Oral #428

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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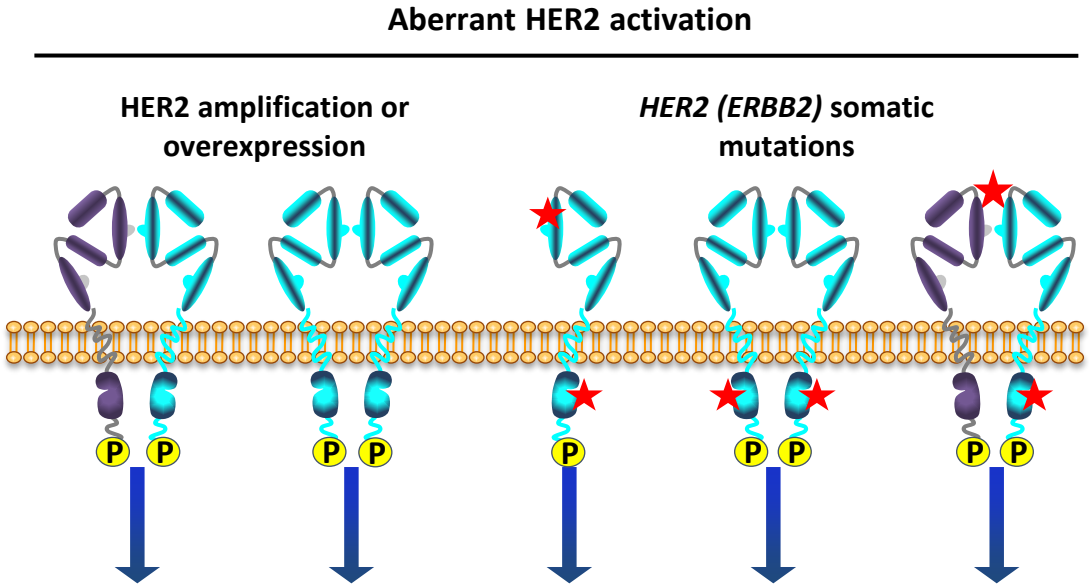
- I will discuss off-label use and/or investigational use of neratinib

Abnormal HER2 activation results in tumor growth



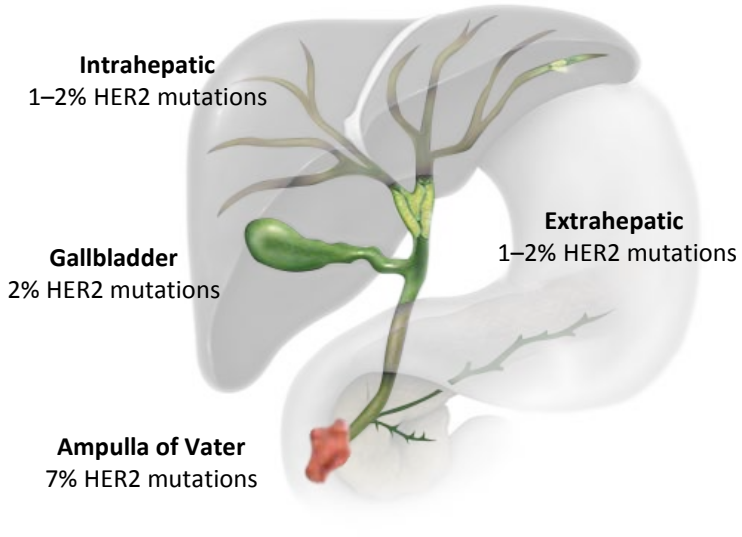
Activation of downstream signal transduction pathways

