Hepatology Snapshot:

Medical therapy of HCC

JOURNAL OF HEPATOLOGY

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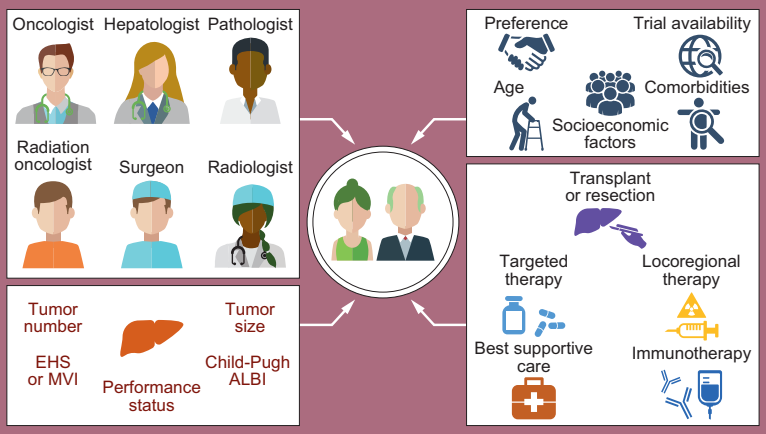
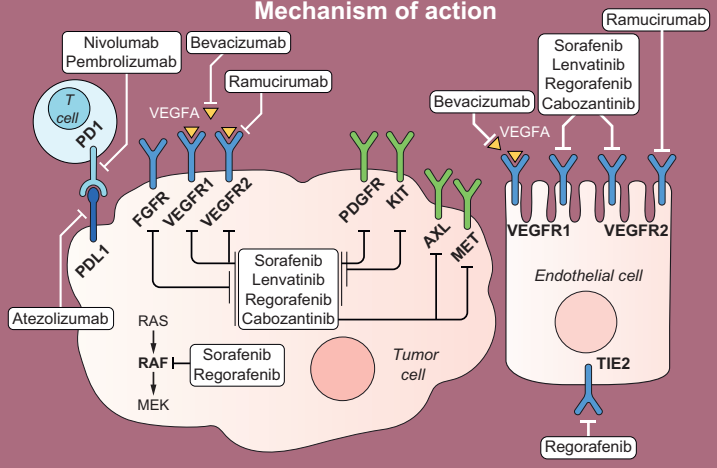
Multidisciplinary discussion



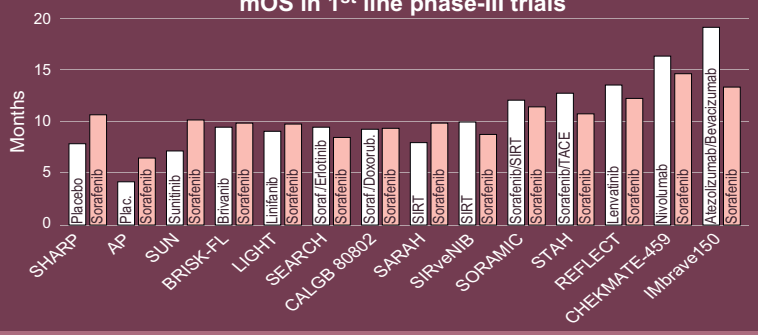
Mechanism of action



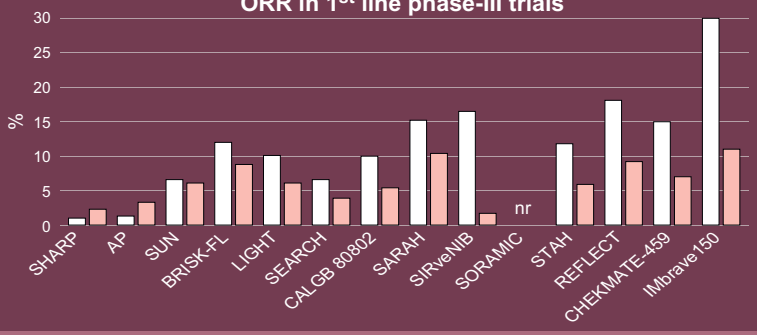
Key efficacy and safety data of phase-III trials

