265 **Oral Abstract Session**

Final results from a phase II study of infigratinib (BGJ398), an FGFR-selective tyrosine kinase inhibitor, in patients with previously treated advanced cholangiocarcinoma harboring an *FGFR2* gene fusion or rearrangement.

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Background: Treatment options for cholangiocarcinoma (CCA) after progression on first-line gemcitabine-based therapy are limited. Fibroblast growth factor receptor 2 (*FGFR2*) gene fusions occur in 13–17% of intrahepatic CCA. A single-arm, phase II study (NCT02150967) evaluated infigratinib, an ATP-competitive FGFR1–3-selective oral tyrosine kinase inhibitor, in previously-treated advanced CCA with *FGFR* fusions/rearrangements. **Methods:** Adult patients with advanced/metastatic CCA with progression on ≥1 line of systemic therapy received infigratinib 125 mg orally for 21 days of each 28-day cycle until unacceptable toxicity or disease progression. All patients received prophylaxis with the oral phosphate binder sevelamer. Primary endpoint: objective response rate (ORR) by independent central review per RECIST v1.1, with duration of response (DOR). Secondary endpoints: progression-free survival (PFS), disease control rate, overall survival, safety, pharmacokinetics. Approximately 160 patients are planned (120/20/20 patients in Cohorts 1/2/3). This analysis focuses on Cohort 1 (patients with *FGFR2* gene fusions or rearrangements without receiving a prior FGFR inhibitor). **Results:** As of 31 March 2020, 108 patients, including 83 (77%) with *FGFR2* fusions, received infigratinib: median age 53 years (range 23–81 years); 54% had received ≥2 prior treatment lines. Median follow-up was 10.6 months (range 1.1–55.9 months). 96 patients (88.9%) discontinued treatment (12 ongoing). Centrally reviewed ORR was 23.1% (95% CI 15.6–32.2) including 1 CR and 24 PRs; median DOR was 5.0 months (range 0.9–19.1 months). Among responders, 8 (32.0%) patients had a DOR of ≥6 months. Median PFS was 7.3 months (95% CI 5.6–7.6 months). Prespecified subgroup analysis: ORR was 34% (17/50) in the second-line setting and 13.8% (8/58) in the third-/later-line setting (3–8 prior treatments). Most common treatment-emergent adverse events (TEAEs, any grade) were hyperphosphatemia (76.9%), eye disorders (67.6%, excluding central serous retinopathy/retinal pigment epithelium detachment [CSR/RPED]), stomatitis (54.6%), and fatigue (39.8%). CSR/RPED occurred in 16.7% of patients (including 1 G3 event; 0 G4). Other common grade 3/4 TEAEs were stomatitis (14.8%; all G3), hyponatremia (13.0%; all G3), and hypophosphatemia (13.0%; 13 G3, 1 G4). **Conclusions:** Infigratinib is associated with promising anticancer activity and a manageable AE profile in patients with advanced, refractory CCA with an *FGFR2* gene fusion or rearrangement. A phase III study of infigratinib versus gemcitabine/cisplatin is ongoing in the front-line setting (NCT03773302). Clinical trial information: NCT02150967. Research Sponsor: QED Therapeutics Inc.

Final results from ClarIDHy, a global, phase III, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (*IDH1*) mutation.