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

1. Bose et al. Cancer Discov 2013;3:224–37

Biliary tract cancer and *HER2* mutations

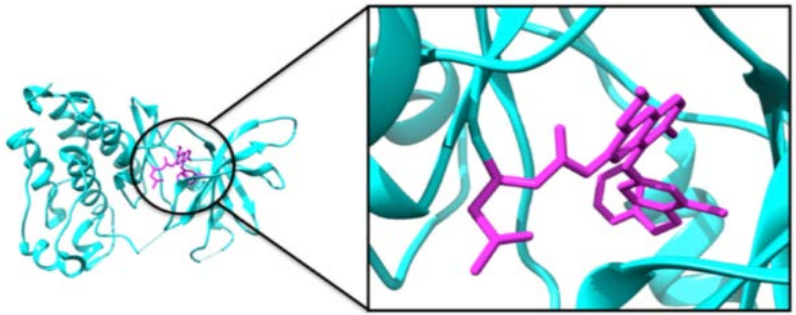
- Heterogeneous and rare disease with poor prognosis; majority of patients present with advanced incurable disease[1]
- Gemcitabine and cisplatin improves OS over gemcitabine for advance disease and is an established front-line standard of care (ABC-02)[1]
- Second-line FOLFOX offers ORR of ~5% and modest 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]



1. Valle et al. N Engl J Med 2010;362:1273–81; 2. Lamarca et al. J Clin Oncol 2019;37(suppl; abstr 4003)
3. Javle et al. Cancer 2016;122:3838–47; 4. Lowery et al. Clin Cancer Res 2018;24:4154–61
5. Wong et al. Cancer 2019;125:1441–8

Neratinib (HKI-272; PB272; NERLYNX®)

- Oral, irreversible, tyrosine kinase inhibitor of EGFR (ERBB1), HER2 (ERBB2), and HER4 (ERBB4)[1]
- Potent inhibition of intracellular signaling, cell proliferation and colony formation of *HER2* mutant and amplified breast tumor cell lines *in vitro*[1,2]



Covalent binding to conserved cysteine residues in the kinase active binding site of EGFR, HER2 and HER4[3]

- Approved in US[4] and Australia[5] for extended adjuvant treatment of patients with early-stage HER2-positive early breast cancer following adjuvant trastuzumab-based therapy; EU[6] 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

1. Rabindran et al. Cancer Res 2004:64:3958–65; 2. Bose et al. Cancer Discov 2013;3:224–37
3. Wissner & Mansour. Arch Pharm Chem Life Sci 2008;341:465–477
4. U.S. Food and Drug Administration. NERLYNX® (neratinib) Prescribing Info
5. Australian Therapeutic Goods Administration. NERLYNX® (neratinib) Product Information
6. European Medicines Agency. NERLYNX® (neratinib) Summary of Product Characteristics

SUMMIT 'basket' study design

***HER2*-mutant tumors**

- **Biliary tract**
- Cervical
- Salivary gland
- Solid tumors (NOS)

→ **Neratinib monotherapy**

- Bladder

→ **Neratinib + Paclitaxel**

- Breast HRc-positive*
- Breast HRc-negative
- Lung
- Colorectal (KRAS/NRAS/BRAF wild-type)

→ **Neratinib* + Trastuzumab#**

*plus fulvestrant (in HR+ breast)
#biosimilar may be used if available

HER2 mutations (documented by local testing)

Primary endpoint
- Objective response rate at first post-baseline tumor assessment (ORR_{first})

Secondary endpoints
- ORR (confirmed)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety
- Biomarkers

Simon 2-stage design
- If ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If ≥4 responses in Stage 2, expand or breakout

Tumor assessments
- RECIST v1.1 (primary criteria)
- PET response criteria (RECIST non-evaluable)

Statistical methods
- ORR_{first}, ORR, CBR: associated 95% CI
- Median PFS: Kaplan-Meier estimate with 95% CI

Key inclusion criteria
- Histologically confirmed cancers for which no curative therapy exists
- Documented *EGFR exon 18, HER2* or *HER4* mutation
- ECOG status of 0–2
- RECIST 1.1 evaluable disease (measurable or non-measurable disease): if RECIST non-measurable, evaluable by other accepted criteria

Key exclusion criteria
- Prior treatment with any pan-HER TKI (eg, lapatinib, afatinib, dacomitinib, neratinib)
- Patients who are receiving any other anticancer agents
- Symptomatic or unstable brain metastases
- Women who are pregnant or breast-feeding

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)

