Trinity College Dublin

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Update on Targeted Therapy for Gastric and Oesophageal Adenocarcinoma

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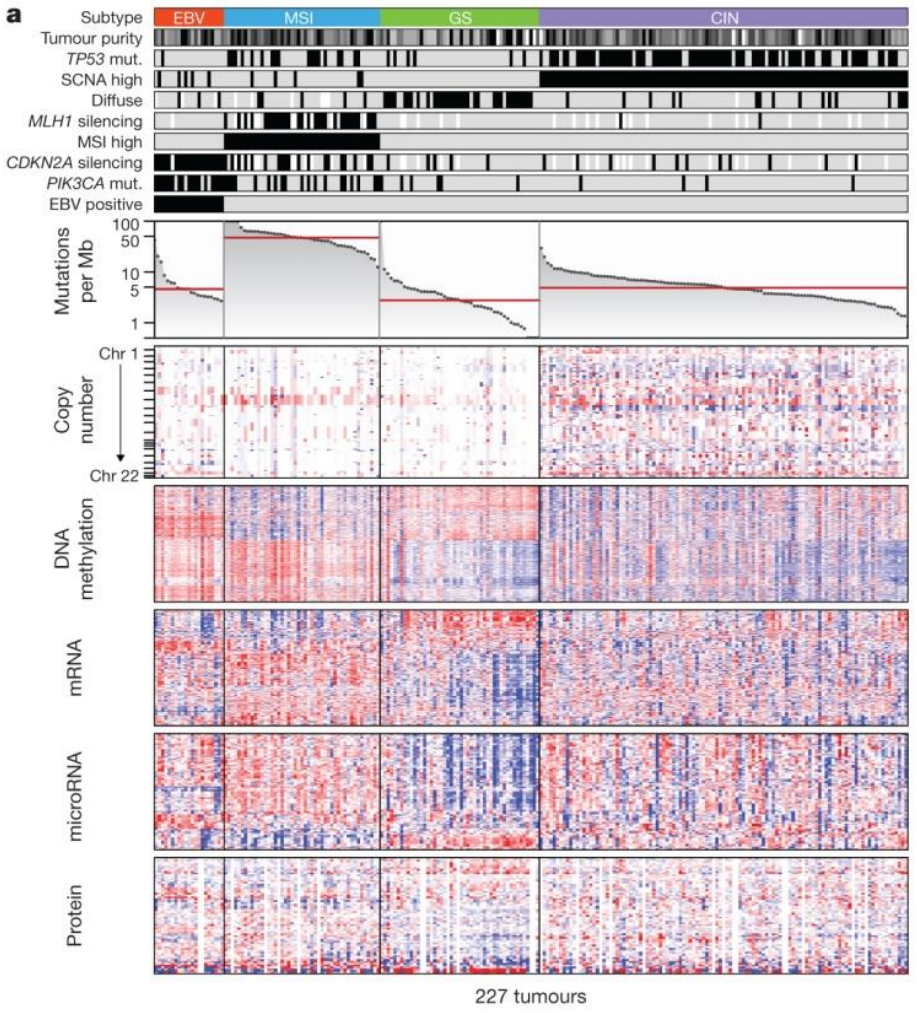
With thanks to our sponsors

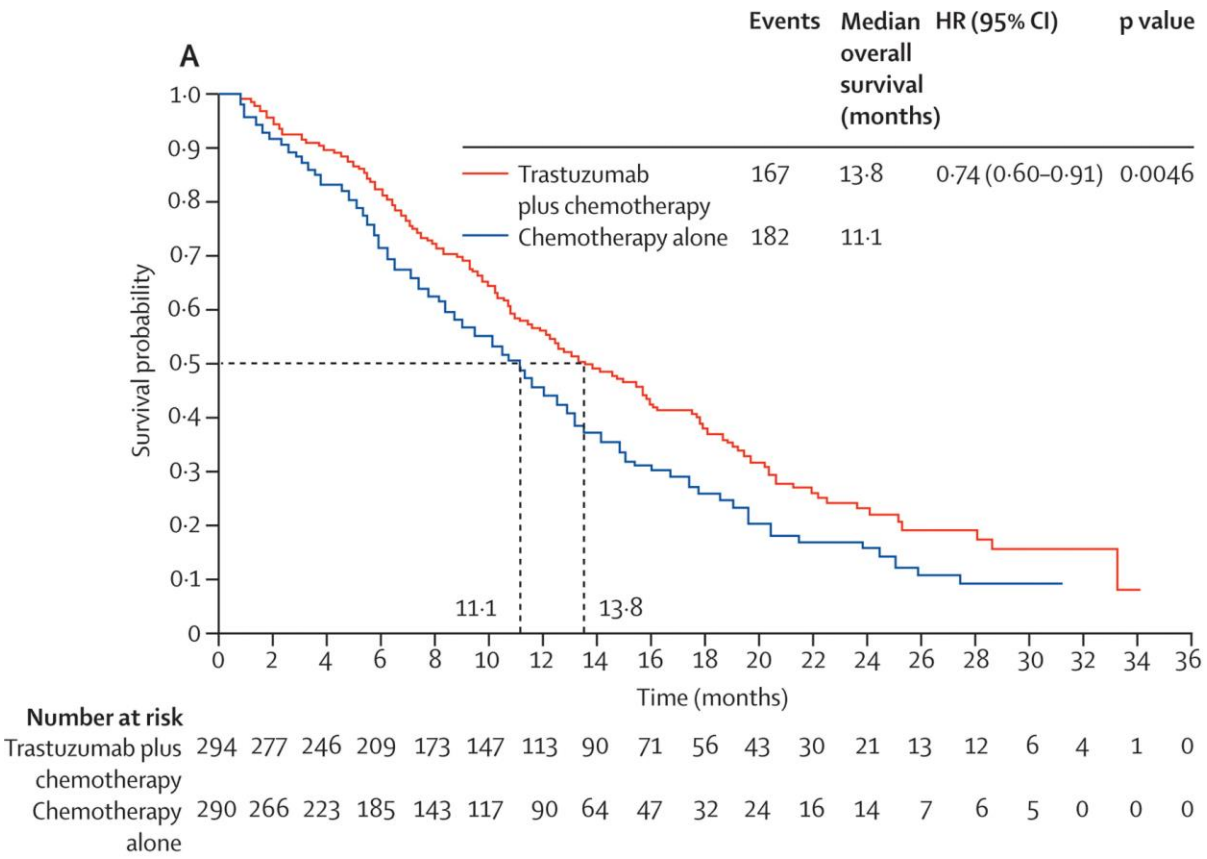
Molecular subtypes of OG adenocarcinoma

- Epstein-Barr virus (EBV)
  - extreme DNA hypermethylation
- Microsatellite instability (MSI)
  - elevated mutation rates & hypermethylation
- Genomically stable (GS)
  - less distinctive genomic alterations
- Chromosomal instability (CIN)
  - aneuploidy & amplification of receptor tyrosine kinases



