# Advances in EGFR Mutant Lung Cancer

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Dana-Farber Cancer Institute

Belfer Center FOR APPLIED CANCER SCIENCE

HARVARD MEDICAL SCHOOL

# Case presentation

- ***53 yo F never smoker presented in 2017 with seizures following 10 lb unintentional weight loss, headaches***
- ***Brain MRI showed at least 5 rim enhancing lesions (5-10 mm), Chest CT showed a 3 cm spiculated cavitary mass in the RLL and mediastinal lymphadenopathy***
- ***CT guided biopsy showed TTF1 positive lung adenocarcinoma***
- ***Rapid molecular testing from tissue revealed a mutation in EGFR (exon 19 deletion). Research testing of ctDNA identified the same mutation in plasma (0.4% allele frequency), confirmed by Guardant testing.***
- ***Started on Osimertinib 80 mg***
- ***All sites of disease regressed, ctDNA cleared, prolonged response for 5 years***

# Case presentation

- *In 2022 started to develop progression of several sites in the brain, requiring SRS and increased dose of osimertinib to 160 mg*
- *Stable until February 2024 when she developed worsening back pain, headaches. Scheduled for brain and spine MRIs but delayed due to a planned vacation in Aruba.*
- *Referred to BWH ED the day after the Super Bowl, imaging showed extensive leptomeningeal spread of disease, Na 120, began seizing in the ED, admitted to the neuro ICU. Began developing cranial nerve palsies.*
- *Guardant testing of plasma negative, palliative RT initiated*
- *CSF obtained and panel genomic testing (Genexus) peformed on cell free DNA, identified EGFR del 19 mutation as well as high level MET amplification*
- *Started on capmatinib (MET inhibitor) together with osimertinib, had complete resolution of her symptoms and has been doing well since*

# EGFR Mutation Discovery – 20 Year Anniversary

*Pasi Janne, MD, PhD*

*Matthew Meyerson, MD, PhD*

*Bruce Johnson, MD*

*William Sellers, MD*

## *EGFR* Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

Science
AAAS

- *First ever evidence of targeted therapy success (pill) in lung cancer*
- *EGFR mutations enriched in women, never smokers, Asian ethnicity*

*Paez, Janne et al., Science 2004*

# Characterization of mechanisms of acquired resistance

*Pasi Janne, MD, PhD*

*Jeff Engelman, MD, PhD*

**_MET_ Amplification Leads to Gefitinib Resistance in Lung Cancer by Activating ERBB3 Signaling**

Jeffrey A. Engelman,[1,2,3] Kreshnik Zejnullahu,[4,5] Tetsuya Mitsudomi,[6] Youngchul Song,[2,3] Courtney Hyland,[7] Joon Oh Park,[4,5] Neal Lindeman,[7] Christopher-Michael Gale,[3] Xiaojun Zhao,[5] James Christensen,[8] Takayuki Kosaka,[6] Alison J. Holmes,[4,5] Andrew M. Rogers,[5] Federico Cappuzzo,[9] Tony Mok,[10] Charles Lee,[7] Bruce E. Johnson,[4,5] Lewis C. Cantley,[2,3] Pasi A. Jänne[4,5*]

[1]Massachusetts General Hospital Cancer Center, Boston, MA 02114, USA. [2]Department of Systems Biology, Harvard Medical School, Boston, MA 02115, USA. [3]Department of Signal Transduction, Beth Israel Deaconess Medical Center, Boston, MA 02115, USA. [4]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA. [5]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA. [6]Department of Thoracic Surgery, Aichi Cancer Center Hospital, Nagoya 464-8681, Japan. [7]Department of Pathology, Brigham and Women's Hospital, Boston, MA 02115, USA. [8]Pfizer Global Research and Development, Department of Research Pharmacology, La Jolla Labs, La Jolla, CA 92121, USA. [9]Istituto Clinico Humanitas, Department on Hematology-Oncology, Rozzano 20089, Italy. [10]Department of Clinical Oncology, Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China.

*To whom correspondence should be addressed. E-mail: pjanne@partners.org

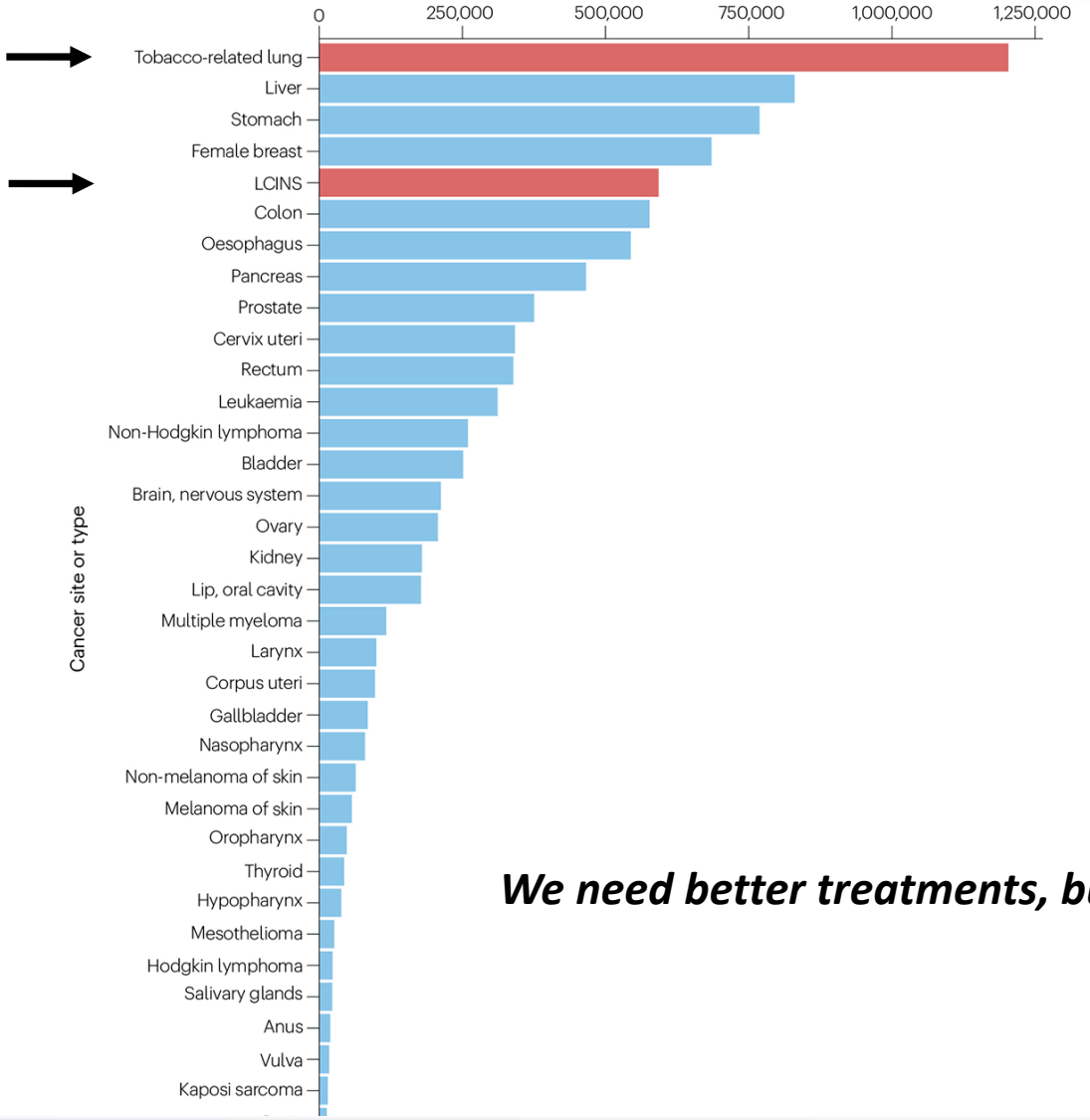
Science
AAAS

***Paez, Janne et al., Science 2004***

- ***Treated EGFR mutant cell line (HCC827) with gefitinib to develop resistant clones***
- ***Identified high level MET amplification as a mechanism to bypass EGFR inhibition***
- ***Now relevant for other targetable oncogenes such as ALK – first generation ALK inhibitor crizotinib blocked ALK and MET, selected for ALK point mutations instead. But new generation specific inhibitors select for MET amplification***

# Lung Cancer in Never Smokers (LCINS)

*Jaclyn Lopiccolo, MD, PhD*




***2020 Global Cancer Deaths***

1. ***Tobacco-related lung cancer***
2. ***Liver cancer***
3. ***Stomach cancer***
4. ***Female breast cancer***
5. ***LCINS***