Efficacy summary

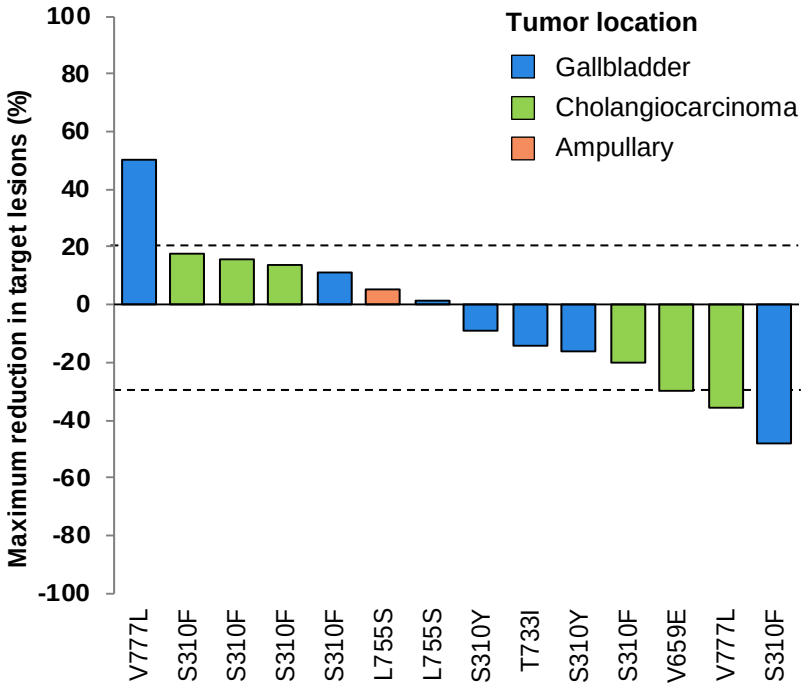
Efficacy endpoint[a]	*HER2*-mutant biliary cohort (n=20)
Objective response (confirmed),[b] n	2
CR	0
PR	2
Objective response rate, % (95% CI)	**10.0 (1.2–31.7)**
DOR for each responder, months	3.0, 3.7
Clinical benefit,[c] n	6
CR	0
PR	2
SD ≥16 weeks	4
Clinical benefit rate, % (95% CI)	**30.0 (11.9–54.3)**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

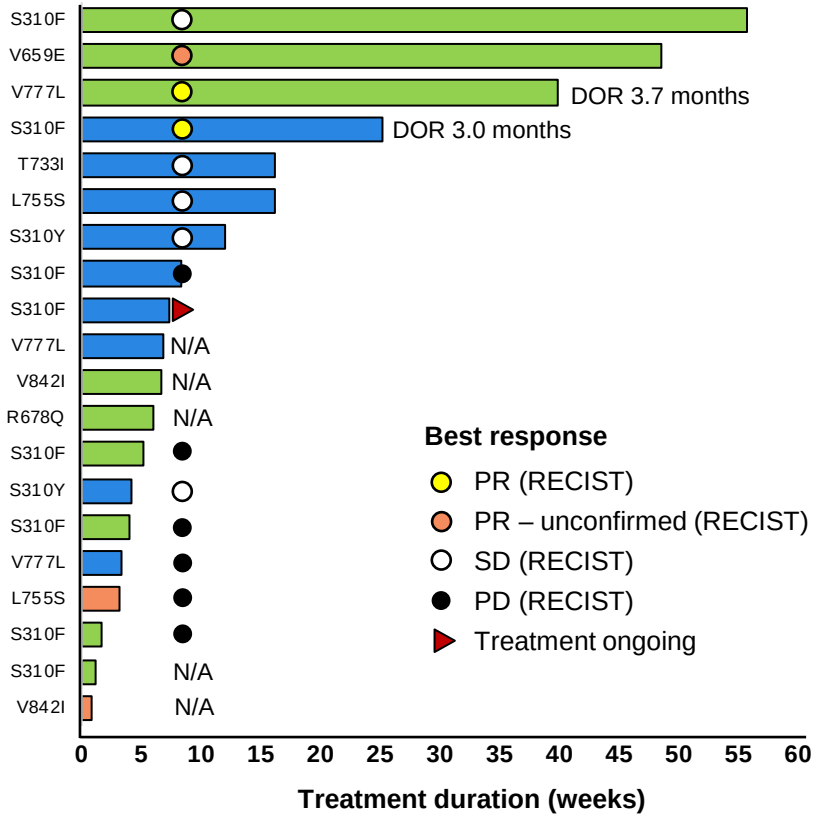
Data cut-off: 1-May-2019

Neratinib monotherapy in *HER2*-mutant biliary cohort

Best change in tumor size



Treatment duration and best response



Response based on investigator tumor assessments (RECIST v1.1)

