Treating *HER2*-mutant advanced biliary tract cancer with neratinib: benefits of HER2-directed targeted therapy in the phase 2 SUMMIT 'basket' trial

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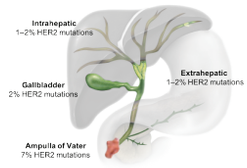
Oral #428

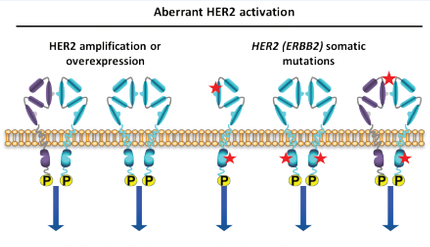
Background

Biliary tract cancer and *HER2* mutations

- Heterogeneous and rare disease with poor prognosis; majority of patients present with advanced incurable disease.[1]
- Gemcitabine and cisplatin improves OS over gemcitabine for advance disease and is an established front-line standard of care (ABC-02).[1]
- Second-line FOLFOX offers ORR of ~5% and modest improvement in OS over best supportive care (ABC-06).[2]
- Somatic *HER2* mutations, mainly missense substitutions, are seen at low frequencies in biliary tract cancers and *HER2* alterations are associated with worse survival in retrospective data sets.[3–5]



Abnormal HER2 activation results in tumor growth



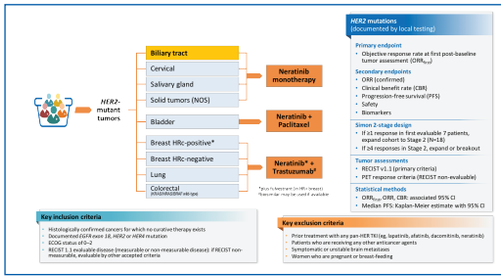
Subset of *HER2* mutations result in constitutive kinase signaling, oncogenic transformation and enhanced tumor growth in preclinical models[6]

Neratinib (HKI-272; PB272; NERLYNX®)

- Oral, irreversible, tyrosine kinase inhibitor of EGFR (ERBB1), HER2 (ERBB2), and HER4 (ERBB4).[7]
- Potent inhibition of intracellular signaling, cell proliferation and colony formation of *HER2* mutant and amplified breast tumor cell lines *in vitro*.[6,7]
- Covalent binding to conserved cysteine residues in the kinase active binding site of EGFR, HER2 and HER4.[8]
- Approved in US[9] and Australia[10] for extended adjuvant treatment of patients with early-stage HER2-positive early breast cancer following adjuvant trastuzumab-based therapy; EU[11] approval for patients with early-stage hormone receptor-positive HER2-positive breast cancer who are less than 1 year from completion of prior adjuvant trastuzumab-based therapy.

Methods

SUMMIT 'basket' study design



Results

Baseline demographics

	HER2-mutant biliary cohort (n=20)
Median age, years (range)	66 (49–78)
Female gender, n (%)	11 (55)
ECOG performance status, n (%)	
0 / 1 / 2	5 (25) / 13 (65) / 2 (10)
Tumor site, n (%)	
Cholangiocarcinoma	9 (45)
Intrahepatic	4 (20)
Extrahepatic	5 (25)
Gallbladder	9 (45)
Ampulla of Vater	2 (10)
Stage at enrollment, n (%)	
M0 / M1	1 (5) / 19 (95)
Patients with prior surgery, n (%)	11 (55)
Patients with prior radiation, n (%)	4 (20)
Prior systemic therapy, n (%)	
Gemcitabine-based	18 (90)
Platinum-doublet	15 (75)
Fluoropyrimidine-based	12 (60)
None	1 (5)
Median no. of prior systemic regimens (range)	2 (0–7)

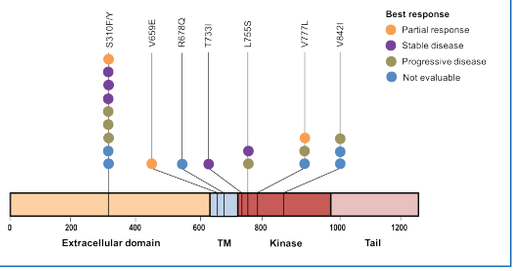
Patient disposition

	HER2-mutant biliary cohort (n=20)
Patients enrolled and received at least one dose of study drug	20 (100.0)
Treatment discontinuation	18 (90.0)
Disease progression	11 (55.0)
Death	2 (10.0)
Adverse event	1 (5.0)
Other[a]	4 (20.0)

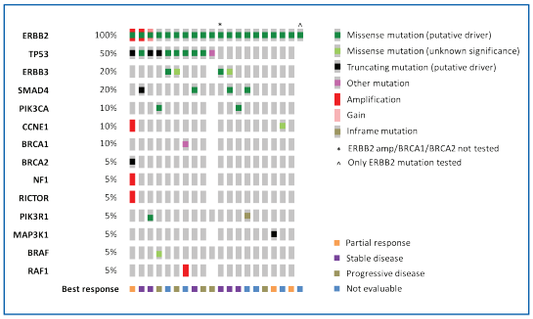
[a]Clinical progression (n=3); clinical progression/adverse event (n=1)

Data cut-off: 1-May-2019

Distribution of mutations in efficacy evaluable, *HER2*-mutant advanced biliary tract cancer patients receiving neratinib



Co-alterations in genes of interest in the *HER2*-mutant advanced biliary cancer cohort