***We need better treatments, but also better early detection***

***Lopiccolo et al., Nat Rev Clin Oncol 2024***

# Discovery of potent/selective inhibitors of mutant EGFR

nature Vol 462|24/31 December 2009|doi:10.1038/nature08622

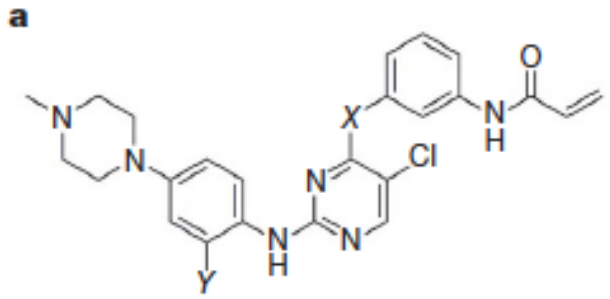
LETTERS

## Novel mutant-selective EGFR kinase inhibitors against EGFR T790M

Wenjun Zhou[1,2]*, Dalia Ercan[3,4]*, Liang Chen[3,4]*, Cai-Hong Yun[1,2]*, Danan Li[3,4], Marzia Capelletti[3,4], Alexis B. Cortot[3,4], Lucian Chirieac[5], Roxana E. Iacob[6,7], Robert Padera[5], John R. Engen[6,7], Kwok-Kin Wong[3,4,8,9], Michael J. Eck[1,2], Nathanael S. Gray[1,2] & Pasi A. Jänne[3,4,8]

*Pasi Janne, MD, PhD*

*Nathanael Gray, PhD*




WZ3146 *X*=O, *Y*=H
WZ4002 *X*=O, *Y*=OMe
WZ8040 *X*=S, *Y*=H

- ***2009 – Early EGFR inhibitors (Gefitinib, Erlotinib) work for ~ 10 mos, no brain penetration***
- ***Today – Mutant-selective inhibitor (Osimertinib) works on average for 2+ years, with brain penetration***
- ***If caught early, osimertinib after surgery (ADAURA) or chemoRT (LAURA) reduces the chance of disease recurrence by 80%***

***Zhou et al., Nature 2009***

# More effective EGFR inhibition selects for small cell transformation

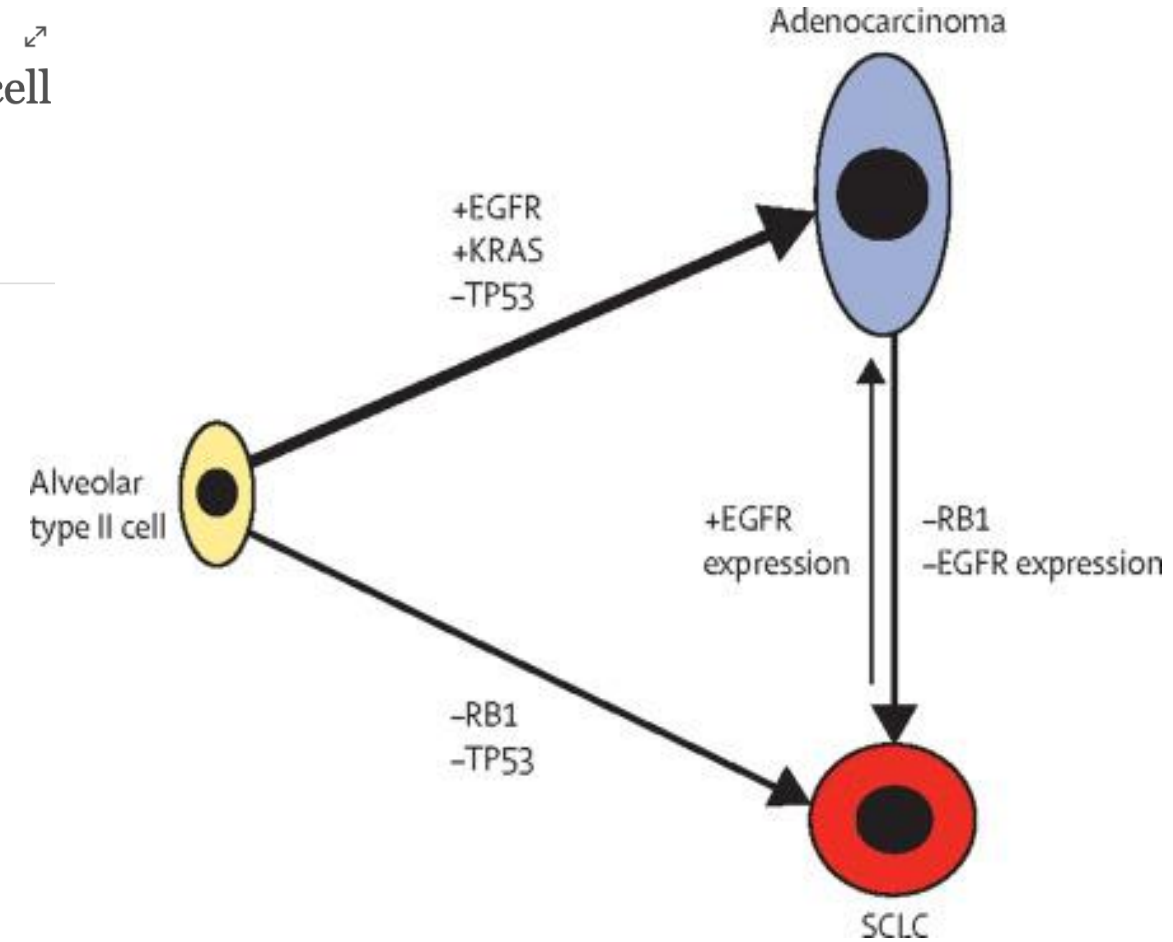
FULL TEXT ARTICLE

## Transformation from non-small-cell lung cancer to small-cell lung cancer: molecular drivers and cells of origin

Matthew G Oser MD, Matthew J Niederst PhD, Lecia V Sequist MD and Jeffrey A Engelman Dr

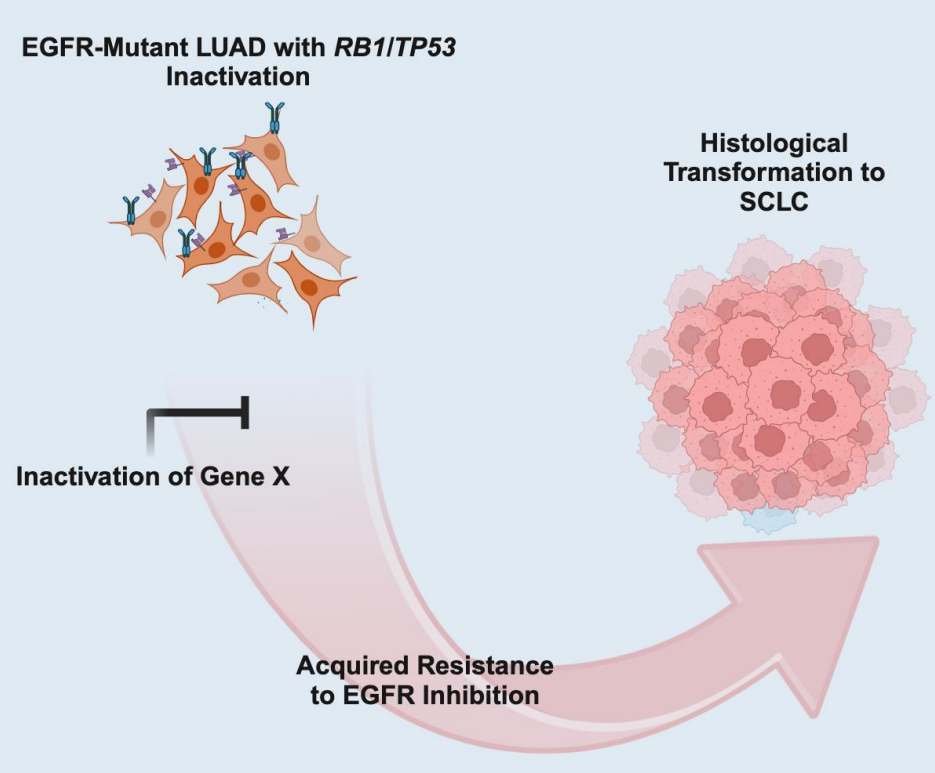
Lancet Oncology, The, 2015-04-01, Volume 16, Issue 4, Pages e165-e172, Copyright © 2015 Elsevier Ltd

