on/1 week off plus PEMBRO 200 mg IV q 3 weeks. In later cohorts, the REG dose could be escalated (160 mg) or reduced (80 mg); the PEMBRO dose is fixed. The primary objective is safety and tolerability. Secondary objectives are to define the maximum tolerated dose (MTD) and recommended phase II dose and assess antitumor activity.

Results: By April 29, 2020, a total of 36 pts were treated with REG 120 mg. Median age was 66 years (range 29–81); 31%/69% of pts were BCLC stage B/C; 100% Child–Pugh A; ECOG status 0/1 was 72%/28%. Dose-limiting toxicities occurred in 4/18 evaluable pts: grade (Gr) 3 ALT/AST increased with Gr 2 bilirubin increased (n=2); Gr 3 rash (n=2). The REG MTD was 120 mg. Gr 3 or 4 treatment-emergent adverse events (TEAEs) occurred in 31/36 pts (86%); the most common are shown in the table below. Incidence of Gr 3 hand–foot skin reaction was 8%, Gr 3 maculopapular rash 6%, and Gr 3 rash 3%; there were no cases of Gr 4 rash. One Gr 5 TEAE was reported (not drug-related). TEAEs led to a REG dose reduction or interruption in 72% of pts and to a PEMBRO dose interruption in 53%. Median treatment duration (range) including pts ongoing was 2.5 months (0.2–15.9) for REG and 3.5 months (0.03–19.2) for PEMBRO. Of 32 evaluable pts, 9 (28%) had a partial response and 20 (63%) had stable disease (RECIST 1.1); disease control rate was 91%.

Table: 990P

TEAEs (Gr 3/4 in ≥10% pts), n (%)	Gr 3	Gr 4
AST increased	7 (19)	0
ALT increased	5 (14)	2 (6)
Hypertension	5 (14)	0
Bilirubin increased	5 (14)	0
Lipase increased	4 (11)	1 (3)

MedDRA v22.0; CTCAE v4.03 grade.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Conclusions: The combination of REG plus PEMBRO for first-line treatment of advanced HCC showed no unexpected safety signals and encouraging antitumor activity. Assessment of REG 80 mg plus PEMBRO is ongoing.

Clinical trial identification: NCT03347292.

Editorial acknowledgement: Editorial assistance provided by Ann Contijoch (Bayer) and Jennifer Tobin (OPEN Health Medical Communications [Choice], with financial support from Bayer).

Legal entity responsible for the study: Bayer.

Funding: Bayer.

