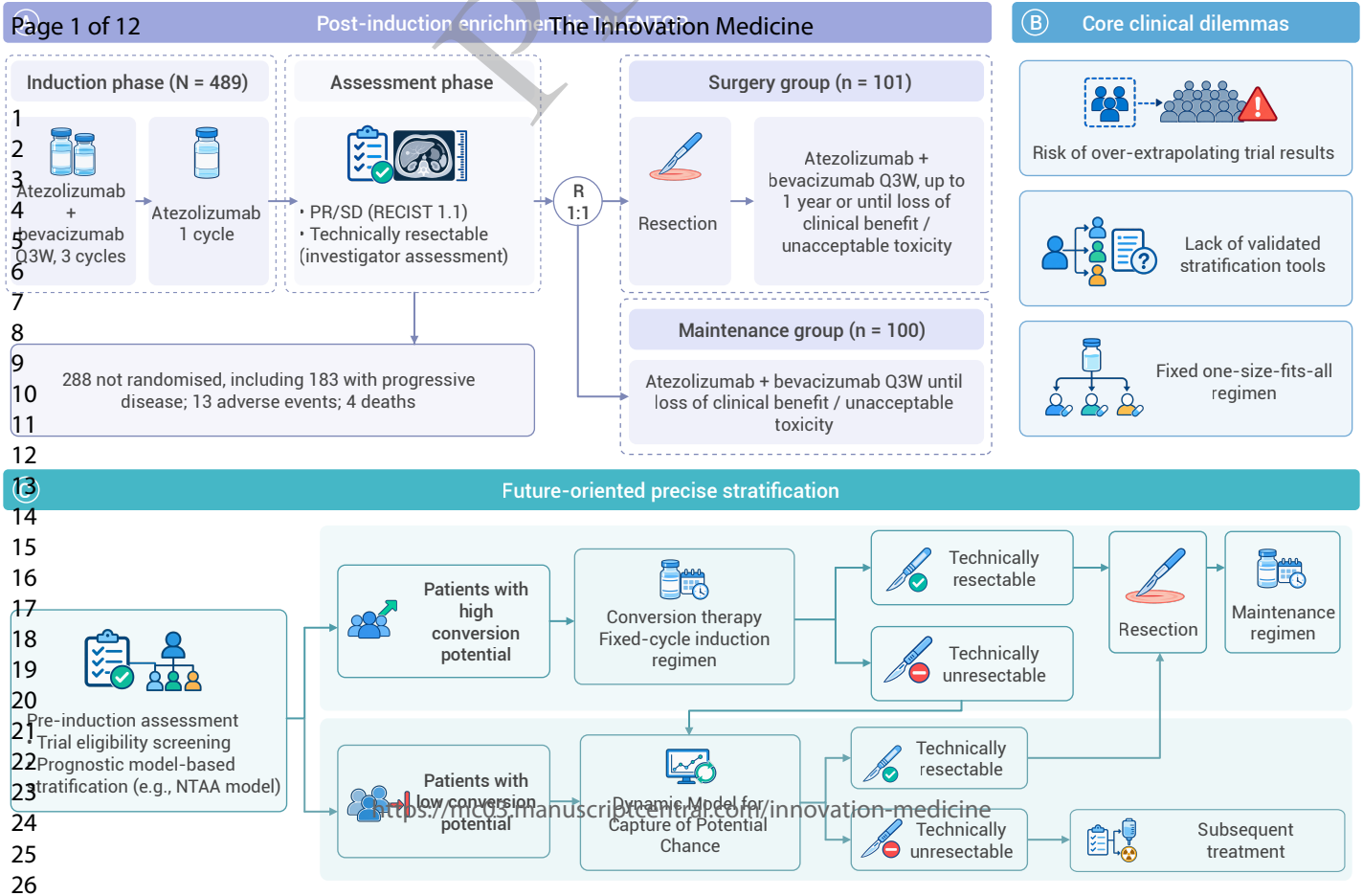


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Interpreting the TALENTOP trial: Conversion resection for locally advanced hepatocellular carcinoma with macrovascular invasion

Shuanggang Chen[1,2], Weijun Fan[1,2,*], Lujun Shen[1,2,*]

[1] Department of Minimally Invasive Interventional Therapy, Sun Yat-Sen University Cancer Center, Guangzhou 510060, China

[2] State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, Guangzhou 510060, China

