Choice of Frontline Therapy for Advanced HCC

VEGF + IO

8:05 – 8:13 AM

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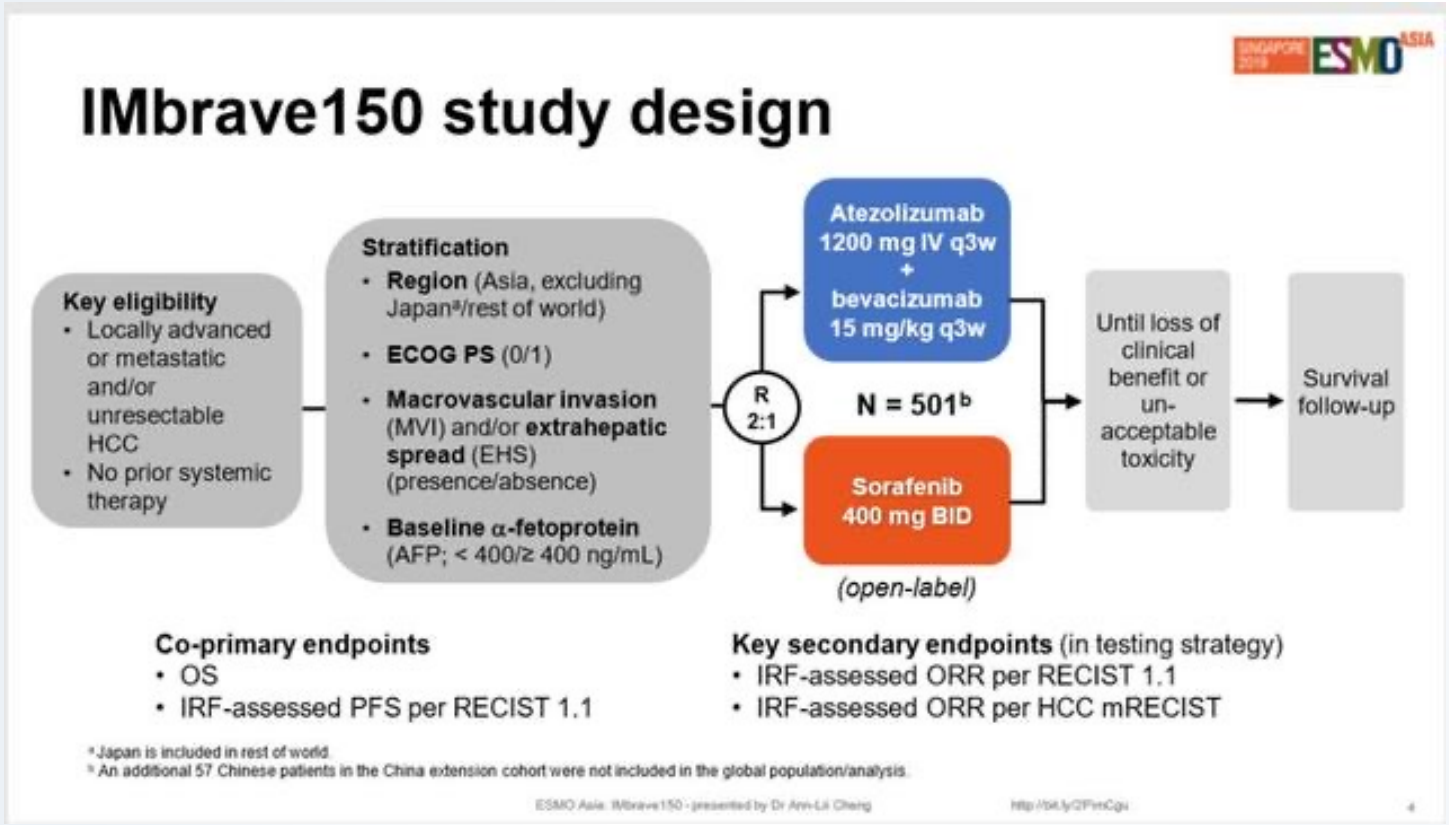
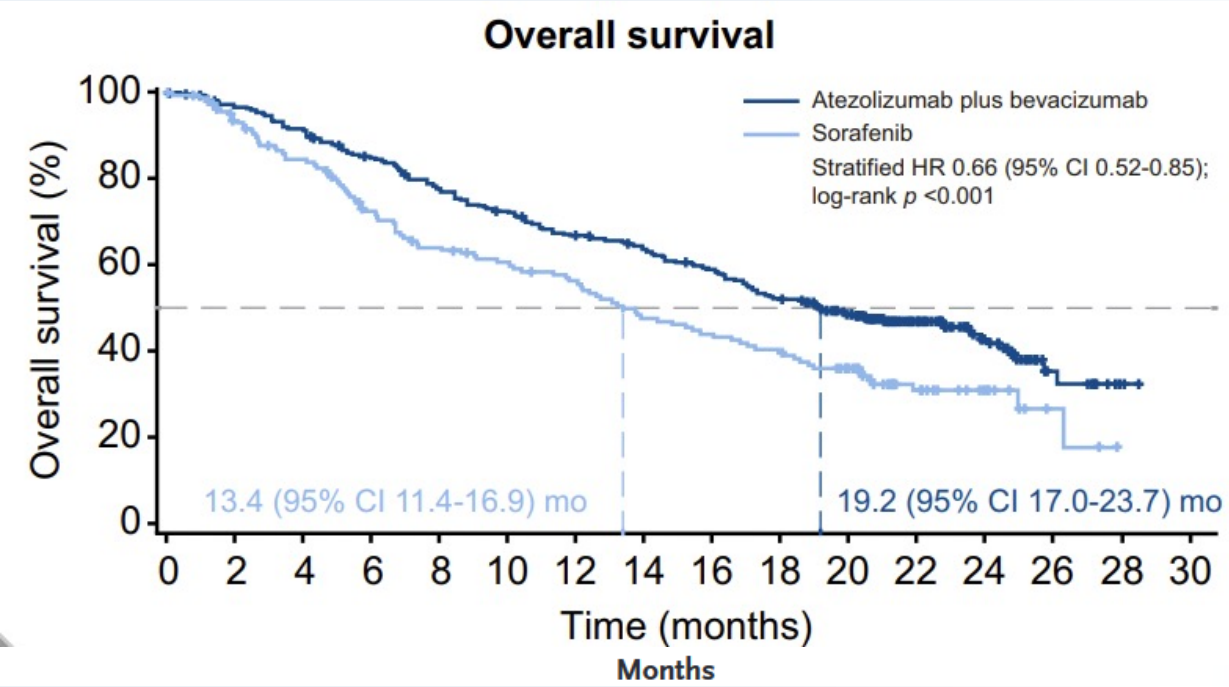
Disclosures