Disclosure: P.R. Galle: Honoraria (self), Advisory/Consultancy, Research grant/Funding (self): Bayer; Honoraria (self), Advisory/Consultancy: BMS; Honoraria (self): AstraZeneca; Honoraria (self), Advisory/Consultancy: Sirtex; Honoraria (self), Advisory/Consultancy: MSD; Advisory/Consultancy: Merck; Honoraria (self), Advisory/Consultancy: Roche; Honoraria (self), Advisory/Consultancy: Eisai; Honoraria (self), Advisory/Consultancy: Ipsen; Advisory/Consultancy: Adaptimmune. R.D. Kim: Advisory/Consultancy, Research grant/Funding (institution): BMS; Advisory/Consultancy, Research grant/Funding (institution): Bayer; Advisory/Consultancy, Speaker Bureau/Expert testimony: Lilly; Research grant/Funding (institution): Eisai. M.W. Sung: Advisory/Consultancy: Bayer; Advisory/Consultancy: Eisai; Advisory/Consultancy: Exelesis. W.P. Harris: Advisory/Consultancy: Exelixis; Advisory/Consultancy: Eisai; Advisory/Consultancy: QED Therapeutics; Advisory/Consultancy: US Department of Justice; Leadership role: Fibrolamellar Cancer Foundation; Leadership role: ASCO; Research grant/Funding (institution): Merck; Research grant/Funding (institution): Bayer; Research grant/Funding (institution): Medimmune; Research grant/Funding (institution): Basilea; Research grant/Funding (institution): Agios; Research grant/Funding (institution): BMS; Research grant/Funding (institution): Boston Scientific; Research grant/Funding (institution): BTG; Research grant/Funding (institution): Halozyme; Officer/Board of Directors: GI Cancer Alliance. D. Waldschmidt: Speaker Bureau/Expert testimony: AstraZeneca; Speaker Bureau/Expert testimony: EISAI; Speaker Bureau/Expert testimony: BMS; Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Celgene; Speaker Bureau/Expert testimony: Incyte; Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Ipsen; Speaker Bureau/Expert testimony: Falk; Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Novartis; Speaker Bureau/Expert testimony: Roche Pharma AG; Speaker Bureau/Expert testimony, Research grant/Funding (institution): Servier; Speaker Bureau/Expert testimony: Shire Baxelta; Speaker Bureau/Expert testimony, Travel/Accommodation/Expenses: Sirtex; Travel/Accommodation/Expenses: Bayer Health Pharma. R. Cabrera: Advisory/Consultancy, Research grant/Funding (institution): Exelixis; Advisory/Consultancy, Research grant/Funding (institution): Eisai; Advisory/Consultancy, Research grant/Funding (institution): Bayer; Advisory/Consultancy, Research grant/Funding (institution): Target PharmaSolutions. U. Mueller: Honoraria (self): ClinStat GmbH; Honoraria (institution): Bayer Pharma. K. Nakajima: Shareholder/Stockholder/Stock options, Full/Part-time employment, Former employee of Bayer: Bayer. T. Ishida: Full/Part-time employment: Bayer. A.B. El-Khoueiry: Honoraria (self), Advisory/Consultancy: Bayer; Honoraria (self), Advisory/Consultancy: BMS; Honoraria (self), Advisory/Consultancy: EISAI; Honoraria (self), Advisory/Consultancy: EMD Serono; Honoraria (self), Advisory/Consultancy: Merck; Honoraria (self): Gilead; Honoraria (self): Roche/Genentech; Advisory/Consultancy: Agenus; Advisory/Consultancy, Research grant/Funding (institution): AstraZenenca; Advisory/Consultancy: CytomX Therapeutics; Advisory/Consultancy: Exelixis; Advisory/Consultancy: Pieris Pharmaceuticals; Advisory/Consultancy: Roche; Research grant/Funding (institution): Astex Pharmaceuticals.

https://doi.org/10.1016/j.annonc.2020.08.1106

991P Sintilimab plus IBI305 as first-line treatment for advanced hepatocellular carcinoma

F. Jia[1], Z. Ren[2], J. Xu[3], G. Shao[4], G. Dai[5], B. Liu[6], A. Xu[7], Y. Yang[8], Y. Wang[9], H. Zhou[10], M. Chen[9]

[1]Deapartment of Liver Surgery, Zhongshan Hospital of Fudan university, Shanghai, China; [2]Department of hepatic oncology, Zhongshan hospital of Fudan university, Shanghai, China; [3]Digestive oncology department, The 5th Medical Center of PLA General Hospital, Beijing, China; [4]Department of interventional therapy, Zhejiang Cancer Hospital, Hangzhou, China; [5]Oncology Department II, Chinese PLA General Hospital, Beijing, China; [6]Oncology, Nanjing Drum Tower Hospital of Nanjing University, Nanjing, China; [7]Oncology, Nantong Tumor Hospital, Nantong, China; [8]Oncology, Innovent Biologics, Inc., Suzhou, China; [9]Oncology, Innovent Biologics, Inc., Beijing, China; [10]Oncology, Innovent Biologics, Inc., Shanghai, China

Background: A phase II/III study, is being conducted to evaluate the efficacy and safety of sintilimab, a PD-1 blockade, plus IBI305, a bevacizumab biosimilar, comparing with sorafenib as first-line treatment for advanced HCC (NCT03794440).