AJ Bass *et al. Nature* **000**, 1-8 (2014) doi:10.1038/nature13480

HER2 targeting in metastatic OG adenocarcinoma

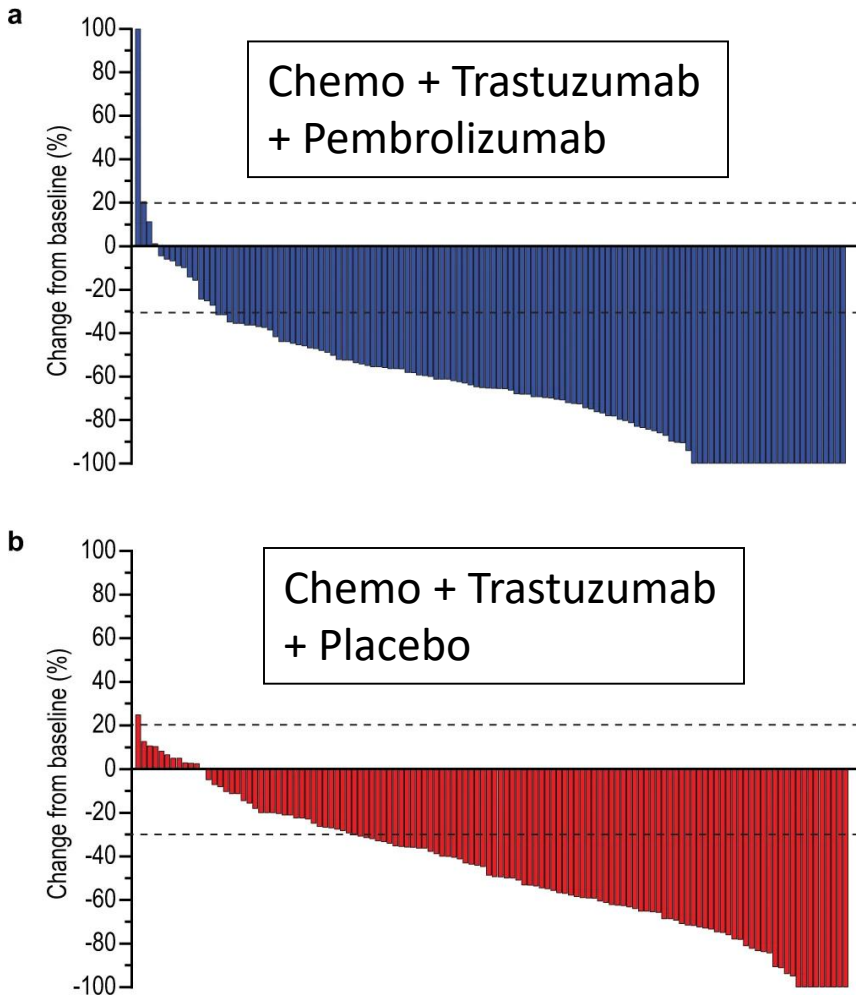


- **ToGA trial :** Trastuzumab+ chemo SOC for HER2 positive advanced OG adenocarcinoma
- 2.7 mo mOS benefit (p=0.004)

Bang et al, LANCET 2010: VOLUME 376, ISSUE 9742

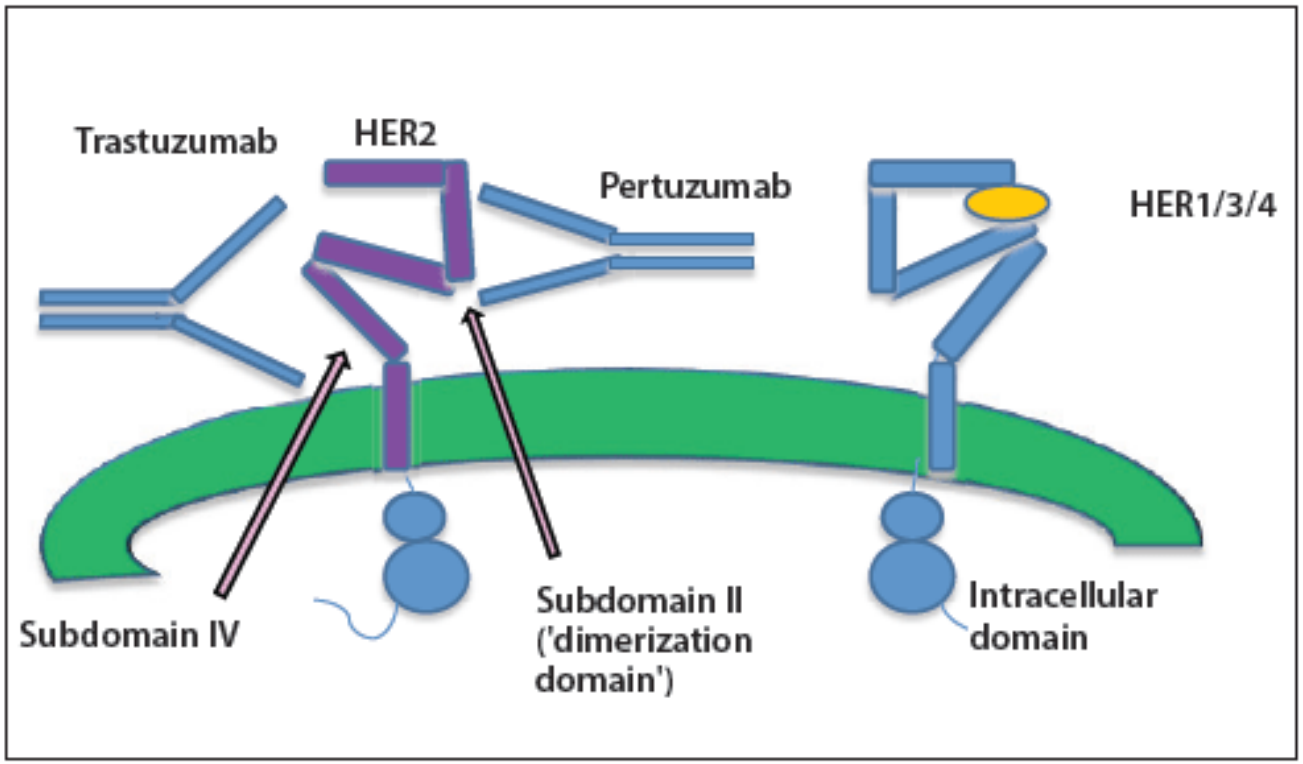
KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer

- Pre-clinical rationale for combination of IO & HER2 targeting
- ORR 74.4% in the pembrolizumab group vs 51.9% in the placebo group. (P = 0.00006)
- Complete response in 11.3% vs 3.1% patients



Janjigian et al, Nature 600:727-730, 2021.