***Matt Oser, MD, PhD***

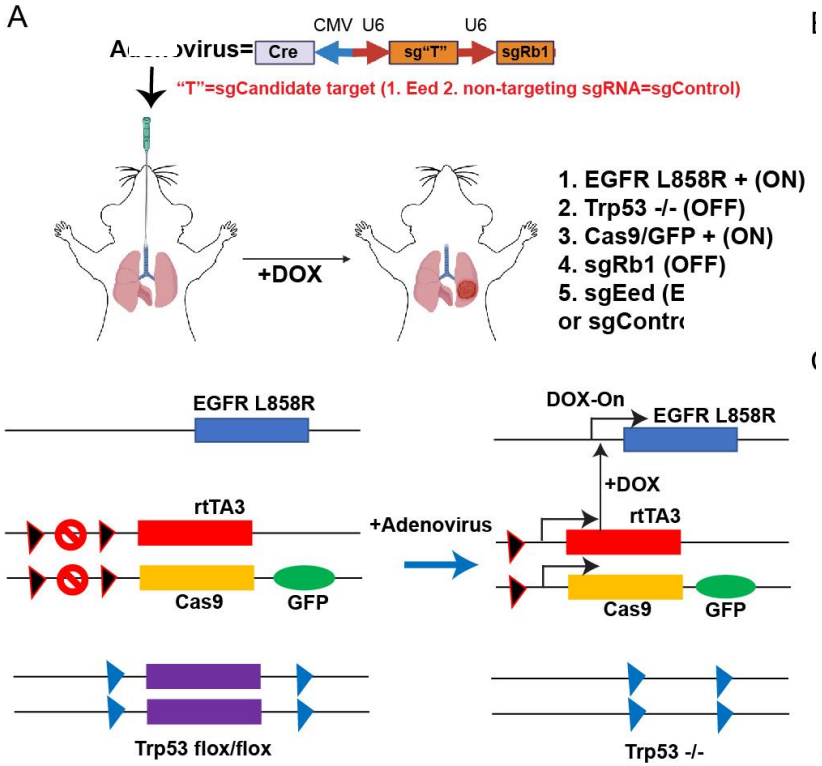


# Modeling therapeutics that could intercept small cell transformation

## LUAD to SCLC Histological Transformation




***How model and eventually therapeutically block SCLC transformation?***




***CRISPR-based somatic gene editing to study therapeutic strategies to block SCLC transformation***

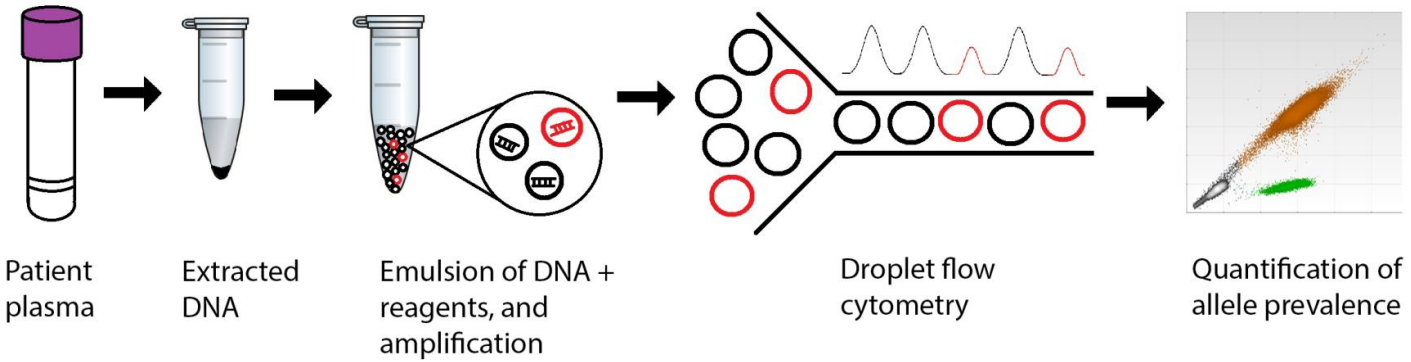
*Matt Oser, MD, PhD*

# Early Detection of EGFR Mutant Lung Adenocarcinoma

*Narjust Florez, MD*

*Christopher Lathan, MD*

*Cloud Paweletz, PhD*

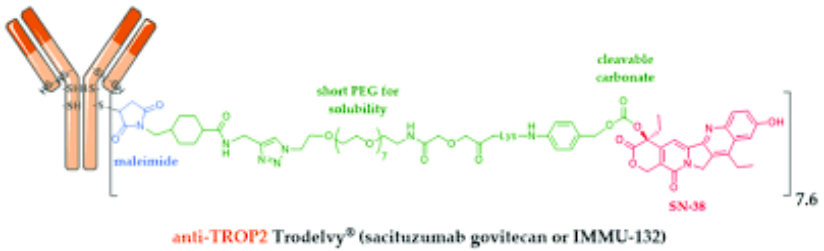



***EGFR mutations can be detected circulating in blood by an ultrasensitive "liquid biopsy" test***

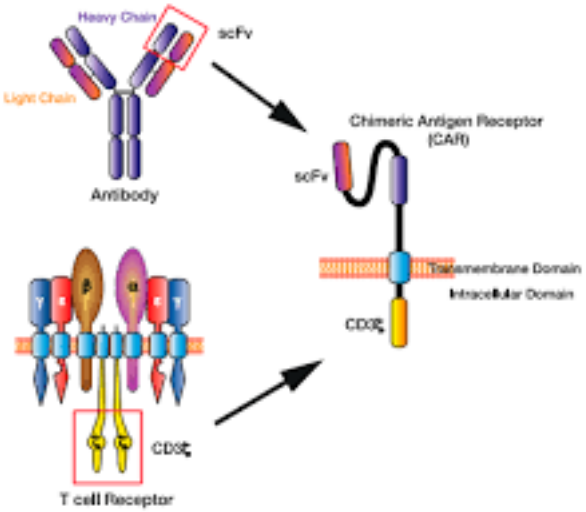
- ***Chest CT screening is only approved for 20 pack year smoking history (ages 50-80)***
- ***Have received generous philanthropic support to initiate this proof of concept blood based screening test in the Asian and Hispanic community where EGFR mutation is most common***

# TROP2 (TACSDT gene) is a cell surface protein targeted by ADCs

***Can we target EGFR mutant lung cancer or eradicate drug tolerant persister cells with a TROP2 targeting antibody drug conjugate (ADC) or a CAR-T cell?***




