HCC: Evolving Concepts in Therapy
Immunotherapy Today

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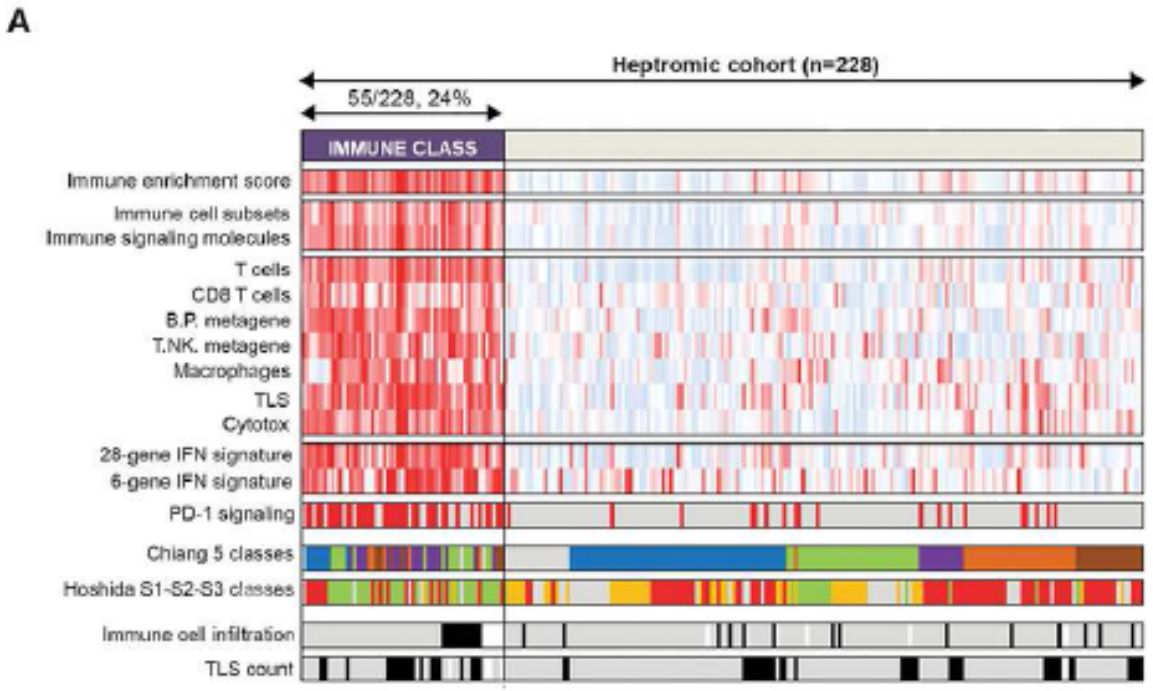
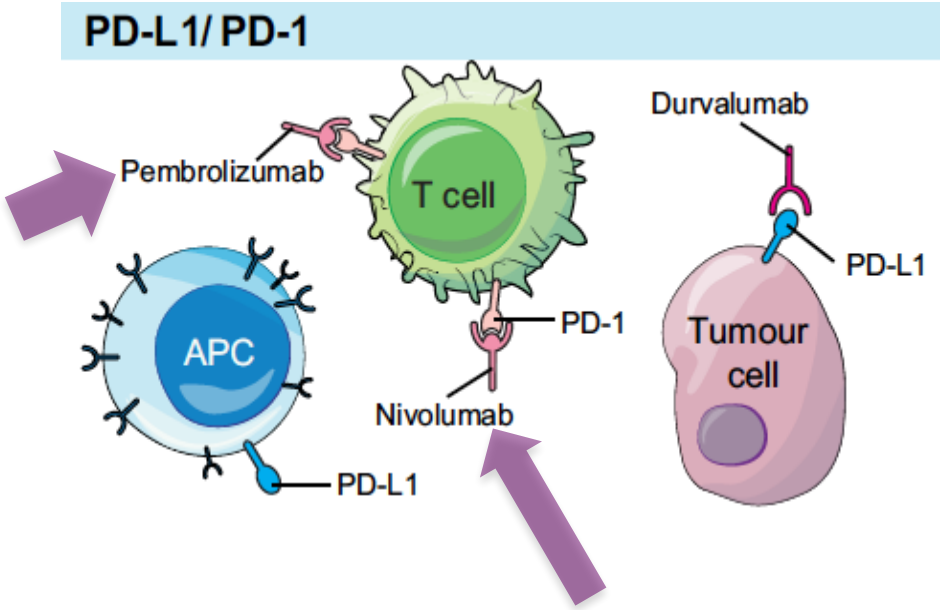
Rationale for immunotherapy: HCC versus other malignant diseases



