Supplementary file 1

Targeted therapy for liver cancer: Current status and future directions

Qian Wang[1*]

[1]School of Medicine, Shandong Xiehe University, 250000, China

Table S1. Strategies to overcome HER2-targeted therapy resistance in HCC, with mechanisms, preclinical evidence, and clinical considerations.

Strategy	Mechanism / Rationale	Examples / Preclinical Evidence	Clinical / Practical Considerations	Reference
Sequential or combination therapy	Bypass HER2 resistance via targeting of downstream pathways (e.g., PI3K/AKT/mTOR)	Combination therapies targeting signaling pathways are explored generally in oncology	Requires biomarker-driven selection; potential for additive toxicity	[1]
Dose modulation / agent switching	Switching HER2-targeted modalities (e.g., ADCs vs mAbs or TKIs)	T-DM1 shows preclinical activity in BTC xenografts proportional to HER2 levels	Feasibility depends on prior treatments and tolerability	[2]
TKI + chemotherapy synergism	Dual inhibition plus chemosensitization, e.g., by blocking drug efflux	Lapatinib inhibits HER2 and ABCB1-mediated gemcitabine efflux in organoids/cell lines	May improve first-line efficacy; monitor overlapping toxicities	[3]
Targeting EMT transcription factors	Reverse EMT-associated resistance	EMT-linked resistance	EMT biomarkers	[1]

	via inhibiting drivers like ZEB1, Axl/Src	reversal demonstrated in general cancer models	needed; off-target effects a concern	
EMT pathway inhibition (e.g., CK2/TGF-β)	Block EMT signaling to restore epithelial phenotype and drug sensitivity	CK2 inhibitor silmitasertib (CX-4945) under Phase II study for CCA	Orphan drug status; potential combination opportunities	[4]
Repurposed metabolic/epigenetic agents	Target metabolic or epigenetic avenues to counter EMT-mediated resistance	General oncology studies suggest these strategies may reverse resistance	Requires identification of relevant epigenetic or metabolic markers	[5]
ADCs following resistance	Deliver cytotoxic payloads selectively to HER2-positive cells	T-DXd shown promising ORRs and control rates in HER2+ BTC, including CCA	Suitable for HER2 IHC 3+; monitor side effects like ILD	[6]

Table S2. Key phase III clinical trials evaluating immune checkpoint inhibitor (ICI) plus tyrosine kinase inhibitor (TKI) combinations versus standard controls in unresectable hepatocellular carcinoma (uHCC), including efficacy outcomes, safety considerations, and references.

Trial (ref)	ICI + TKI (arm)	Control	Phase	Primary PFS result	Primary/Final OS result	Reference
COSMIC-312 (Lancet Gastro Hepatol 2024).	Atezolizumab + Cabozantinib	Sorafenib	III	**PFS improved**: median PFS ~6.8 vs 4.2 months (investigational vs sorafenib); HR favoured combo.	**No OS benefit** in primary analysis (OS not significantly improved). Toxicity higher with combo; more dose reductions/discontinuations.	[7]
LEAP-002 (Merck/Eisai; long-term follow-up, ASCO 2025).	Pembrolizumab + Lenvatinib	Lenvatinib + placebo (lenvatinib alone)	III	**No significant PFS benefit globally** (primary analysis did not meet superiority).	**No statistically significant OS benefit** in the global cohort; some prespecified/post-hoc subgroups (e.g., Japanese cohort) show more favourable OS signals on exploratory analysis. Safety: higher grade ≥3 TRAEs with combo.	[8,9]
CARES-310 (NCT03764293; final OS analysis/ASCO 2024–25).	Camrelizumab + Rivoceranib	Sorafenib	III	**PFS improved** (statistically significant vs sorafenib).	**OS improved**: final overall survival analysis reported significant OS benefit for the ICI+TKI arm vs sorafenib in first-line uHCC. Safety: notable hypertension, liver enzyme elevations; regulatory interactions ongoing (CRLs/NDAs).	[10]
Context / meta-commentary	—	—	—	Multiple Phase-III studies show **consistent PFS gains** for some	—	[11,12]

				ICI+TKI combos, but **OS benefits are heterogeneous**; differences likely reflect trial design, control arm choice, subsequent therapies and regional/subgroup effects.		

Table S3. Summary of the main biomarker technologies advancing precision medicine in HCC, emphasizing their advantages, clinical applications, and implementation difficulties.

Biomarker/Technology	Description	Advantages	Challenges	References
Predictive & Prognostic Biomarkers	Prognostic biomarkers show the fate of the illness regardless of treatment, whereas predictive biomarkers predict how well a patient will respond to therapy.	steers clear of ineffective treatments and support individualized treatment plans.	Lack of uniformity; restricted regulatory clearance and validation.	[13,14]
Liquid Biopsy (ctDNA)	using circulating tumor DNA to identify tumor-specific mutations (such as TERT, TP53, and CTNNB1) without invasive procedures.	allows for the real-time tracking of tumor development and response to therapy.	demands economical implementation and excellent analytical sensitivity.	[15,16]

Tissue-based Genomic Profiling	thorough examination of copy number changes, gene fusions, and mutations to find potential treatment targets.	makes it easier to find targets that can be used for precise treatment.	costly technology and difficult interpretation.	[17,18]
Transcriptomic Profiling	HCC is divided into molecular subtypes based on immunological and metabolic characteristics to enable customized treatment.	enhances the prediction of immunotherapy response and directs combo regimens.	Subtype overlaps; interaction with clinical operations is required.	[19]
Artificial Intelligence (AI) & Machine Learning (ML)	combining clinical and multi-omics data to help with decision-making, predict therapy response, and stratify risk.	improves adaptive treatment planning and biomarker identification.	Challenges with clinical uptake, data integration, and interpretability.	[20,21]

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