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Background: CCA is a rare cancer for which there are limited effective therapies. *IDH1* mutations occur in ~20% of intrahepatic CCAs, resulting in production of the oncometabolite D-2-hydroxyglutarate, which promotes oncogenesis. IVO (AG-120) is a first-in-class, oral, small-molecule inhibitor of mutant *IDH1* (m*IDH1*). ClarIDHy aimed to demonstrate the efficacy of IVO vs PBO in pts with unresectable or metastatic m*IDH1* CCA. The primary endpoint was met with significant improvement in progression-free survival (PFS) by independent radiology center (IRC) with IVO vs PBO (hazard ratio [HR] = 0.37, $p < 0.0001$). Objective response rate (ORR) and stable disease for IVO were 2.4% (3 partial responses) and 50.8% (n = 63) vs 0% and 27.9% (n = 17) for PBO. IVO pts experienced significantly less decline in physical and emotional functioning domains of quality of life at cycle 2 day 1 vs PBO pts (nominal $p < 0.05$). **Methods:** Pts with m*IDH1* CCA were randomized 2:1 to IVO (500 mg PO QD) or matched PBO and stratified by prior systemic therapies (1 or 2). Key eligibility: unresectable or metastatic m*IDH1* CCA based on central testing; ECOG PS 0–1; measurable disease (RECIST v1.1). Crossover from PBO to IVO was permitted at radiographic progression. Primary endpoint: PFS by IRC. Secondary endpoints included overall survival (OS; by intent-to-treat), ORR, PFS (by investigator), safety, and quality of life. The planned crossover-adjusted OS was derived using the rank-preserving structural failure time (RPSFT) model. **Results:** As of 31 May 2020, ~780 pts were prescreened for an *IDH1* mutation and 187 were randomized to IVO (n = 126) or PBO (n = 61); 13 remain on IVO. Median age 62 y; M/F 68/119; 91% intrahepatic CCA; 93% metastatic disease; 47% had 2 prior therapies. 70% of PBO pts crossed over to IVO. OS data were mature, with 79% OS events in IVO arm and 82% in PBO. Median OS (mOS) was 10.3 months for IVO and 7.5 months for PBO (HR = 0.79; 95% CI 0.56–1.12; one-sided p = 0.093). The RPSFT-adjusted mOS was 5.1 months for PBO (HR = 0.49; 95% CI 0.34–0.70; $p < 0.0001$). Common all-grade treatment emergent adverse events (TEAEs, $\geq$ 15%) in the IVO arm: nausea 41%, diarrhea 35%, fatigue 31%, cough 25%, abdominal pain 24%, decreased appetite 24%, ascites 23%, vomiting 23%, anemia 18%, and constipation 15%. Grade $\geq$ 3 TEAEs were reported in 50% of IVO pts vs 37% of PBO pts, with grade $\geq$ 3 treatment-related AEs in 7% of IVO pts vs 0% in PBO. 7% of IVO pts experienced an AE leading to treatment discontinuation vs 9% of PBO pts. There were no treatment-related deaths. **Conclusions:** IVO was well tolerated and resulted in a favorable OS trend vs PBO despite a high rate of crossover. These data – coupled with statistical improvement in PFS, supportive quality of life data, and favorable safety profile – demonstrate the clinical benefit of IVO in advanced m*IDH1* CCA. Clinical trial information: NCT02989857. Research Sponsor: Agios Pharmaceuticals, Inc.

IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC).

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Background: Atezo + bev has been approved globally for pts with unresectable HCC who have not received prior systemic therapy, based on results from IMbrave150 (NCT03434379). At a median of 8.6 mo follow-up, both coprimary endpoints were met, with statistically significant and clinically meaningful improvements observed with atezo + bev vs sor for OS (HR, 0.58 [95% CI, 0.42, 0.79]; $P<0.001$) and independently-assessed progression-free survival (PFS; per RECIST 1.1; HR, 0.59 [95% CI, 0.47, 0.76]; $P<0.001$) (Finn, et al. *N Engl J Med* 2020). Here, we report an updated OS analysis for IMbrave150. **Methods:** The global, multicenter, randomized, open-label, Phase III study IMbrave150 enrolled 501 systemic treatment-naive pts with unresectable HCC, ≥1 measurable untreated lesion (RECIST 1.1), Child-Pugh class A liver function and ECOG PS 0/1. Pts were randomized 2:1 to receive either atezo 1200 mg IV q3w + bev 15 mg/kg IV q3w or sor 400 mg bid until unacceptable toxicity or loss of clinical benefit per investigator. This post hoc, descriptive OS analysis was conducted with 12 mo of additional follow up from the primary analysis. **Results:** 501 pts were enrolled, including 336 to atezo + bev and 165 to sor. At the clinical cut-off date of Aug 31, 2020, median follow-up was 15.6 mo and 280 OS events were observed. Median OS was 19.2 mo with atezo + bev vs 13.4 mo with sor (HR, 0.66 [95% CI, 0.52, 0.85]; $P=0.0009$). Survival at 18 mo was 52% with atezo + bev and 40% with sor. Survival benefit with atezo + bev over sor was generally consistent across subgroups and with the primary analysis. The updated objective response rate (ORR; 29.8% per RECIST 1.1) with atezo + bev was in line with the primary analysis, with more pts achieving complete response (CR; 7.7%) than previously reported. Additional response data are in Table. Safety was aligned with the primary analysis, with no new signals identified. **Conclusions:** IMbrave150 showed consistent clinically meaningful treatment benefit and safety with 12 mo of additional follow-up. The combination provides the longest survival seen in a front-line Phase III study in advanced HCC, confirming atezo + bev as a standard of care for previously untreated, unresectable HCC. Clinical trial information: NCT03434379. Research Sponsor: F. Hoffmann-La Roche, Ltd.

