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Abstract #653P
ESMO 2024

A PHASE 1 DOSE ESCALATION STUDY OF EBC-129, A FIRST-IN CLASS, ANTI N-GLYCOSYLATED CEACAM5 & CEACAM6 ANTIBODY-DRUG CONJUGATE (ADC) IN PATIENTS WITH SOLID TUMORS

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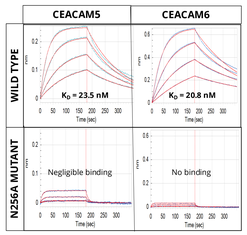
BACKGROUND:

EBC-129 is a humanised IgG1 mAb (EBC-092), linked to monomethyl auristatin E (MMAE) via the cleavable mc-vc-PAB linker and a DAR of 3.5. It targets a conformational epitope unique to N256-glycosylated CEACAM5 & CEACAM6 (N256 C5/C6) which confers tumour specificity. EBC-129 can internalise and inhibit tumour growth independently, via both receptors, see **Fig. 1**. C6 (and not C5) was shown to be predictive for overall survival in PDAC and gastric cancers.

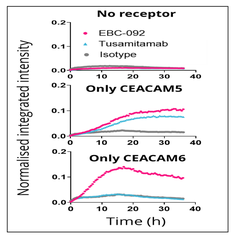
Figure 1. Molecular characterisation of EBC-129

EBC-129 only binds to N256-glycosylated CEACAM5/6



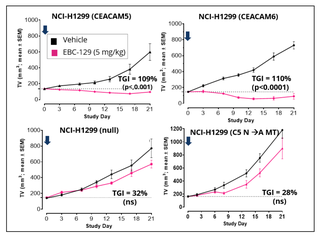
BLI determination (Octet) using HEK-293 6E-produced antigen

Internalisation specific for CEACAM5/6 expressing cells



Isogenic NCI-H1299 cancer cells (WT: null, or overexpressing C5/C6) analysed in Incucyte S3

Equal efficacy via N-glycosylated CEACAM5 or CEACAM6 receptor

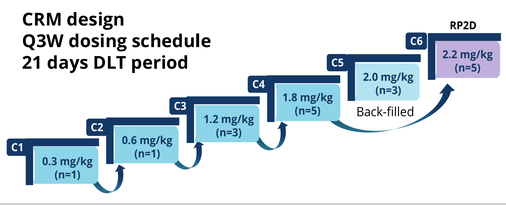


Efficacy studies using isogenic NCI-H1299 xenograft models in NOD-SCID mice (n=6/grp) after 1x 5 mg/kg EBC-129

METHODS:

The multicentre Phase 1A dose escalation study used a Bayesian design to establish the recommended Phase 2 dose (RP2D) of EBC-129. Patients (pts) failing standard therapies, with adequate organ function and ECOG 0-1 were eligible (see below), and received doses between 0.3 and 2.2 mg/kg every 3 weeks, until disease progression (**Fig. 2**). The primary endpoint was safety; secondary endpoints included efficacy and PK. Prospective central assessment of archival tissue to determine IHC positivity (≥20% at 2+ or 3+) was performed centrally using a validated assay with a mouse N256-C5/6 specific mAb, EBC-413 (**Fig. 3**).

Figure 2. Schematic representation of Part A Dose Escalation

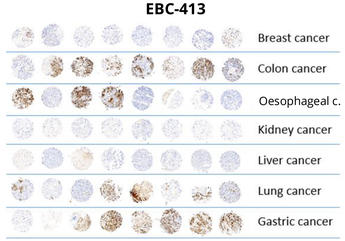


Patient Demographics

Age (Y; Med [R])	**72.9 (53.0-98.3)**
Sex (M : F [%])	**77.8 : 22.2**
Race (Asian : White [%])	**55.6 : 44.4**
Prior lines (Med [R])	**3 (1 -9)**
Tumor type (%)	
PDAC	**33%**
CRC	**28%**
Oesophageal (SCC/ADC)	**22%**
Gastric	**6%**
NEPC	**6%**
Appendiceal	**6%**

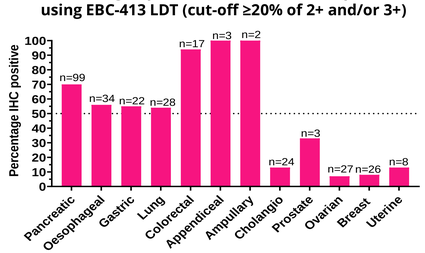
Fig. 3. IHC (using EBC-413*) shows highest expression of N256-CEACAM5/6 in pancreatic, GI and lung cancers

Multi-tumour TMA stained with EBC-413



** Parental mouse IgG1 mAb of EBC-092*

EBC-129 antigen prevalence in clinical samples tested using EBC-413 LDT (cut-off ≥20% of 2+ and/or 3+)