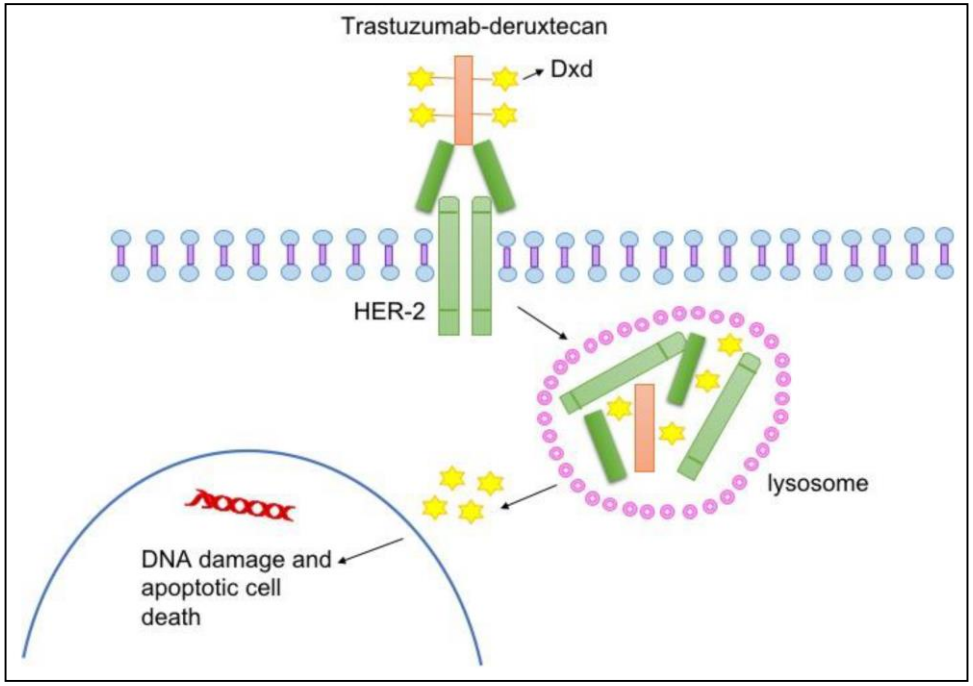
Dual HER2 Targeting?



- No benefit to addition of pertuzumab to Trastuzumab in advanced disease
- Await results in pre / peri-op setting
  - TRAP-2 study
  - INNOVATION study

O'Sullivan et al, Oncology Vol 28 No 3,
Hecht et al, J Clin Oncol . 2016 Feb 10;34(5):443-51

