Targeting *HER2* (*ERBB2*) mutation-positive advanced biliary tract cancers with neratinib: results from the phase 2 SUMMIT 'basket' trial

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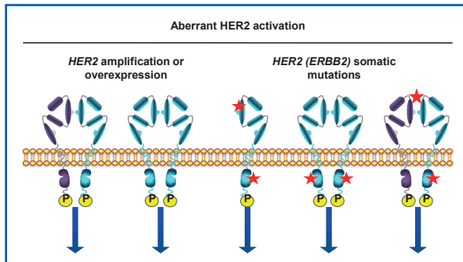
Background

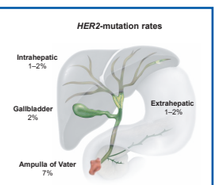
HER2 activation results in enhanced tumor growth in preclinical models



Subset of *HER2* mutations result in constitutive kinase signaling, oncogenic transformation and enhanced tumor growth in preclinical models[1]

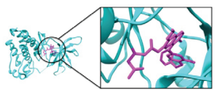
Biliary tract cancer and *HER2* mutations

- Biliary tract cancer is a heterogeneous and rare disease with poor prognosis; majority of patients present with advanced incurable disease.[2]
- Gemcitabine + cisplatin improves overall survival (OS) compared with gemcitabine for advanced disease and is an established front-line standard of care (ABC-02).[2]
- Second-line FOLFOX results in an objective response rate (ORR) of ~5% and modest improvement in OS compared with best supportive care (ABC-06).[3]
- Somatic *HER2* mutations, mainly missense substitutions, are seen at low frequencies in biliary tract cancers and *HER2* alterations are associated with poor survival in retrospective data sets.[4–6]



Neratinib (HKI-272; PB272; NERLYNX®)

- Neratinib is an oral, irreversible, tyrosine kinase inhibitor of EGFR (ERBB1), HER2 (ERBB2), and HER4 (ERBB4).[7]
- Neratinib results in potent inhibition of intracellular signaling, cell proliferation and colony formation of *HER2*-mutant and amplified breast tumor cell lines *in vitro*.[1,7]

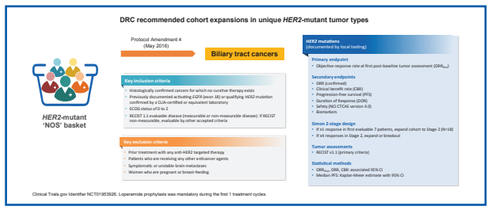


Neratinib binds covalently to conserved cysteine residues in the kinase active binding site of EGFR, HER2 and HER4[8]

- Neratinib is approved for the extended adjuvant treatment of patients with early-stage HER2-positive breast cancer; it is also approved for use in combination with capecitabine for the treatment of advanced or metastatic HER2-positive breast cancer patients with who have received ≥2 prior anti-HER2 therapies.[9–11]

Methods

SUMMIT: a multi-histology, open-label, phase 2 'basket' study of neratinib in patients with somatic *HER2* mutations



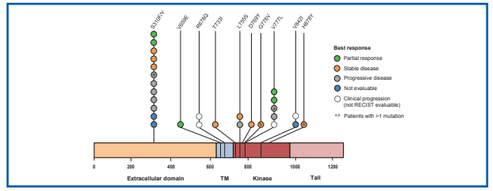
Results

Baseline demographics

	HER2-mutant biliary cohort (n=25)
Median age, years (range)	65 (49–78)
Female gender, n (%)	13 (52)
ECOG performance status, n (%) 0 / 1 / 2	6 (24) / 17 (68) / 2 (8)
Tumor site, n (%) Cholangiocarcinoma Intrahepatic Extrahepatic Gallbladder Ampulla of Vater	 11 (44) 6 (24) 5 (20) 10 (40) 4 (16)
Stage at enrollment, n (%) M1	 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 Platinum-based Fluoropyrimidine-based None	 24 (96) 23 (92) 18 (72) 1 (4)

Data cut-off date: 19-Oct-2020

Distribution of mutations in efficacy evaluable, *HER2*-mutant advanced biliary tract cancer patients receiving neratinib (n=25)



Patient disposition

	HER2-mutant biliary cohort (n=25)
Subjects enrolled and received at least one dose of study drug, n (%)	25 (100)
Reasons for treatment discontinuation, n (%) Disease progression Death Adverse event Clinical progression	24 (96) 15 (60) 1 (4)* 4 (16)# 4 (16)

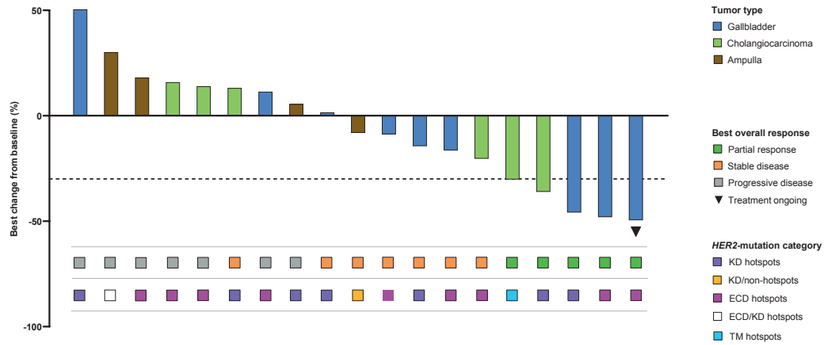
*Reason of death is progressive disease. #Four AEs are related to disease under study (biliary tract carcinoma)
Data cut-off date: 19-Oct-2020

