Targeting *HER2* mutation-positive advanced biliary tract cancers with neratinib: Final results from the phase 2 SUMMIT 'basket' trial

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Background

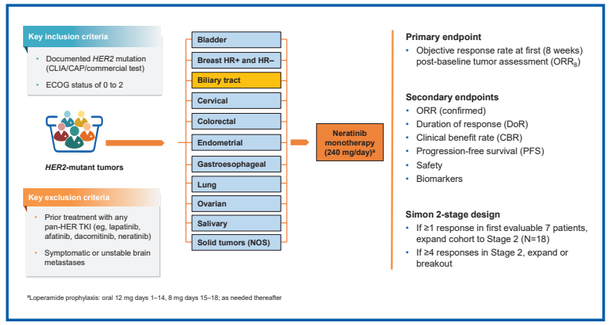
- *HER2* mutations are infrequent genomic events in biliary tract cancers (BTCs) and are associated with poor overall survival (OS) in patients with metastatic disease.[1]
- HER2 overexpression is associated with an increased risk of disease recurrence in patients with resected BTC.[2] There is limited data on targeting HER2 in BTC harboring activating somatic *HER2* mutations.
- Neratinib, an irreversible, pan-HER, oral tyrosine kinase inhibitor (TKI), interferes with constitutive receptor kinase activation[3–5] and has demonstrated activity in several *HER2*-mutant solid tumors.[6–8]
- SUMMIT is an open-label, single-arm, multi-cohort, phase 2, 'basket' trial of neratinib in patients with solid tumours harbouring oncogenic *HER2* somatic mutations (NCT01953926).
- In the initial study report from SUMMIT, the antitumor activity of neratinib appeared to be dependent on both histology and mutation. One of the first seven patients enrolled in the *HER2*-mutant BTC cohort achieved a partial response (PR), meeting Simon two-stage criteria for cohort expansion.[8]
- Here, we report the final results of the expanded *HER2*-mutant BTC cohort in SUMMIT.

Methods

Study design

- The design of the SUMMIT multi-histology 'basket' study is shown in Figure 1.

Figure 1. SUMMIT multi-histology 'basket' study design: Neratinib monotherapy cohorts



[a]Loperamide prophylaxis: oral 12 mg days 1–14, 8 mg days 15–18; as needed thereafter

Genomic analysis

- Archival or pre-treatment formalin-fixed, paraffin-embedded (FFPE) tumor tissue was required for study entry. Plasma was collected before treatment, on treatment (every other cycle), and at treatment discontinuation.
- Tumor DNA was extracted from FFPE tissue or plasma and sequenced using Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT)[9] or MSK-ACCESS.[10]
- Custom targeted *HER2* single-gene sequencing was performed in select cases using plasma samples. Somatic alterations were annotated with OncoKB (version date December 24, 2021).

Statistics

- Baseline characteristics, activity, and safety were summarised in the safety analysis set (all patients receiving at least one neratinib dose).
- The Clopper-Pearson method was used to calculate ORR and CBR 95% confidence intervals (CIs). Kaplan-Meier methodology was used to determine PFS estimates with 95% CIs.
- All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) or the survival package (version 3.1-12) from R (version 4.0.2).

Results

Table 1. Baseline demographics

	HER2-mutant biliary cohort (n=25)
Median age, years (range)	65 (49–78)
Female sex, n (%)	13 (52)
ECOG performance status, n (%)	
0 / 1 / 2	6 (24) / 17 (68) / 2 (8)
Tumor site, n (%)	
Cholangiocarcinoma	11 (44)
Intrahepatic	6 (24)
Extrahepatic	5 (20)
Gallbladder	10 (40)
Ampulla of Vater	4 (16)
M1 stage at enrollment, n (%)	25 (100)
Patients with prior surgery, n (%)	16 (64)
Patients with prior radiation, n (%)	5 (20)
Median no. of prior systemic regimens (range)	2 (0–7)
Prior systemic therapy, n (%)	
Gemcitabine-based	24 (96)
Platinum-based	23 (92)
Fluoropyrimidine-based	18 (72)
None	1 (4)

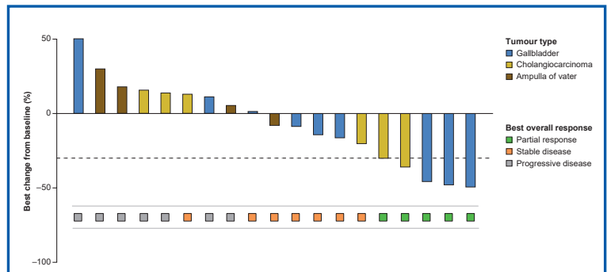
ECOG = Eastern Cooperative Oncology Group. Data cut-off: Jan 22, 2021.