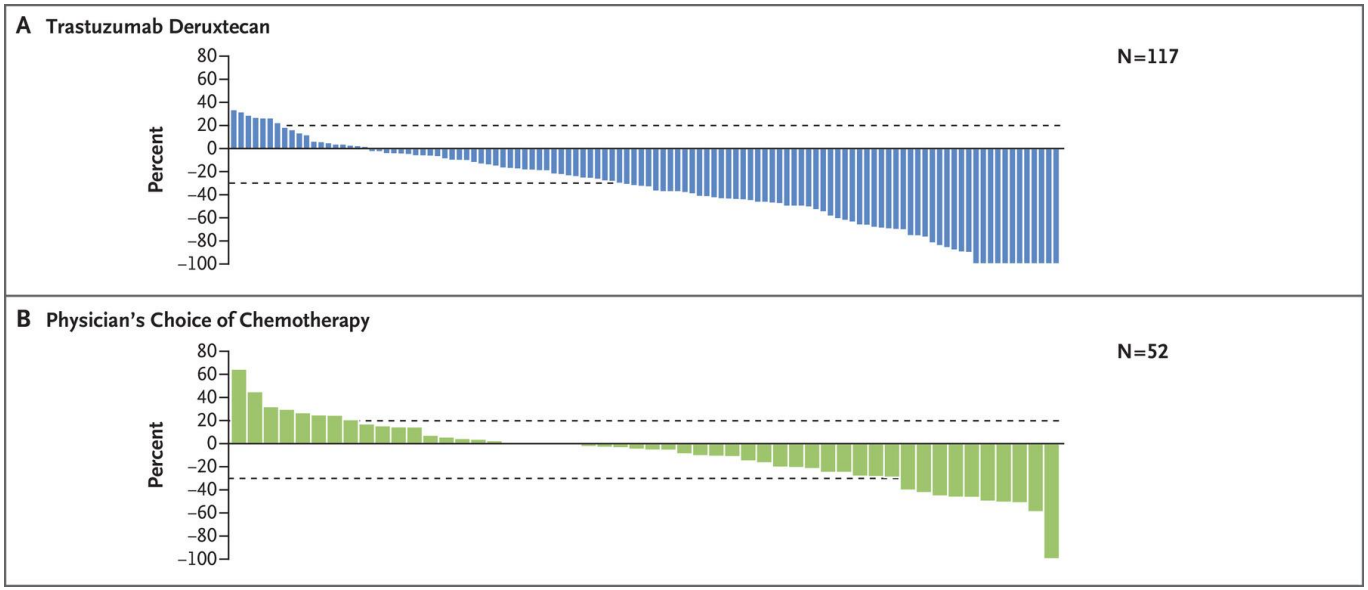
Trastuzumab Deruxtecan

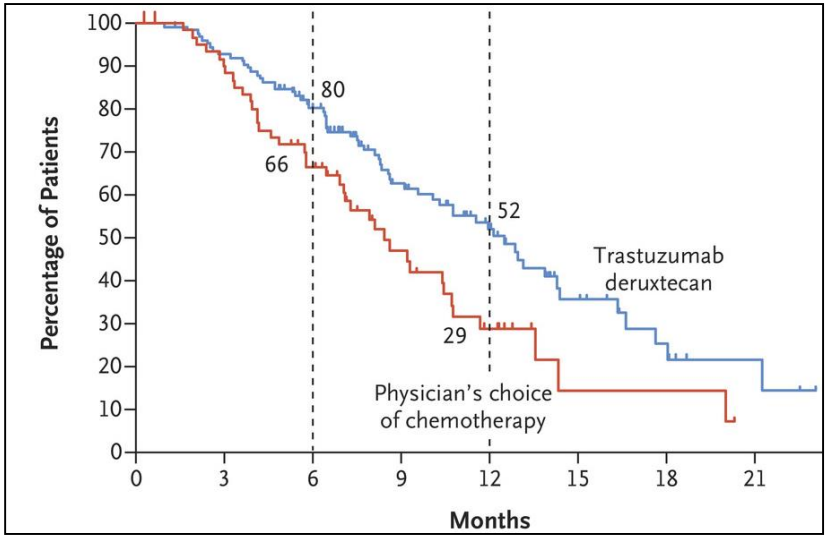


- Drug-to-antibody ratio approx 8
- Internalisation following HER-2 binding on tumour cells
- Cleavage by lysosomal enzymes
- Membrane permeable topoisomerase 1 inhibitor enters nucleus
- Penetrates adjacent tumour cells (HER2 low or neg)

Int. J. Mol. Sci. 2021, 22(9), 4774

Trastuzumab Deruxtecan – DESTINY GASTRIC -01

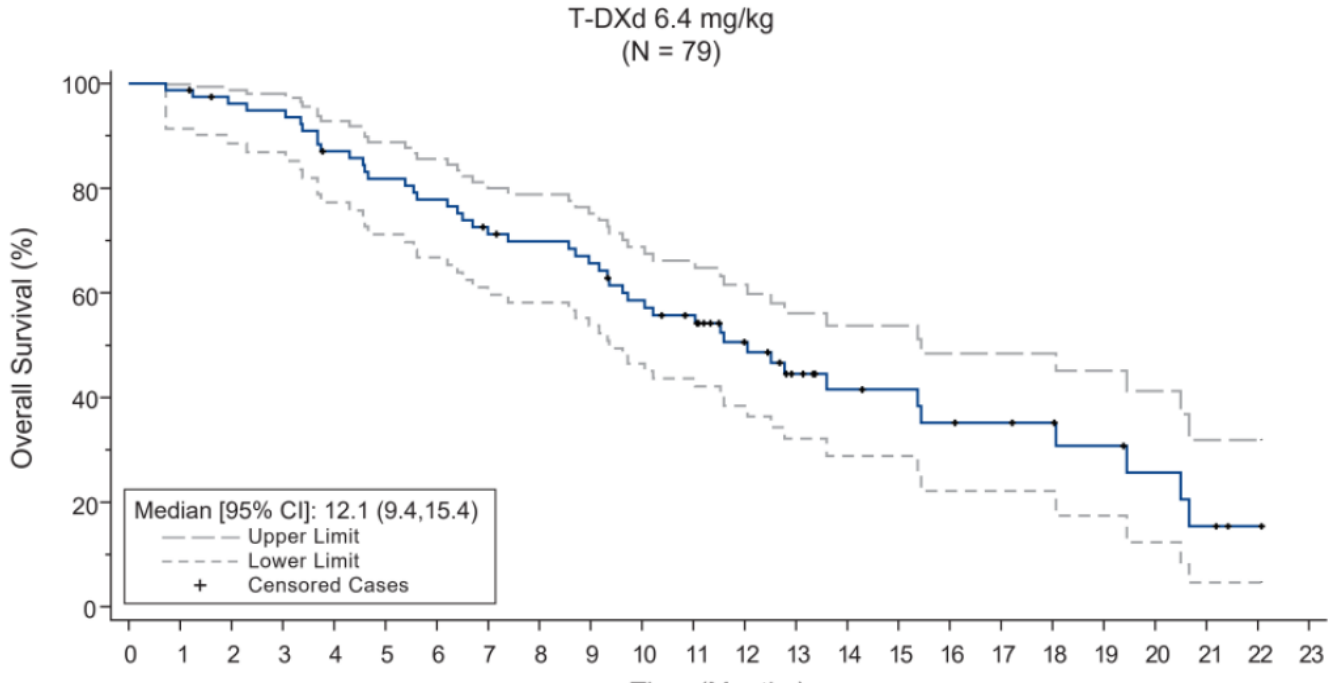




- T-Dxd vs chemo (2:1), n=187
- At least 2 prior regimens, 1 tras
- ORR 51% vs 15% (p<0.001)
- mOS 12.5 vs 8.4 mo (HR .59, p=0.01)
- HER2 testing on archival tissue only

N Engl J Med 2020; 382:2419-2430

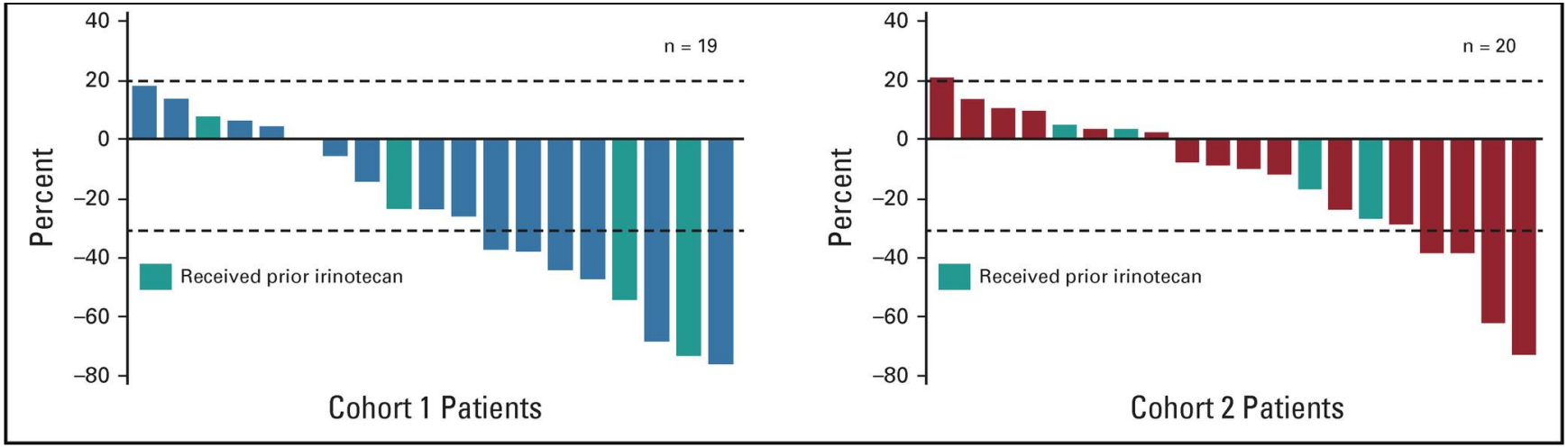
Trastuzumab Deruxtecan – DESTINY GASTRIC -02