RESULTS - Safety & PK

As of 13 Aug 2024, 18 pts received ≥1 dose of EBC-129 (see demographics). The MTD was 2.2 mg/kg,. Two DLTs were observed (G4 febrile neutropenia @ 2.2 mg/kg; G3 AST ↑ @ 2 mg/kg). The most common TRAEs were Gr 1-2 infusion-related reactions (83%). Transient Gr 3/4 neutropenia was the most common G3/4 event. No recurrence was seen after growth factor support. Other than 1 treatment-aggravated pre-existing G1 neuropathy @ 2.2 mg/kg (G1) no other neuropathy was seen; see **Tables 1 & 2**. Exposures for conjugated antibody (cAb) and other PK parameters increased proportionally with dose and did not show accumulation in Cycle 5 **(Fig. 4 & Table 3).**

Table 1. TEAEs where Preferred Term is > 10% - Part A Safety Analysis Set (Data cut-off 19 Jul 2024)

Preferred Term	EBC-129 dose (mg/kg)						TOTAL
	0.3	0.6	1.2	1.8	2.0	2.2	
	N=1	N=1	N=3	N=5	N=3	N=5	N=18
Chills*	0	1 (100%)	3 (100%)	4 (80%)	3 (100%)	2 (40%)	**13 (72%)**
Pyrexia*	0	1 (100%)	3 (100%)	3 (60%)	2 (67%)	3 (60%)	**12 (67%)**
Neutrophil count decreased/neutropenia	0	0	0	5 (100%)	3 (100%)	4 (80%)	**12 (67%)**
Nausea*	0	0	1 (33%)	2 (40%)	3 (100%)	1 (20%)	**7 (39%)**
WBC decreased	0	0	0	3 (60%)	2 (67%)	1 (20%)	**6 (33%)**
Fatigue	0	1 (100%)	1 (33%)	2 (40%)	0	1 (20%)	**5 (28%)**
Diarrhoea	1 (100%)	0	0	0	1 (33%)	2 (40%)	**4 (22%)**
Platelet count decreased	0	0	0	1 (20%)	2 (67%)	1 (20%)	**4 (22%)**
Anaemia	0	0	2 (67%)	0	1 (33%)	0	**3 (17%)**
Dyspnoea*	0	0	2 (67%)	0	1 (33%)	0	**3 (17%)**
Vomiting*	0	0	1 (33%)	0	1 (33%)	1 (20%)	**3 (17%)**
AST increased	0	0	0	1 (20%)	1 (33%)	1 (20%)	**3 (17%)**
Myalgia	0	0	0	1 (20%)	1 (33%)	1 (20%)	**3 (17%)**
Infusion related reactions*	0	0	0	1 (20%)	1 (33%)	0	**2 (11%)**
Decreased appetite	0	0	1 (33%)	1 (20%)	0	0	**2 (11%)**
Abdominal pain upper	1(100)	0	0	0	0	1 (20%)	**2 (11%)**
Amylase increased	0	0	0	1(20%)	0	1 (20%)	**2 (11%)**
Dyspepsia	0	0	0	0	0	2 (40%)	**2 (11%)**
Hypokalaemia	0	0	0	0	0	2 (40%)	**2 (11%)**
Hypomagnesaemia	0	0	0	0	0	2 (40%)	**2 (11%)**

** All these AEs were part of infusion related reactions (IRRs) with a total overall incidence of 83%*

***Table 2.* Summary of ≥ Grade 3 related TEAEs**

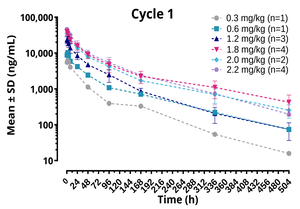
Preferred Term	1.2 mg/kg N=3	1.8 mg/kg N=5	2.0 mg/kg N=3	2.2 mg/kg N=5	TOTAL N=18
Neutrophil count decreased/Neutropenia	0	4 (80%)	3 (100%)	3 (60%)	**10 (55%)**
Anaemia	1 (33%)	0	1 (33%)	0	**2 (11%)**
WBC count decreased	0	0	1 (33%)	1 (20%)	**2 (11%)**
AST increased	0	0	1 (33%)	0	**1 (6%)**
Diarrhoea	0	0	1 (33%)	0	**1 (6%)**
Vomiting	0	0	0	0	**1 (6%)**
Hypoxia	0	0	0	0	**1 (6%)**
Blood bilirubin increased	0	0	0	0	**1 (6%)**
Dizziness	0	0	0	0	**1 (6%)**
Lipase increased	0	1 (20%)	0	0	**1 (6%)**
Amylase increased	0	1 (20%)	0	0	**1 (6%)**
Febrile neutropenia	0	0	0	1 (20%)	**1 (6%)**

Table 3. Interim PK parameters for cAb in human serum (ECLIA)
Phoenix® WinNonLin® NCA analysis

