Developmental therapeutics

LBA33 A first-in-human phase I study of a novel KRAS G12D inhibitor HRS-4642 in patients with advanced solid tumors harboring KRAS G12D mutation

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Background: *KRAS* G12D mutation is one of the most prevalent subtypes in *RAS* mutant cancers. However, no results of KRAS G12D inhibitors from any clinical trials have been reported yet. HRS-4642 is a highly selective KRAS G12D inhibitor. Here, we report preliminary results of the dose escalation part of a first-in-human phase 1 study of HRS-4642 in patients (pts) with advanced *KRAS* G12D mutant solid tumors.

Methods: Pts with histologically confirmed advanced solid tumors harboring *KRAS* G12D mutation who failed prior standard of care were enrolled to receive HRS-4642 i.v. at doses of 15, 50, 100, 200, and 300 mg QW in 21-day cycles. Dose escalation part allowed pts with *KRAS* mutation. An accelerated titration followed by a Bayesian optimal interval design is used to guide dose escalation and determine the maximum tolerated dose (MTD). The primary endpoints were safety, MTD, and recommended phase 2 dose (RP2D).

Results: At data cutoff on Aug 4, 2023, 18 pts were enrolled (lung adenocarcinoma n=10, colorectal adenocarcinoma n=5, appendiceal mucinous adenocarcinoma, ovarian cancer, and pancreatic cancer n=1 each). Pts had received a median of 3 lines of prior treatment (range 2-7). No DLTs were observed and the MTD was not reached yet. Grade ≥3 adverse events (AEs) were observed in 9 pts (50.0%). 6 pts (33.3%) had grade ≥3 treatment-related AEs (TRAEs), being hypercholesterolemia (16.7%), increased lipase (11.1%), and anemia (11.1%). No dose dependent trend was observed in the incidence of AEs. Serious TRAEs were observed in one patient (grade 2 increased ALT and grade 1 increased AST). No pts discontinued treatment or died due to TRAEs. 13 pts with baseline target lesions had at least one post-baseline assessment, and one NSCLC patient at 200 mg had partial response. 11 pts (61.1%) had stable disease and 6 (33.3%) experienced target lesion shrinkage, including lung and colorectal cancers. HRS-4642 exposure was approximately proportional to dose with a half-life of around 40 hours.

Conclusions: HRS-4642 showed a tolerable safety profile and preliminary anti-tumor activity in advanced solid tumors harboring *KRAS* G12D mutation. Dose escalation is ongoing and expected to proceed to dose expansion soon.

Clinical trial identification: NCT05533463.

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LBA34 Trastuzumab deruxtecan (T-DXd) for pretreated patients (pts) with HER2-expressing solid tumors: Primary analysis from the DESTINY-PanTumor02 (DP-02) study

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Background: T-DXd has shown significant survival benefit for pts with HER2-expressing breast and gastric cancers. Interim DP-02 data showed a promising objective response rate (ORR) and duration of response (DOR) in HER2-expressing tumors (ASCO 2023). Here we report the primary analysis including progression-free (PFS) and overall survival (OS).

Methods: This open-label, Phase 2 study (NCT04482309) evaluated T-DXd (5.4 mg/kg Q3W) in pts with HER2-expressing (immunohistochemistry [IHC] 3+/2+ by local or central testing), locally advanced/metastatic disease after ≥1 systemic treatment (Tx), or without alternative Tx options. Primary endpoint was investigator-assessed confirmed ORR. Secondary endpoints included safety, DOR, PFS and OS.

Results: At data cut off (Jun 2023), 267 pts with biliary tract (BTC), bladder (URO), cervical (CC), endometrial (EC), ovarian (OC), pancreatic (PC), or other tumors had received Tx (median [m] follow up: 12.75 [range 0.4–31.6] months [mo]); 72.3% received ≥2 prior lines of therapy. In all pts, investigator-assessed ORR (95% CI) was 37.1% (31.3, 43.2); mDOR (95% CI) was 11.3 mo (9.6, 17.8); mPFS (95% CI) was 6.9 mo (5.6, 8.0); and mOS (95% CI) was 13.4 mo (11.9, 15.5). In pts with IHC 3+ expression (central; n=75) ORR was 61.3% (49.4, 72.4); mDOR was 22.1 mo (9.6, not reached); mPFS was 11.9 mo (8.2, 13.0); and mOS was 21.1 mo (15.3, 29.6). Table shows ORR, PFS and OS by tumor type in all pts and IHC 3+. Grade (G) ≥3 Tx-related adverse events (AEs) occurred in 40.8% of pts; 8.6% discontinued Tx due to Tx-related AEs. Adjudicated Tx-related interstitial lung disease/pneumonitis occurred in 10.5% (n=28) of pts (9.0% [n=24] G≤2; 1.1% [n=3] G5).

