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# National Cancer Policy Forum

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SVP Immuno-Oncology, Early Development and Translational  
Oncology

July, 2018



Modeling to Predict Efficacy:

VEGFR Inhibition



Randomization to Detect ESoE:

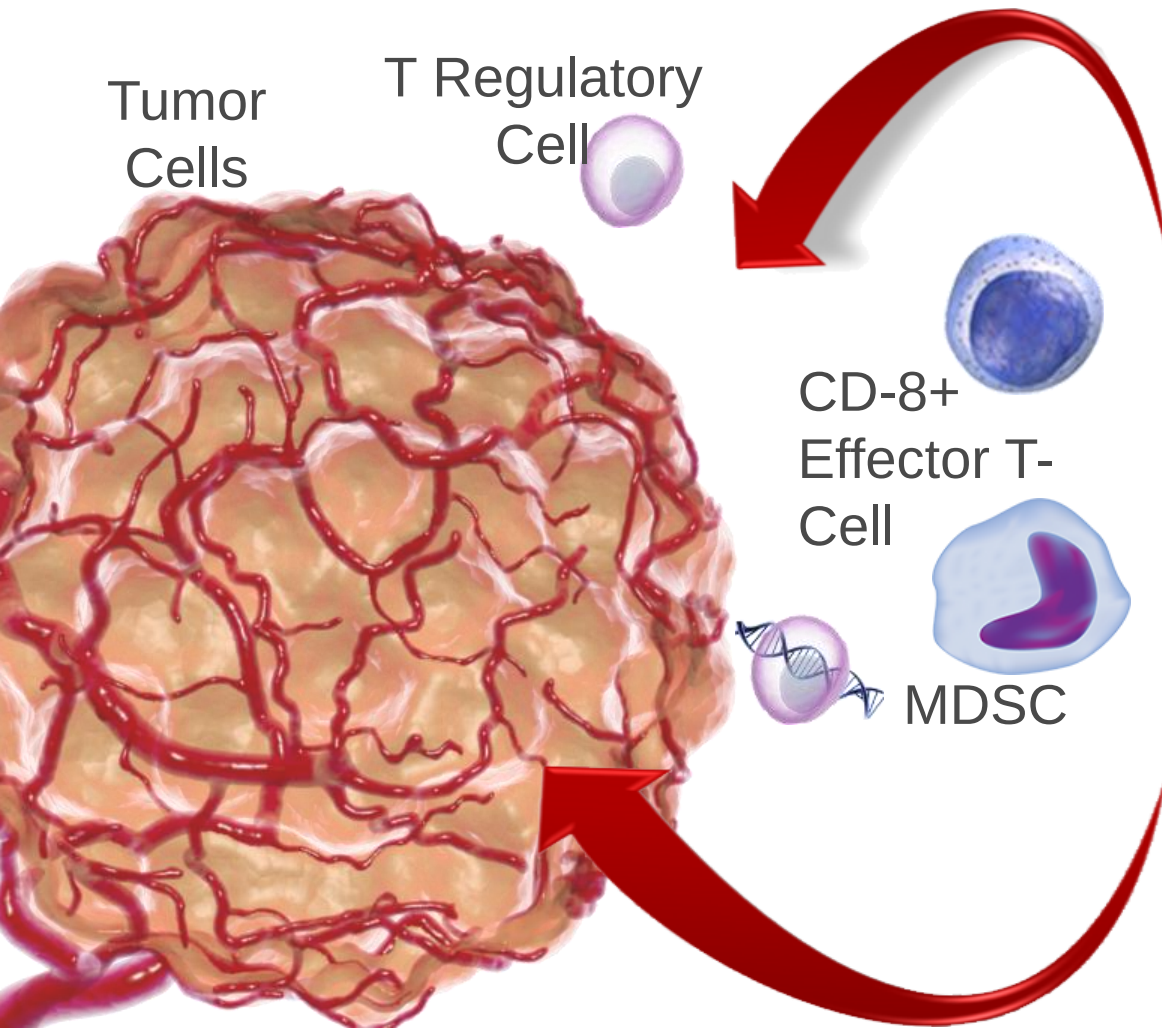
CDK4/6 Inhibition



RWD to Determine Efficacy:

PARP Inhibition

# Rationale for Combining Anti-Angiogenic Treatment With Anti-PD-L1



VEGFR2 is selectively expressed by FOXP3<sup>high</sup> CD4<sup>+</sup> Treg

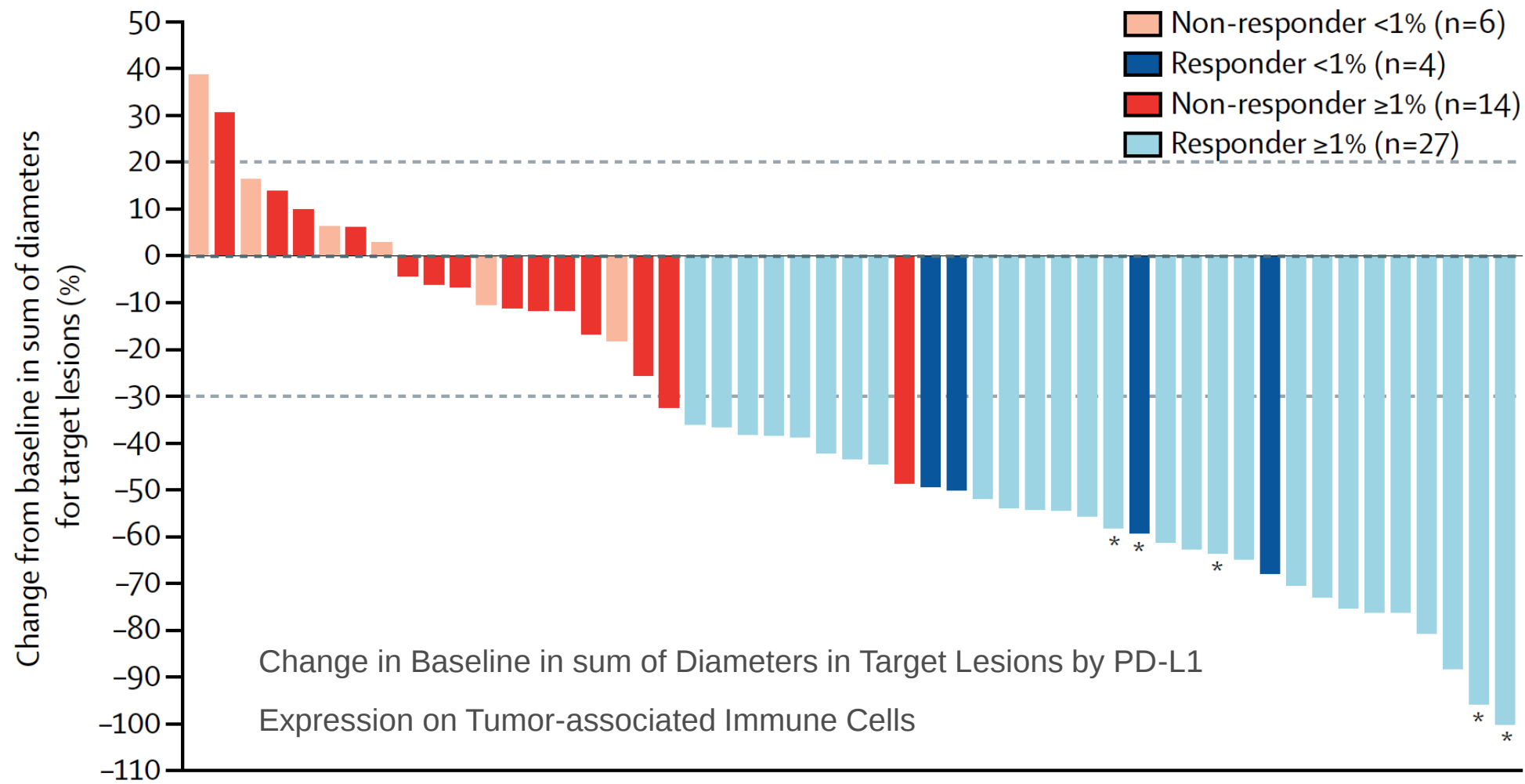
Eur J Immunol , 2009, Suzuki et al.