No.

IMBrave150


IMbrave150 study design
Key eligibility
• Locally advanced or metastatic and/or unresectable HCC
• No prior systemic therapy
Stratification
• Region (Asia, excluding Japan[a]/rest of world)
• ECOG PS (0/1)
• Macrovascular invasion (MVI) and/or extrahepatic spread (EHS) (presence/absence)
• Baseline α-fetoprotein (AFP; < 400/≥ 400 ng/mL)
R 2:1
Atezolizumab 1200 mg IV q3w + bevacizumab 15 mg/kg q3w
N = 501[b]
Sorafenib 400 mg BID
(open-label)
Until loss of clinical benefit or un-acceptable toxicity
Survival follow-up
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.

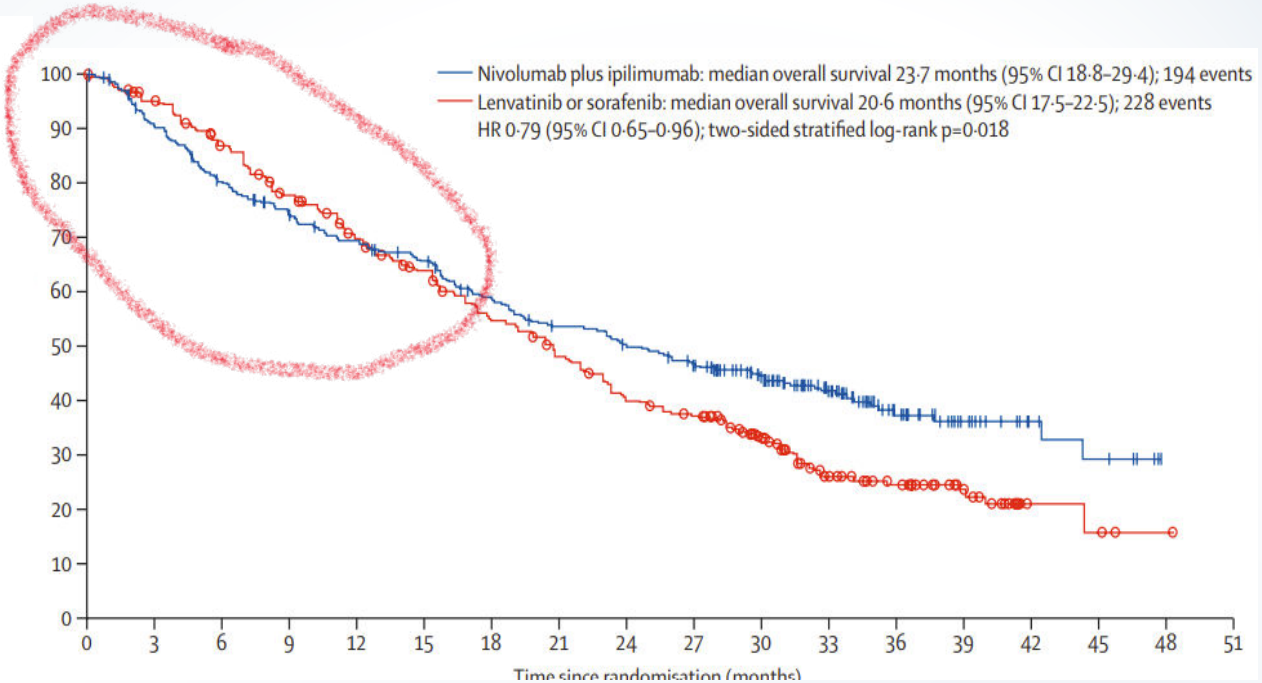
IMbrave150: OS



At 12 months: survival 67.2% v 54.6%

mOS 19.2 v 13.4 months, p <0.0001
ORR 30% vs 11%

CheckMate 9DW: OS



OS 23.7m vs 20.6m

Toxicity

IMbrave150

Table 3. Adverse Events from Any Cause.

Variable	Atezolizumab–Bevacizumab (N=329)	Sorafenib (N=156)
	number (percent)	
Patients with an adverse event from any cause	323 (98.2)	154 (98.7)
Grade 3 or 4 event*	186 (56.5)	86 (55.1)
Grade 5 event†	15 (4.6)	9 (5.8)
Serious adverse event	125 (38.0)	48 (30.8)
Adverse event leading to withdrawal from any trial drug	51 (15.5)	16 (10.3)
Withdrawal from atezolizumab–bevacizumab	23 (7.0)	—
Adverse event leading to dose modification or interruption of any trial drug	163 (49.5)	95 (60.9)
Dose interruption of any trial treatment	163 (49.5)	64 (41.0)
Dose modification of sorafenib	—	58 (37.2)

