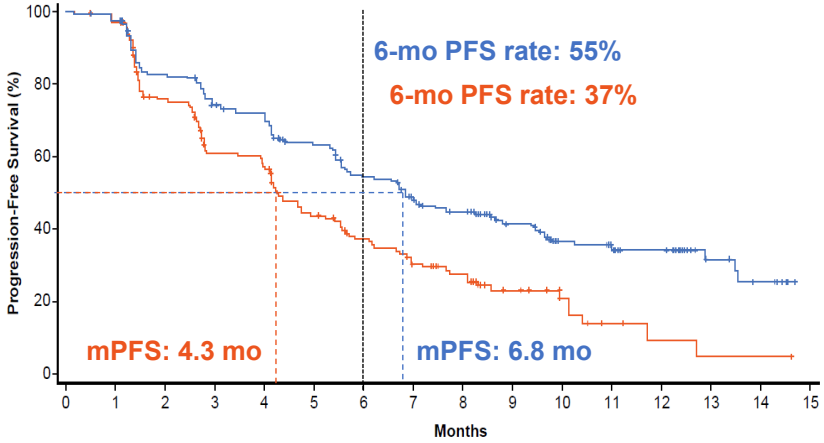
Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b] *P* = 0.0006[b,c]	



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

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.

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.

Cheng AL, et al. Presented at ESMO Asia 2019

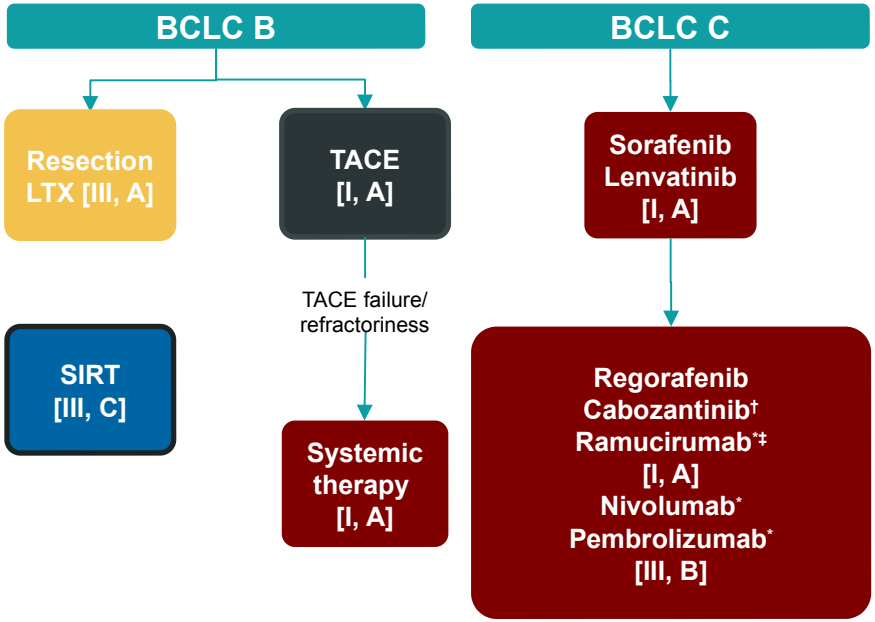
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 4): iv238–iv255, 2018
doi:10.1093/annonc/mdy308

CLINICAL PRACTICE GUIDELINES

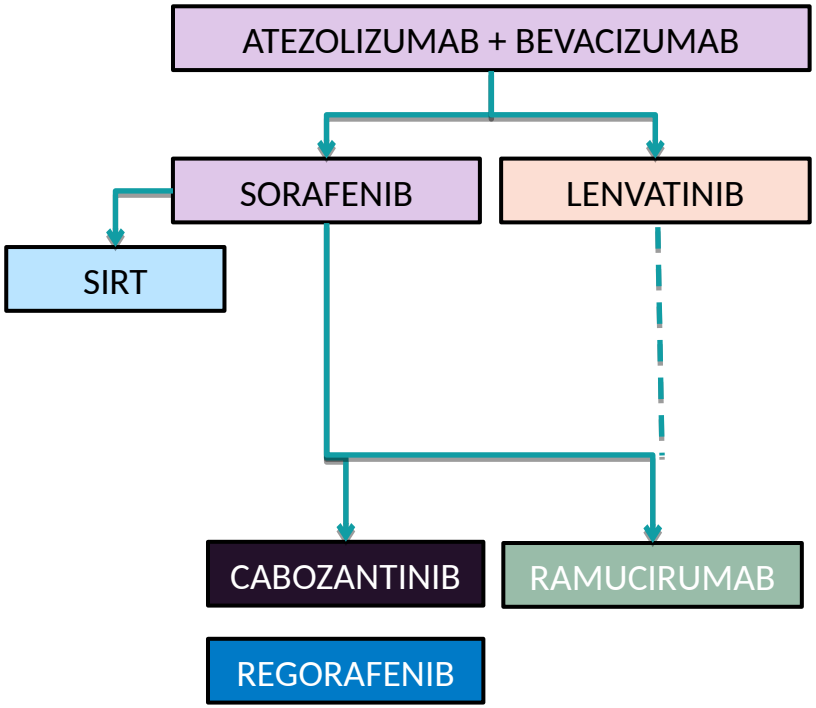
Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