Simultaneous blockade of PD-1 and VEGFR2 induced synergistic anti-tumour effect *in vivo*, in various models  
Clin & Exp Immunology, 2013, Yasuda et al.

Anti-angiogenesis therapies may partially depend on their effects on vessel normalization and the consequent reprogramming of the immune TME

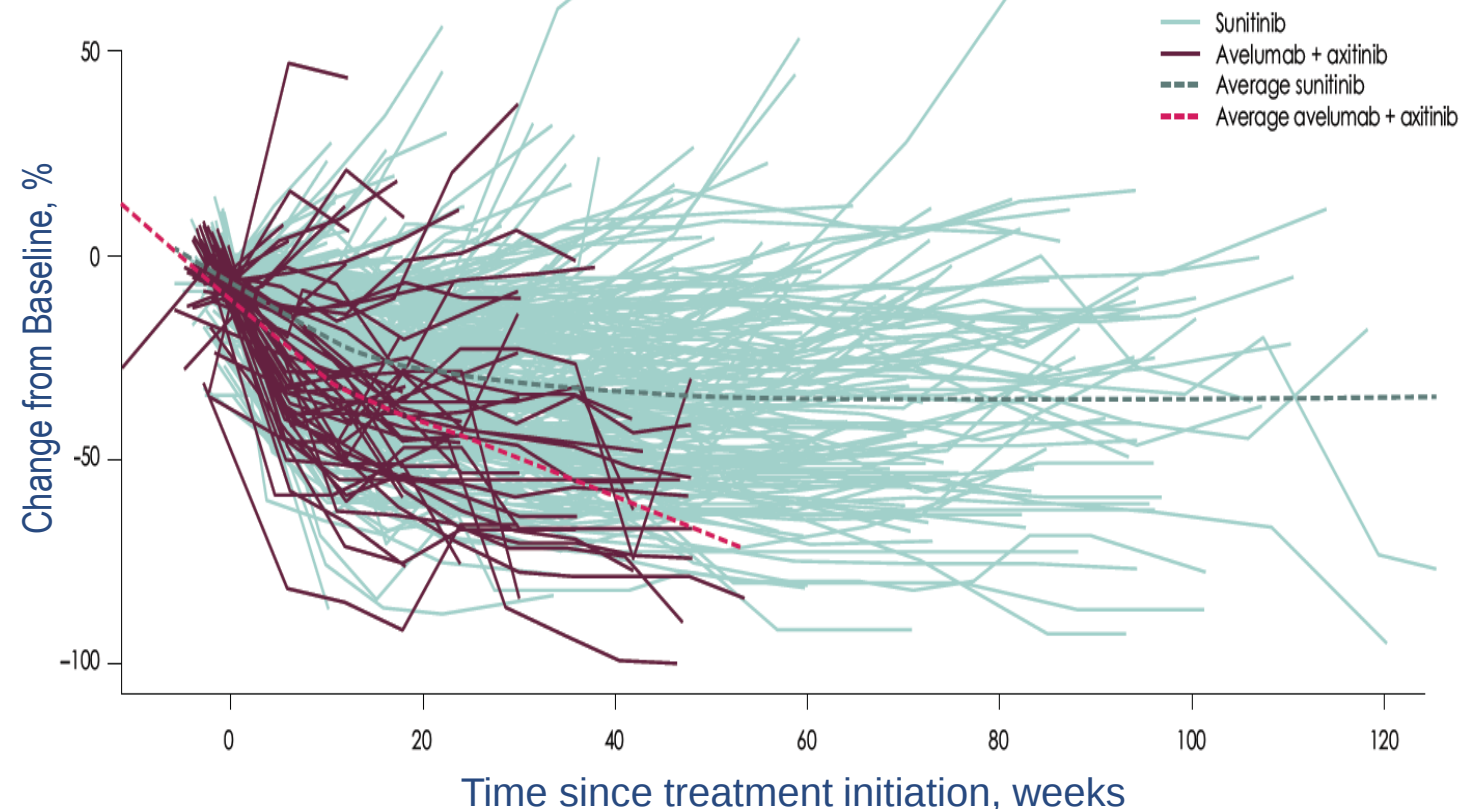
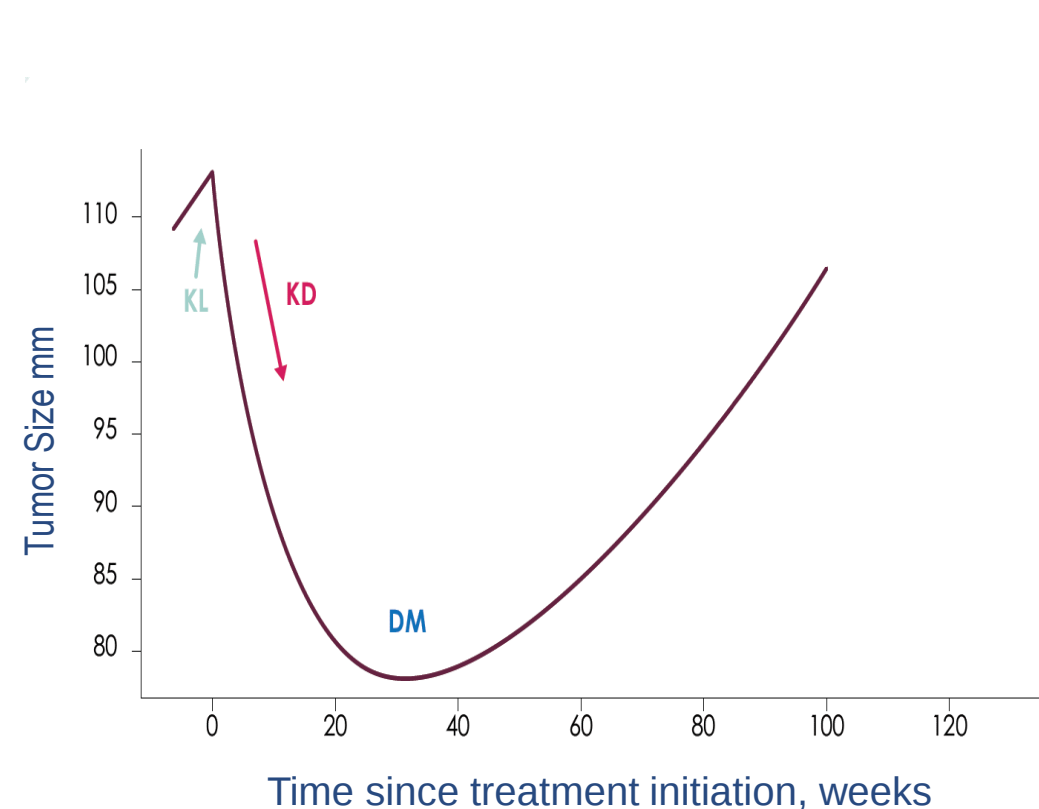
Tian, L, Nature, 544, 250–254, 13 April 2017