**TROP2 ADC**




**TROP2 CAR-T cell**

***Eric Smith M.D. PhD***

***Elliott Brea M.D. PhD***

***Simon Baldacci M.D. PhD***

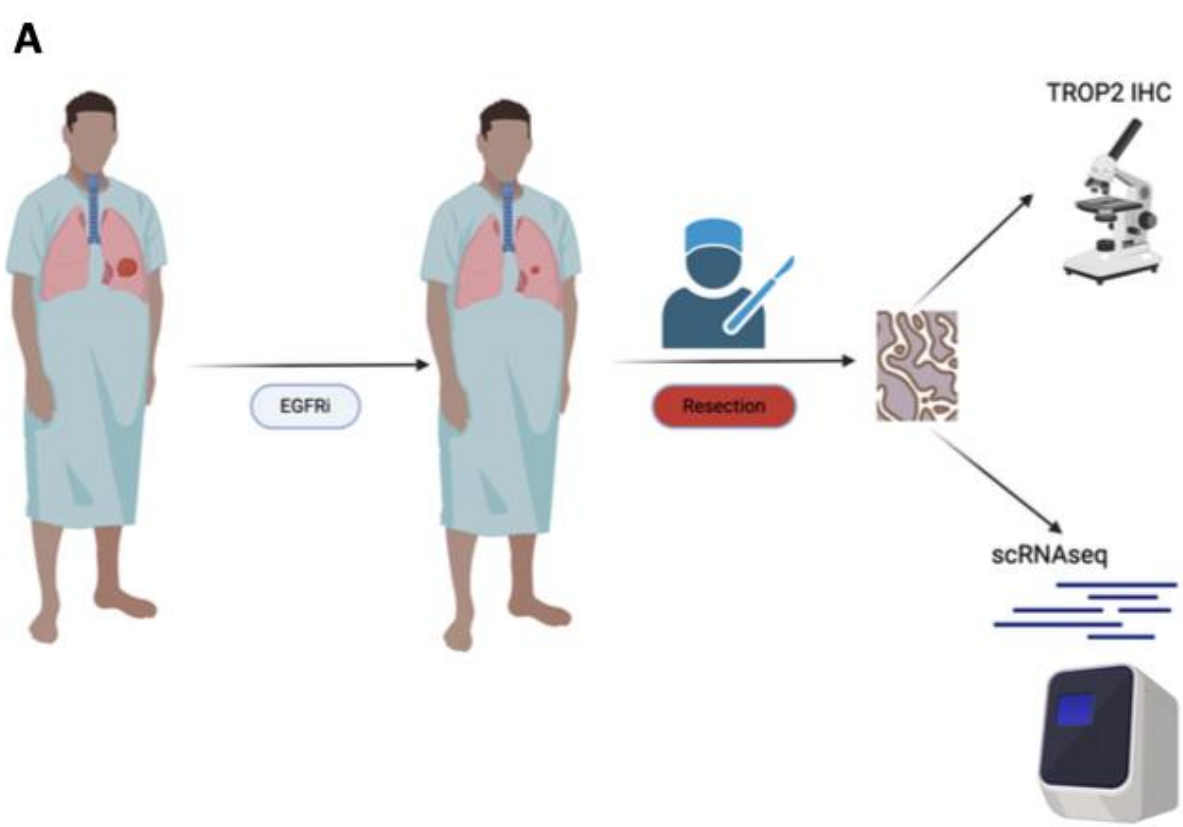
***Francesco Facchinetti M.D. PhD***

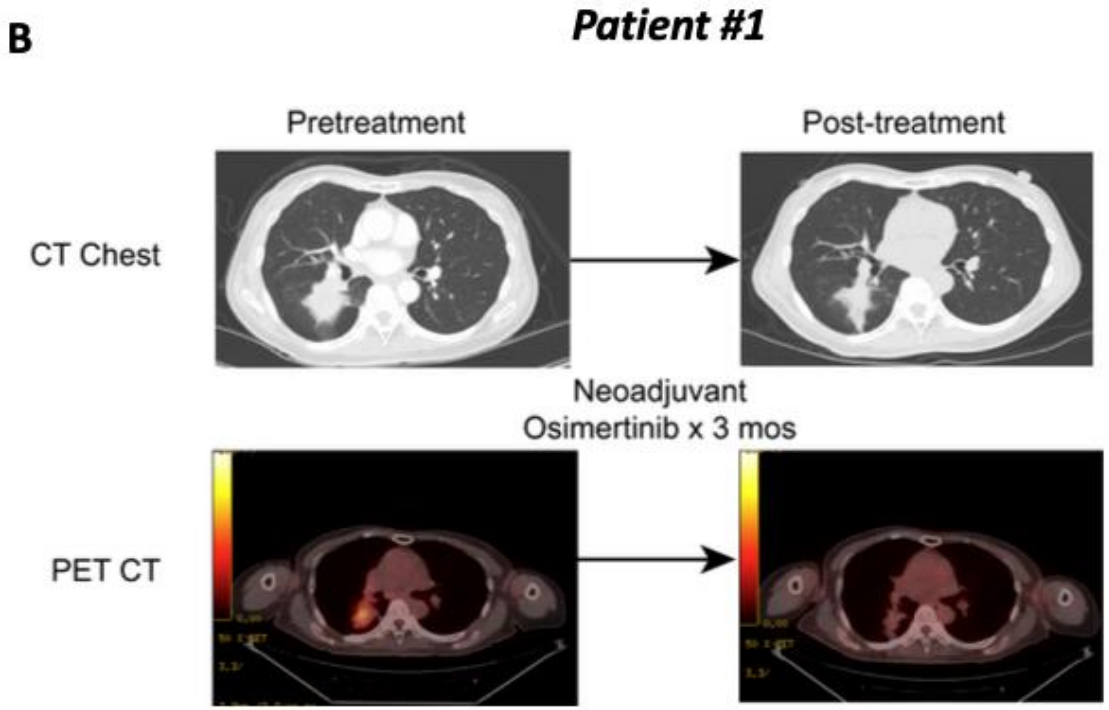
NIH NATIONAL CANCER INSTITUTE

LUNGSTRONG Raising for Research

# Unlike an ADC, CAR-Ts are living drugs and can expand, kill cells with low antigen density

# TROP2 is up-regulated by Osimertinib in *EGFR* mutant lung cancer



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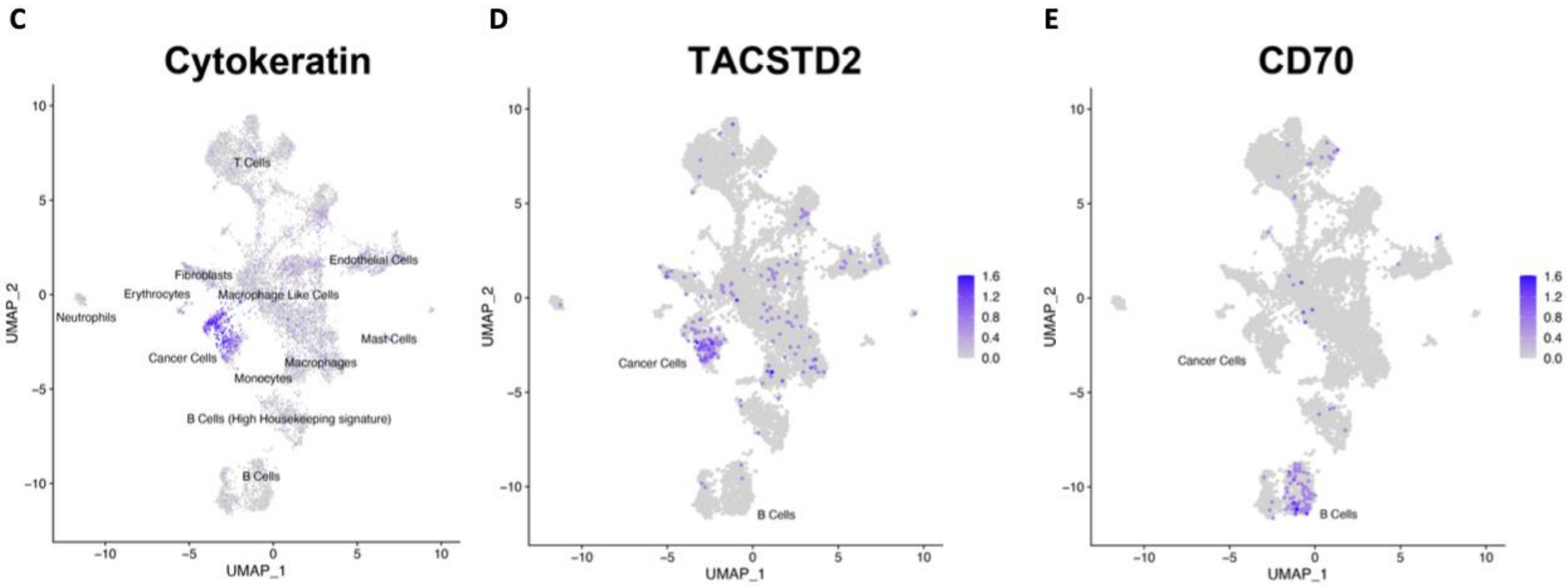
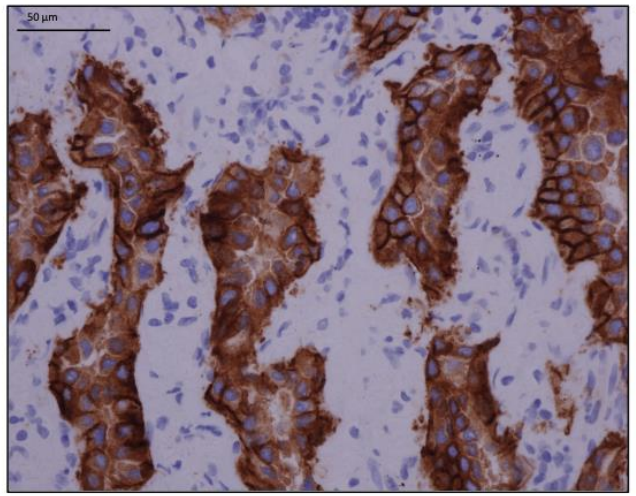


