Immunological mechanisms of resistance to CDK4/6 inhibitors in breast cancer

Tumor Immune Microenvironment: A Holistic Approach

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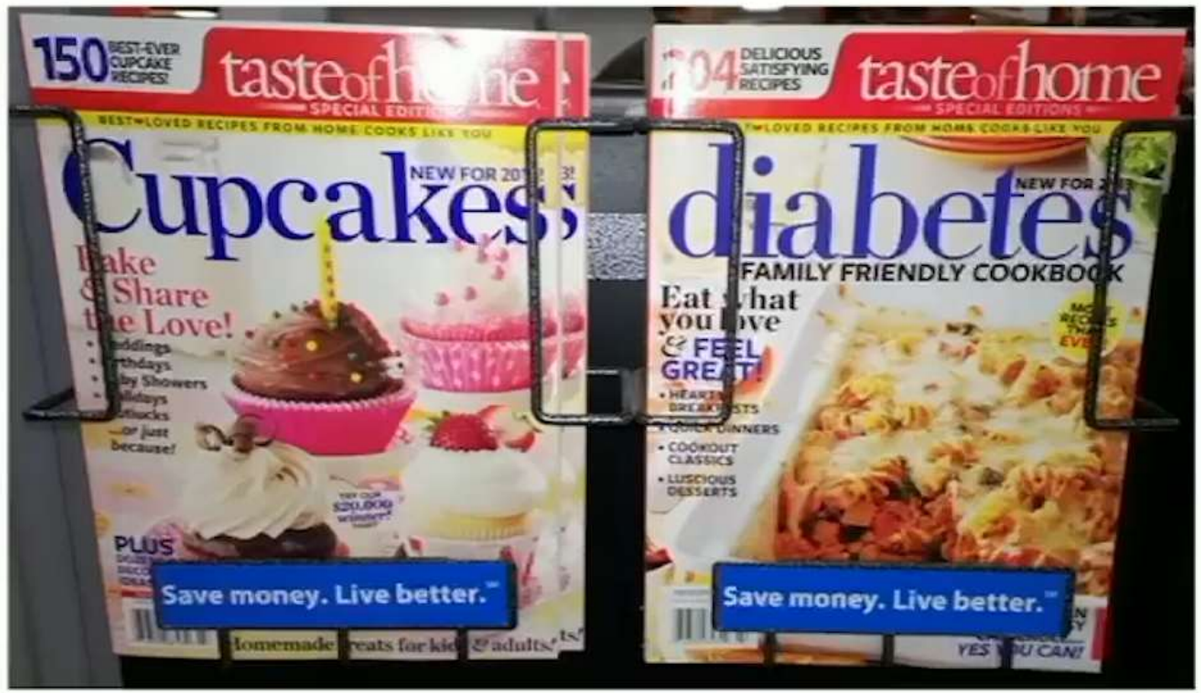
Lorenzo Galluzzi, *Ph.D.*

Weill Cornell Medical College – New York, US
Yale School of Medicine – New Haven, CT
Université Paris Descartes – Paris

Disclosures

Boehringer Ingelheim, AstraZeneca, OmniSEQ, Onxeo
The Longevity Labs, Noxopharm, Inzen, Promontory

Consultant, SAB Member or Stock Option Holder



Breast cancer

BREAST CANCER IN WOMEN: KNOW THE SUBTYPE

It's important for guiding treatment and predicting survival.

KNOW THE SCIENCE

HR = Hormone receptor
HR+ means tumor cells have receptors for the hormones estrogen or progesterone, which can promote the growth of HR+ tumors. Hormone therapies like tamoxifen can be used to treat HR+ tumors.

HER2 = Human epidermal growth factor receptor
HER2+ means tumor cells overexpress (make high levels of) a protein, calle HER2/neu, which has been shown to be associated with certain aggressive types of breast cancer. Trastuzumab and some other therapies can target ce that overexpress HER2.