# Axitinib + Avelumab, 1L RCC, Change in Tumor Burden



# Potential Impact of avelumab + axitinib on Tumor Size Compared with Historical Data of sunitinib as Evaluated by a Modeling and Simulation Approach

Avelumab + axitinib appear to have a greater impact on tumor burden than sunitinib



# Axitinib + Pembrolizumab in 1L RCC: Phase 1 Overall Survival

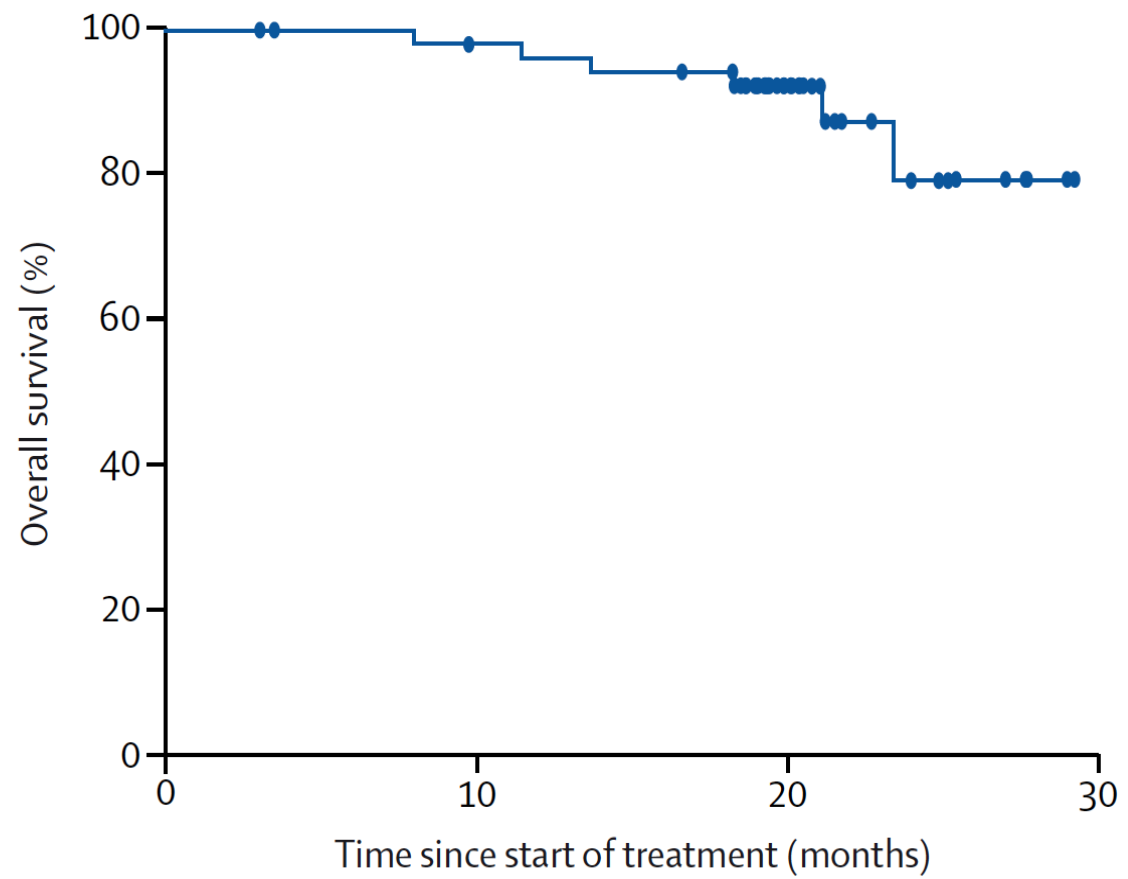


## 1L RCC Ph 3 Studies

- Nivolumab + NKT214 (IL-2PEG)
  - Axitinib + Avelumab
  - Axitinib + Pembrolizumab
  - Lenvatinib + Pembrolizumab
  - Cabozantinib + Nivolumab
  - Bevacizumab + Atezolizumab\*
  - Nivolumab + Ipilimumab\*\*
- Ph 1/2