Methods: In phase II, the safety run-in part, adults with advanced or metastatic HCC (histologically diagnosed or clinical diagnosed for cirrhosis per AASLD guideline) were enrolled to receive sintilimab (200 mg IV Q3W) plus IBI305 (15 mg/kg IV Q3W). The primary endpoint is safety profile. In phase III part, following the same inclusion and exclusion criteria, it is planned to enroll 546 pts. Eligible patients were randomized (2:1) to receive sintilimab (200 mg IV Q3W) plus IBI305 (15 mg/kg IV Q3W) or sorafenib (400 mg orally, BID). The primary endpoints are OS and PFS by IRC per RECIST 1.1. The phase III part is ongoing and patient enrollment has completed. We reported the results from phase II part herein.

Results: As of Feb 3rd, 2020, 24 pts were enrolled in phase II part. With a median treatment duration of 9.2 months, 18 (75%) pts experienced TRAEs. Grade ≥ 3 TRAEs were reported in 6 (25%) pts, including proteinuria (3 [12.5%]), hepatic function abnormal (2 [8.3%]), hyperthyroidism (1 [4.2%]) and immune-mediated hepatitis (1 [4.2%]). No TRAE resulted in treatment discontinuation and death. With a median follow-up of 9.0 months, the median OS was not reached and the 6-month OS rate was 87.1%. The median PFS was 8.4 months (95% CI, 5.6, not reached) and the 6-month PFS rate was 60.9%. The ORR assessed by the investigator per RECIST 1.1 was 25.0% and DCR was 83.3%.

Conclusions: The data from phase II part showed acceptable safety profile and promising efficacy of sintilimab plus IBI305 as first-line treatment for advanced HCC.

Clinical trial identification: NCT03794440.

Legal entity responsible for the study: Innovent Biologics, Inc. Innovent Biologics, Inc.

Funding: Innovent Biologics, Inc.

Disclosure: Y. Yang, Y. Wang, H. Zhou, M. Chen: Full/Part-time employment: Innovent Biologics, Inc.. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.1107

992P Yttrium-90 glass microspheres in the treatment of early and advanced hepatocellular carcinoma: The LEGACY study

R. Salem[1], G.E. Johnson[2], A. Riaz[1], V. Bishav[3], E. Kim[3], S. Padia[4]

[1]Radiology, Northwestern Feinberg School of Medicine, Chicago, IL, USA; [2]Radiology, University of Washington, Seattle, WA, USA; [3]Radiology, Mount Sinai Health System, New York City, NY, USA; [4]Radiological Sciences, University of California Los Angeles Medical Center, Los Angeles, CA, USA

Background: Neoadjuvant locoregional therapies are key to bridging hepatocellular carcinoma (HCC) patients to transplantation or resection. The primary endpoints of LEGACY were to evaluate local tumor control and duration of response in unresectable HCC following radiation treatment with Y90 glass microspheres as either a neoadjuvant or stand-alone therapy.

Methods: LEGACY is a retrospective, single-arm, multi-center study conducted at 3 US sites. Study patients included all eligible consecutive HCC patients who received treatment with Y90 glass microspheres (TheraSphere®) between January 2014 and December 2017. Patients were Child-Pugh A, ECOG 0 or 1, with solitary tumors (≤8 cm). Primary efficacy endpoints were Objective Response Rate (ORR) and Duration of Response (DoR). ORR was defined as complete response (CR) or partial response (PR) to treatment based upon mRECIST criteria and was confirmed with subsequent imaging. DoR was evaluated in patients who achieved response. Pre- and post- treatment images were evaluated through a blinded, independent, central review process.

Results: A total of 162 eligible patients were included in the study. ORR was 72.2% (117/162; 95% CI = 64.9%, 78.5%). Forty-five (27.8%) patients were deemed unevaluable due to transplant or resection (n=20), lack of confirmatory imaging (n=20), or for other reasons (n=5). Most patients with a confirmed response experienced DoR ≥ 6 months (89/117, 76.1%, 95% CI = 67.6%, 82.9%). Treatment with Y90 glass microspheres demonstrated suitability as neoadjuvant therapy to transplant or resection (n=45) or as solitary treatment (n=50). Median overall survival (OS) for the intent-to-treat population was 57.9 months, with 3-year OS of 86.6% (51 patients at risk). Liver function, including albumin and bilirubin, were maintained throughout the study follow-up for 92.9% (118/127) and 85.3% (110/129) of patients, respectively.