HR+/HER2- ····→ aka "Luminal A"

73% of all breast cancer cases

- Best prognosis
- Most common subtype for every race, age, and poverty level

HR-/HER2- ····→ aka "Triple Negative"

13% of all breast cancer cases

- Worst prognosis
- Non-Hispanic blacks have highest rate of this subtype at every age and poverty level

HR+/HER2+ ····→ aka "Luminal B"

10% of all breast cancer cases

- Little geographic variation by state

HR-/HER2+ ····→ aka "HER2-enriched"

5% of all breast cancer cases

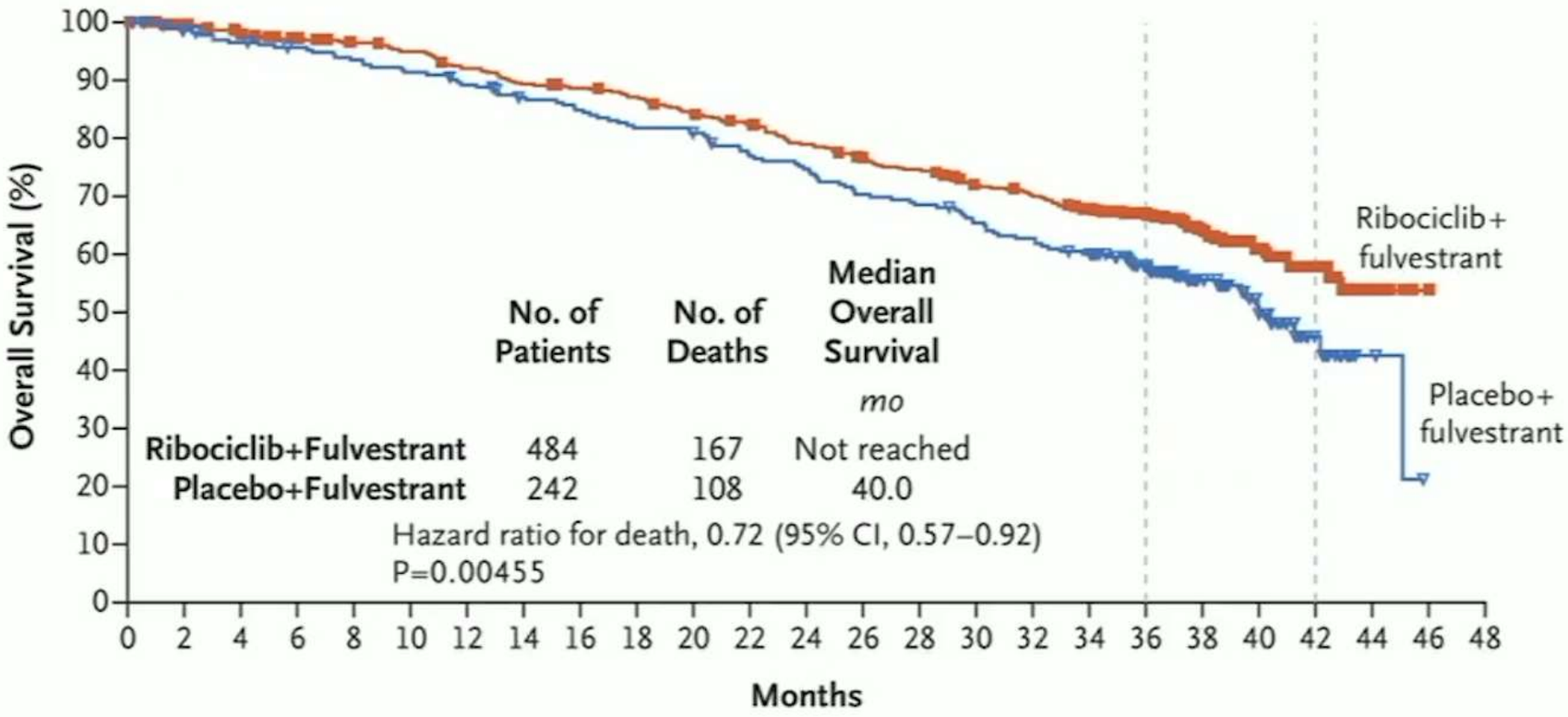
- Lowest rates for all races and ethnicities

www.cancer.gov

Source: Special section of the Annual Report to the Nation on the Status of Cancer, 1975-2011.