# TROP2 is up-regulated by Osimertinib in *EGFR* mutant lung cancer

F

***Patient #1***

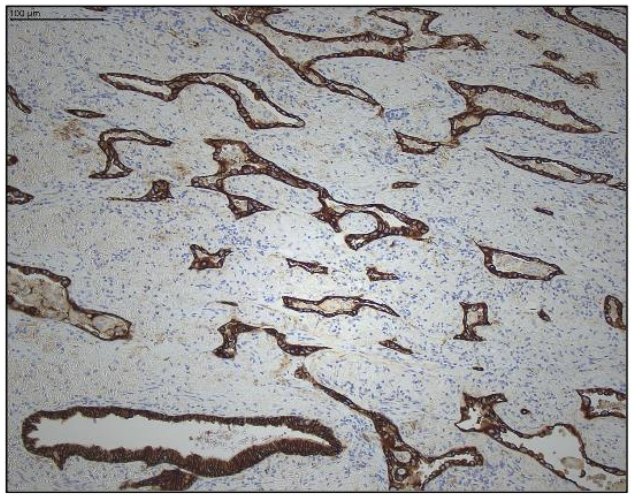
TROP2 H-score 270



Post-neoadjuvant osimertinib

***Patient #2***

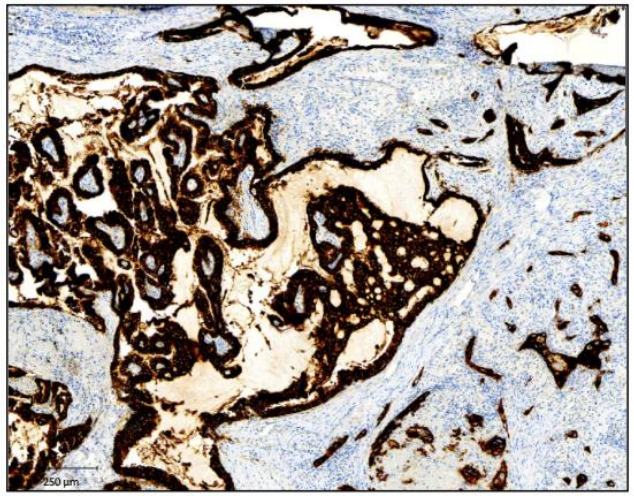
TROP2 H-score 270



Post-"neoadjuvant"
Osimertinib + carboplatin + pemetrexed

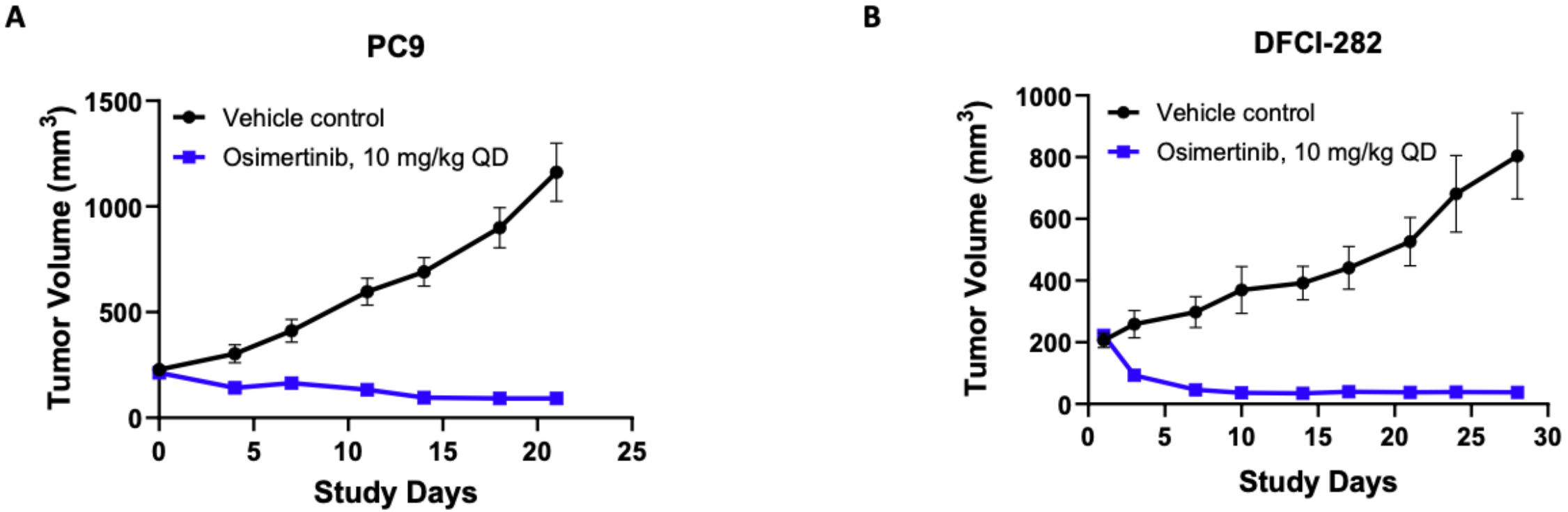
***Patient #3***

TROP2 H-score 300



Post-neoadjuvant afatanib

# TROP2 is up-regulated by Osimertinib in *EGFR* mutant lung cancer



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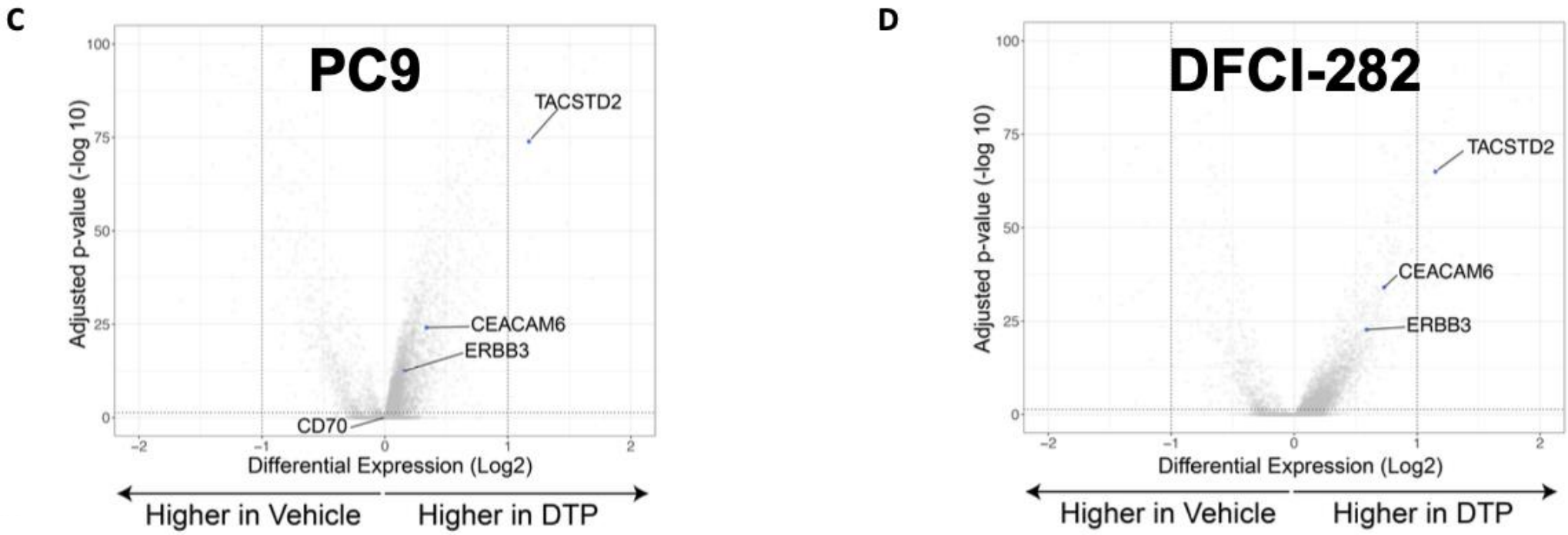