Sia D et al, Gastroenterol 2017

Disease	PD-L1 ≥ 1%	Response Rate (Overall/PD-L1≥ 1%)
Malignant Melanoma	83-84%	40%
Lung cancer	63%	20%/15-40%
Head and neck cancer	85-86%	10-15%/15-23%
Hepatocellular carcinoma	20-25%	14-18%/20-28%



- Immune class reported 24% in HCC
- HCC ranking in the low range of PD-L1 expression & RR to PD-1 inhibitors single agent

Results of immunotherapy single agent phase III in advanced HCC

Advanced stages

First line

CheckMate-459
(nivolumab versus sorafenib)

Yau T et al, ESMO 2019

Second line

KEYNOTE-240
(pembrolizumab versus placebo)

Finn R et al, J Clin Oncol 2019

Negative phase III trials

Overall Survival (OS)

The combination of atezolizumab + bevacizumab sets the first line for advanced hepatocellular carcinoma

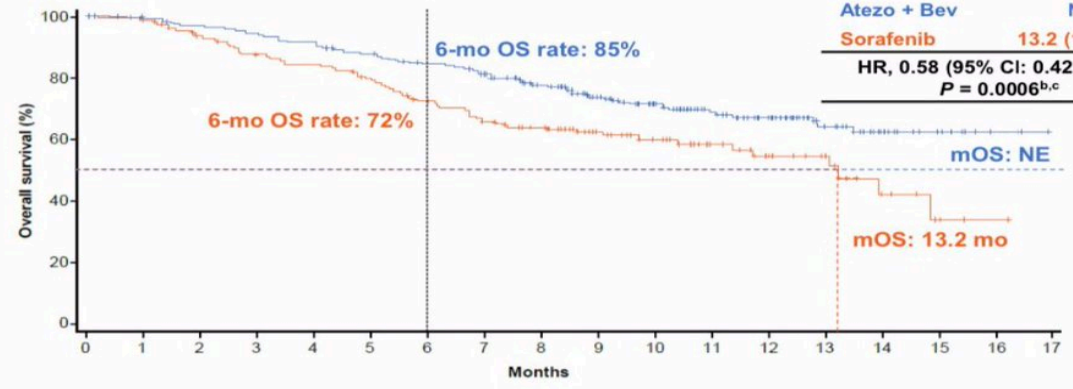
IMbrave 150 Phase 3 Study

Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma

SINGAPORE 2019 ESMO ASIA

SINGAPORE
22-24 NOVEMBER 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

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.