	SHARP		REFLECT		IMbrave150		RESORCE		CELESTIAL		REACH-2	
	Sorafenib n = 299	Placebo n = 303	Lenvatinib n = 478	Sorafenib n = 476	Atezo/Bev n = 335	Sorafenib n = 165	Regorafenib n = 379	Placebo n = 194	Cabozantinib n = 470	Placebo n = 237	Ramucirumab n = 197	Placebo n = 95
ALBI 1	nr	nr	66%	72%	54%	53%	39%	42%	39%	43%	43%	44%
ALBI 2	nr	nr	34%	28 %	46%	47%	61%	58%	61%	57%	57%	56%
mOS	10.7	7.9	13.6	12.4	19.2	13.4	10.6	7.8	10.2	8.0	8.5	7.3
mPFS	5.5	2.8	7.3	3.6	6.9	4.3	3.1	1.5	5.2	1.9	2.8	1.5
ORR	2%	1%	19%	7%	30%	11%	11%	4%	4%	1%	4%	1%
CR	0%	0%	<1%	<1%	8%	1%	1%	0%	0%	0%	0%	0%
PR	2%	1%	18%	6%	22%	11%	10%	4%	4%	1%	4%	1%
DCR	43%	32%	73%	59%	74%	55%	65%	36%	64%	33%	60%	39%
TrAEs Grade 3/4	45%	32%	57%	49%	44%	46%	50%	17%	68%	37%	59%	44%
Stop due to AEs	11%	5%	9%	7%	7%	10%	10%	4%	16%	16%	11%	3%
Treatment duration	5.3	4.3	5.7	3.7	8.4/7.0	2.8	3.6	1.9	3.8	2.0	3.0	2.0

mOS in 1st line phase-III trials



ORR in 1st line phase-III trials



Sequential systemic treatment

Standard
Atezolizumab + Bevacizumab [I, A]

Option
Lenvatinib [I, A], Sorafenib [I, A]

Standard after Sorafenib

Cabozantinib [I, A]
Regorafenib [I, A]
Ramucirumab [I, A]

Option after Atezolizumab + Bevacizumab or Lenvatinib

Sorafenib [V, C]
Cabozantinib [V, C]
Lenvatinib [V, C]
Regorafenib [V, C]
Ramucirumab [V, C]

Points to consider

Lenvatinib
- Higher ORR compared to sorafenib
- Only tested in 1st line

Atezolizumab/Bevacizumab
- Risk of upper GI bleeding
- Caution: autoimmune disease, transplantation
- Only tested in 1st line

Sorafenib
- Only tested in 1st line
- Experience in CP B

Regorafenib
- Only tested in patients that tolerated sorafenib

Cabozantinib
- Tested in 2nd and 3rd line after sorafenib

Ramucirumab
- Only AFP^{high}
- Only tested after sorafenib

IO: Nivolumab ± ipilimumab and pembrolizumab approved by FDA

Response
- Predictor of OS
- Downsizing to local therapies?

QoL
- Infusional regimens with superior QoL

Biomarkers
- Only AFP established
- Additional biomarkers required

Sequence
- Timely switch from local to systemic therapies
- No optimal sequences for systemic therapies established

Liver function
- ALBI *vs.* CPS
- Prognostic/predictive value?
- Risk of deterioration
- Monitoring recommended

Keywords: Hepatocellular carcinoma; Immunotherapy; Targeted therapies; Molecular therapy; Tyrosine kinase inhibitor; VEGF

Received 2 February 2021; received in revised form 11 May 2021; accepted 14 May 2021.

Treatment strategies in patients with hepatocellular carcinoma (HCC) range from liver transplantation and surgical resection, through transarterial and percutaneous local therapies, to systemic treatments.[1] To ensure that the individual patient is matched with the optimal therapy, not only the stage of the tumor but also the underlying liver disease have to be taken into account. Clinical decision making for patients with HCC requires a multidisciplinary team that longitudinally re-evaluates and adapts therapeutic strategies. While local therapies remain the mainstay of early disease stages, we have recently seen a paradigm shift in patients with intermediate HCC. Instead of the repetitive use of local therapies, an early conversion towards systemic treatments in patients that fail to reach a radiological response is now advocated.[2] This development was promoted by the recent advances in systemic treatments and an increasing recognition that preservation of liver function is critical to take full advantage of existing therapeutic options.

