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A Phase 1/2 Study of Safety and Efficacy of the Arginase Inhibitor INCB001158 Plus Chemotherapy in Patients With Advanced or Metastatic Biliary Tract Cancers

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Study Overview

- INCB001158 is a small-molecule arginase inhibitor that restores arginine levels and alleviates myeloid-derived immunosuppression in the tumor microenvironment

Key Inclusion Criteria
- Age ≥18 years
- Presence of measurable disease per RECIST v1.1
- ECOG score 0–1
- Baseline tumor biopsy mandatory
- **Phase 1:** Histologically/cytologically confirmed advanced or metastatic solid tumors that progressed after prior standard therapy*
- **Phase 2:** Histologically/cytologically confirmed advanced (unresectable) or metastatic BTC, with no prior systemic treatment†

Primary Endpoints
- Safety, tolerability, and RP2D of INCB001158 in combination with gemcitabine/cisplatin
- ORR

Secondary Endpoints
- DOR, DCR, PFS

Other Endpoints
- PK, pharmacodynamics, biomarkers

BID, twice daily; BOIN, Bayesian optimal interval; BTC, biliary tract cancer; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, Recommended Phase 2 Dose.
* There was no limit to the number of prior treatment regimens. † Not including adjuvant therapy completed at least 6 months prior to enrollment. Precise BTC population per protocol: intra- or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma. ‡ Gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 (Days 1 and 8 of 21-day cycle).

Safety Profile

Most Common Adverse Events

Phase 1 Most Common TEAEs (>30%) in the INCB001158 + Gemcitabine/Cisplatin Cohort (RP2D in Gray)

	Any Grade			Grade ≥3			Related to INCB001158			Related to Gemcitabine/Cisplatin		
TEAE, n (%)	50 mg (n=7)	75 mg (n=4)	100 mg (n=4)	50 mg (n=7)	75 mg (n=4)	100 mg (n=4)	50 mg (n=7)	75 mg (n=4)	100 mg (n=4)	50 mg (n=7)	75 mg (n=4)	100 mg (n=4)
Any	**7 (100)**	**4 (100)**	**4 (100)**	**7 (100)**	**1 (25)**	**4 (100)**	**3 (43)**	**3 (75)**	**3 (75)**	**6 (86)**	**4 (100)**	**4 (100)**
Anemia	5 (71)	2 (50)	**3 (75)**	1 (14)	0	**2 (50)**	1 (14)	1 (25)	**1 (25)**	5 (71)	1 (25)	**3 (75)**
WBC count decreased	4 (57)	1 (25)	**2 (50)**	2 (29)	0	**2 (50)**	0	0	**0**	4 (57)	1 (25)	**2 (50)**
Platelet count decreased	5 (71)	0	**1 (25)**	4 (57)	0	**1 (25)**	0	0	**0**	5 (71)	0	**1 (25)**
Constipation	1 (14)	2 (50)	**2 (50)**	0	0	**0**	0	0	**0**	0	0	**0**
Neutrophil count decreased	4 (57)	0	**1 (25)**	4 (57)	0	**1 (25)**	0	0	**0**	4 (57)	0	**1 (25)**

- INCB001158 100 mg BID was chosen as the recommended phase 2 dose

Phase 2 Most Common TEAEs (>25%) in the BTC Cohort (n=33)

TEAE, n (%)	Any Grade	Grade ≥3	Related to INCB001158	Related to Gemcitabine/Cisplatin
Any	**33 (100)**	**29 (88)**	**24 (73)**	**28 (85)**
Fatigue	16 (48)	3 (9)	11 (33)	10 (30)
Anemia	15 (45)	7 (21)	3 (9)	13 (39)
Nausea	13 (39)	2 (6)	4 (12)	8 (24)
Neutrophil count decreased	11 (33)	10 (30)	3 (9)	11 (33)
Constipation	10 (30)	0	1 (3)	1 (3)
Platelet count decreased	10 (30)	3 (9)	2 (6)	10 (30)
Vomiting	10 (30)	4 (12)	1 (3)	6 (18)
Pyrexia	9 (27)	1 (3)	0	3 (9)