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

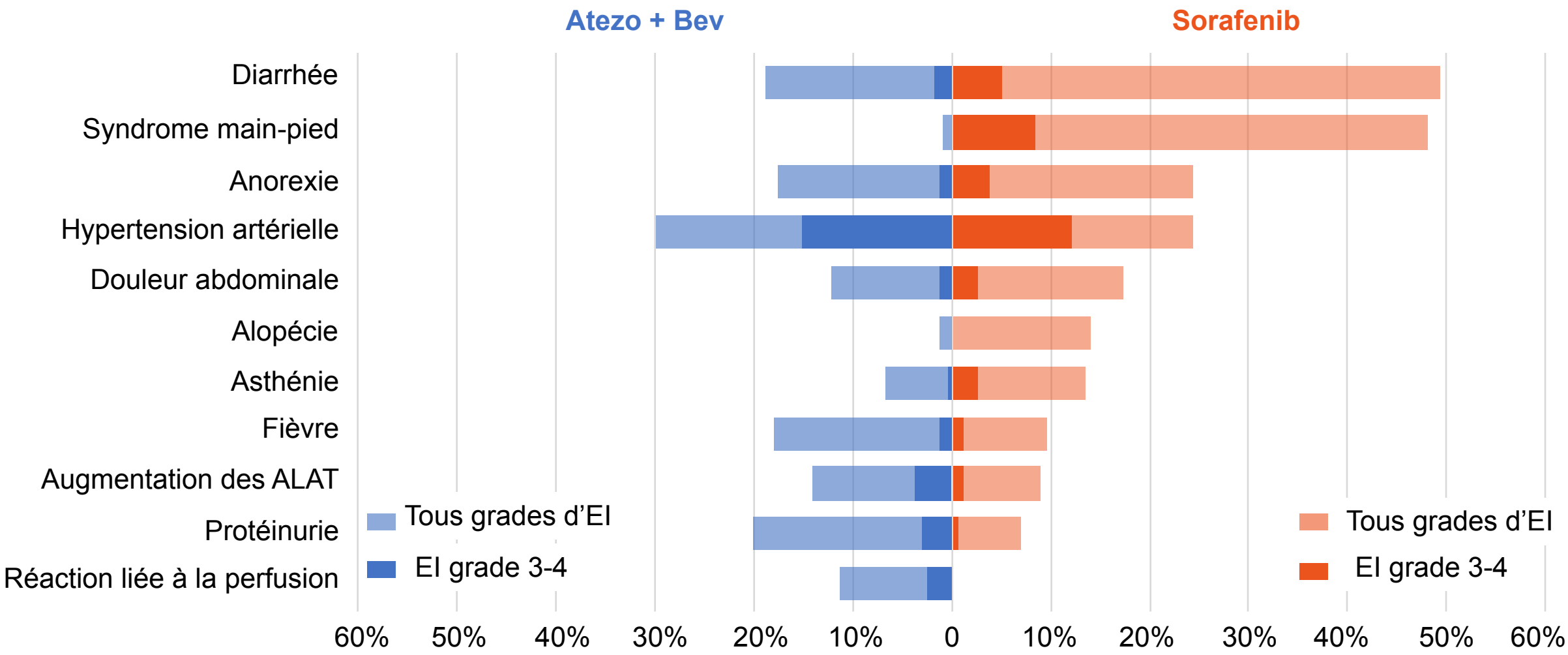
The safety and tolerability profile of atezolizumab + bevacizumab was in line with the known safety profiles of each individual component and the underlying disease

Treatment with atezolizumab + bevacizumab resulted in a clinically meaningful delay in deterioration of patient-reported quality of life vs sorafenib

Atezolizumab + bevacizumab should be considered a practice-changing treatment for patients with unresectable HCC who have not received prior systemic therapy