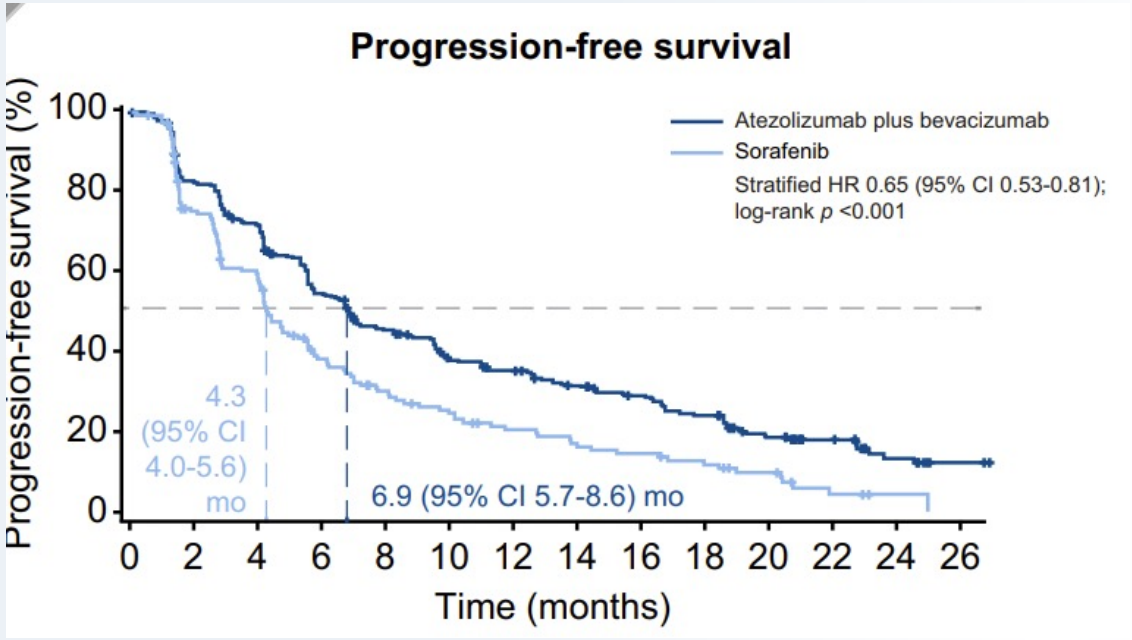
* Numbers represent the highest grades assigned.
† Grade 5 events in the atezolizumab–bevacizumab group included gastrointestinal hemorrhage (in 3 patients), pneumonia (in 2 patients), empyema, gastric ulcer perforation, abnormal hepatic function, liver injury, multiple-organ dysfunction syndrome, esophageal varices hemorrhage, subarachnoid hemorrhage, respiratory distress, sepsis, and cardiac arrest (in 1 patient each); grade 5 events in the sorafenib group included death (in 2 patients), hepatic cirrhosis (in 2 patients), cardiac arrest, cardiac failure, general physical health deterioration, hepatitis E, and peritoneal hemorrhage (in 1 patient each).

CheckMate 9DW

"Treatment-related deaths in the nivolumab plus ipilimumab group were from immune-mediated hepatitis (four patients), hepatic failure (three patients), hepatic insufficiency (one patient), decompensated cirrhosis (one patient), diarrhoea-colitis (one patient), autoimmune haemolytic anaemia (one patient), and dysautonomia (one patient). Treatment-related deaths in the lenvatinib or sorafenib group were from hepatorenal syndrome (one patient), ischaemic stroke (one patient), and acute kidney injury (one patient)."