Ph 3

Approved



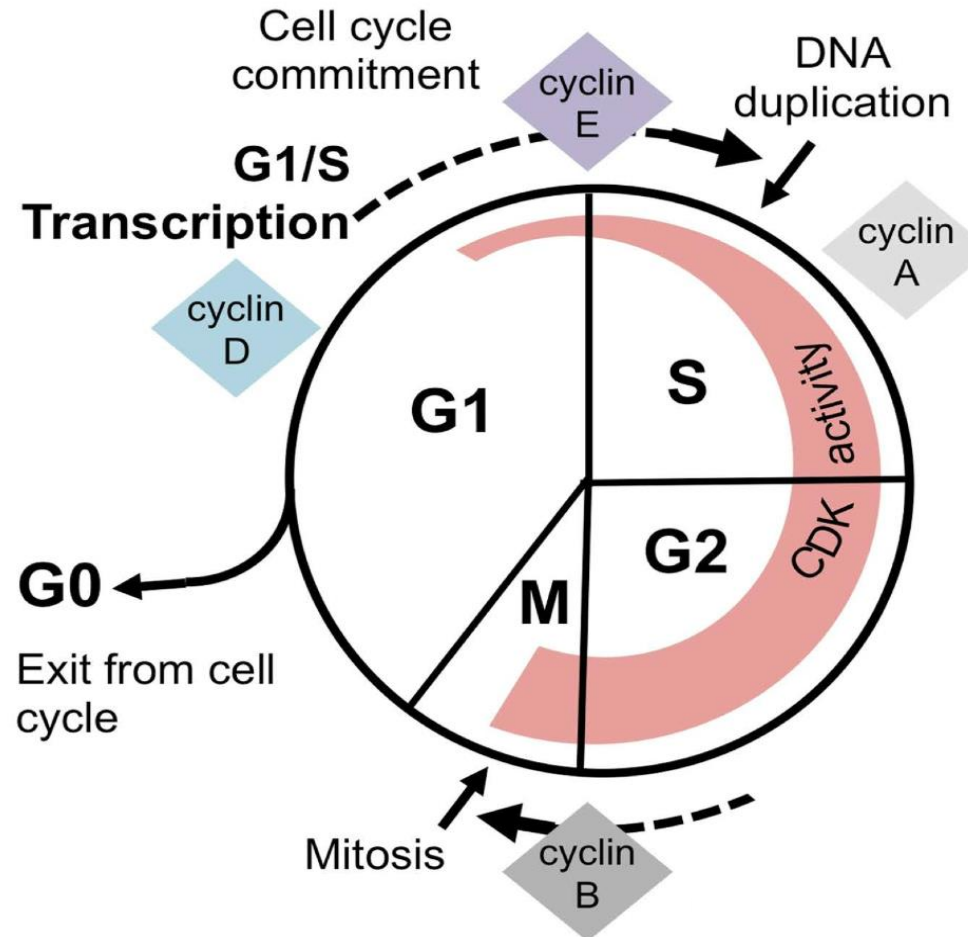
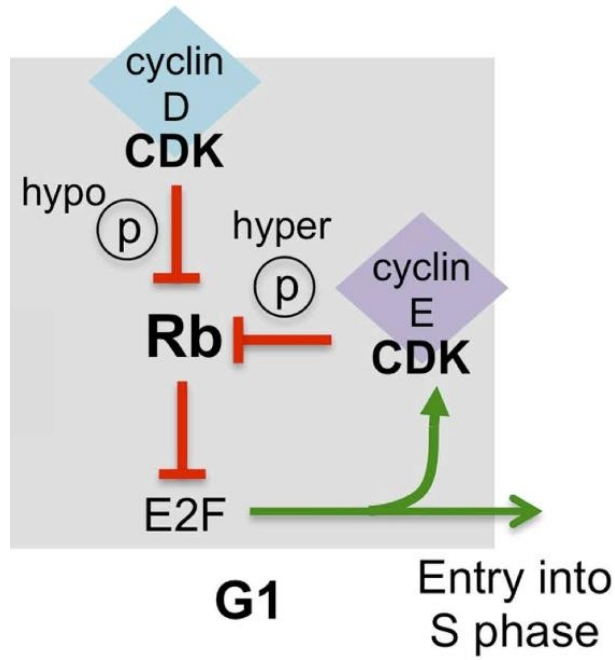
|                |     |     |      |      |
|----------------|-----|-----|------|------|
| Number at risk | 52  | 48  | 27   | 0    |
| (censored)     | (0) | (3) | (21) | (46) |