- Phase II single arm, n=79, Western patients
- HER2 status on biopsy post progression on Trastuzumab
- mOS 12.1 months (9.4 – 15.4), mPFS 5.6 months (4.2 – 8.3)
- ORR 41.8%

Ku et al, ESMO 2022

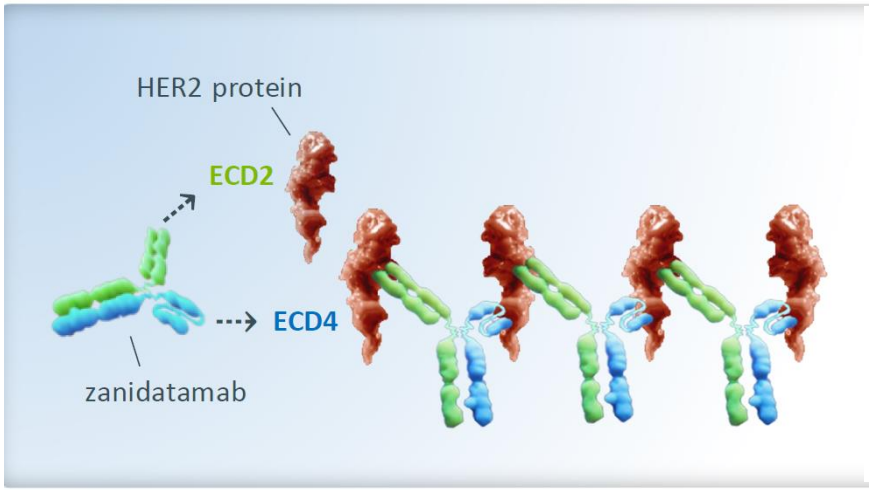
DESTINY GASTRIC-01: HER2 low…

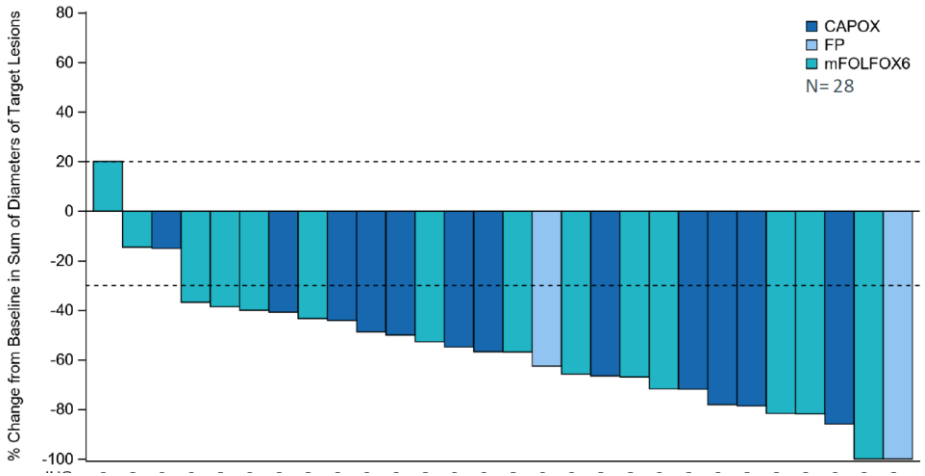


- Exploratory cohort 1, IHC 2+/ISH–; exploratory cohort 2, IHC 1+
- No prior HER-2 directed therapy
- N=45 (C1 21, C2 24)
- Median OS 7.8 months (cohort 1) & 8.5 months (cohort 2)
- ORR 26.3% (cohort 1) & 9.5% (cohort 2)