***Correspondence:** shenlj@sysucc.org.cn (L.S.); fanwj@sysucc.org.cn (W.F.)

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Atezolizumab plus bevacizumab (T+A) constitutes the first-line standard-of-care regimen for BCLC stage C unresectable hepatocellular carcinoma (HCC).[1,2] For patients with CNLC stage Ⅲa HCC complicated by macrovascular invasion and absence of extrahepatic metastasis, systemic therapy may achieve tumour downstaging to render curative resection feasible.[1] Despite prognostic benefits associated with conversion resection shown in prior retrospective cohorts, high-level phase Ⅲ prospective evidence remained scarce until the publication of the TALENTOP trial in The Lancet.[1] Nevertheless, its distinctive post-hoc enrichment design confers inherent methodological limitations that merit careful interpretation. This commentary evaluates the trial design, key observations, methodological shortcomings and real-world translational implications to inform clinical decision-making and future investigations.

TALENTOP was not constructed to compare upfront hepatectomy against primary T+A therapy in untreated patients with macrovascular-invasive HCC. Patients harbouring main portal vein tumour thrombus face prohibitive peri-operative morbidity and excessive early recurrence following primary surgical resection; accordingly, international clinical guidelines categorise such presentations as unresectable disease.[1] In this multicentre randomised trial, all 489 enrolled participants received four-cycle T+A induction without any baseline risk-stratification. Eligibility for subsequent randomisation required radiological partial response or stable disease per RECIST 1.1 criteria, alongside confirmed R0 resectability validated by a two-tier independent multidisciplinary team (MDT) panel. Notably, RECIST 1.1

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predominantly assesses tumour dimensional shrinkage and is well-documented to underestimate intra-tumoural necrosis in vascular-rich HCC treated with anti-angiogenic agents. Reliance on this morphological criterion alone may misclassify therapeutic response and overlook substantial pathological tumour regression invisible on cross-sectional imaging. This dual-review MDT mechanism was implemented specifically to reduce subjective assessment bias and minimise inter-institutional variability in judging surgical candidacy, a long-standing pain point within HCC conversion practice. Beyond tumour response evaluation, serial hepatic functional reserve assessment throughout induction is equally indispensable, as liver parenchymal injury can disqualify patients from curative surgery even when tumour shrinkage appears satisfactory. Only 201 (41.1 %) of the initial cohort proceeded to random assignment. A total of 183 patients were excluded due to progressive disease, reflecting substantial primary therapeutic resistance within this high-risk population. Disease progression during induction frequently precludes subsequent curative-intent interventions and pushes patients toward palliative-only management, highlighting the clinical costs of unselected induction strategies. Further participants dropped out secondary to deteriorating hepatic function, impaired performance status, or immune-related adverse events. Such substantial pre-randomisation attrition underscores the practical dilemma of universal unselected induction: many patients endure prolonged systemic exposure without ever gaining access to potential curative options.

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The trial achieved its composite primary endpoint of time-to-treatment-failure (TTF). Median TTF reached 20.4 months within the surgical-resection arm versus 11.8 months in the continuous-maintenance group (HR 0.60, 95 %CI 0.39-0.91, P=0.015). Among 83 patients who successfully underwent hepatectomy, R0-resection rate was 93 % and pathological complete response rate reached 28 %. It should be emphasised that radiologically assessed stable disease represents merely a necessary, rather than sufficient, prerequisite for curative surgery. Surgical eligibility demands additional anatomical evidence of tumour-thrombus regression, widespread tumour necrosis, and spatial confinement of viable malignant lesions within resectable hepatic segments, which can only be comprehensively judged through formal MDT consensus review. The widely cited 17 % overall resection rate across the full intention-to-treat cohort is heavily confounded by trial-specific randomisation mechanics. Half of all MDT-confirmed R0-resectable subjects were allocated to non-surgical maintenance therapy. After adjusting for randomisation-imposed restrictions and 17.8 % pre-operative dropout among surgical-arm participants, the real-world conversion rate is estimated at approximately 34 % (41.1 % *82.2 %). This numerical distinction carries tangible significance for pre-treatment patient counselling and informed consent, preventing inappropriate extrapolation of trial-derived surgical yields to routine clinical practice.

Mature overall-survival data remain unavailable at the current follow-up time-point. Numerically higher 24-month overall-survival rates observed in the surgical cohort (83 % versus 67 %) failed to reach statistical significance. Early crossing of survival

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curves highlights the intrinsic trade-offs associated with conversion hepatectomy: although resection facilitates durable oncological control, it is accompanied by non-trivial peri-operative hazards. Grade 3-4 adverse events occurred more frequently in patients receiving surgical intervention (39 % vs 21 %), and both treatment-related deaths documented within the trial arose in the hepatectomy group. Collectively, curative conversion resection should be reserved for rigorously pre-screened candidates after multidisciplinary risk-benefit appraisal. Given immature OS endpoints and elevated peri-operative hazards, clinicians should not over-emphasize TTF gains in isolation. Instead, decision-making must integrate tumour response, hepatic functional reserve, performance status, and MDT-confirmed resectability, while awaiting definitive long-term survival evidence from the TALENTOP trial.

