Conclusions: Patients with solitary, unresectable, advanced HCC treated with Y90 glass microspheres had high response rates, clinically meaningful DoR, and comparable OS to existing curative therapy. Radiation treatment with Y90 glass microspheres is an effective means of treating solitary HCC while preserving liver function.

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993P NBTXR3 radiation enhancing hafnium oxide nanoparticles: RP2D for the treatment of HCC and liver metastases

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Background: NBTXR3, functionalized hafnium oxide nanoparticles, administered by intratumoral injection (ITI) and activated by radiotherapy (RT), such as stereotactic body RT (SBRT), increases energy deposit inside tumor cells and subsequently tumor cell death compared to RT alone, while sparing healthy tissues. This innovative approach, which does not engage liver and renal functions, might benefit patients (pts) with unresectable liver cancers.

Methods: Phase I/II clinical trial to evaluate NBTXR3 administered by ITI activated by SBRT (45 Gy / 3 fractions / 5-7 days or 50 Gy / 5 fractions / up to 15 days) in pts with hepatocellular carcinoma (HCC) or liver metastases [NCT02721056]. Phase I 3+3 dose escalation scheme with 5 NBTXR3 dose levels: 10, 15, 22, 33, and 42% of baseline tumor volume. Primary endpoints include Recommended Phase II Dose (RP2D) determination and early DLT incidence. Secondary endpoints include safety profile, liver disease scores evolution, and early efficacy by response rate (mRECIST/RECIST 1.1).

Results: Enrolment at all dose levels is complete, 23 pts treated: 6 pts at 10% (2 SBRT doses tested due to organ constraints), 4 pts each at 15% and 22% (due to fiducial displacement and ITI shift), 3 pts at 33% and 6 pts at 42%. No early DLT was observed at any dose level. 1 SAE (late onset G3 bile duct stenosis) related to NBTXR3 and RT occurred at 22%. No clinically meaningful changes in Child-Pugh score and APRI were observed post-treatment. There were 11 AEs related to NBTXR3 and/or ITI, of which grade 3 AEs were: 2 abdominal pain (ITI related) and 1 bile duct stenosis (NBTXR3 related) No grade 4-5 AEs were observed. CT-scan showed NBTXR3 within tumor without leakage to healthy tissues. To date, the best observed responses assessed by MRI in target lesions from evaluable pts for HCC (n=11) were 5 CR, 5 PR, 1 SD and for metastases (n=7) 5 PR, 2 SD.

Conclusions: NBTXR3 has demonstrated a very good safety and tolerability profile in these patient populations. The RP2D has been determined to be 42% of tumor volume. Early efficacy results highlight the potential for NBTXR3 to address an unmet medical need in pts with unresectable primary or metastatic liver cancer.

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994P Stem cell-like subtypes revealed by integrative multi-omics analysis in early-stage hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) is lethal malignancy with second highest worldwide cancer mortality. Cancer stem cell in HCC has been regarded as a major cause of cancer progression. However, molecular and clinical features of stem cell-like HCC contributing aggressive tumor biology and therapeutic resistance remain unclear.

Methods: Transcriptomic signatures was identified by analyzing single-cell transcriptomic data from human fetal and mature hepatocytes and applied to 6 HCC cohorts (total n = 1263). Later, supervised and unsupervised approaches were applied to analyze proteomic data and multiple genomic data such as somatic mutations, mRNA expression, miRNA expression, and copy number alterations were integrated with proteomic data to uncover most correlated genomic alterations with functional products. Clinical significance of subtypes was tested and validated in multiple cohorts of HCC patients.

Results: Integrative analysis of genomic and proteomic data uncovered three subtypes of HCC. Hepatic stem (HS) subtype is characterized by strong stem cell features, vascular invasion, and poor prognosis. Hepatoblast (HB) subtype has moderate stem cell features but high genomic instability and low immune activity. Mature hepatocyte (MH) subtype is characterized by low genomic instability. Importantly, 3 subtypes are highly conserved in two most important pre-clinical models, established HCC cell lines (n = 81) and patient-derived HCC xenograft models (n=168). Most strikingly, 3 subtypes are significantly associated with sorafenib treatment and response to immunotherapy. We further validated subtype-specific sensitivity to sorafenib in HCC cell lines and PDX models. Because these subtypes are highly associated with currently available treatments, our findings may provide the foundation for rationalized marker-based clinical trials.

Conclusions: We identified two distinct stem cell-like subtypes with biomarkers in the tumor tissue. Each subtype has distinct response to immunotherapy and subtype-specific drug response for target agents as well as unique pathway dependencies. Our findings may offer the foundation of biomarker based clinical trials for new therapeutic approaches to refractory HCC patients.

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995P CTNNB1 mutations in Chinese HCC patients and immune microenvironment related analysis

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Background: *CTNNB1*, encoding β-catenin and associated with regulation of WNT pathway, plays an important role in development of hepatocellular carcinoma (HCC). It was reported as an immune-resistant biomarker in HCC. However, the landscape of *CTNNB1* mutations in Chinese HCC patients and mechanisms of *CTNNB1* mutations underlying immune resistance remain unclear.

Methods: FFPE tumor and matched blood samples of 1303 Chinese HCC patients were analyzed in a CAP & CLIA certified laboratory using next-generation sequencing targeting 450 cancer genes. IHC staining was performed on FFPE tissue sections of 672 HCC patients using anti-PD-L1 antibody 28-8 or 22C3. A total of 408 HCC patients from public database were also included to evaluate the relationship between *CTNNB1* mutations and tumor infiltrating lymphocytes (TILs). Mutational data was collected from TCGA and immune cell infiltration data was downloaded from TIEMR website.

Results: *CTNNB1* mutations were detected in 20.2% of Chinese HCC patients, and 98.5% mutations were SNV/Indels. D32-S37 within the β-TRCP binding site was hotspot region (55.0%). Compared with wild-type cohort, mutational frequencies of *ARID2* (10.3% vs. 4.9%, P<0.01) and *NFE2L2* (7.6% vs. 3.3%, P<0.01) were significantly higher in patients with *CTNNB1* mutations, whereas *TP53* (44.5% vs. 64.7%, P<0.01), *RB1* (1.9% vs. 16.2%, P<0.01), *AXIN1* (6.1% vs. 14.7%, P<0.01) mutations and 11q13 amplification (4.6% vs. 10.4%, P<0.01) were less abundant. *CTNNB1* mutations were found to be significantly correlated with TMB-H (top 20% of HCC, 29.7% vs. 20.4%, P<0.01), but not correlated with PD-L1 expression (CPS>1). TILs analysis revealed that CD4+, CD8+ T cells, dendritic cells, macrophages and