Table 2. Efficacy summary

Efficacy endpoint[a]	*HER2*-mutant biliary cohort (n=25)
Objective response at first assessment (Week 8), n/N, %	2/18 (11.1)
Objective response (confirmed),[b] n	4
CR	0
PR	4
Objective response rate, % (95% CI)	**16.0** (4.5–36.1)
Best overall response, n (%)	**5 (20.0)**
DOR for each responder, months	**3.0, 3.6, 3.7, 4.7**
Clinical benefit,[c] n	7
CR	0
PR	4
SD ≥16 weeks	3
Clinical benefit rate, % (95% CI)	**28.0** (12.1–49.4)
Median PFS,[d] months (95% CI)	2.8 (1.1–3.7)
Median OS, months (95% CI)	5.4 (3.7–11.7)

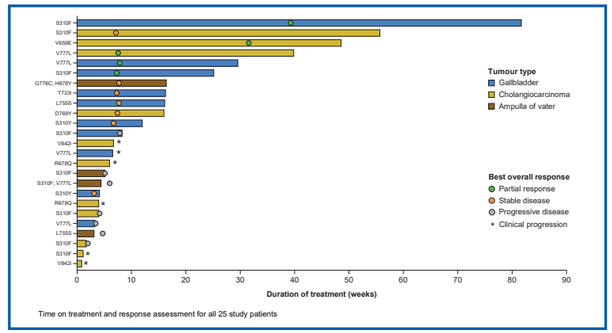
[a]Response is based on investigator tumor assessments per RECIST v1.1; [b]Objective response rate is defined as either a complete or partial response that is confirmed no less than 4 weeks after the criteria for response are initially met; [c]Clinical benefit rate is defined as confirmed CR or PR or SD for at least 16 weeks (within ± 7-day visit window); [d]Kaplan-Meier analysis. CR = complete response; DOR = duration of response; PFS = progression-free survival; PR = partial response; OS = overall survival; SD = stable disease.

Figure 2. Waterfall plot for 19 patients with RECIST-evaluable disease



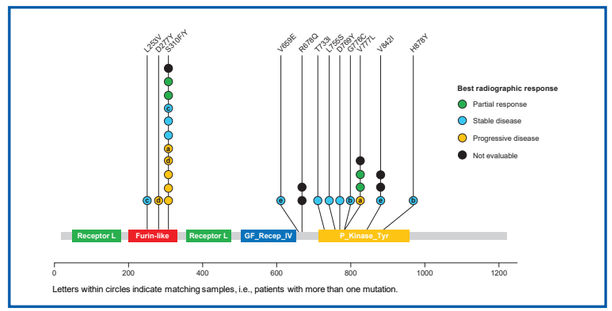
Six patients who were not evaluable are not depicted. Dotted line at –30% indicates partial response

Figure 3. Treatment and response assessment



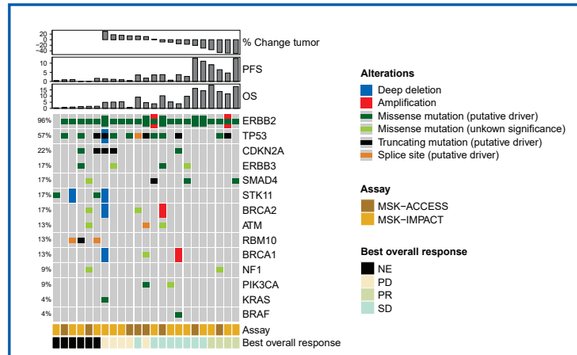
Time on treatment and response assessment for all 25 study patients