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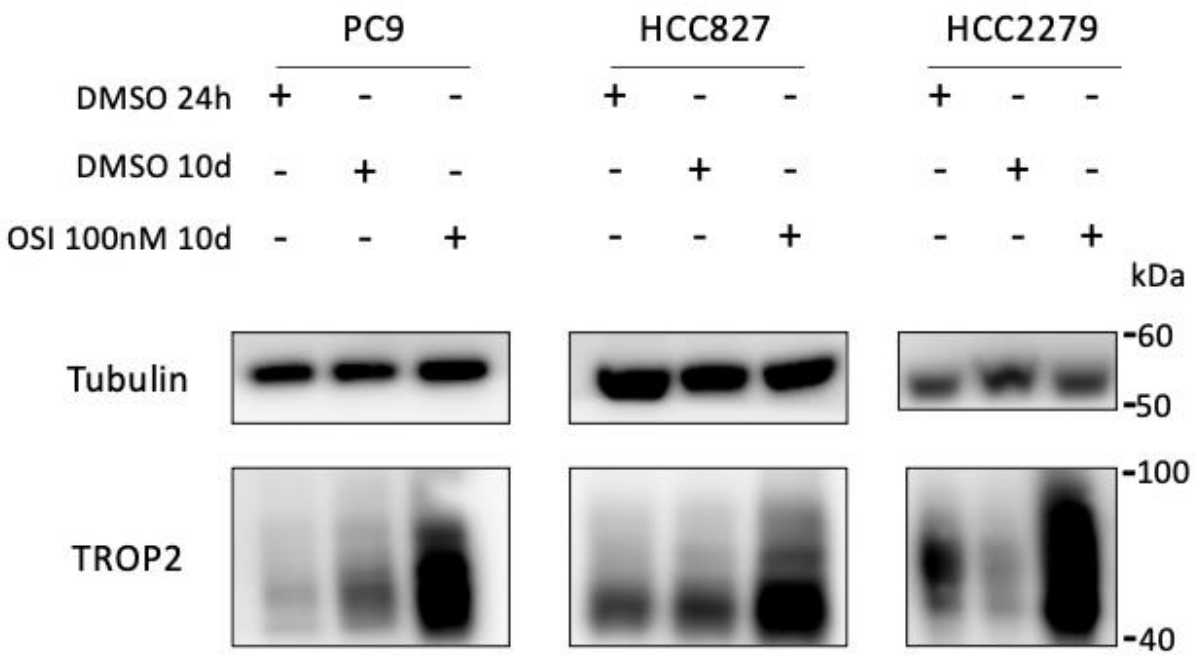
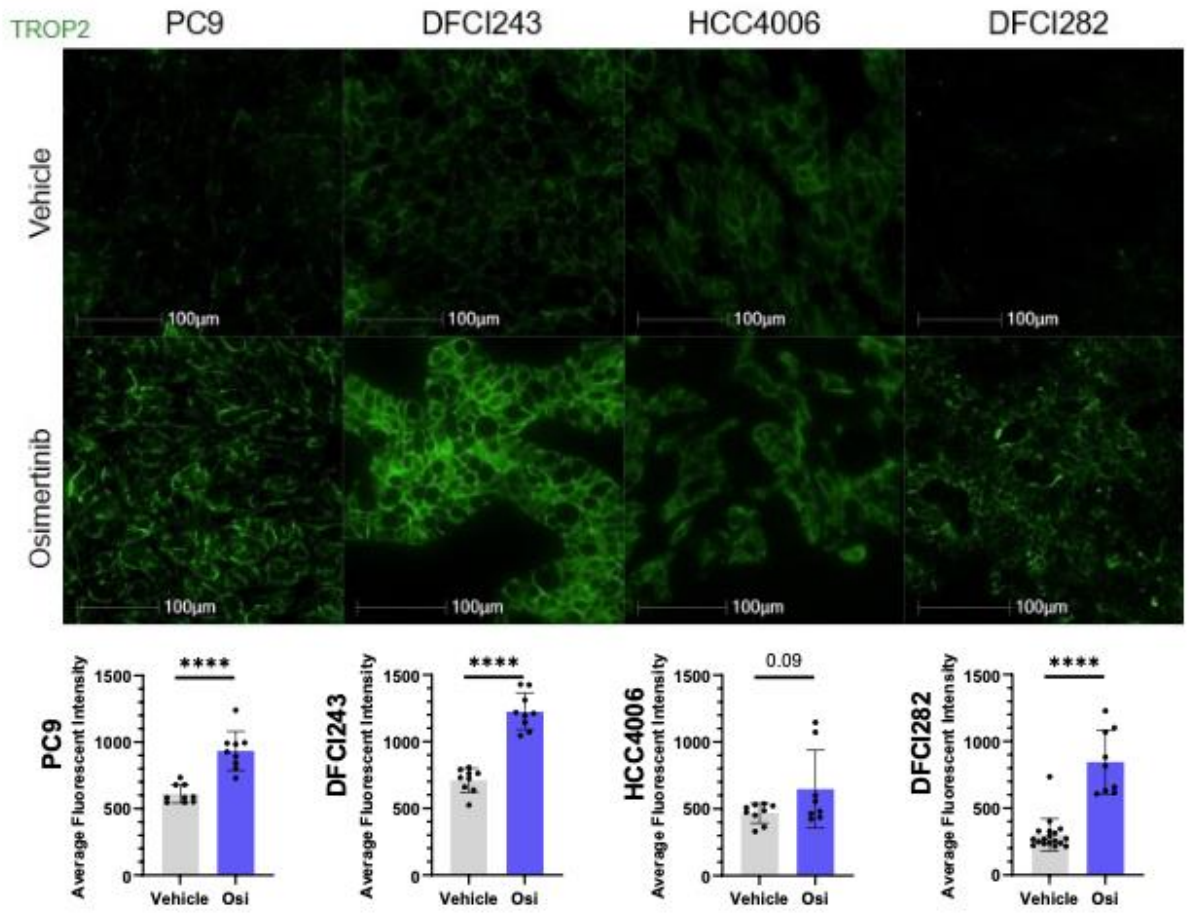
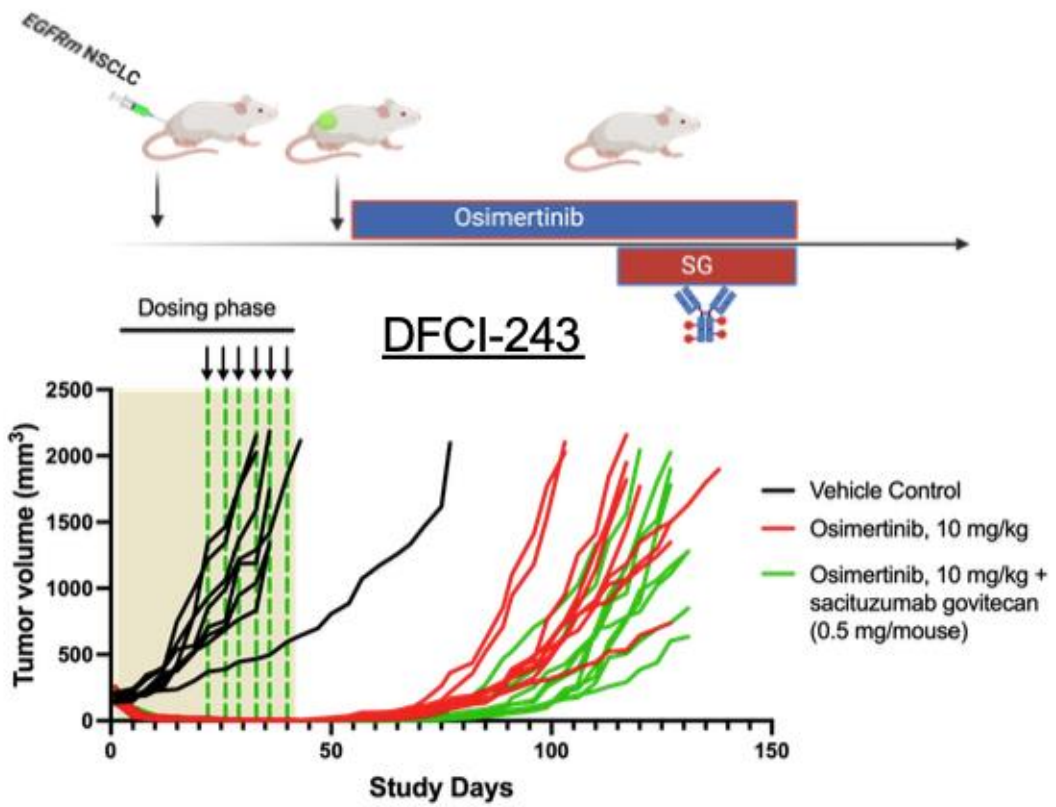


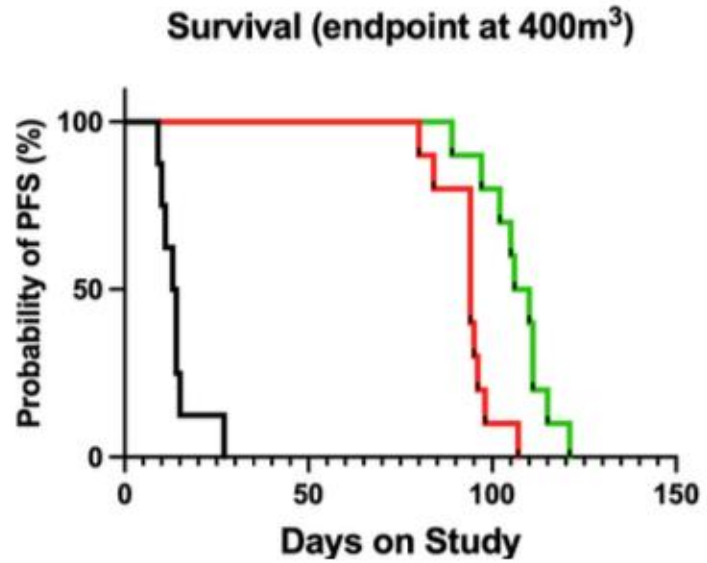



# Sacitizumab govitecan (TROP2 ADC) delays regrowth but no cures

G




H



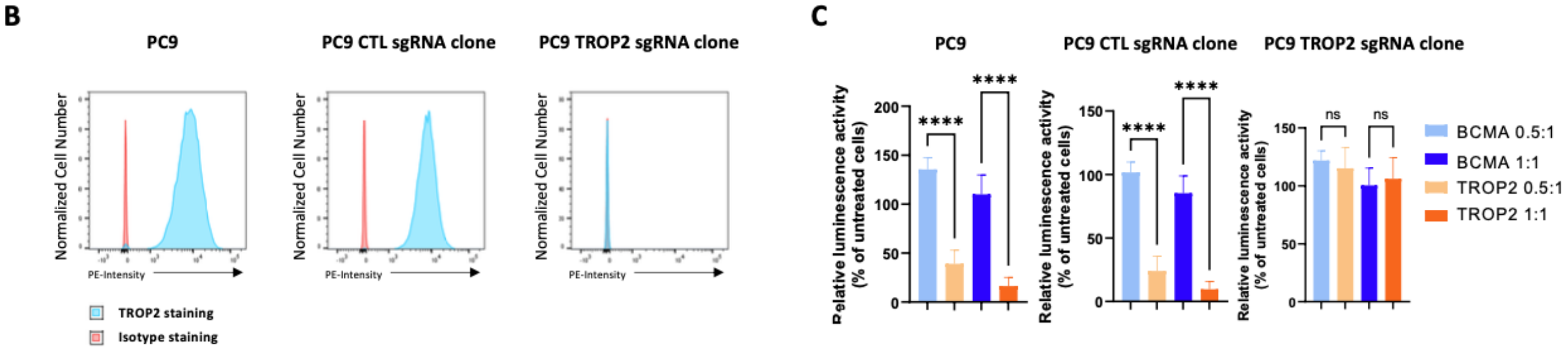

| | Median survival (days) |
|---|---|
| Vehicle control | 13.5 |
| Osimertinib, 10 mg/kg qd | 94 |
| Osimertinib + Sacituzumab govitecan q2w | 108 |