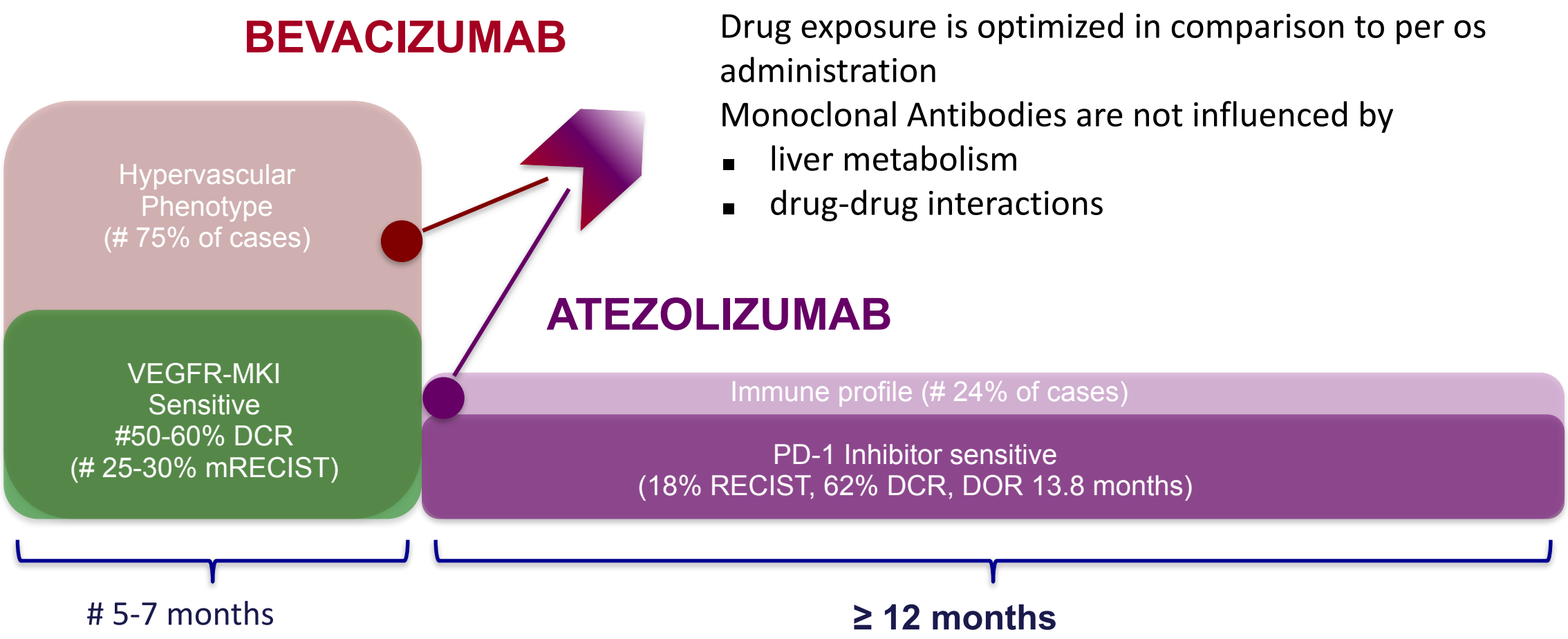
Treatment-related grade 3-4 adverse events (AEs) occurred in 36% of patients receiving atezolizumab (Tecentriq) and bevacizumab (Avastin) and 46% of patients receiving sorafenib

Tolerance of atezolizumab + bevacizumab in first line for advanced hepatocellular carcinoma



Finn RS *et al. NEJM* 2020;382:1894-1905.