Dose (mg/kg)	C_{max} (µg/mL)	$AUC_{0\text{-}21D}$ (h*µg/mL)	T_{max} (h)	$AUC_{0\text{-}inf}$ (h*µg/mL)	$t_{1/2}$ (h)	
1.2	25 ± 4.2	855 ± 27	2.0 (0.5-2.0)	865 ± 23	88 ± 9.8	Cycle 1
1.8	39.1 ± 8.1	1,750 ± 512	0.5 (0.5-0.5)	1,830 ± 573	134 ± 19	Cycle 1
2.0	36 ± 1.4	1,480 ± 66	0.5 (0.5-0.5)	1,530 ± 91	122 ± 18	Cycle 1
2.2	46 ± 5.0	1,890 ± 287	0.5 (0.5-0.5)	1,920 ± 285	92 ± 12	Cycle 1
1.2	20	781	0.5	782	51	Cycle 5
1.8	37 ± 2.1	2,145 ± 361	0.5 (0.5-0.5)	2,310 ± 382	158 ± 12	Cycle 5
2.2	35	1,280	0.5	1,300	111	Cycle 5

Mean ± SD, with exception of T_{max} (median (min-max))

Figure 4. Serum conc. vs time (cAb)

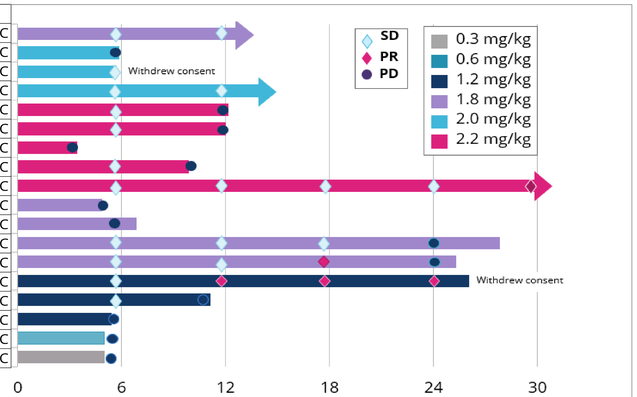


RESULTS - Efficacy

Of 18 evaluable pts, there were 3 PRs (2 oesophageal adenocarcinomas and 1 pancreatic adenocarcinoma), and 8 patients with SD. 3 pts are currently still ongoing (**Figs. 5 and 6**).

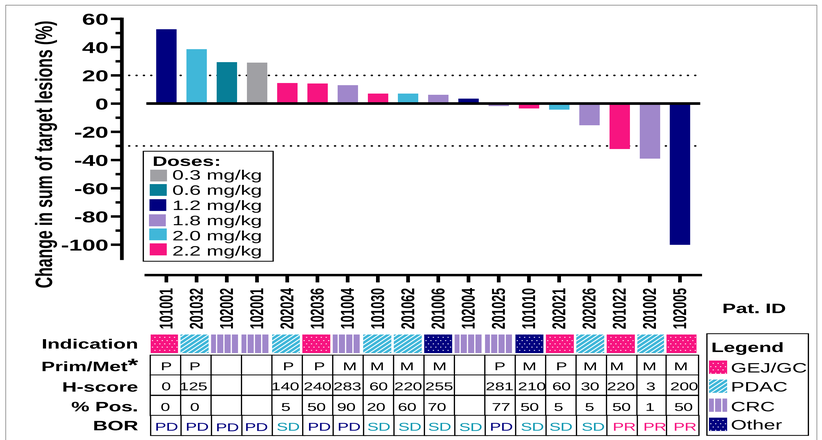
Figure. 5. Patient duration on treatment and time to response

Pat. ID	Indication
202026	Pancreatic ADC
201032	Pancreatic ADC
210062	Pancreatic ADC
202021	Gastric ADC
101030	Pancreatic ADC
202024	Pancreatic ADC
102036	GEJ ADC
101010	NEPC
201022	Oesophageal ADC
101004	CRC
201025	Caecum ADC
201025	Appendix ADC
201006	Pancreatic ADC
201005	Oesophageal ADC
102004	CRC
101001	Oesophageal SCC
102002	CRC
102001	CRC



ADC: adenocarcinoma
SCC: squamous cell carcinoma

Figure. 6 Waterfall plot, showed best overall response of target lesions



** Origin of archival tissue; P: primary tumour; M: metastatic lesion*

CONCLUSION

EBC-129 is the first ADC to target N256C5/6 and confers equal activity independently via both receptors. EBC-129 demonstrated promising early activity in heavily pre-treated pts. Reversible IRRs and neutropenia were the most common AEs. Expansion cohorts in IHC$^+$ gastroesophageal adenocarcinomas or other IHC$^+$ cancers, and in PDAC (IHC positive or ≥ 1% expression at 3+) are ongoing.