JCO 41, no. 4 (February 01, 2023) 816-825

Next generation HER2 targeting: Zanidatimab

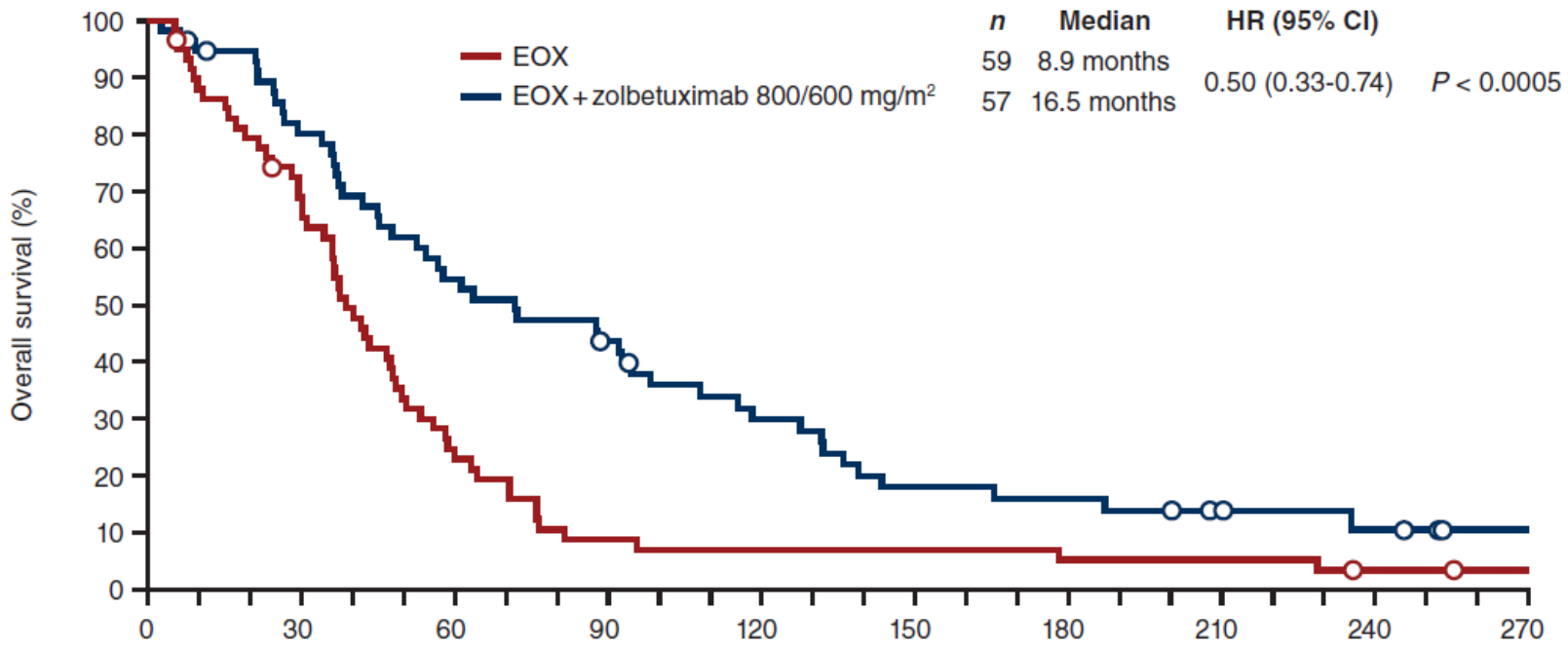




- Humanised bispecific antibody, binds to juxtamembrane & dimerization domains of HER2
  - Binds adjacent HER2 proteins
- Phase II: 1st line Zanidatimab & chemo
  - ORR 75%
  - mPFS 12 months
- Phase I: Zanidatimab + chemo + Tislelizumab
  - ORR 75%, DCR 100%
- HERIZON GEA 01 study – ongoing phase 3, Zanidatimab + chemo +/- Tisleluzumab

Ku et al, ESMO 2021

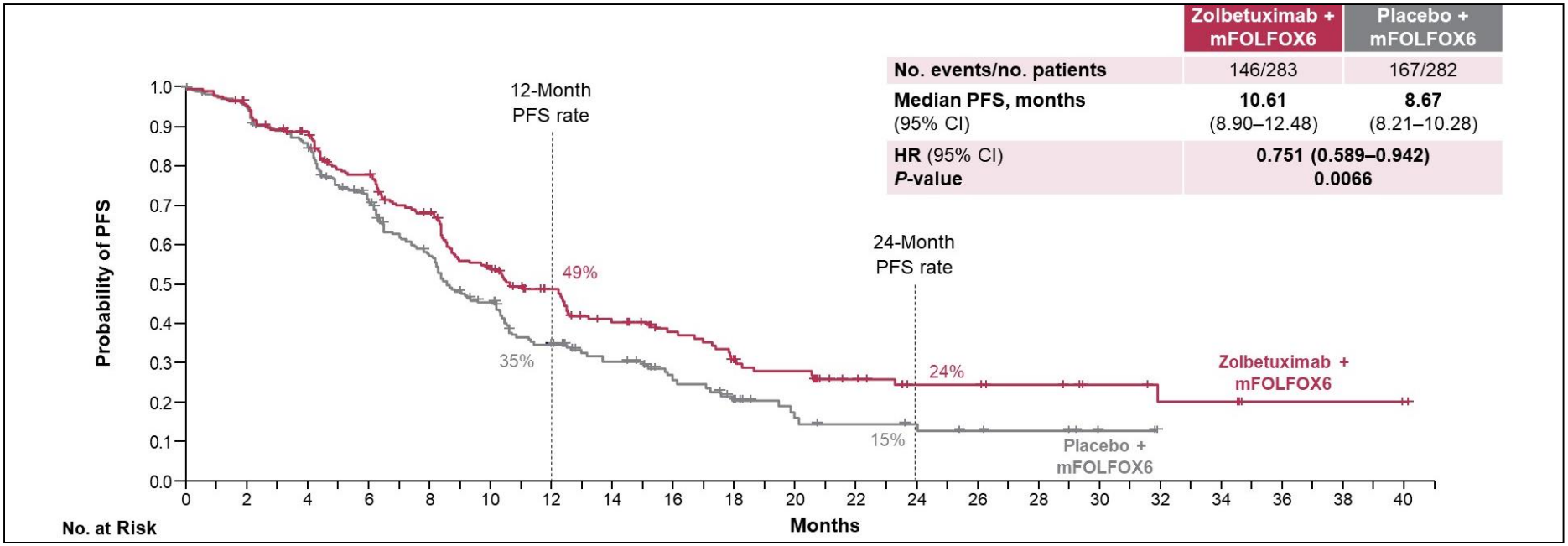
Claudin 18 - Zolbetuximab



- FAST study: PIIb, EOX +/- Zolbetuximab, n=161
- Claudin-18 positive > 40% cells, 1st line therapy
- Median OS 13 vs 8.3 mo (p<0.005)
- Benefit greatest in patients Claudin-18 positive > 70% cells