Associating VEGF and PD-L1 inhibition using monoclonal antibodies



Drug exposure is optimized in comparison to per os administration

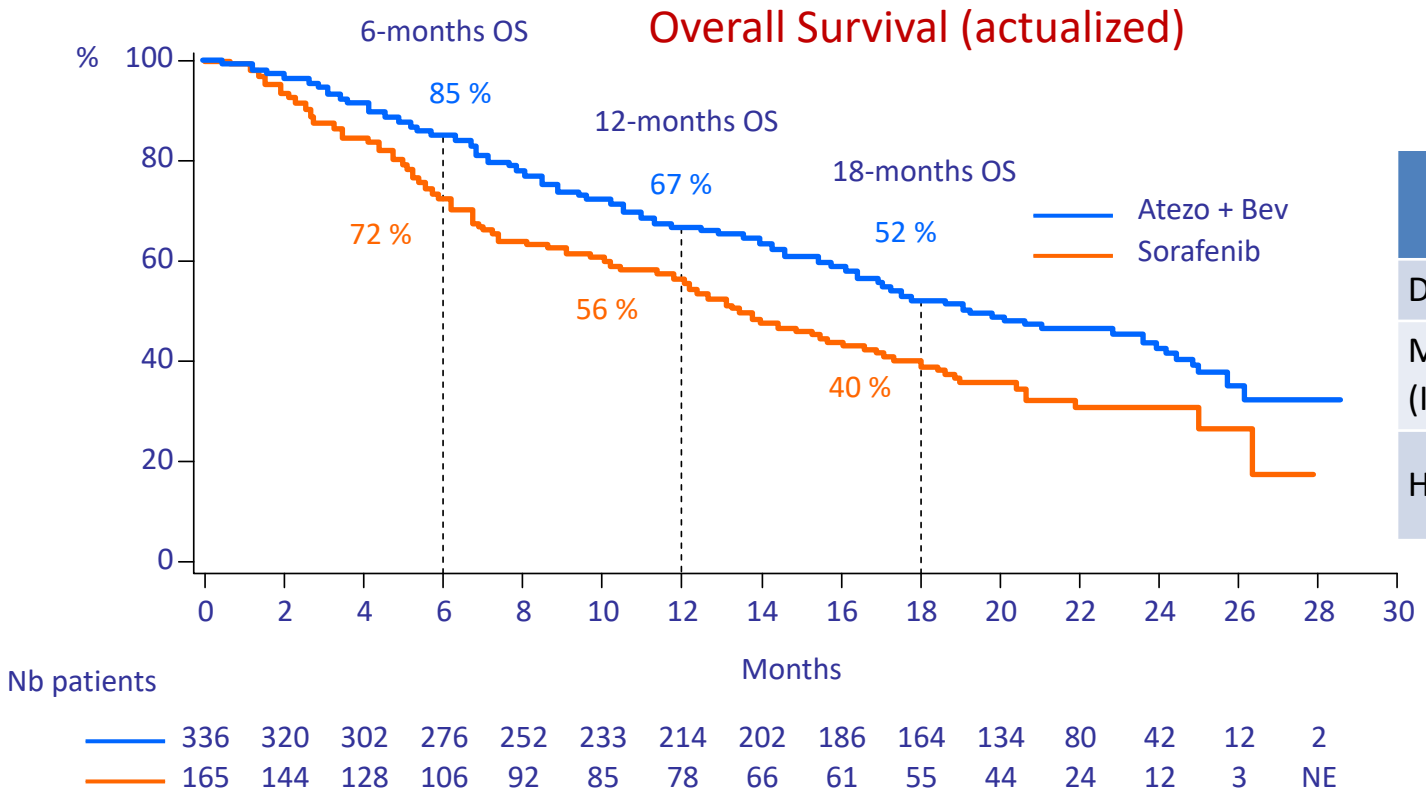
Monoclonal Antibodies are not influenced by

- liver metabolism
- drug-drug interactions

Sia D, Gastroenterol 2017; Finn RS, J Clin Oncol 2019; Finn RS, NEJM 2020

IMbrave150: Updated overall survival (OS) of atezolizumab + bevacizumab for advanced hepatocellular carcinoma

- First analysis conducted after median follow up of 8.6 months (Finn RS et al. N Engl J Med 2020)
- Updated analysis performed after additional 12 months follow up, i.e. median FU of 15.6 months



	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Death, n (%)	180 (54)	100 (61)
Median OS, months (IC 95%)	19.2 (17.0-23.7)	13.4 (11.4-16.9)
HR (IC 95%)	0.66 (0.52-0.85) p = 0.0009	