Updated ORR and DOR per independently-assessed RECIST 1.1 and HCC mRECIST.

	Atezo + Bev n = 326 RECIST 1.1	Sor n = 159 RECIST 1.1	Atezo + Bev n = 325 HCC mRECIST	Sor n = 158 HCC mRECIST
Confirmed ORR (95% CI), %	29.8 (24.8, 35.0)	11.3 (6.9, 17.3)	35.4 (30.2, 40.9)	13.9 (8.9, 20.3)
CR, n (%)	25 (7.7)	1 (0.6)	39 (12.0)	4 (2.5)
PR, n (%)	72 (22.1)	17 (10.7)	76 (23.4)	18 (11.4)
SD, n (%)	144 (44.2)	69 (43.4)	121 (37.2)	65 (41.1)
Median DOR (95% CI), mo	18.1 (14.6, NE)	14.9 (4.9, 17.0)	16.3 (13.1, 21.4)	12.6 (6.1, 17.7)

DOR, duration of response; HCC mRECIST, modified RECIST for HCC; NE, not estimable; PR, partial response; SD, stable disease.

Pembrolizumab (pembro) vs placebo (pbo) in patients (pts) with advanced hepatocellular carcinoma (aHCC) previously treated with sorafenib: Updated data from the randomized, phase III KEYNOTE-240 study.

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Background: KEYNOTE-240 (NCT02702401) examined the anti-PD-1 antibody pembro and demonstrated improvement in OS and PFS vs pbo in pts with aHCC previously treated with sorafenib. However, the study did not meet prespecified statistical significance criteria for OS and PFS. Median OS (final analysis) was 13.9 mo for pembro vs 10.6 mo for pbo (HR 0.781; 95% CI 0.611-0.998). At the first interim analysis when PFS and ORR were prespecified to be tested, median PFS was 3.0 mo for pembro vs 2.8 mo for pbo (HR 0.775; 95% CI 0.609-0.987) and ORR was 16.9% (CR, n = 3) for pembro and 2.2% (CR, n = 0) for pbo. AEs were consistent with the known safety profile of pembro. Longer-term data from KEYNOTE-240 after ~1.5 years of additional follow-up are reported. **Methods:** Adults with confirmed aHCC who experienced failure (progression or intolerance) to sorafenib therapy were randomized 2:1 to pembro 200 mg IV Q3W + best supportive care (BSC) or pbo + BSC for ≤35 cycles or until confirmed progression/unacceptable toxicity, pt withdrawal of consent, or investigator decision. Dual primary end points were OS and PFS, assessed by blinded independent central review (BICR) per RECIST v1.1. Secondary end points included ORR, DOR, DCR, TTP (all assessed by BICR per RECIST v1.1), and safety. **Results:** Of 413 pts, 278 were randomized to pembro and 135 to pbo. As of July 13, 2020, median time from randomization to data cutoff was 39.6 mo (range 31.7-48.8) for pembro and 39.8 mo (31.7-47.8) for pbo. Median OS was 13.9 mo (95% CI 11.6-16.0) for pembro and 10.6 mo (8.3-13.5) for pbo (HR 0.771; 95% CI 0.617-0.964). Estimated OS rates at 24 and 36 mo for pembro and pbo were 28.8% and 20.4% and 17.7% and 11.7%, respectively. Median PFS was 3.3 mo (95% CI 2.8-4.1) for pembro and 2.8 mo (1.6-3.0) for pbo (HR 0.703; 95% CI 0.559-0.885). Estimated PFS rate at 24 mo was 11.8% for pembro and 4.8% for pbo. ORR was 18.3% (95% CI 14.0-23.4) for pembro and 4.4% (1.6-9.4) for pbo. Median time to response was 2.7 mo (95% CI 1.2-16.9) for pembro and 2.9 mo (1.1-6.9) for pbo. Median DOR was 13.9 mo (range 1.5+ to 41.9+) for pembro and 15.2 mo (2.8-21.9) for pbo; 45.1% of responders in pembro arm and 33.3% of responders in pbo arm had DOR ≥12 mo. DCR was 61.9% for pembro and 53.3% for pbo. Best overall responses were 10 CR, 41 PR, 121 SD, and 85 PD for pembro and 0 CR, 6 PR, 66 SD, and 54 PD for pbo. The median TTP was 4.0 mo (95% CI 2.8-5.3) for pembro and 2.8 mo (1.6-3.0) for pbo. No new or unexpected AEs occurred. The frequency of sponsor-assessed immune-mediated hepatitis events did not increase with additional follow-up. There continued to be no HBV or HCV viral flare events. **Conclusions:** In previously treated pts with aHCC, improvement in OS and PFS was maintained over time with pembro vs pbo, and the safety profile remained consistent over time. These data support the benefit:risk profile of pembro. Clinical trial information: NCT02702401. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Nivolumab (NIVO) plus ipilimumab (IPI) combination therapy in patients (Pts) with advanced hepatocellular carcinoma (aHCC): Long-term results from CheckMate 040.