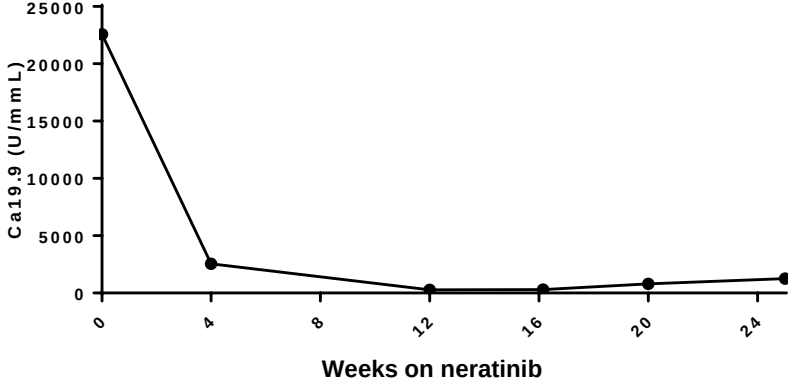
DOR = duration of response; N/A = no post-baseline assessment available

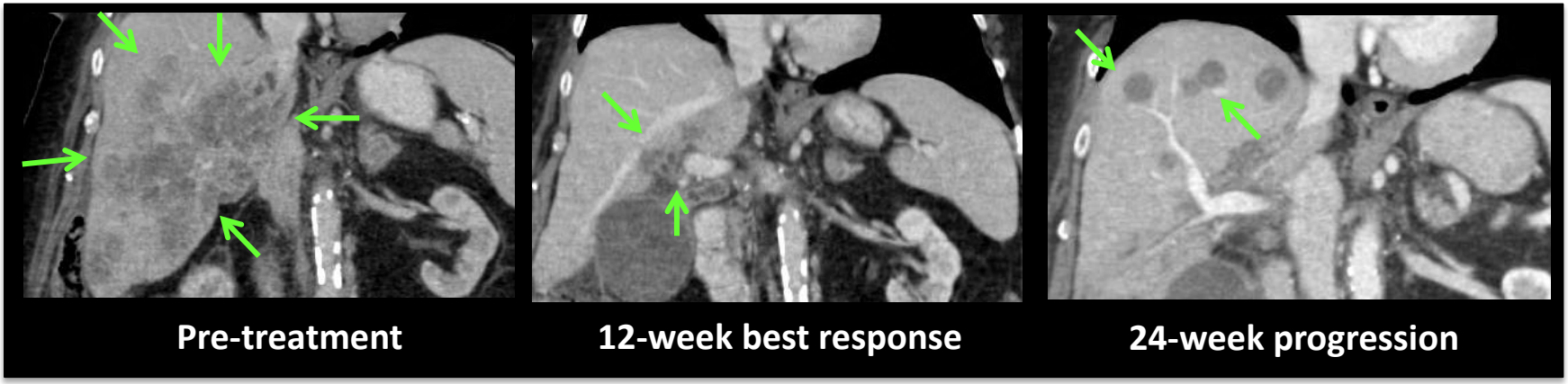
NOTE: of the 20 patients enrolled to the biliary tract cohort, 5 patients did not have a post-baseline tumor assessment and 1 patient is pending first assessment