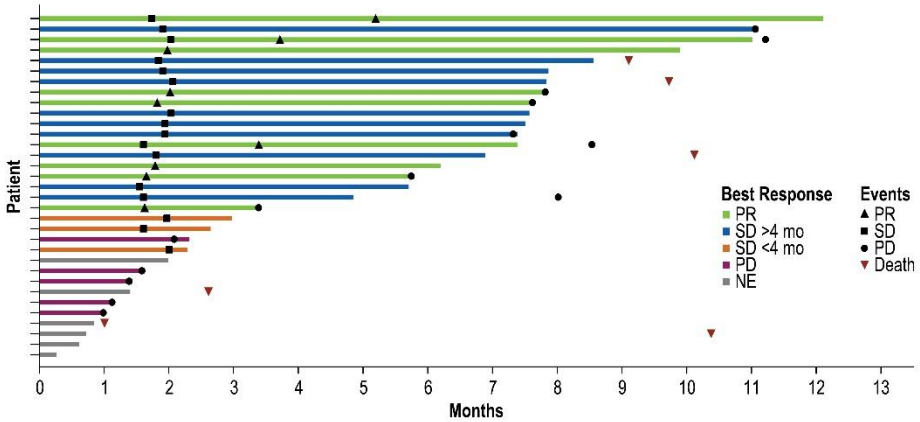
BID, twice daily; BTC, biliary tract cancer; RP2D, Recommended Phase 2 Dose; TEAE, treatment-emergent adverse event; WBC, white blood cell.

Tumor Response

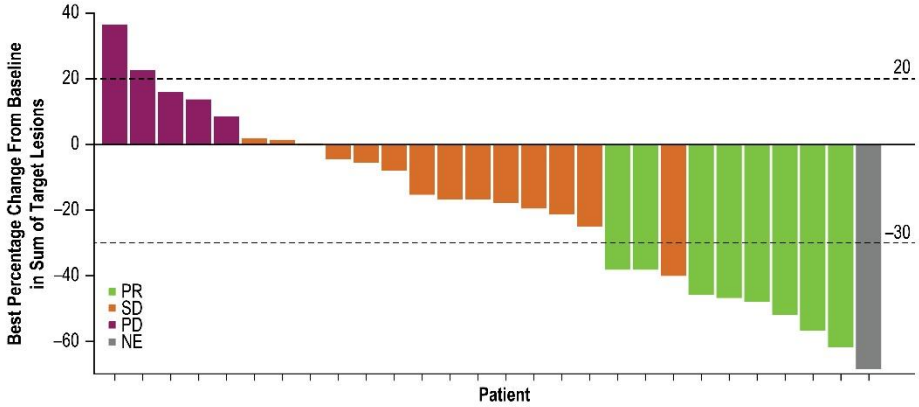
*Phase 2 Tumor Expansion: BTC Cohort**

- ORR was 24.2% (8/33; 95% CI, 11.1%–42.3%); SD occurred in 42.4% of patients, rendering a DCR of 66.7% (95% CI, 48.2%–82.0%)
  - ORR and DCR for gemcitabine/cisplatin alone are 19%–26.1% and 65%–81.4%, respectively[1-4]

Time on Treatment and Overall Response†



Percentage Change From Baseline in Target Lesions†



BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

* Statistical analyses performed on the intention-to-treat population, n=33 dosed patients. † NE includes patients who discontinued prior to postbaseline tumor assessment and those who had nonmeasurable disease.

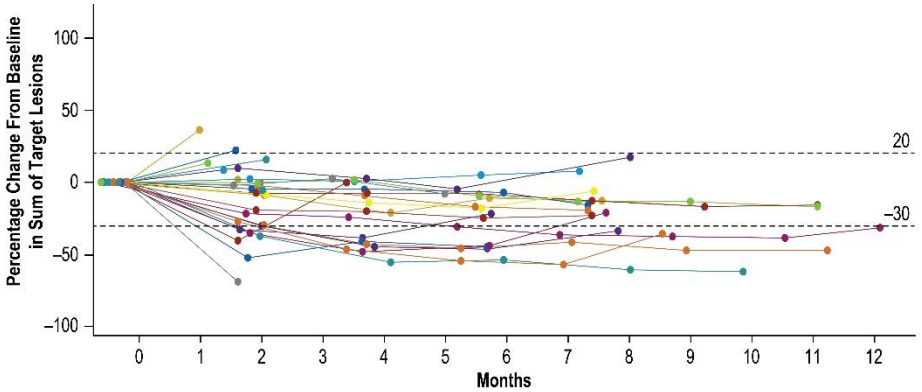
1. Kang MJ, et al. *Acta Oncologica*. 2012;51:860-866. 2. Valle J, et al. *N Engl J Med.* 2010;362:1273-1281. 3. Valle JW, et al. *Lancet Oncol.* 2015;16:967-978. 4. Okusaka T, et al. *Br J Cancer*. 2010;103:469-474.