Efficacy summary

Efficacy endpoint[a]	*HER2*-mutant biliary cohort (n=25)
Objective response (confirmed),[b] n CR PR **Objective response rate,** % (95% CI)	4 0 4 **16.0 (5–36)**
Best overall response, n (%)	**5 (20.0)**
DOR for each responder, months	**3.0, 3.6+, 3.7, 4.7**
Clinical benefit,[c] n CR PR SD ≥16 weeks **Clinical benefit rate,** % (95% CI)	7 0 4 3 **28.0 (12–49)**
Median PFS,[d] months (95% CI)	**2.8 (1.1–3.7)**
Median OS, months (95% CI)	**5.4 (3.7–11.7)**

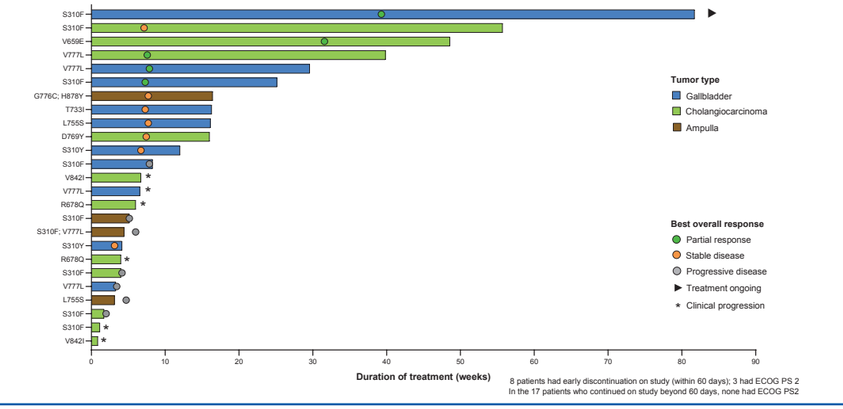
[a]Response is based on investigator tumor assessments per RECIST v1.1; [b]Objective response rate (ORR) is defined as either a complete or partial response that is confirmed no less than 4-weeks after the criteria for response are initially met; [c]Clinical benefit rate (CBR) is defined as confirmed CR or PR or stable disease (SD) for at least 16 weeks (within +/− 7-day visit window); [d]Kaplan-Meier analysis. DOR, duration of response; PFS, progression-free survival; OS, overall survival
Data cut-off date: 19-Oct-2020

Best percentage change in target lesion size from baseline in efficacy-evaluable patients (n=19)



Response based on investigator tumor assessments (RECIST v1.1)
NOTE: of the 25 patients enrolled, 19 patients had baseline RECIST-evaluable disease

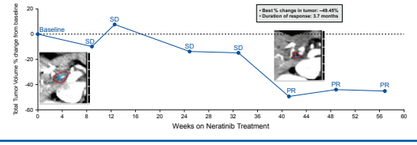
Best responses and duration of treatment (n=25)



8 patients had early discontinuation on study (within 60 days); 3 had ECOG PS 2
In the 17 patients who continued on study beyond 60 days, none had ECOG PS2

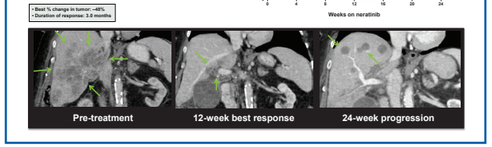
Advanced *HER2*-mutant gallbladder patient with rapid and durable response to neratinib

- 67-year-old female
- Stage IV adenocarcinoma of the gallbladder
- *HER2 (S310F)* mutation
- Progressive disease after 1st-line gemcitabine + cisplatin and 2nd-line capecitabine and oxaliplatin



Advanced *HER2*-mutant gallbladder patient with rapid and marked response to neratinib

- 71-year-old patient
- Stage IV adenocarcinoma of the gallbladder
- *HER2 S310F/ERRB2* amplification
- Progressive disease after gemcitabine + cisplatin, FOLFOX and FOLFIRI



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

Adverse event, n (%)	*HER2*-mutant biliary tract cancer cohort (n=25)	
	All grades	Grade 3 or 4
Patients with at least 1 adverse event, n (%)	25 (100.0)	18 (72.0)
Diarrhea	14 (56.0)*	6 (24.0)#
Vomiting	12 (48.0)	1 (4.0)
Fatigue	10 (40.0)	0
Nausea	10 (40.0)	0
Abdominal pain	9 (36.0)	3 (12.0)
Decreased appetite	7 (28.0)	0
Constipation	6 (24.0)	0
Aspartate aminotransferase increased	4 (16.0)	1 (4.0)
Dehydration	4 (16.0)	2 (8.0)
Dizziness	4 (16.0)	0
Dry mouth	4 (16.0)	0
Pyrexia	4 (16.0)	0

*None of the diarrhea events resulted in dose discontinuation within the biliary tract cancer cohort; 1 patient was hospitalized, and 4 patients reduced study drug due to diarrhea events. #No Grade 4 diarrhea events were reported. Two grade 5 events were reported: general deterioration (n=1) and sepsis (n=1)
Data cut-off date: 19-Oct-2020

Summary and conclusions

- Neratinib is safe and tolerable in patients with advanced biliary tract cancers with somatic *HER2* mutations:
  - Although the study did not meet its prespecified criteria for further expansion, the antitumor activity of neratinib appears comparable to current standards of care, with similar PFS and OS in heavily pretreated patients.
  - A subset of biliary tract cancer patients had tumor shrinkage or extended disease control, suggesting single-agent anti-tumor activity in this rare population.
  - The major observed toxicities were manageable gastrointestinal adverse events and were consistent with expectations.
  - A limitation of the study is the small sample size and inclusion of poor ECOG PS patients, leading to a high proportion of non-evaluable patients.
- Analysis of co-mutations and copy number variations is ongoing and may inform future combination strategies.

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