**, 0.0016

# Designing a TROP2 CAR-T cell

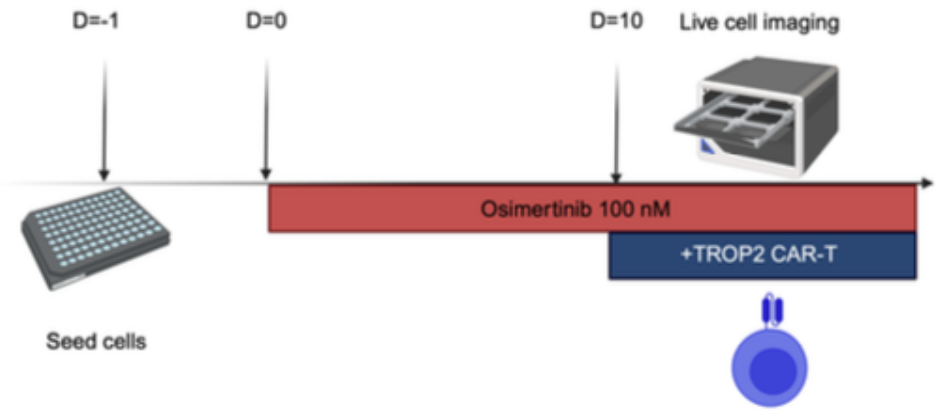

- ***Have also engineered novel TROP2 binders that target multiple extracellular domains***
- ***Can further engineer gating strategies to mitigate off tumor on target toxicity***