TALENTOP implemented a uniform 12-month peri-operative T+A adjuvant regimen to minimise inter-group heterogeneity and guarantee trial standardisation. Biologically, prolonged systemic therapy could theoretically eradicate microscopic residual disease and suppress occult micrometastases in high-risk HCC with macrovascular invasion. However, this one-size-fits-all therapeutic paradigm lacks supporting evidence for individualised real-world deployment. Findings from the IMbrave050 phase Ⅲ study demonstrate that adjuvant T+A confers only short-term recurrence-free-survival advantages without translating into sustained overall-survival benefit.[3] Cumulative risks of haemorrhage, hepatocellular injury, and immune-mediated toxicities escalate during extended dual-agent treatment courses, posing particular threats to patients with compromised baseline hepatic reserve. To

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date, no high-quality evidence defines the optimal duration of post-resection adjuvant therapy. Circulating tumour DNA (ctDNA) monitoring holds promise for guiding adjuvant de-escalation, yet its analytical standardisation and cost-effectiveness remain incompletely validated for routine HCC workflows.[3] Patients achieving postoperative pathological complete response may receive unnecessary overtreatment, whereas individuals with high-risk residual disease may receive sub-therapeutic intervention. Therefore, treatment duration ought to be dynamically adjusted according to postoperative histopathological response, hepatic functional reserve, treatment tolerance, and circulating tumour DNA-derived molecular relapse biomarkers.[3]

Clinicians must refrain from broad extrapolation of TALENTOP outcomes to unselected CNLC Ⅲa HCC populations. Observed TTF improvements apply exclusively to patients achieving adequate tumour control and MDT-validated R0 resectability following induction therapy. Indiscriminate administration of T+A induction for every patient with macrovascular invasion exposes substantial numbers of individuals to avoidable toxicities, heavy economic burdens, and ongoing risks of tumour progression throughout treatment cycles. Baseline prognostic stratification remains an unmet clinical need to mitigate futile therapeutic exposure. Our internally validated NTAA prognostic model, originally developed for BCLC B HCC patients receiving transarterial chemoembolization, incorporates tumour-burden metrics, alpha-fetoprotein values, and hepatic-function parameters.[4] Importantly, NTAA cannot be implemented in routine clinical practice at present, as it has not yet been validated in patients receiving T+A conversion therapy. The composite set of these

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biological variables theoretically harbours predictive potential for identifying individuals with favourable conversion probability, which merits prospective external validation. While exhibiting favourable discriminative performance in retrospective TACE-treated cohorts, this tool still requires independent external validation before widespread clinical adoption. Even with robust predictive biomarkers, surgical candidacy still hinges on systematic MDT-driven anatomical assessment and cannot be inferred from imaging-derived stable disease alone.

Important conceptual distinctions separate TALENTOP from CARES-009, another landmark phase 2/3 trial recently published in The Lancet.[5] CARES-009 investigated peri-operative camrelizumab-apatinib therapy for patients with primarily resectable HCC and intermediate-to-high recurrence risk. While both studies advance the integration of surgical and systemic management for HCC, TALENTOP addresses conversion pathways for initially unresectable macrovascular-invasive tumours, whereas CARES-009 targets neoadjuvant-adjuvant strategies for resectable disease. Their respective conclusions are complementary yet non-interchangeable within real-world clinical workflows.[5]

Future research priorities encompass the establishment of standardized pre-induction assessment workflows to stratify patients into subgroups of high and low conversion potential, as conceptualized in Figure 1. Prospective external validation of baseline predictive tools including the NTAA model is urgently needed, which may reduce the proportion of patients subjected to futile induction cycles. For patients with high conversion potential, an optimal induction regimen and duration should be explored;

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for those with low conversion potential, dynamic model-guided re-evaluation of induction strategy is warranted. Fixed four-cycle induction schedules should give way to response-adapted treatment timelines that optimise surgical timing according to individual tumour dynamics. Further interpretation will become feasible once mature overall-survival end-points from TALENTOP become accessible, clarifying whether TTF gains can be translated into durable long-term survival. Additional evidence generation is required for under-represented subgroups, including non-HBV-associated HCC and elderly patient cohorts. Beyond oncological endpoints, patient-reported outcome metrics deserve greater attention to balance tumour-oriented efficacy against treatment-related quality-of-life impairment. Large-scale real-world registry datasets will also complement randomised trial evidence by reflecting unselected patient populations encountered in daily practice. Consensus criteria guiding adjuvant-therapy discontinuation, informed by postoperative histology and serial ctDNA monitoring, also require formal establishment. Collectively, such advances will foster safer, personalised conversion-treatment algorithms for locally advanced HCC.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors report no conflict of interest.