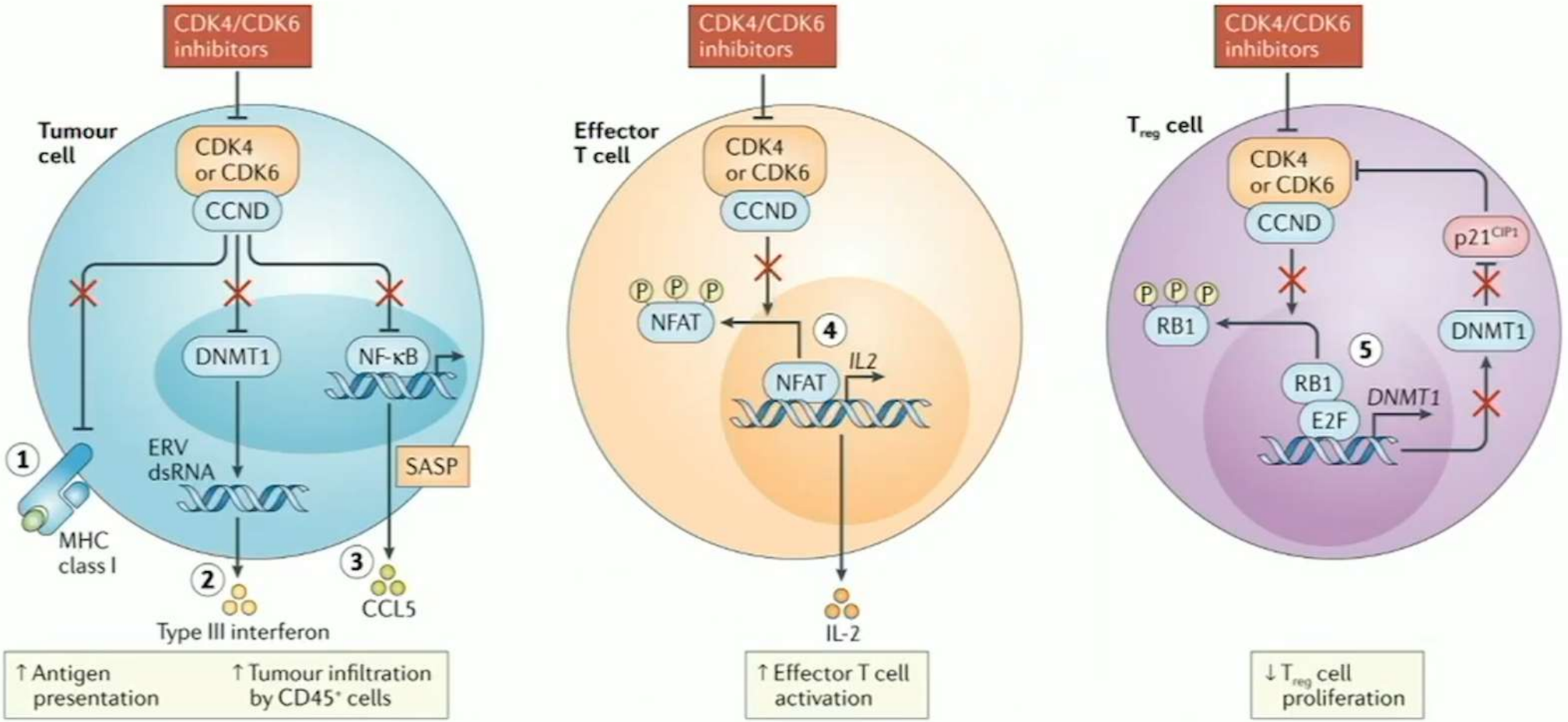
Clinical efficacy of CDK4/6 inhibitors plus hormonotherapy

CDK4/6i are cytostatic agents that block cell cycle progression at the G_1-S transition



Slamon et al., NEJM 2020

Immunotherapeutic effects of CDK4/6i



Petroni et al., Nat Rev Immunol 2020

Hypothesis

CDK4/6i control ER$^+$ breast cancer at least in part via immunostimulatory effects

Resistance to CDK4/6 may involve immunosuppression

Efficacy can be boosted with non-overlapping immunostimulatory agents, such as RT

Why RT?