# TROP2 CAR-T cells kill EGFR mutant cells



# TROP2 CAR-T cells eradicate EGFR DTPs

**E**



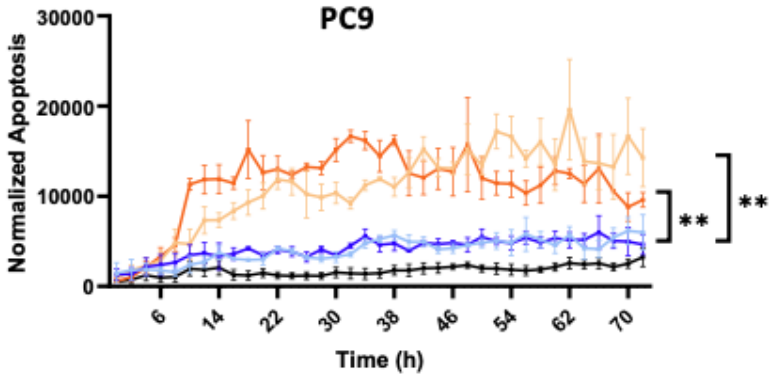

Osimertinib

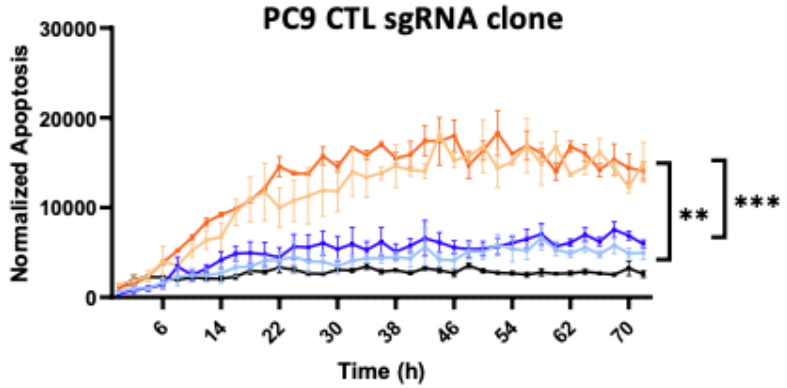
Osimertinib + BCMA CAR-T 0.5:1

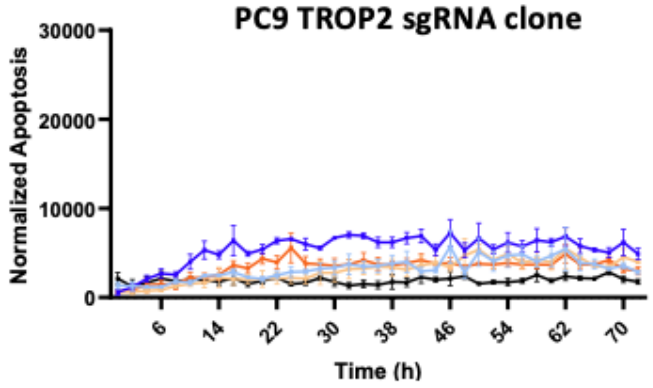
Osimertinib + BCMA CAR-T 1:1

Osimertinib + TROP2 CAR-T 0.5:1

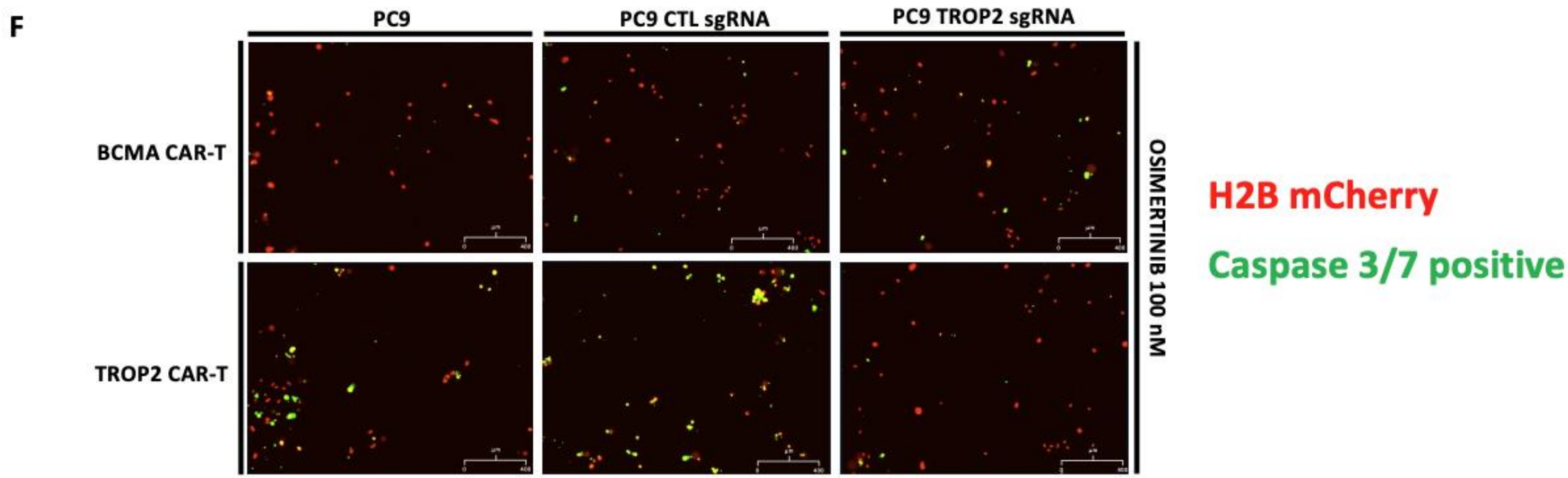
Osimertinib + TROP2 CAR-T 1:1



# TROP2 CAR-T cells eradicate EGFR DTPs



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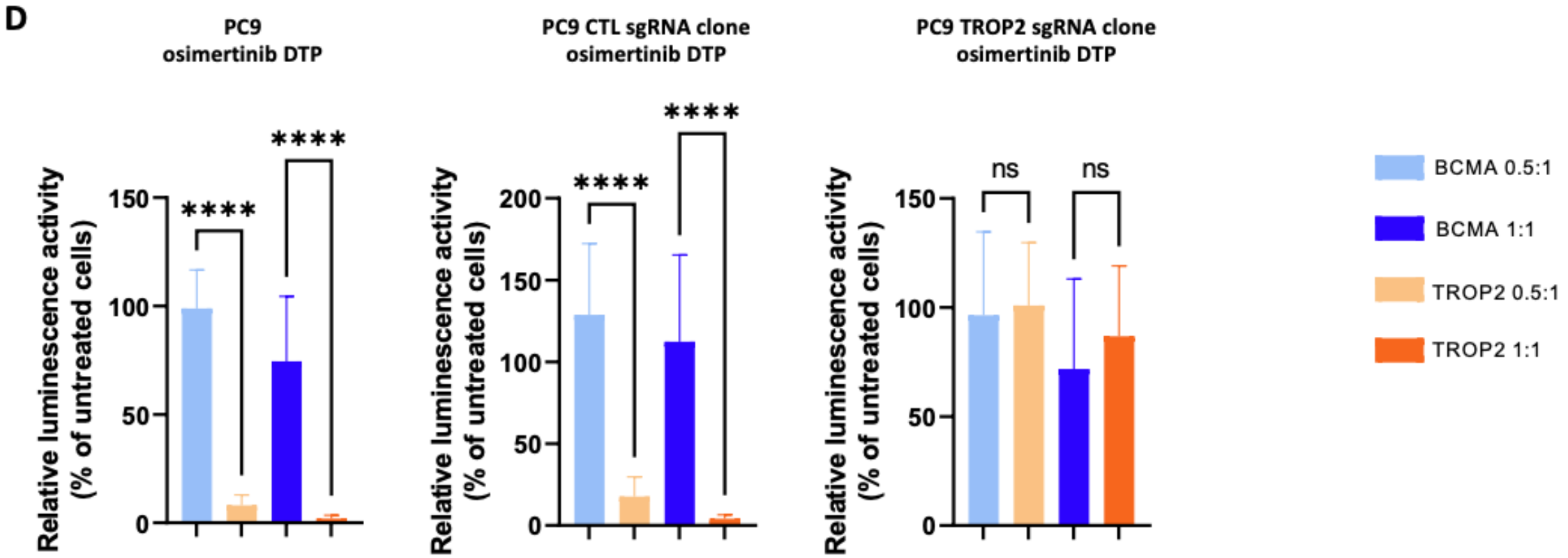
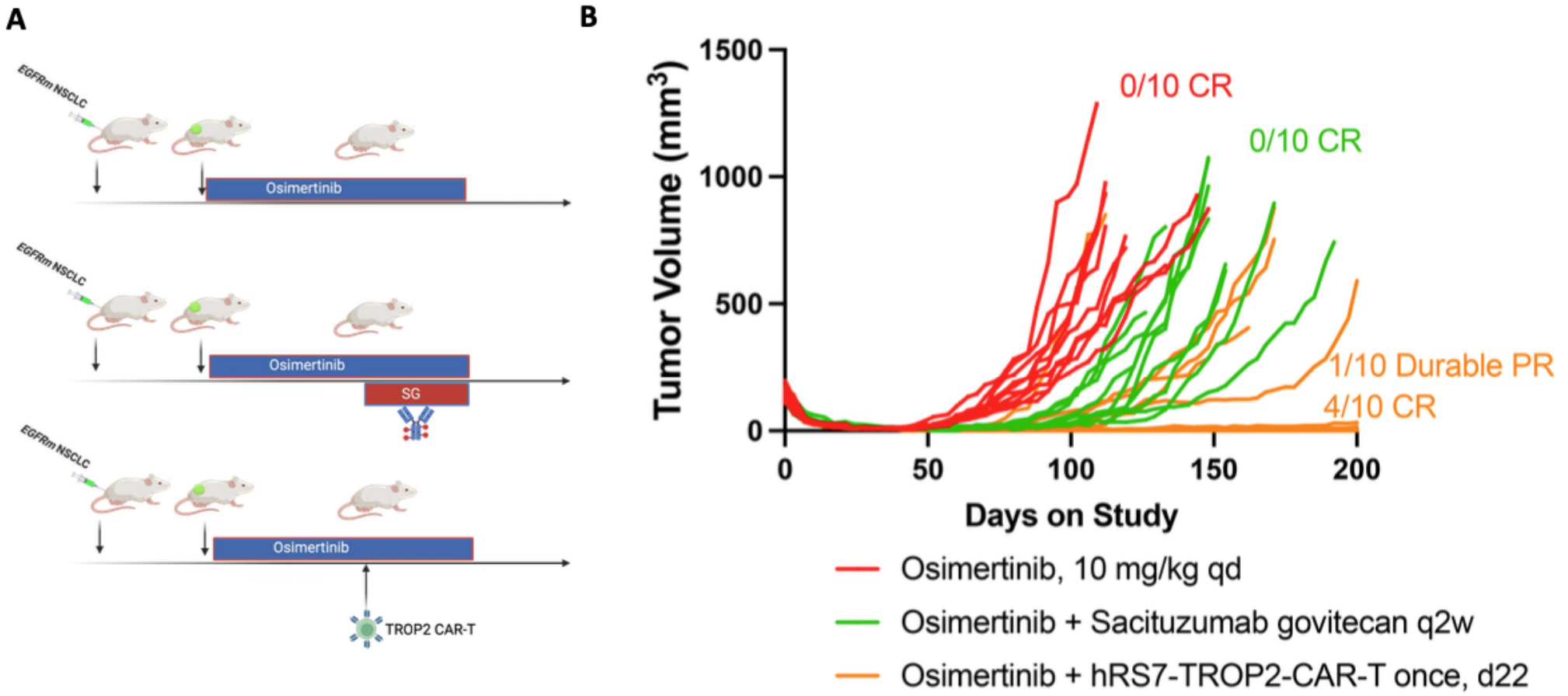


# A single infusion of TROP2 CAR-T cells generates durable responses in EGFR Patient derived xenografts



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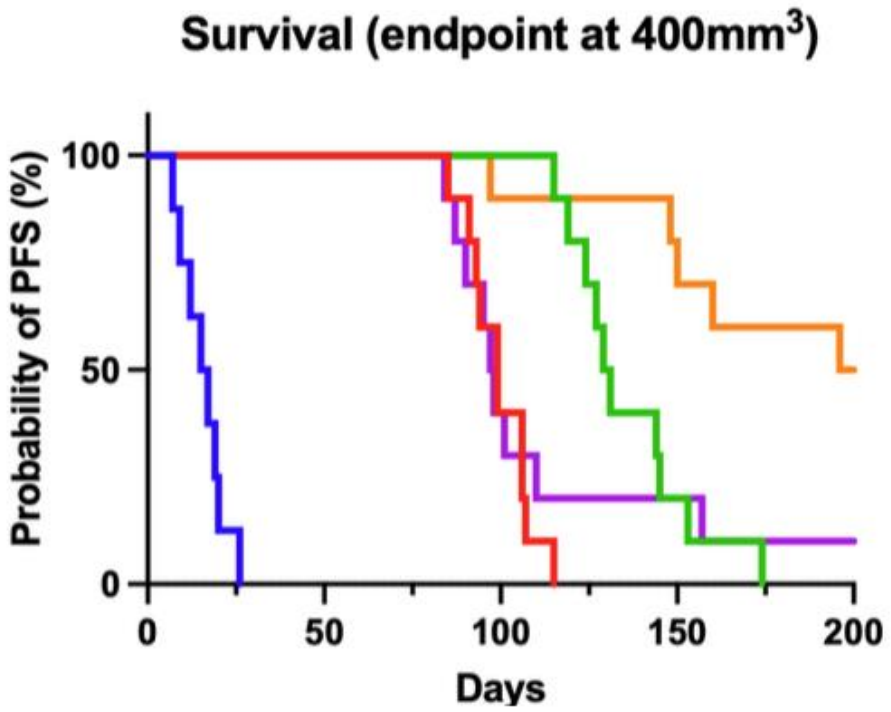


Vehicle control
Osimertinib
Osimertinib + Sacituzumab govitecan q2w
Osimertinib + BCMA-CAR-T once
Osimertinib + hRS7-TROP2-CAR-T once

| | Median survival (days) |
|---|---|
| Vehicle control | 16 |
| Osimertinib | 99 |
| Osimertinib + Sacituzumab govitecan q2w | 130 |
| Osimertinib + BCMA-CAR-T once | 97.5 |
| Osimertinib + hRS7-TROP2-CAR-T once | >200 |

ns, 0.2643
**, 0.0054
** , 0.0014

# Thank You!