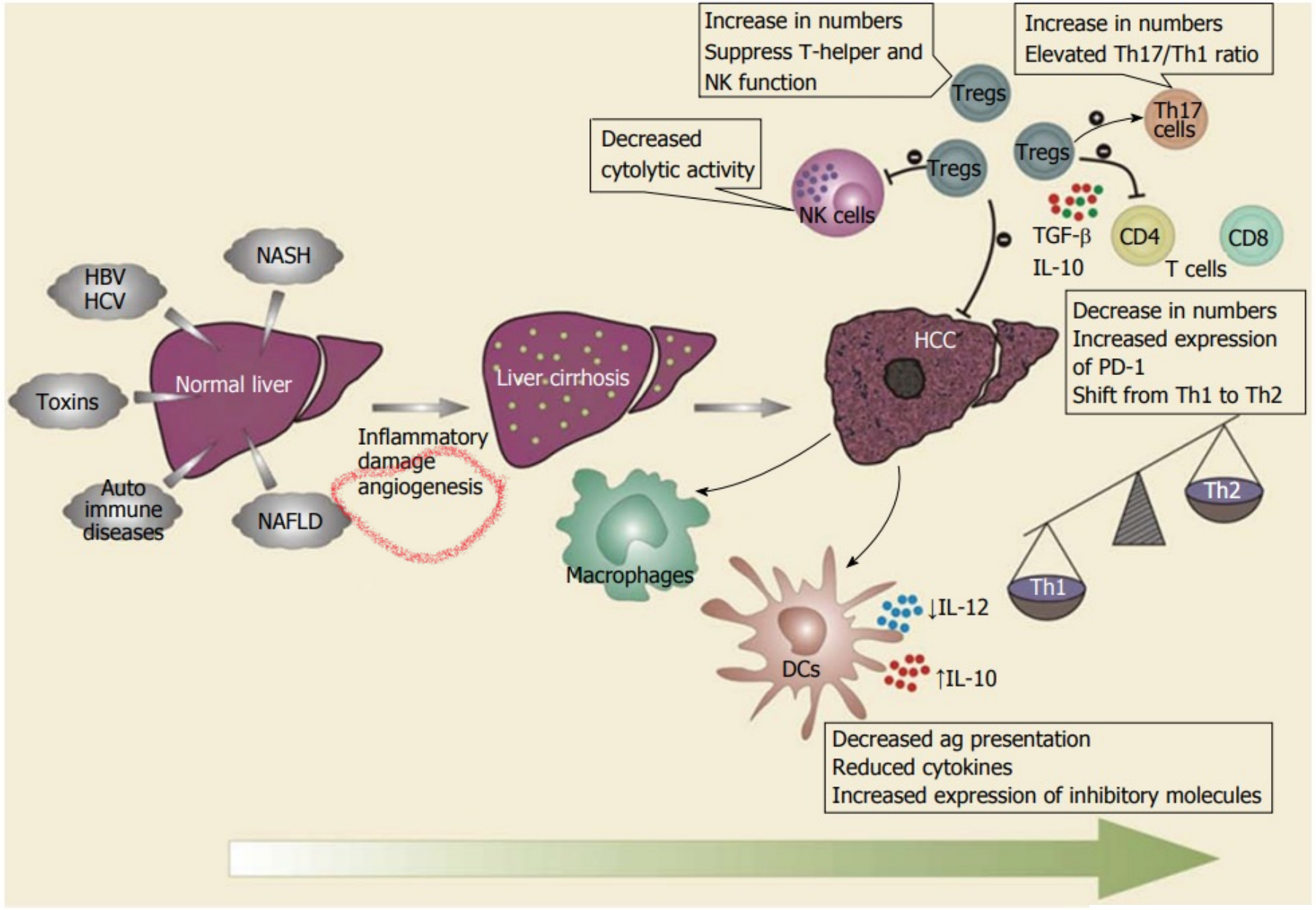
PFS

IMbrave150



CheckMate 9DW

Median PFS 9.1 vs 9.2



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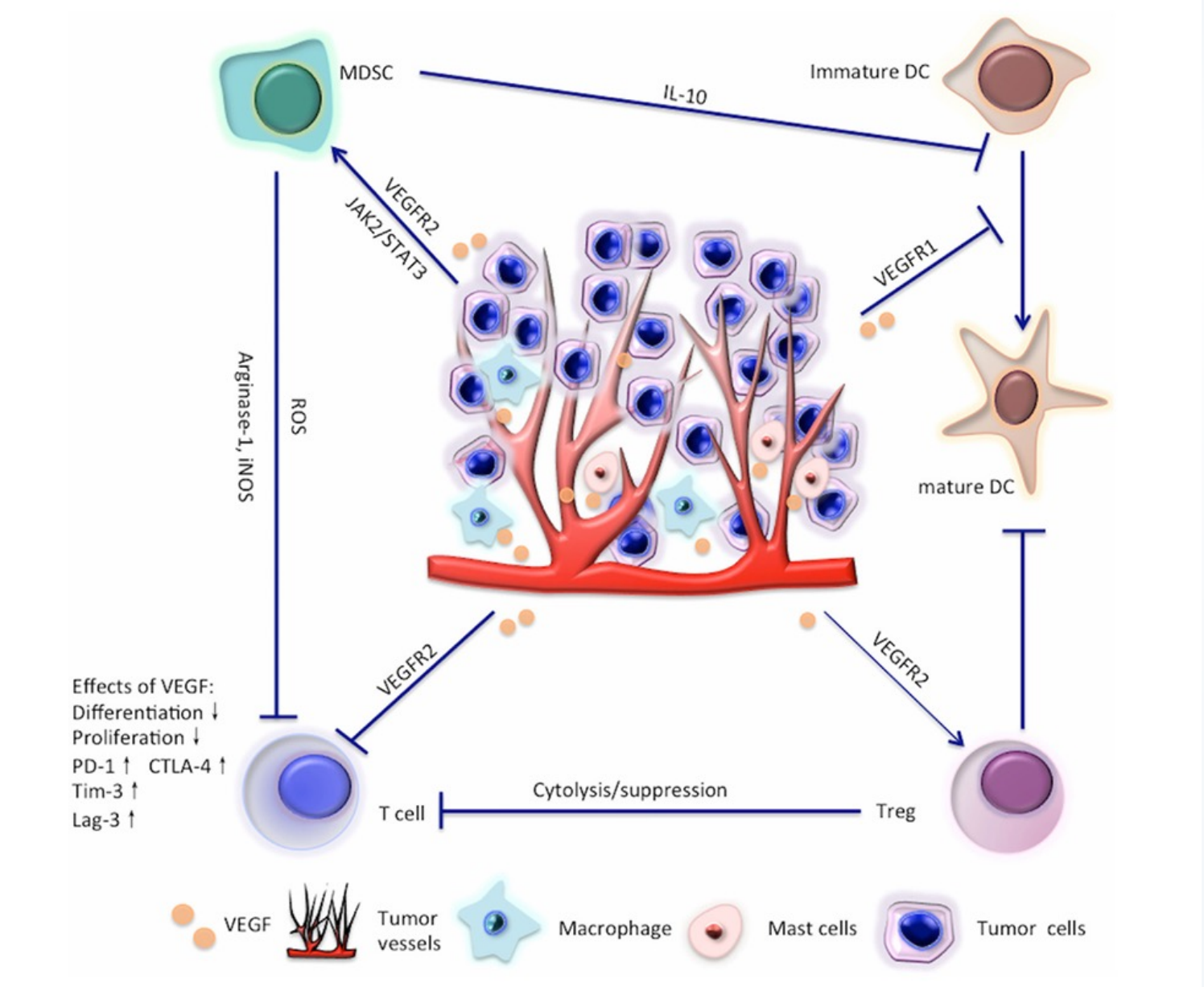

MDSC
IL-10
Immature DC
VEGFR2
JAK2/STAT3
VEGFR1
Arginase-1, iNOS
ROS
mature DC
VEGFR2
VEGFR2
Effects of VEGF:
Differentiation ↓
Proliferation ↓
PD-1 ↑ CTLA-4 ↑
Tim-3 ↑
Lag-3 ↑
T cell
Cytolysis/suppression
Treg
VEGF
Tumor vessels
Macrophage
Mast cells
Tumor cells