RT is a cytostatic/cytotoxic agent that blocks cell cycle progression at the G_2-M transition

RT drives multiple immunostimulatory effects beyond those driven by CDK4/6i

Potential for synergy

Rodriguez-Ruiz et al, Nat Immunol 2020

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Weill Cornell Medicine

Weill Cornell Medicine
Sandra and Edward Meyer Cancer Center

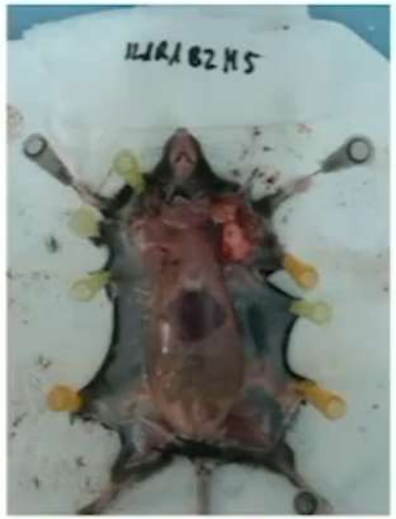
Weill Cornell Medicine
Englander Institute for Precision Medicine

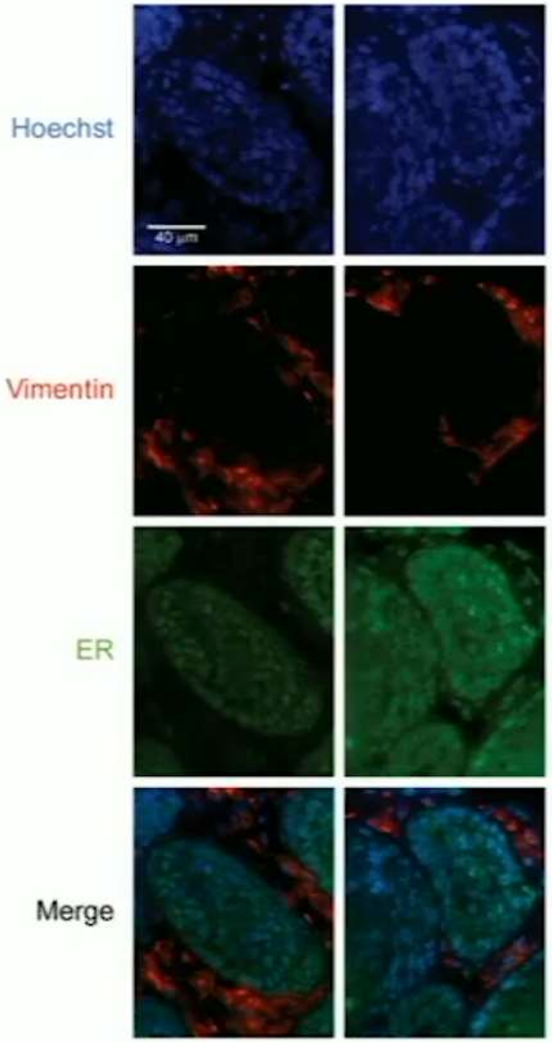
RT as a combinatorial partner to CDK4/6 inhibitors