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Background: NIVO 1 mg/kg + IPI 3 mg/kg Q3W (4 doses) followed by NIVO 240 mg Q2W is approved in the US for sorafenib-treated pts with aHCC based on initial results from CheckMate 040 (NCT01658878), which reported objective response rate (ORR) of 32% and median overall survival (mOS) of 22.8 months (mo).[1] We present 44-mo long-term follow-up results from the CheckMate 040 NIVO+IPI cohort. **Methods:** Pts were randomized to 3 arms: [A] NIVO 1 mg/kg + IPI 3 mg/kg Q3W (4 doses) or [B] NIVO 3 mg/kg + IPI 1 mg/kg Q3W (4 doses), each followed by NIVO 240 mg Q2W, or [C] NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W. Treatment continued until intolerable toxicity or disease progression. Safety and tolerability, ORR (blinded independent central review per RECIST v1.1), duration of response (DOR), disease control rate (DCR), and OS were assessed. Data cutoff was May 26, 2020. **Results:** 148 pts were randomized. Minimum follow-up was 44 mo. mOS remained at 22.2 mo in arm A, 12.5 mo in arm B, and 12.7 mo in arm C; 36-mo OS rates were 42%, 26%, and 30%, respectively. Durable responses were achieved across treatment arms, with DOR approaching 4 years in some cases. DCR was higher in arm A than arms B and C. In all arms, responses were observed regardless of baseline programmed death ligand 1 expression ($<1\%$ or $\geq 1\%$) or baseline alpha-fetoprotein level (<400 μg/L or ≥ 400 μg/L). Pts with hepatitis B or C virus (HBV or HCV) etiology had higher ORR than uninfected pts in arms B (29% vs 43% vs 9%) and C (31% vs 42% vs 0%). ORR was independent of etiology in arm A (HBV, 32%; HCV, 29%; uninfected, 31%). Additional efficacy data are in the table. There were no additional discontinuations due to treatment-related adverse events or immune-mediated adverse events (IMAEs) since the primary analysis. IMAEs were reported more frequently in arm A than arms B and C; the most common were rash, hepatitis, and adrenal insufficiency. Most IMAEs were reversible and resolved when treated using established algorithms. **Conclusions:** At a minimum follow-up of 44 mo, second-line NIVO1+IPI3 continued to demonstrate clinically meaningful responses and long-term survival benefit in aHCC. The safety profile was manageable and no new safety signals were identified with longer follow-up. Clinical trial information: NCT01658878. Research Sponsor: Bristol Myers Squibb and ONO Pharmaceutical Company Ltd.