Anti-VEGF therapy and HCC

Inhibition angiogenesis

Normalization of vasculature -> improves immune cell infiltration

Synergizes with immune checkpoint inhibitors in modification of TME

Antiangiogenic therapies in HCC (other than bevacizumab)

Drug	Target
Lenvatinib	VEGFR-1-3, FGFRs, PDGFR-α, RET, and KIT.
Sorafenib	VEGFR-1-3, PDGFR-beta, c-kit, FLT-3, RET
Regorafenib	VEGFR-1-3, PDGFR-beta, FGFR1, RET
Ramucirumab	VEGFR-2 ab
Cabozantinib	VEGFR-2, c-Met, c-kit, RET, FLT-3

VEGF + IO

VEGFi is essential in HCC management

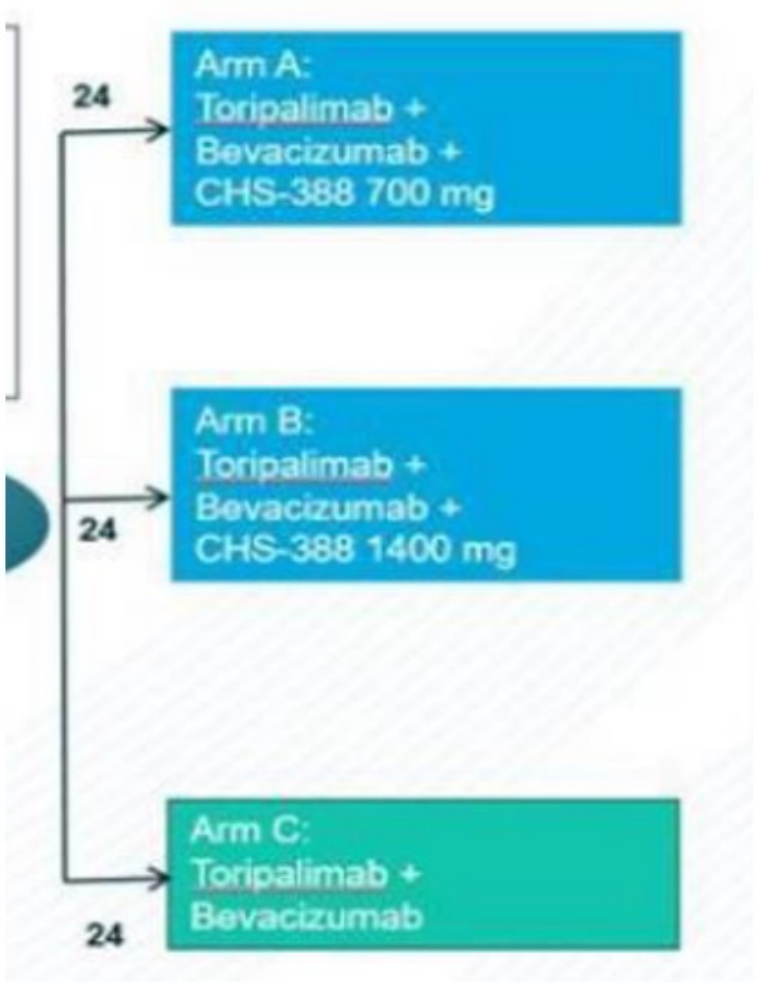
Angiogenesis

Tumor microenvironment alteration

Acceptable safety profile

CHS-388-202

A Randomized Phase 2 Study of Casdozokitug in Combination With Toripalimab Plus Bevacizumab in Participants With Unresectable and/or Locally Advanced or Metastatic Hepatocellular Carcinoma



The drugs

Toripalimab: humanized IgG4K mAb specific for human PD-1; binding to PD-1 is more prolonged than other PD-1 blockers

Bevacizumab

CHS-388, aka casdozokitug: IgG1 mAb targeting IL-27 (cytokine involved in blocking anti-tumor immune response).

All three drugs are given via IV.
Drugs administered on D1 of 21d cycle

Thank you