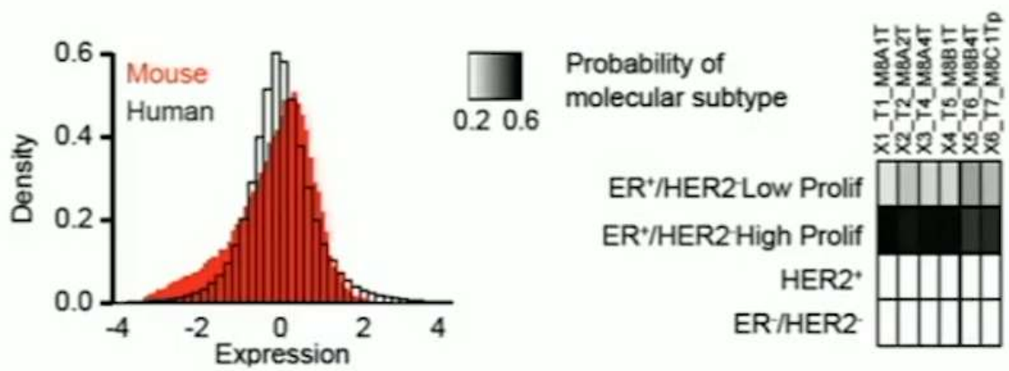
Giulia Petroni

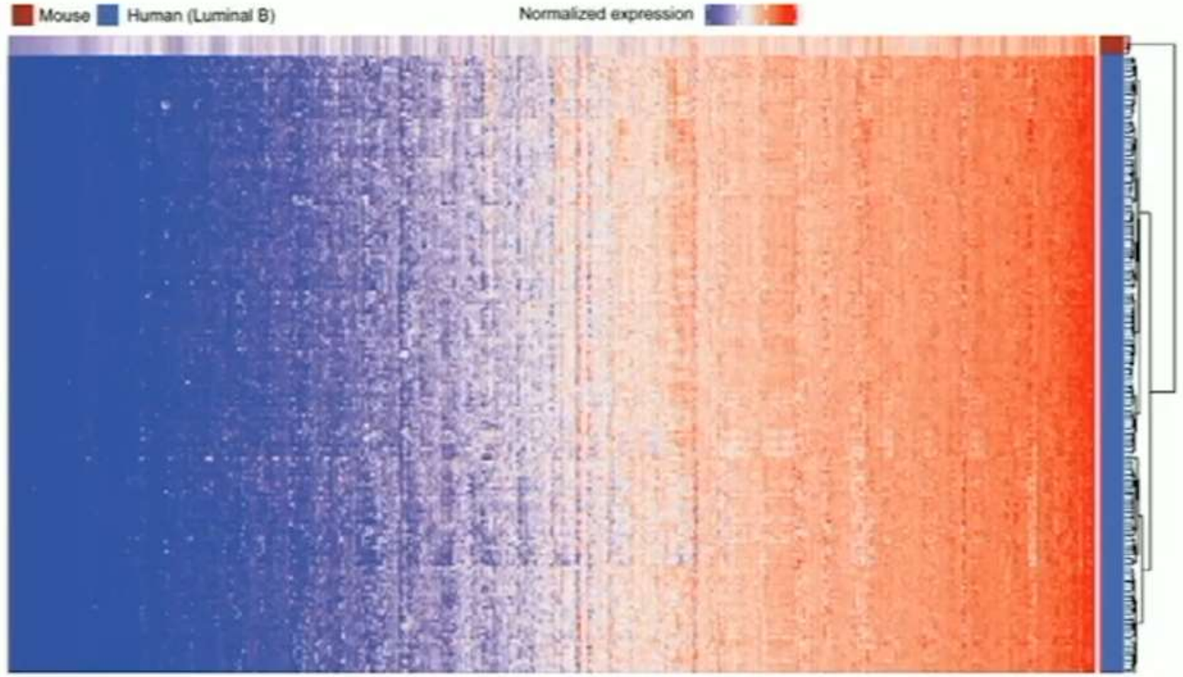
Claudia Galassi

M/D-driven tumors - A unique model of luminal B breast cancer





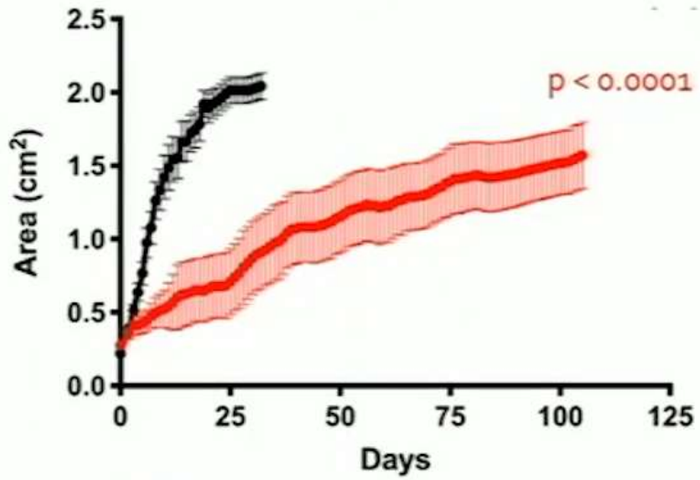


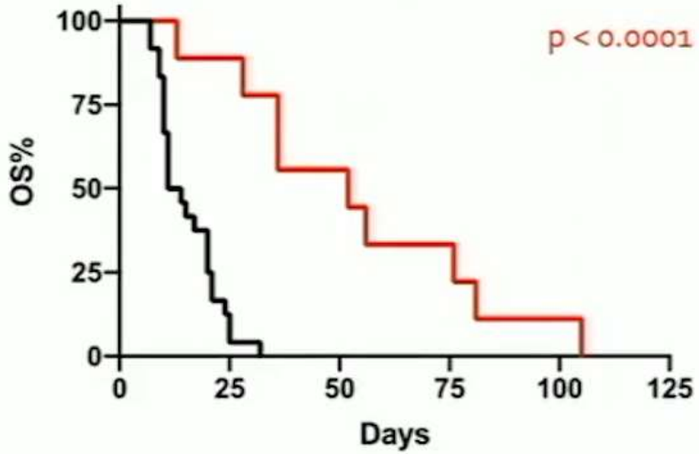


Buque et al. – Nat Commun 2020

Sensitivity to treatment

Sensitivity to CDK4/6 inhibitors





Median OS

Control (n=24): **12.5d**

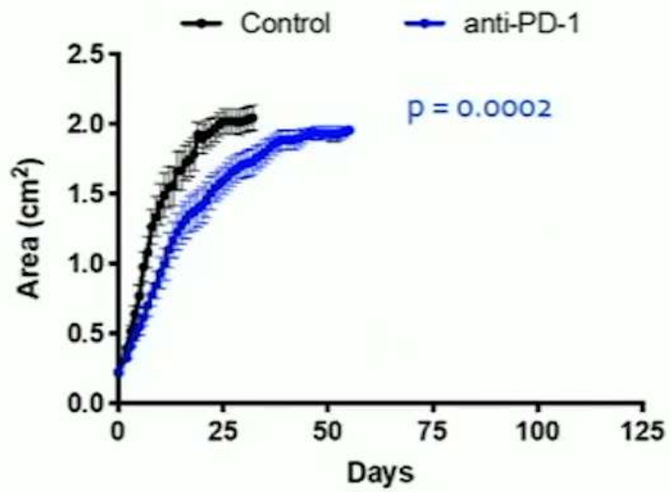
Palbociclib (n=9): **52d**

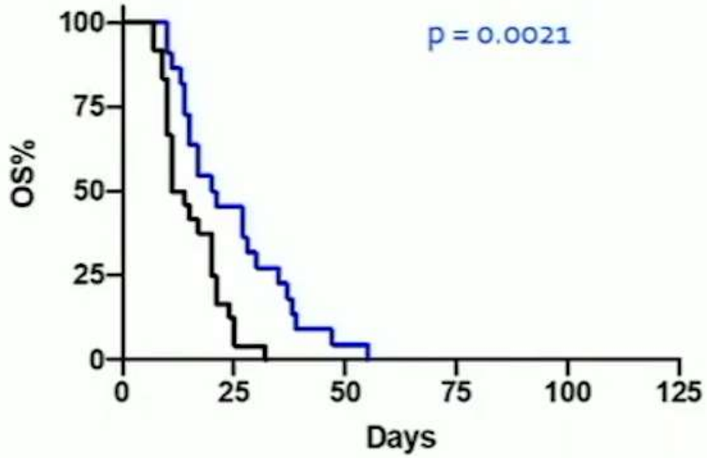
Median OS

Control (n=24): 12.5d

anti-PD-1 (n=22): **20.5d**

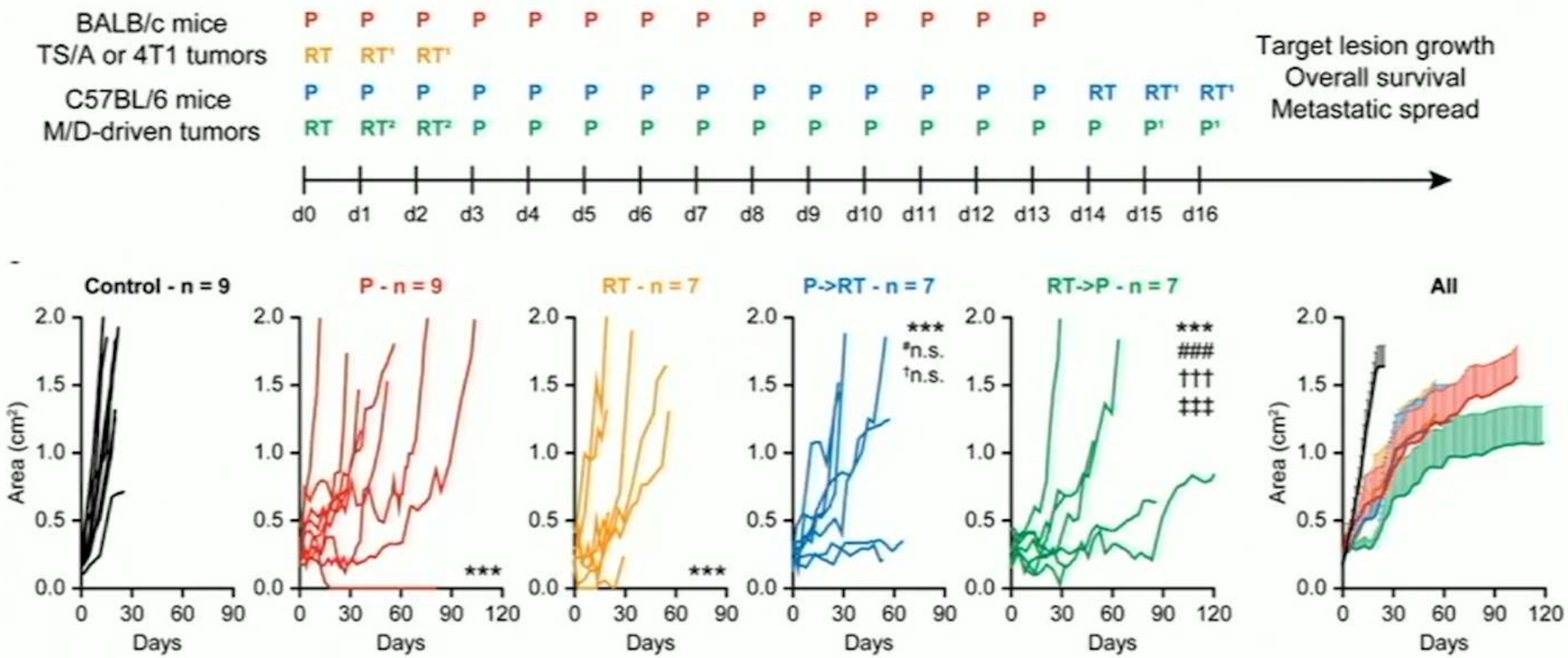