Data cut-off: 1-May-2019

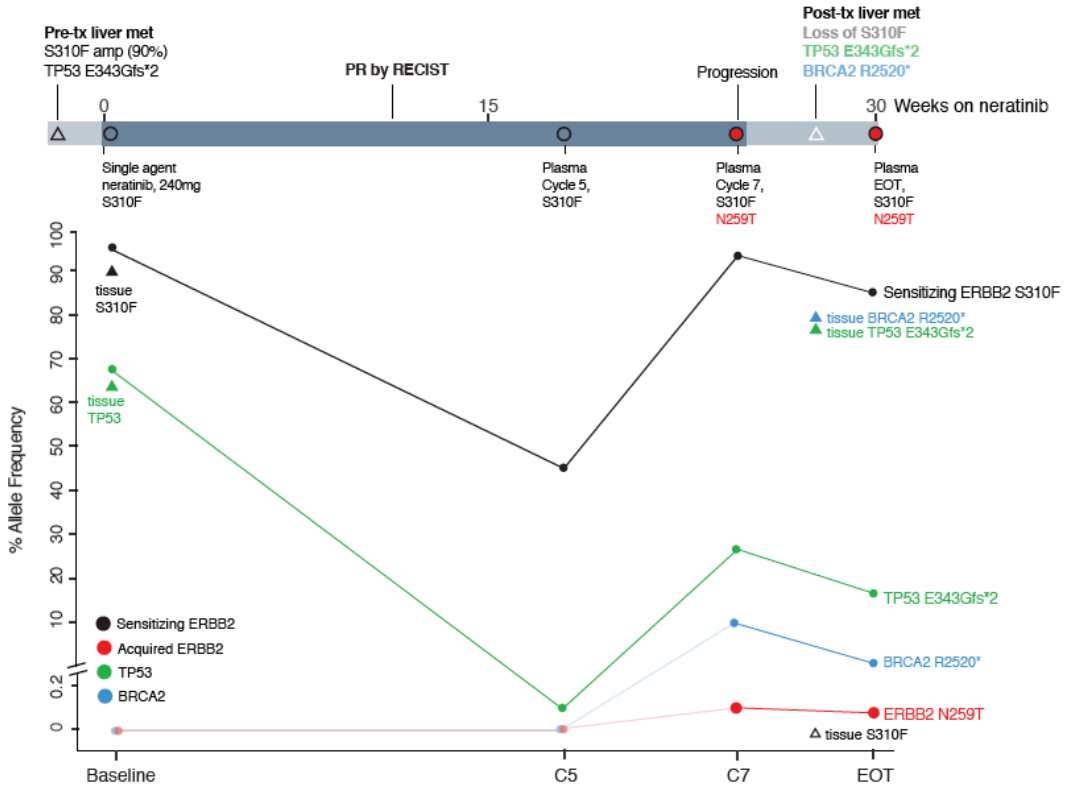
Advanced *HER2*-mutant gallbladder patient with rapid and marked response to neratinib

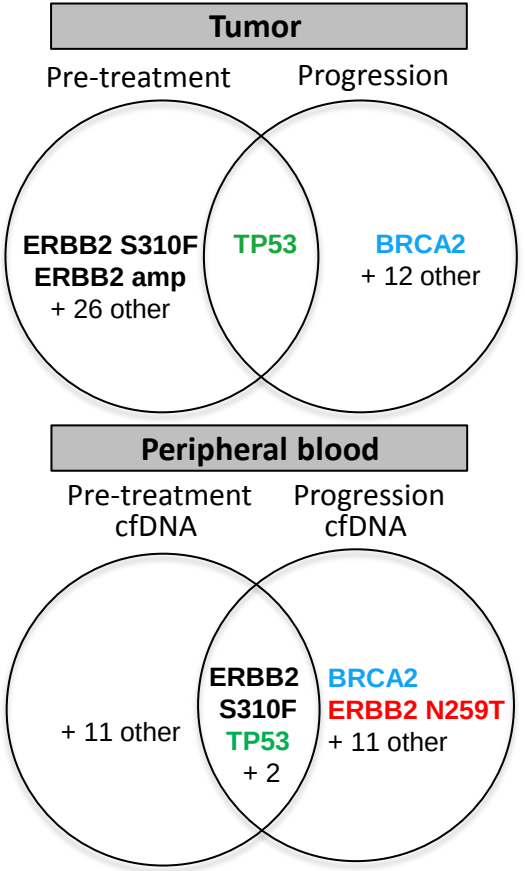
- 71-year old with *HER2 S310F/ERRB2* amplified Stage IV adenocarcinoma of the gallbladder with progression of disease on gemcitabine and cisplatin, FOLFOX and FOLFIRI





Polyclonal resistance emerges in gallbladder responder





Courtesy of Dr. Helen Won, MSKCC

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. #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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