DATA AND CODE AVAILABILITY

Not applicable.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

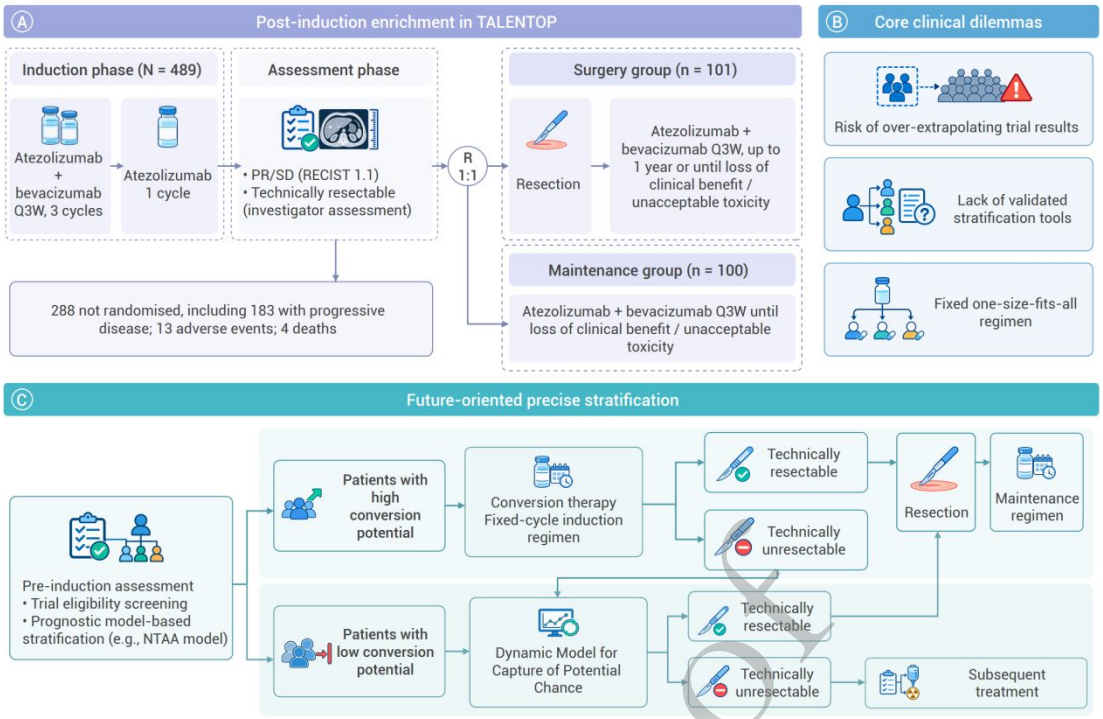


Figure 1. Study design of the TALENTOP trial and proposed framework for future-oriented precise stratification for locally advanced hepatocellular carcinoma with macrovascular invasion. (A) The upper-left panel illustrates the post-induction enrichment design of the TALENTOP trial. A total of 489 patients received four-cycle induction therapy with atezolizumab plus bevacizumab. Patients achieving PR or SD by RECIST version 1.1 and assessed as technically resectable underwent 1:1 randomisation to either the surgery group or the maintenance-therapy group. Of the enrolled participants, 288 patients were not randomised owing to progressive disease, adverse events, death, or other reasons. (B) The upper-right panel summarises core clinical dilemmas raised by the TALENTOP trial, including unselected patient cohorts, fixed one-size-fits-all regimen, lack of validated baseline stratification tools, and the risk of over-extrapolating trial results to real-world populations. (C) The bottom panel depicts a conceptual workflow for future-oriented

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precise stratification. Following pre-induction assessment containing trial eligibility screening and prognostic-model-based stratification (e.g., the NTAA model), patients are categorised into subgroups with high or low conversion potential. Patients with high conversion potential are assigned an optimal induction regimen and duration, whereas patients with low conversion potential require dynamic model-guided evaluation of induction strategy. After re-assessment of technical resectability, subsequent management pathways are implemented, including optimal maintenance regimen and duration for candidates suitable for resection, or optimal subsequent treatment modality for patients remaining technically unresectable.

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