Poor sensitivity to PD1 blockade





Buque et al., Nat Comm 2020; Petroni et al., Clin Cancer Res 2021

RT plus CDK4/6 inhibitors in M/D-driven tumors



Critical role of treatment schedule

CIMER clinical trial

Petroni et al., Clin Cancer Res 2021

Open questions

What happens in the context of hormonotherapy?

What are the immunological consequences of treatment?

Open question

How do γδ T cells accumulate in tumors responding to CDK4/6 inhibitors?

Conclusions

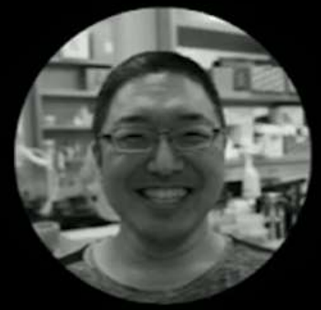
γδ T cells stand out as prominent candidates to underlie resistance to CDK4/6i +/- RT in patients

RT limits immunosuppression by γδ T cells to extend the efficacy of CDK4/6i, at least in preclinical settings

IL17 blockage may be considered as a clinically viable strategy to ameliorate the efficacy of CDK4/6i

lab galluzzi

Giulia Petroni



Takahiro Yamazaki

Aitziber Buqué

Norma Bloy

Claudia Galassi

Emma Guilbaud

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Beatriz Alvarez Abril

Vanessa Klapp

Ai Sato

KEEP CALM AND DO EPIC THINGS

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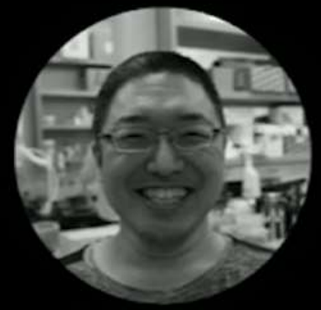

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