Sahin et al, Ann Oncol 32:5 2021

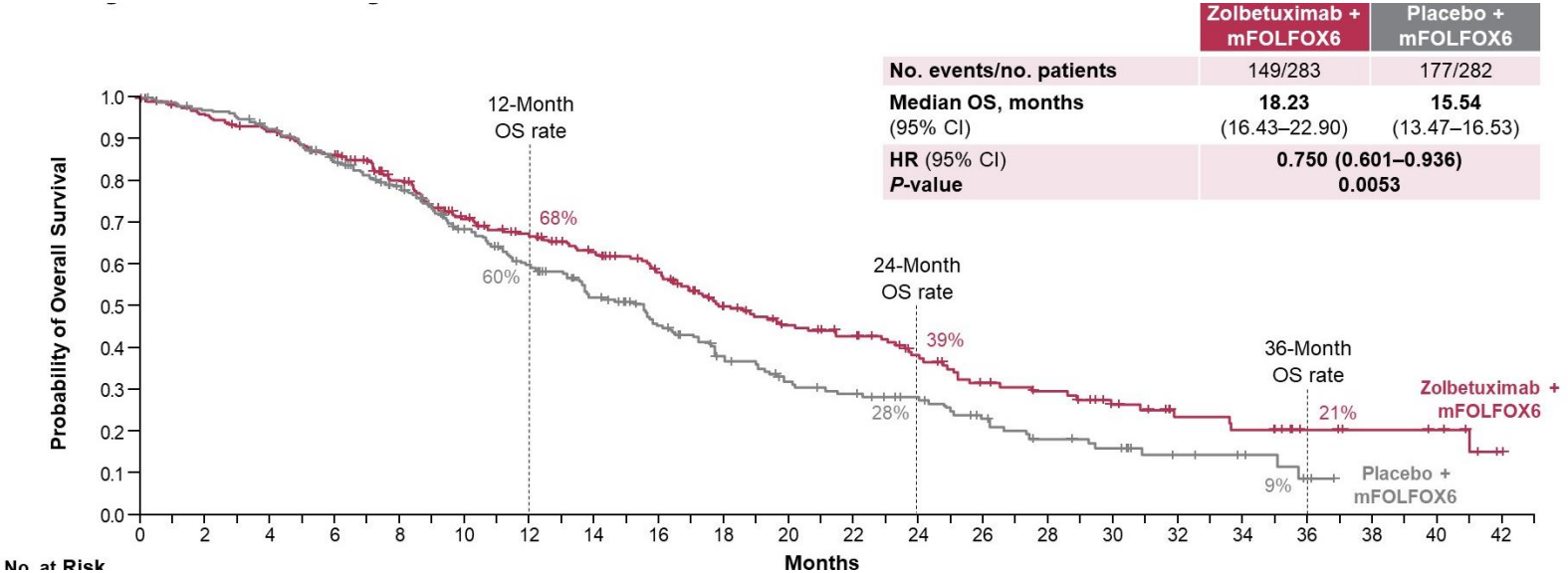
Claudin-18 : Zolbetuximab, SPOTLIGHT



- N=556, LA/met advanced GEJ/gastric, Claudin 18 positive > 75% cells
- HER2 negative, 1st line therapy
- FOLFOX +/- Zolbetuxumab
- Primary end-point PFS

Shitara et al, GI ASCO 2023

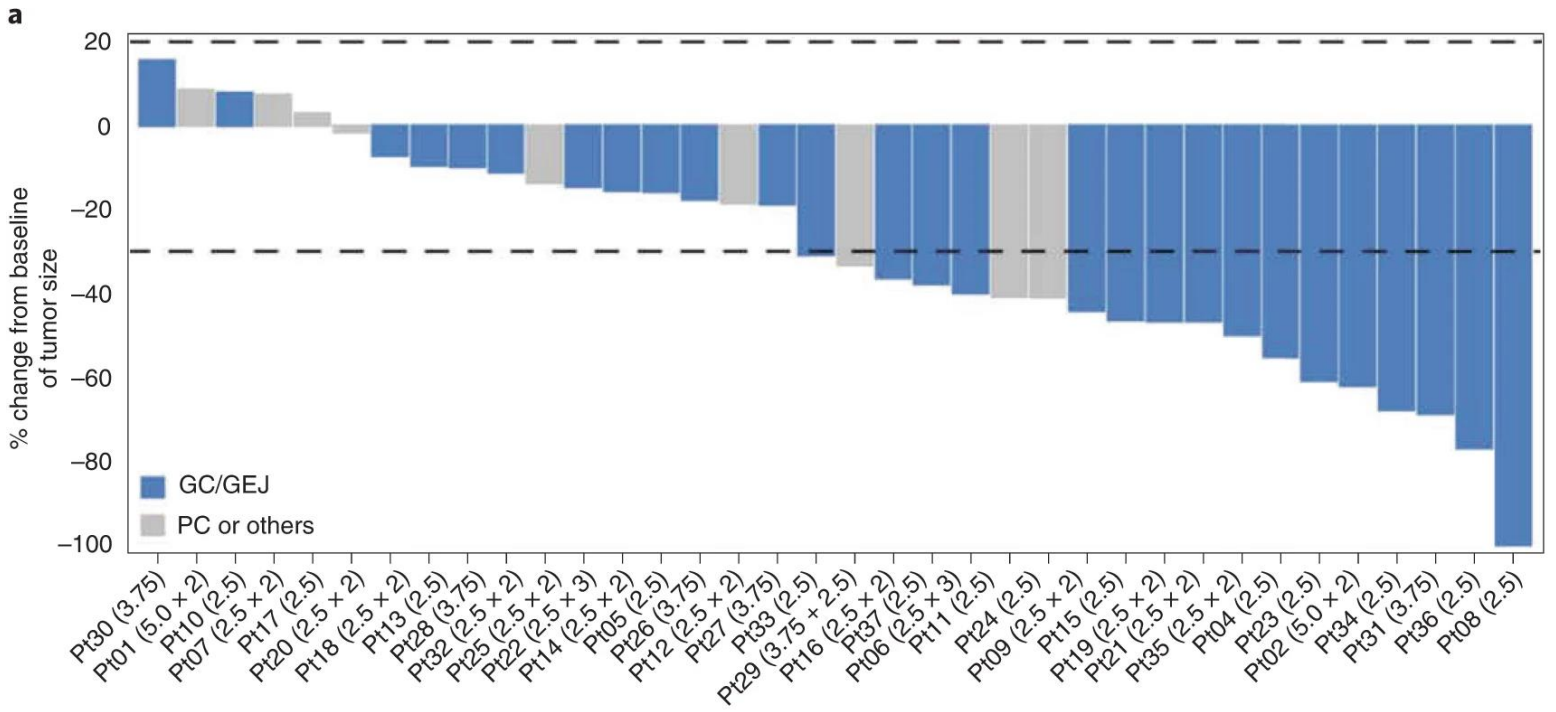
Claudin-18 : Zolbetuximab : SPOTLIGHT



	Zolbetuximab + mFOLFOX6 (N = 211)	Placebo + mFOLFOX6 (N = 211)
Patients[a], n	128	131
ORR[b], % (95% CI)	60.7 (53.72–67.30)	62.1 (55.17–68.66)
BOR[c,d], n (%)		
CR	12 (5.7)	7 (3.3)
PR	116 (55.0)	124 (58.8)
SD	45 (21.3)	52 (24.6)
PD	14 (6.6)	14 (6.6)
Median DOR[b], months, (95% CI)	8.51 (6.80–10.25)	8.11 (6.47–11.37)
3rd quartile, months (95% CI)	29.9 (10.41–NE)	15.5 (13.27–NE)