Table: LBA34

	n		ORR, %		mPFS, mo (95% CI)		mOS, mo (95% CI)	
	All	IHC 3+	All	IHC 3+	All	IHC 3+	All	IHC 3+
Total	267	75	37.1	61.3	6.9 (5.6, 8.0)	11.9 (8.2, 13.0)	13.4 (11.9, 15.5)	21.1 (15.3, 29.6)
BTC	41	16	22.0	56.3	4.6 (3.1, 6.0)	7.4 (2.8, 12.5)	7.0 (4.6, 10.2)	12.4 (2.8, NR)
URO	41	16	39.0	56.3	7.0 (4.2, 9.7)	7.4 (3.0, 11.9)	12.8 (11.2, 15.1)	13.4 (6.7, 19.8)
CC	40	8	50.0	75.0	7.0 (4.2, 11.1)	NR (3.9, NR)	13.6 (11.1, NR)	NE (3.9, NR)
EC	40	13	57.5	84.6	11.1 (7.1, NR)	NR (7.3, NR)	26.0 (12.8, NR)	26.0 (18.9, NR)
OC	40	11	45.0	63.6	5.9 (4.0, 8.3)	12.5 (3.1, NR)	13.2 (8.0, 17.7)	20.0 (3.8, NR)
PC	25	2	4.0	0	3.2 (1.8, 7.2)	5.4 (2.8, NR)	5.0 (3.8, 14.2)	12.4 (8.8, NR)
Other	40	9	30.0	44.4	8.8 (5.5, 12.5)	23.4 (5.6, NR)	21.0 (12.9, 24.3)	24.3 (11.1, NR)

NR, not reached

Conclusions: We observed durable responses to T-DXd and clinically meaningful PFS and OS in pretreated pts across HER2-expressing tumors, with safety consistent with the known profile. These data support T-DXd as a potential tumor-agnostic treatment in HER2-expressing tumors. (Funded by BioNTech; ClinicalTrials.gov number; NCT04503278).

Clinical trial identification: NCT04482309.

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LBA35 BNT211-01: Interim results from a repeat dose escalation study of CLDN6 CAR-T cells manufactured with an automated process ± a CLDN6-encoding CAR-T cell-amplifying RNA Vaccine (CARVac)

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Background: Chimeric antigen receptor (CAR) T cells targeting CLDN6 ± CARVac showed promising activity against relapsed/refractory (r/r) CLDN6+ tumors (*ESMO* 2022 LBA38). We present data from a repeat 3+3 dose escalation trial with CAR T cells manufactured by an automated process and increased CARVac dosage.

Methods: BNT211-01 is recruiting patients (pts) with CLDN6-positive r/r solid tumours and no further treatment options. Following lymphodepletion, CAR T cells are flat dosed at 4 dose levels (DLs, 1×10^6 up to $2\text{-}5\times10^8$ CAR-T cells) ± repeat CLDN6 CARVac dosing (1×50 µg, then 100 µg doses). Primary endpoints are safety and tolerability. Additional endpoints are efficacy and pharmacokinetics.

Results: As of 24.07.2023, 38 pts primarily with ovarian cancer (n=14) and germ cell tumors (n=11) have been treated. Treatment related TEAEs ≥G3 were observed in 23 (61%) pts, including 20 (53%) pts with TEAEs related to CAR T cells. From 21 pts treated with the combination, 9 (43%) pts had TEAEs ≥G3 related to both IMPs, and 2 (10%) to CARVac. Related TESAEs have been observed in 8 pts (21%). DLTs occurred in 2 pts from different cohorts, G4 CRS at 5×10^8 CAR-T cells and G4 pancytopenia at 1×10^8, hence an MTD could not be determined. One death was assessed as treatment-related after the data cut-off. CRS was predominantly (95%) G1-2 and observed in 18 (47%) pts. 2 cases each of G1 ICANS and G1 hemophagocytic lymphohistiocytosis were reported (both 5%). Of 28 efficacy-evaluable patients, 9 pts (32%) had partial responses (PRs) and a further 9 had stable disease ([SD], unconfirmed overall response rate [ORR]: 32%, disease control rate [DCR]: 64%). Of 19 pts treated with ≥ $1\text{x}10^8$ CAR T cells, 8 PRs and 8 SDs resulted in an ORR of 42% and a DCR of 84%. CAR-T expansion was dose dependent, with improved persistence by addition of CARVac.

Conclusions: CLDN6 CAR T cells ± CARVac demonstrated encouraging antitumor activity. Addition of CARVac improved CAR-T cell persistence. The safety profile in terms of CRS, ICANS and DLTs observed is in line with previously reported observations. We intend to present data on up to 42 pts, with a data cut-off of 10.09.2023.

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