Finn RS, ASCO GI® 2021, 267

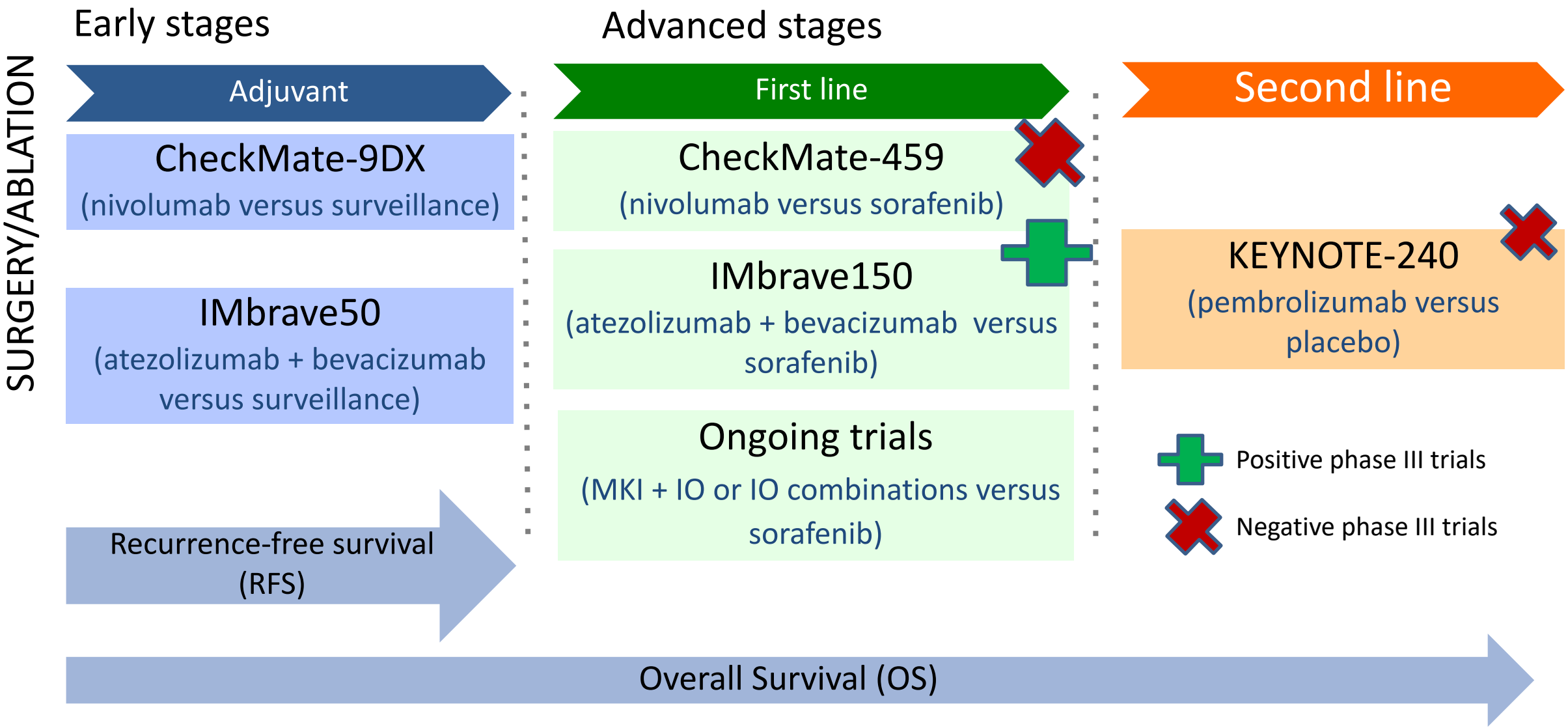
IMbrave150: Updated tumor response and duration of atezolizumab + bevacizumab for advanced hepatocellular carcinoma

Updated Tumor Response and Duration

	RECIST 1.1		mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Objective response Complete response Partial response	30 % 8 % 22 %	11 % < 1 % 11 %	35 % 12 % 23 %	14 % 3 % 11 %
Stable disease	44 %	43 %	37 %	41 %
Disease control rate	74 %	55 %	73 %	55 %
Progression	19 %	25 %	20 %	25 %
Ongoing response	56 %	28 %	50 %	27 %
Median duration of response, months (IC 95%)	18.1 (14.6-NE)	14.9 (4.9-17)	16.3 (13.1-21.4)	12.6 (6.1-17.7)

Finn RS, ASCO GI® 2021, 267

Phase III of immunotherapy in HCC across disease stages



Immunotherapy today in HCC – Summary

- PD-1 inhibitors single agent phase III did not reached OS primary endpoint in 1L and 2L, possibly linked to weakness of target relevance in the overall population
- In first line, combining VEGF and PD-L1 inhibition using antibodies is superior to previous standard with oral VEGFR-MKI sorafenib (OS, PFS) in IMbrave 150 trial
- The high rate of OR by RECIST (≥30%) observed with atezolizumab + bevacizumab in advanced HCC makes it attractive for neoadjuvant/downstaging strategies
- Other immunotherapy agents (CTLA4 inhibitors) or immunotherapy + VEGFR-MKI combinations are actively investigated in first line in HCC
- Trials are ongoing in the adjuvant setting with immunotherapy used as single agent or in combination

Thank you for your attention !