Sorafenib was the first drug to receive approval for the systemic treatment of HCC in 2007.[3] This milestone was followed by a series of negative trials; it is only in the last 4 years that additional drugs and combinations have been approved for both first- and second-line treatment. Lenvatinib demonstrated non-inferiority to sorafenib in the REFLECT study, with a superior objective response rate, and was approved as an alternative first-line treatment.[4] In second-line, 3 drugs were tested after sorafenib and approved by FDA and EMA: regorafenib (RESORCE),[5] ramucirumab (REACH-2)[6] and cabozantinib (CELESTIAL).[7] 3 drugs that were tested against placebo after sorafenib were endorsed by the FDA and EMA: regorafenib (RESORCE) is recommended for patients that tolerated and progressed on sorafenib,[5] while ramucirumab (REACH-2)[6] and cabozantinib (CELESTIAL) demonstrated efficacy in second-line.[7]

All of the aforementioned drugs are tyrosine kinase inhibitors (TKIs), with distinct, but partially overlapping target profiles. Notably, a "common denominator" of the TKIs is their vascular endothelial growth factor receptor (VEGFR) activity.[3] There is increasing evidence that VEGF-directed therapies not only act on the tumor vasculature, but also profoundly modulate the immune infiltrate in tumors. The importance of VEGF signaling was highlighted by 2 additional approvals: ramucirumab (REACH-2), the first monoclonal VEGFR2 antibody, was approved in patients with AFP ≥400 ng/ml as the first (and thus far the only) biomarker-guided therapy in HCC.[6] Most recently, IMbrave150 reported benchmark results for the combination of the VEGFA antibody bevacizumab with the PD-L1 (programmed cell death 1 ligand 1) antibody atezolizumab.[8,9] This was the first therapy that demonstrated a significant overall survival benefit compared with sorafenib, and is now the standard front-line treatment of advanced HCC. Atezolizumab/bevacizumab also marks the transition towards immunotherapy (IO) combinations in HCC. While this is the only IO regimen approved by the EMA, the FDA granted accelerated approval to nivolumab ± ipilimumab and pembrolizumab in second-line based on phase I/II efficacy data from CHECKMATE-040 and KEYNOTE-224.[10,11]

With multiple options available, sequential systemic therapy is strongly recommended. *Post hoc* analyses from the first-line REFLECT, and the second-line RESORCE and CELESTIAL trials indicated that a median overall survival of over 20 months is now feasible with systemic therapies. To what extent median overall survival can be further prolonged, especially after introduction of atezolizumab/bevacizumab as a standard of care in front line, remains to be determined, and so far, there are no data available on second-line regimens following lenvatinib or atezolizumab/bevacizumab. To improve individualised treatments and to avoid unnecessary liver toxicity and adverse events, biomarkers need to be established that are capable of guiding treatment decisions upfront or early on during therapy. Currently, IO-based systemic therapies are not only under investigation in the early stage as neoadjuvant/adjuvant treatments but also in the intermediate stage in combination with or even instead of locoregional therapies. The deep responses observed under systemic therapies might not only result in efficient downsizing, but also downstaging of tumors, facilitating a "stage migration to the left" with the introduction of local therapies following systemic treatment with potentially curative intent.

Financial support

AS and AV have received funding from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) - SFB/TRR 209 - 314905040, and Vo959/9-1 (to AV). AV is supported by the European-Latin- American ESCALON consortium, funded by the EU Horizon2020 program. AS is supported by the German Cancer Aid -70114101.

Conflict of Interest

Honoraria for Speaker, consultancy and advisory role to AV: Roche, Bayer, Sanofi, BMS, Lilly, Novartis, EISAI, AstraZeneca, Merck, Ipsen, PierreFabre, MSD. Honoraria for Speaker, consultancy and advisory role to AS: Roche, BMS and Servier.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

AV and AS: Writing manuscript and designing figure.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.05.017.

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