Figure 4. Lollipop diagram of the *HER2* gene annotated with centrally confirmed mutations and tumor responses (n=23)



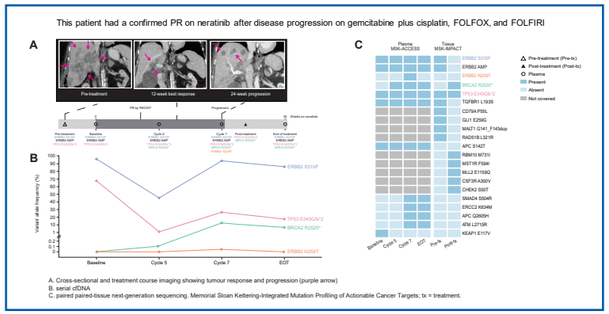
Letters within circles indicate matching samples, i.e., patients with more than one mutation.

Figure 5. OncoPrint of co-occurring genomic alterations (n=23)



OncoPrint is annotated with objective response, central next-generation sequencing confirmation assay best tumor shrinkage, PFS, and OS. NE = not estimable.

Figure 6. Polyclonal resistance to neratinib in 71-year-old woman with adenosquamous carcinoma of the gallbladder harbouring *HER2*-amplified/*S310F* mutation



A. Cross-sectional and treatment course imaging showing tumour response and progression (purple arrow)
B. serial ctDNA
C. paired paired-tissue next-generation sequencing. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets: tx = treatment.

Table 3. Incidence of treatment-emergent adverse events (≥15%)

Adverse event, n (%)	*HER2*-mutant biliary tract cancer cohort (n=25)		
	All grades	Grade 1 or 2	Grade 3 or 4
Patients with at least 1 adverse event, n (%)			
Diarrhea*	14 (56)	8 (32)	6 (24)*
Vomiting	12 (48)	11 (44)	1 (4)
Fatigue	10 (40)	10 (40)	0
Nausea	10 (40)	10 (40)	0
Abdominal pain	8 (32)	6 (24)	2 (8)
Decreased appetite	7 (28)	7 (28)	0
Constipation	6 (24)	6 (24)	0
Aspartate aminotransferase increased	4 (16)	3 (12)	1 (4)
Dehydration	4 (16)	2 (8)	2 (8)
Dizziness	4 (16)	4 (16)	0
Dry mouth	4 (16)	4 (16)	0
Pyrexia	4 (16)	4 (16)	0

All 25 patients had at least one adverse event (AE); 16 (64%) had one or more serious AEs, two (8%) had serious treatment-related AEs, and five (20%) had treatment-emergent AEs and/or clinical progression leading to treatment discontinuation. *Diarrhea was the most common AE. Loperamide prophylaxis was used as follows: oral 12 mg days 1–14, 8 mg days 15–18; as needed thereafter; †There was no grade 4 diarrhea. Two patients had a grade 5 AE: one died because of general deterioration and one because of sepsis.

Summary and conclusions

- The SUMMIT trial has reported encouraging activity of neratinib in patients with *HER2*-mutant biliary cancers, with especially promising tumor responses in patients with cholangiocarcinoma or gallbladder cancer.
- The major observed toxicities were manageable gastrointestinal AEs and were consistent with expectations.
- Limitations of the study are the small sample size and inclusion of patients with poor ECOG performance status, leading to a high proportion of non-evaluable patients.
- In the *HER2*-mutant breast and *HER2*-mutant lung cohorts of SUMMIT,[11,12] addition of trastuzumab to neratinib prolonged and deepened responses; the same approach should be explored for *HER2*-mutant biliary cancer.

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Acknowledgements

- The authors would like to thank all patients and their families for participating in the SUMMIT study.
- SUMMIT was sponsored by Puma Biotechnology Inc. This work was also supported in part by a Cancer Center Support Grant (P30 CA008748) and Cycle for Survival.
- Puma Biotechnology Inc. funded medical writing/editing assistance for this poster, which was provided by Miller Medical Communications Ltd.

Presented at the 2022 ASCO Annual Meeting, 3–7 June, 2022, Chicago, IL, USA