A. Vogel[1], A. Cervantes[2], I. Chau[3], B. Daniele[4], J. M. Llovet[5,6,7], T. Meyer[8,9], J.-C. Nault[10], U. Neumann[11], J. Ricke[12], B. Sangro[13], P. Schirmacher[14], C. Verslype[15], C. J. Zech[16], D. Arnold[17] & E. Martinelli[18], on behalf of the ESMO Guidelines Committee*



Systemic Therapy of HCC

2020?



Ongoing Phase 3 Clinical Trials in HCC

Trial	IO Agent	Non-IO Agent	Comparator	Population
RATIONALE-301	Tislelizumab		Sorafenib*	Advanced stage
HIMALAYA	Durvalumab Durvalumab + Tremelimumab		Sorafenib	
Imbrave 150	*Atezolizumab*	*Bevacizumab*	*Sorafenib*	
LEAP-002	Pembrolizumab	Lenvatinib	Sorafenib	
COSMIC-312	Atezolizumab	Cabozantinib	Sorafenib	
EMERALD-1	Durvalumab Durvalumab	Bevacizumab	Placebo	Intermediate stage in combination with TACE
Checkmate 9DX	Nivolumab		Placebo	Early stage post resection/ablation
Keynote-937	Pembrolizumab		Placebo	
EMERALD-2	Durvalumab Durvalumab	Bevacizumab	Placebo	

* non-inferiority is tested

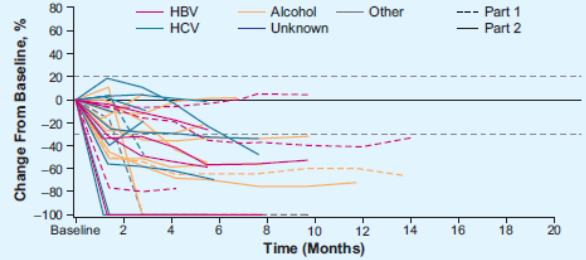
Combination Systemic Therapy of HCC

Multi-TKI + Anti-PD-1

Pembrolizumab 200 mg IV d1 **+**
Lenvatinib 12 or 8 mg daily PO, q3wk

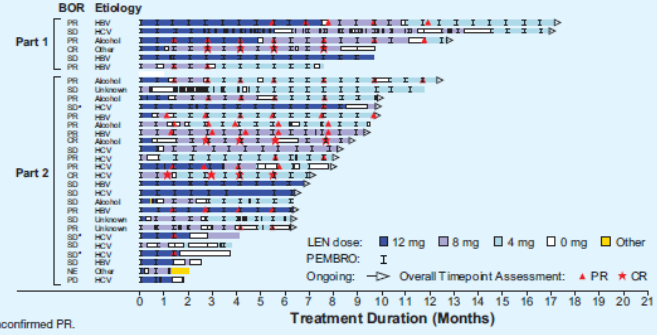
- N=30
- **ORR 53.3%** by RECIST 1.1 IIR
- Median DOR 8.3 months
- Median PFS 9.69 months
- Grade ≥ 3 TEAE 73%
- **SAE 50%, 13% fatal** (1 SBP, 1 ARDS, 1 perforation)
- Expansion cohort underway

Figure 3. Percentage Change in Tumor Size Over Time by mRECIST per Independent Imaging Review (Efficacy Analysis Set)



HBV/HCV, hepatitis B or C virus; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

Figure 4. Duration of Treatment and Response Assessments by mRECIST per Independent Imaging Review (Safety Analysis Set)

