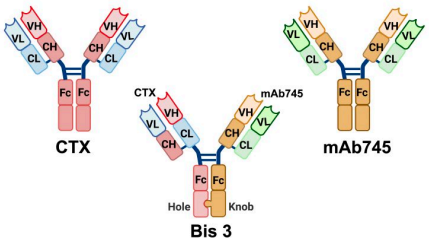
Bispecific EGFR/MERTK Antibody to Overcome Resistance to Tagrisso in Lung Cancer

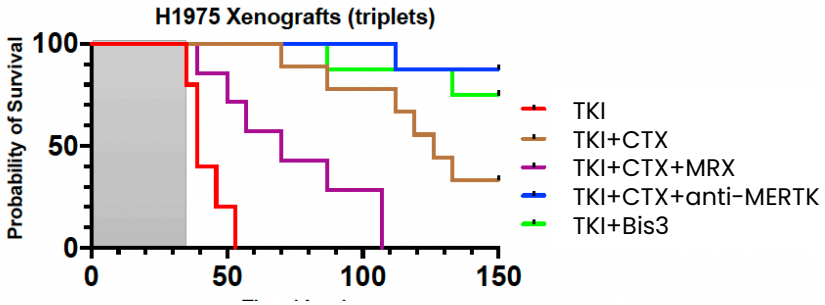
Therapeutics

Reference Number: **2493** \ Principal Investigator: **Prof. Yosef Yarden** \ Patent Status: **Filed**

Lung cancer patients treated with the blockbuster drug Osimertinib (Tagrisso) eventually develop resistance. We identified a novel MERTK-dependent escape mechanism, that occurs even in the absence of new mutations and is estimated to account for more than 60% of resistance cases. Bis3, a bispecific EGFR/MERTK antibody, promotes degradation of both receptors and works synergistically with TKIs to achieve durable tumor response.



	MERTK KD (M)	EGFR KD (M)
mAb745	2.42e-12	-
CTX	-	1.65e-10
Bis 3	9.88e-12	1.65e-09



TKI: Osimertinib
Cetuximab (CTX): anti-EGFR antibody
MRX-small molecule MERTK inhibitor
H1975 cells carry EGFR T790M mutation

APPLICATIONS

- First-line combination therapy with EGFR TKIs to prevent emergence of resistance
- Second-line therapy for patients relapsing on TKIs

DEVELOPMENT STAGE

- Bis3 demonstrated dual EGFR/MERTK degradation and robust suppression of proliferation and survival in drug-tolerant persisters *in vitro*
- In 3D spheroids, Bis3 + osimertinib strongly inhibited growth across EGFR mutations
- *In vivo* (xenografts and PDXs), Bis3 + TKI markedly delayed relapse, including in exon-20 models.
- Human IgG1 CrossMab format; ready for advancement toward IND-enabling studies
- Ongoing studies are addressing efficacy of Bis3 on various exon-20 mutations as well as EGFR-C797S animal models.

DIFFERENTIATION

Simultaneous degradation of EGFR and MERTK

Single therapeutic molecule, replacing combined anti-EGFR and anti-MERTK monoclonals

Efficacy across EGFR mutations including Exon-20

REFERENCES

- Suvendu Giri et al, BioRxiv, 2025