	[A] NIVO1+IPI3 Q3W (n = 50)	[B] NIVO3+IPI1 Q3W (n = 49)	[C] NIVO3 Q2+IPI1 Q6W (n = 49)
ORR, n (%)	16 (32)	15 (31)	15 (31)
Complete response	4 (8)	3 (6)	1 (2)
Partial response	12 (24)	12 (24)	14 (29)
Stable disease	9 (18)	5 (10)	9 (18)
Progressive disease	20 (40)	24 (49)	21 (43)
DCR, % (95% CI)	54 (39-68)	43 (29-58)	49 (34-64)
Median DOR, mo (range)	17.5 (5-47+)	22.2 (4-44+)	16.6 (4-49+)
mOS, mo (95% CI)	22.2 (9.4-NE)	12.5 (7.6-16.4)	12.7 (7.4-30.5)
12-mo OS rate, % (95% CI)	61 (46-73)	56 (41-69)	51 (36-64)
24-mo OS rate, % (95% CI)	46 (32-59)	30 (18-44)	42 (28-56)
36-mo OS rate, % (95% CI)	42 (28-55)	26 (14-39)	30 (18-43)

NE, not evaluable.

1. Yau T, et al. *JAMA Oncology.* 2020; epub ahead of print.

TACTICS: Final overall survival (OS) data from a randomized, open label, multicenter, phase II trial of transcatheter arterial chemoembolization (TACE) therapy in combination with sorafenib as compared with TACE alone in patients (pts) with hepatocellular carcinoma (HCC).

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Background: To date many trials have been conducted to compare the efficacy and toxicity between TACE plus molecular targeted agents and TACE alone; all of them failed to show its clinical benefit in terms of progression free survival (PFS) or OS. In TACTICS trial (NCT01217034) TACE plus sorafenib significantly improved PFS over TACE alone in patients with unresectable HCC. (*Gut 2020;69:1374-1376*). Here we will report a final OS analysis from TACTICS trial with predefined mature OS events. **Methods:** Patients with unresectable HCC were randomized to TACE plus sorafenib (n=80) or TACE alone (n=76). Patients in the combination group received sorafenib 400 mg once daily for 2–3 weeks before TACE, followed by 800 mg twice daily during on-demand conventional TACE sessions until time to untreatable (unTACEable) progression (TTUP), defined as untreatable tumor progression, transient deterioration to Child-Pugh C or appearance of vascular invasion/extrahepatic spread. Co-primary endpoints were progression-free survival (PFS), which is defined as TTUP, or time to any cause of death and OS. Multiplicity was adjusted by gatekeeping hierarchical testing. **Results:** At the cut-off date of July 31, 2020, 131 OS events were observed. Median OS was 36.2 mo with TACE plus sorafenib vs 30.8 mo with TACE alone (HR, 0.861 [95%CI, 0.607, 1.223]; *P*=0.40). ΔOS was 5.4 mo. Updated PFS was 22.8 mo with TACE plus sorafenib vs 13.5 mo with TACE alone (HR, 0.661[95%CI, 0.466, 0.938]; *P*=0.02). Post-trial treatments with active procedures/agents were observed in 47 (58.8%) in TACE plus sorafenib and in 58 (76.3%) with TACE alone. Anticancer procedures in TACE alone group include resection/ablation in 14, transarterial therapy in 53 and radiation in 7. Anticancer medications in TACE alone include targeted agents in 40 (29 sorafenib, 5 regorafenib, 3 lenvatinib, 3 ramucirumab), other systemic chemotherapy in 5 and immunotherapy in 5. Safety was consistent with the primary analysis, with no new signals identified. **Conclusion:** In TACTICS, TACE plus sorafenib did not show OS benefit as compared with TACE alone although significantly better PFS was consistently observed. OS in TACE plus sorafenib in TACTICS trial showed the longest OS (36.2 mo) with the longest ΔOS (5.4 mo) as compared with the previous 5 TACE combination trials. The major reason for negative OS result was speculated that many post-trial active treatments were performed in control arm (76.3%), which implies that OS endpoint in TACE combination trial may not be feasible anymore in current era of sequential therapy with many active locoregional and systemic treatments. Clinical trial information: NCT01217034. Research Sponsor: Japan Liver Oncology Group.