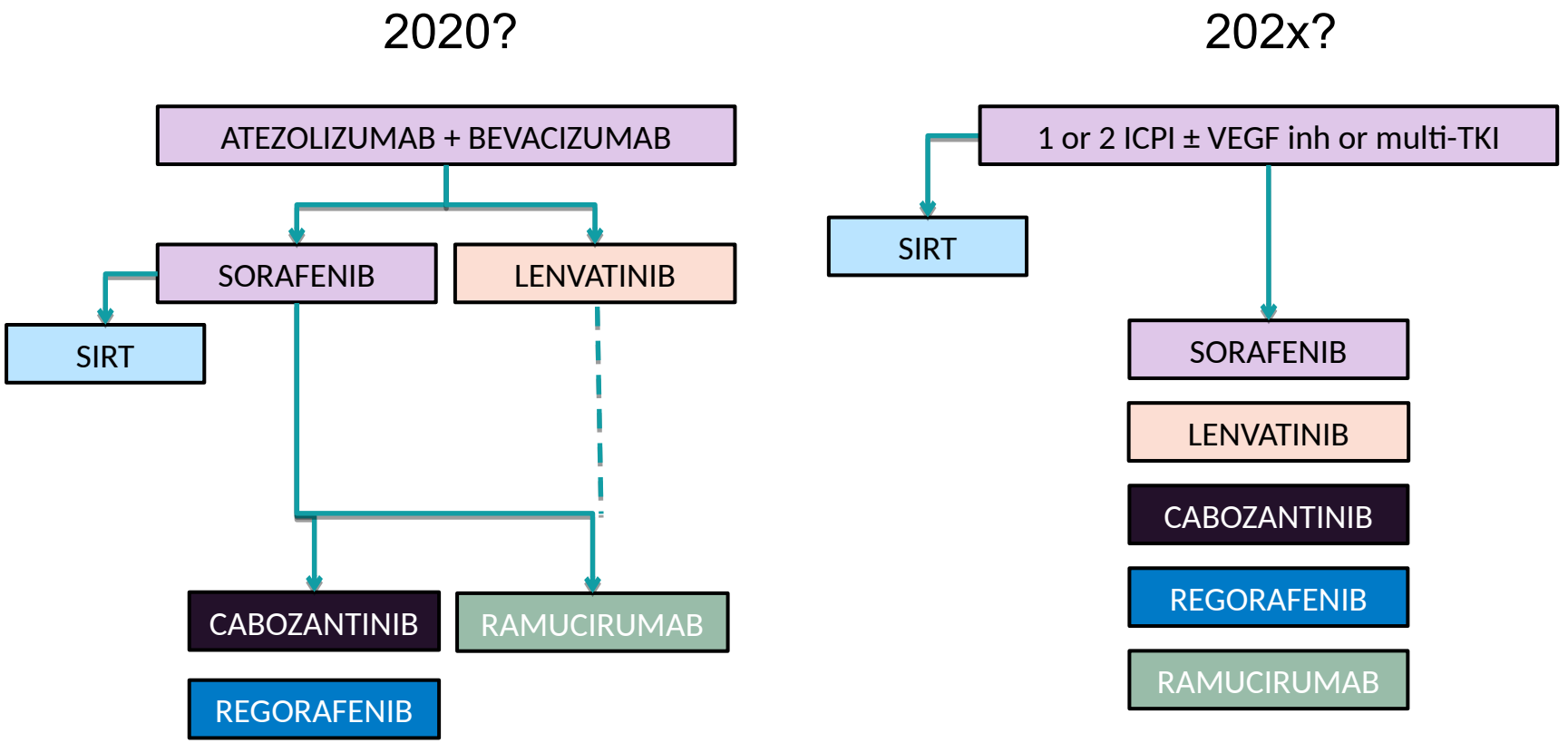


*Unconfirmed PR.

BOR, best overall response; CR, complete response; HBV/HCV, hepatitis B or C virus; LEN, lenvatinib; NE, not evaluable; PD, progressive disease; PEMBRO, pembrolizumab; PR, partial response; SD, stable disease.

Ikeda M, et al. Presented at AACR 2019

Systemic Therapy of HCC



Take-Home Messages

- Immunotherapy through ICPIs is likely to have a large impact on HCC management due to the ability to produce durable and clinically relevant responses with few side effects.
- The combination of Atezolizumab and Bevacizumab may become the standard of care for 1L therapy (and this will impact downstream options).
- Single agents and combinations of ICPIs with other ICPIs, VEGF inhibitors or multi-TKIs are being tested in across tumor stages.
- Combinations of ICPIs with VEGF inhibitors or multi-TKIs carry significant toxicities in cirrhotic patients that demand a specific work-up for diagnosis and management.

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Review

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Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma

Bruno Sangro[1,*], Stephen L. Chan[2,3], Tim Meyer[4], María Reig[5], Anthony El-Khoueiry[6], Peter R. Galle[7]

Summary

Immune checkpoint inhibitors (ICIs) have reshaped cancer therapy. ICIs enhance T cell activation

Keywords: Immunotherapy; Nivolumab; Pembrolizumab; Tremelimumab; Durvalumab;

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