Shitara et al, GI ASCO 2023

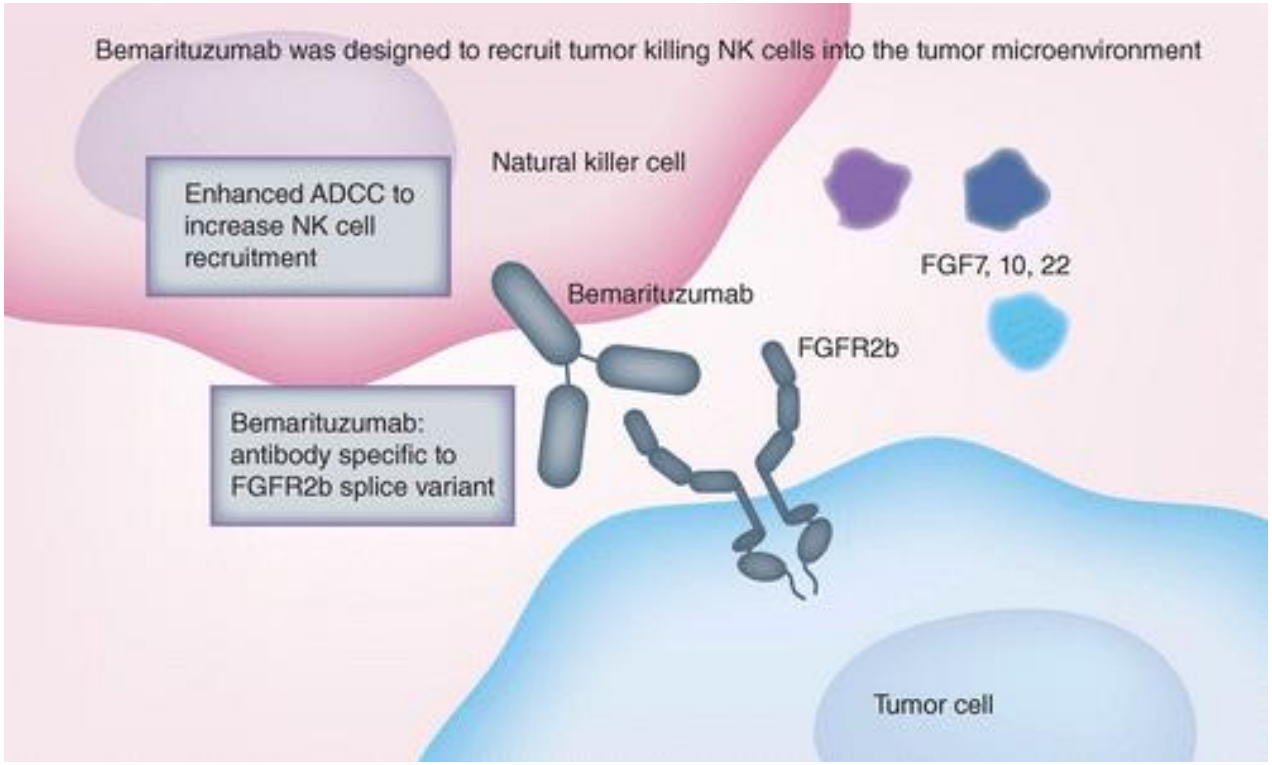
Claudin-18 : CAR-T



- CLDN18.2-targeted CAR T cells (CT041)
- Open-label, single-arm, ph I study, n= 37 pts, prior treatment
- CLDN18.2-positive GI cancers
- Gastric/GEJ cancers, ORR 57.1%, DCR 75.0%
- 6-month OS rate 81.2%.

Nature Medicine volume 28, 1189–1198 (2022)

Targeting FGFR…Bemarituzumab



- 5-10% GEJ adenoca have FGFR2 amplification
- Anti-FGFR2b antibody
  - binds to the FGFR2b receptor,
  - Inhibits FGF ligand binding & receptor internalization / degredation
  - Antibody-dependent cell-mediated cytotoxicity

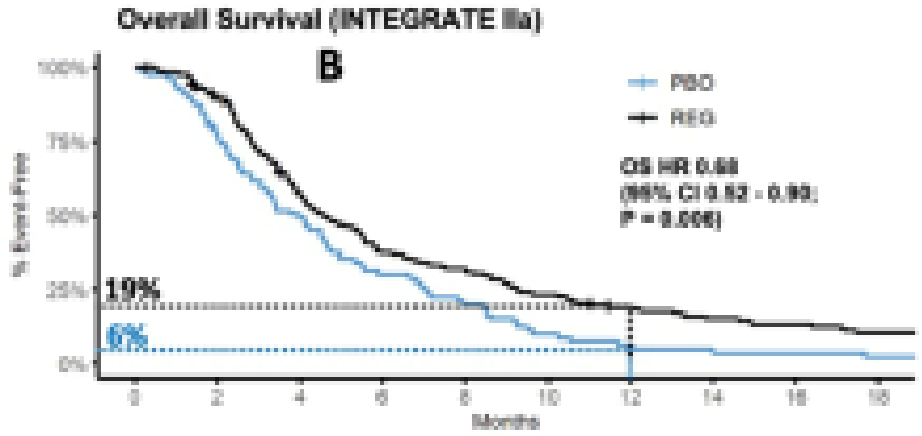
FUTURE ONCOLOGY VOL. 15, NO. 18

FIGHT study – FGFR2b targeting

- Randomised double-blind placebo controlled P II study, N=155 patients FGFR2b overexpressing advanced gastric/GEJ ca
- FOLFOX + Bemarituzumab / placebo
- Median PFS 9·5 (7.3 – 12.9) vs 7·4 months (5·8–8·4), **p= 0.073**
- ORR 47% vs 33%, **p =0.11**
- Median OS significantly longer in bemarituzumab arm : not reached vs 12.9 months (HR, 0.58; 95% CI, 0.35-0.95; *P* =.027)
- Post hoc analysis (median fu 12.5 months), median OS 19.2 vs 13.5 months (HR, 0.60; 95% CI, 0.38-0.94)
- Randomised Phase III: FORTITUDE 101 & 102

Wainberg et al, Lancet Oncol 2022

VEGF-targeting : INTEGRATE IIa Trial



- 251 patients with advanced gastric/GEJ cancer, randomised 2:1 to Regorafenib vs placebo
- > 2 prior lines of treatment
- OS superior in the regorafenib arm: HR 0.68, p=.006
- 12-month OS rate 19% vs 6%
- Deterioration in global quality of life delayed in the regorafenib arm compared with the placebo arm (*P* =.0043)

Pavlakis et al, GI ASCO 2023

Conclusions

- Promising results – how to sequence will be next challenge?
- Combinations of targeted therapy & IO most likely to have greatest impact
- CAR T-cell immunotherapy targets (surface antigens)
  - HER2
  - CEA
  - MUC-1
  - Mesothelin
  - Folate receptor 1
  - EpCAM
- Tissue acquisition is important for our patients….

Thank you for attending our first UKIOG Annual Meeting

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