Tumor Response and Progression-Free Survival

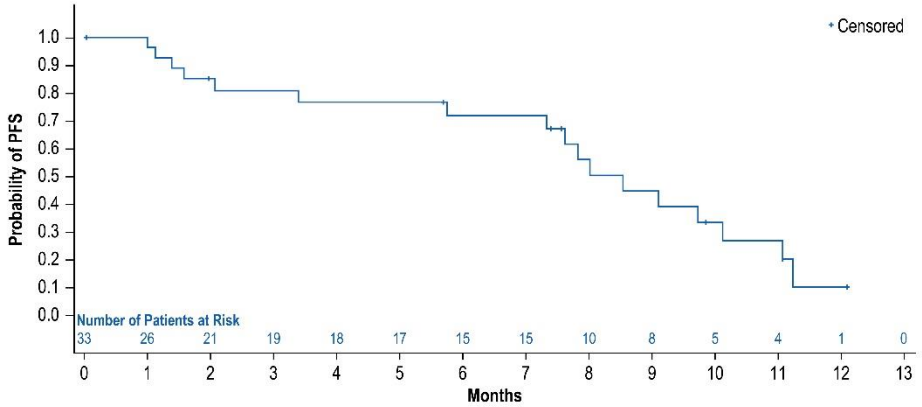
*Phase 2 Tumor Expansion: BTC Cohort**

- Median DOR (95% CI) for INCB001158 100 mg BID + gemcitabine/cisplatin was 5.8 (4.1–NR) months
- Median PFS (95% CI) was 8.5 (5.7–10.1) months
  - Median PFS for gemcitabine/cisplatin alone is 5.7–8.0 months[1-4]

Percentage Change in Tumor Lesions Over Time†



PFS



BID, twice daily; BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; NR, not reached; PFS, progression-free survival.

* Statistical analyses performed on the intention-to-treat population, n=33 dosed patients. † Scheduled study visits took place at Weeks 8, 16, 24, 32, 40, 48, and 56.

1. Kang MJ, et al. *Acta Oncologica*. 2012;51:860-866. 2. Valle J, et al. *N Engl J Med.* 2010;362:1273-1281. 3. Valle JW, et al. *Lancet Oncol.* 2015;16:967-978. 4. Okusaka T, et al. *Br J Cancer*. 2010;103:469-474.

Conclusions

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- Preliminary data suggest that addition of INCB001158 to gemcitabine/cisplatin was tolerable and did not result in significant added toxicity
- INCB001158 of 100 mg BID was identified as the recommended phase 2 dose
- Response rates and PFS in phase 2 suggest that some patients with BTC may benefit from this combination as first-line treatment
  - Earlier studies of first-line gemcitabine/cisplatin in patients with BTC reported ORR of 19%–26.1% and median PFS of 5.7–8.0 months[1-4]
  - Preliminary results of INCB001158 + gemcitabine/cisplatin show an ORR of 24.2% and a median PFS of 8.5 months
- INCB001158 is currently under investigation for solid tumors and hematological malignancies, and future translational analyses are planned

BID, twice daily; BTC, biliary tract cancer; ORR, objective response rate; PFS, progression-free survival.

1. Kang MJ, et al. *Acta Oncologica*. 2012;51:860-866. 2. Valle J, et al. *N Engl J Med.* 2010;362:1273-1281. 3. Valle JW, et al. *Lancet Oncol.* 2015;16:967-978. 4. Okusaka T, et al. *Br J Cancer*. 2010;103:469-474.