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.

Editorial acknowledgement: Alexandra Greenberg-Worisek, PhD, MPH (Boston Scientific Corporation).

Legal entity responsible for the study: The authors.

Funding: Biocompatibles UK Ltd/Boston Scientific Corporation.

Disclosure: R. Salem: Advisory/Consultancy: Boston Scientific; Advisory/Consultancy: Eisai; Advisory/Consultancy: Genentech; Advisory/Consultancy: Cook; Advisory/Consultancy: BD. G.E. Johnson: Advisory/Consultancy: Boston Scientific; Advisory/Consultancy: Genentech. A. Riaz: Speaker Bureau/Expert testimony, In 2017 and 2018: BTG. V. Bishav: Speaker Bureau/Expert testimony: Boston Scientific. E. Kim: Advisory/Consultancy: Boston Scientific; Advisory/Consultancy: Eisai; Advisory/Consultancy: Bristol Myers Squibb; Advisory/Consultancy: Guerbet; Advisory/Consultancy: Ethicon. S. Padia: Advisory/Consultancy: Boston Scientific; Advisory/Consultancy: Bristol Meyer Squibb; Research grant/Funding (self): Varian.

https://doi.org/10.1016/j.annonc.2020.08.1108

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

T. de Baere[1], M. Pracht[2], Y. Rolland[3], J. Durand-Labrunie[4], N. Jaksic[3], F. Nguyen[5], J-P. Bronowicki[6], V. Vendrely[7], V. Croisé-Laurent[8], E. Rio[9], S. Le Sourd[10], P. Saïd[11], P. Gustin[1], C. Perret[9], D. Peiffert[12], E. Deutsch[4], E. Chajon[13]

[1]Interventional Radiology, Institut Gustave Roussy, Villejuif, France; [2]Medical Oncology Department, Centre Eugene - Marquis, Rennes, France; [3]Interventional Radiology, Centre Eugene - Marquis, Rennes, France; [4]Radiation Oncology, Institut Gustave Roussy, Villejuif, France; [5]Radiotherapy, Institut Gustave Roussy, Villejuif, France; [6]Gastroenterology, CHRU de Nancy, Vandoeuvre-lès-Nancy, France; [7]Radiotherapy, CHU de Bordeaux, Pessac, France; [8]Radiotherapy, CHRU de Nancy, Vandoeuvre-lès-Nancy, France; [9]Radiotherapy, Institut de Cancérologie de l'Ouest, Nantes, France; [10]Medical Oncology Department, Centre Eugene - Marquis, Rennes, France; [11]Biometry, Nanobiotix, Corp., Paris, France; [12]Radiotherapy, Institut de Cancérologie de Lorraine, Nancy, France; [13]Radiation Oncology, Centre Eugene - Marquis, Rennes, France

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.

Clinical trial identification: NCT02721056.

Legal entity responsible for the study: Nanobiotix.

Funding: Nanobiotix.

Disclosure: T. de Baere: Honoraria (self): Nanobiotix. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.1109

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

J-S. Lee[1], S.H. Lee[2], S. Lee[3], A. Kaseb[3], S.Y. Yim[4]

[1]Systems Biology Department, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA; [2]Surgery, Cha Bundang Medical Center, Sungnam, Republic of Korea; [3]GI Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA; [4]Gastroenterology, Korea University, Seoul, Republic of Korea

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.

Legal entity responsible for the study: The authors.

Funding: National Cancer Institute/NIH.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2020.08.1110

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

K. Dong[1], G. Xu[2], M. Lei[3], S. Zhao[4], M. Yao[5]

[1]Hepatobiliary surgery, Sichuan Academy of Medical Sciences·Sichuan Provincial People's Hospital, Chengdu, China; [2]Department of liver neoplasms, Jiangxi Cancer Hospital, Nanchang, China; [3]Department of Medicine, OrigiMed, Shanghai, China; [4]Department of Computer Oncology, OrigiMed, Shanghai, China; [5]Department of Information and Knowledge, OrigiMed, Shanghai, China

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