Efficacy summary

Efficacy endpoint[a]	*HER2*-mutant biliary cohort (n=20)
Objective response (confirmed),[b] n	2
CR	0
PR	2
Objective response rate, % (95% CI)	**10.0 (1.2–31.7)**
DOR for each responder, months	3.0, 3.7
Clinical benefit,[c] n	6
CR	0
PR	2
SD ≥16 weeks	4
Clinical benefit rate, % (95% CI)	**30.0 (11.9–54.3)**
Median[d] PFS (95% CI), months	**1.8 (0.9–3.7)**

[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

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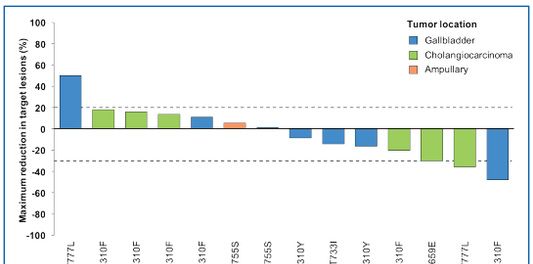
Best change in tumor size



Response based on investigator tumor assessments (RECIST v1.1); DOR = duration of response; N/A = no post baseline assessment available
NOTE: of the 20 patients enrolled in the biliary tract cohort, 5 did not have a post-baseline tumor assessment and 1 is pending first assessment

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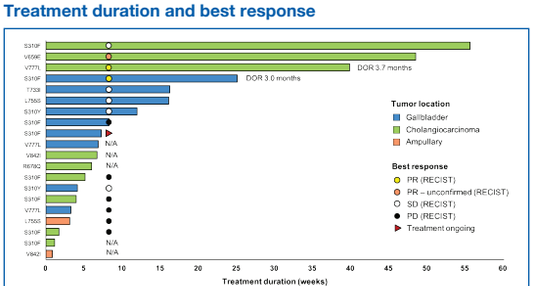
Treatment duration and best response

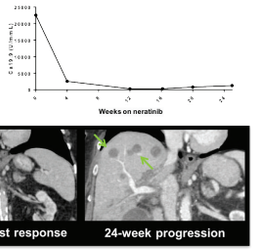


Response based on investigator tumor assessments (RECIST v1.1); DOR = duration of response; N/A = no post-baseline assessment available

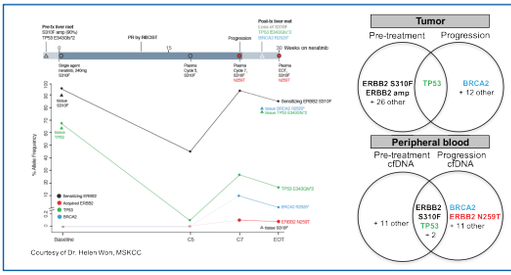
Data cut-off: 1-May-2019

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

- 71-year old with *HER2 S310F/ERBB2* amplified Stage IV adenocarcinoma of the gallbladder with progression of disease on gemcitabine and cisplatin, FOLFOX and FOLFIRI



Polyclonal resistance emerges in gallbladder responder



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

Adverse event, n (%)	*HER2*-mutant biliary tract cancer cohort (n=20)		*HER2*-mutant cancer monotherapy cohort (n=242)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Patients with at least 1 adverse event, n (%)	20 (100.0)	14 (70.0)	232 (95.9)	126 (52.1)
Vomiting	11 (55.0)	1 (5.0)	79 (32.6)	7 (2.9)
Diarrhea	10 (50.0)*	4 (20.0)*	160 (66.1)	45 (18.6)
Fatigue	8 (40.0)	0	71 (29.3)	5 (2.1)
Nausea	8 (40.0)	0	94 (38.8)	4 (1.7)
Abdominal pain	7 (35.0)	2 (10.0)	47 (19.4)	10 (4.1)
Decreased appetite	6 (30.0)	0	56 (23.1)	1 (0.4)
Constipation	5 (25.0)	0	84 (34.7)	2 (0.8)
Aspartate aminotransferase increased	4 (20.0)	0	25 (10.3)	7 (2.9)
Abdominal distension	3 (15.0)	0	10 (4.1)	0
Ascites	3 (15.0)	1 (5.0)	7 (2.9)	2 (0.8)
Asthenia	3 (15.0)	1 (5.0)	21 (8.7)	2 (0.8)
Dehydration	3 (15.0)	2 (10.0)	24 (9.9)	10 (4.1)
Dry mouth	3 (15.0)	0	12 (5.0)	0

*None of the diarrhea events resulted in dose discontinuation within the biliary tract cancer cohort; 1 patient was hospitalized and 2 patients reduced study drug due to diarrhea events. [a]No Grade 4 diarrhea events were reported. Grade 4 and 5 events were considered unrelated to neratinib (investigator assessment). Two grade 5 events were reported: general deterioration (n=1) and sepsis (n=1)

Data cut-off: 1-May-2019

Summary and conclusions

- Neratinib is safe and tolerable in patients with advanced biliary tract cancers with somatic *HER2* mutations:
  - The major observed toxicities were manageable gastrointestinal adverse events and were consistent with toxicities observed in prior clinical investigations of *HER2*-mutated solid tumors.
- A subset of biliary tract cancer patients had tumor shrinkage or extended disease control suggesting single-agent anti-tumor activity in this rare population:
  - Disease control was observed in both cholangiocarcinoma and gallbladder cancer.
  - A limitation of the study is the small sample size; ongoing enrollment will obtain a more accurate estimation of efficacy in this unique population.
- Further correlative studies from serial tumor biopsies and cfDNA are undergoing analysis to interrogate both innate and acquired resistance mechanisms.

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