\*IMmotion 151 Reported positive PFS, Feb 2018  
\*\*FDA approves nivolumab + ipilimumab combination for intermediate or poor-risk RCC, April, 2018





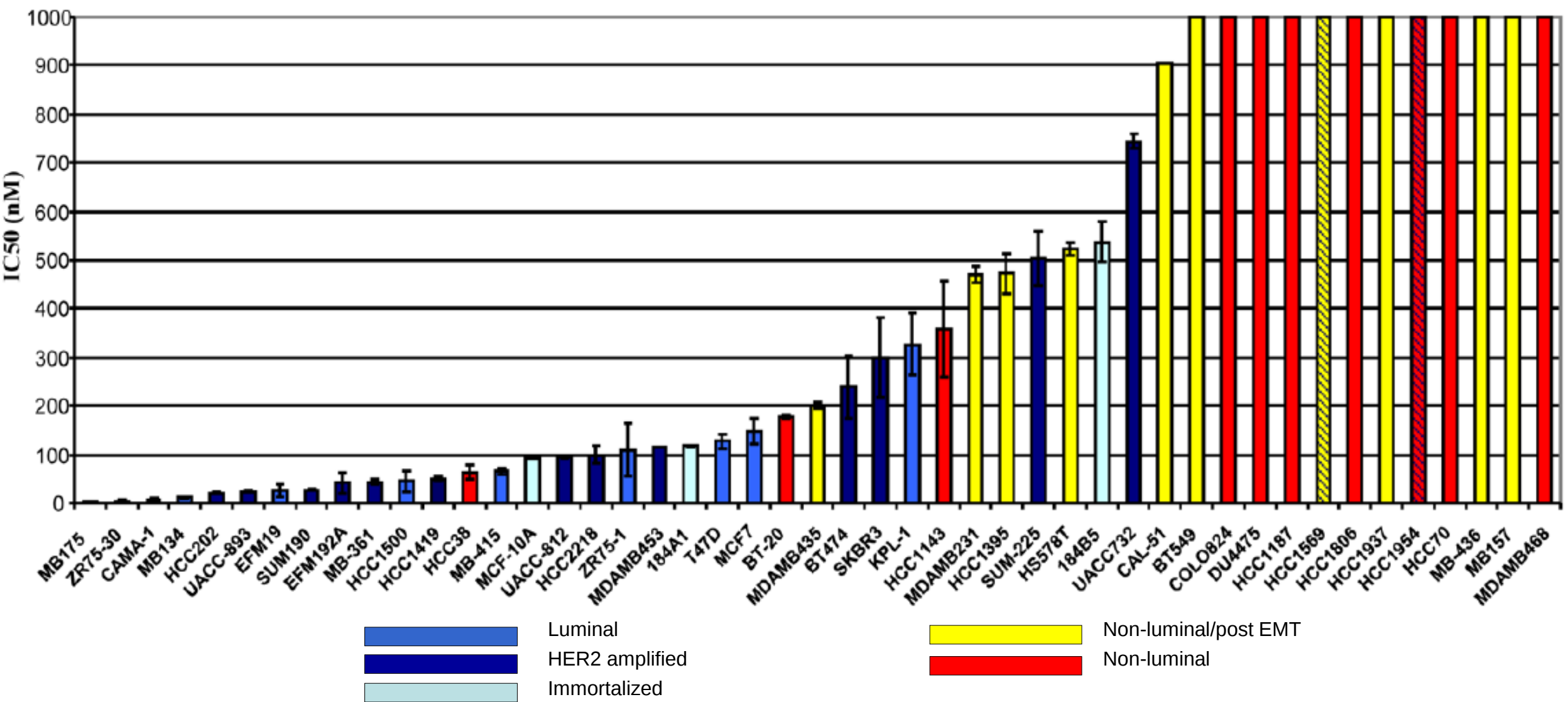
# Targeting the Cell Cycle: CDK4/6 Inhibition and Immunity



CDK4 expression and activity are necessary to establish IL-2 responsiveness in T-lymphocytes

Modiano et al, J Immunol, Dec 2000, 165: 6693

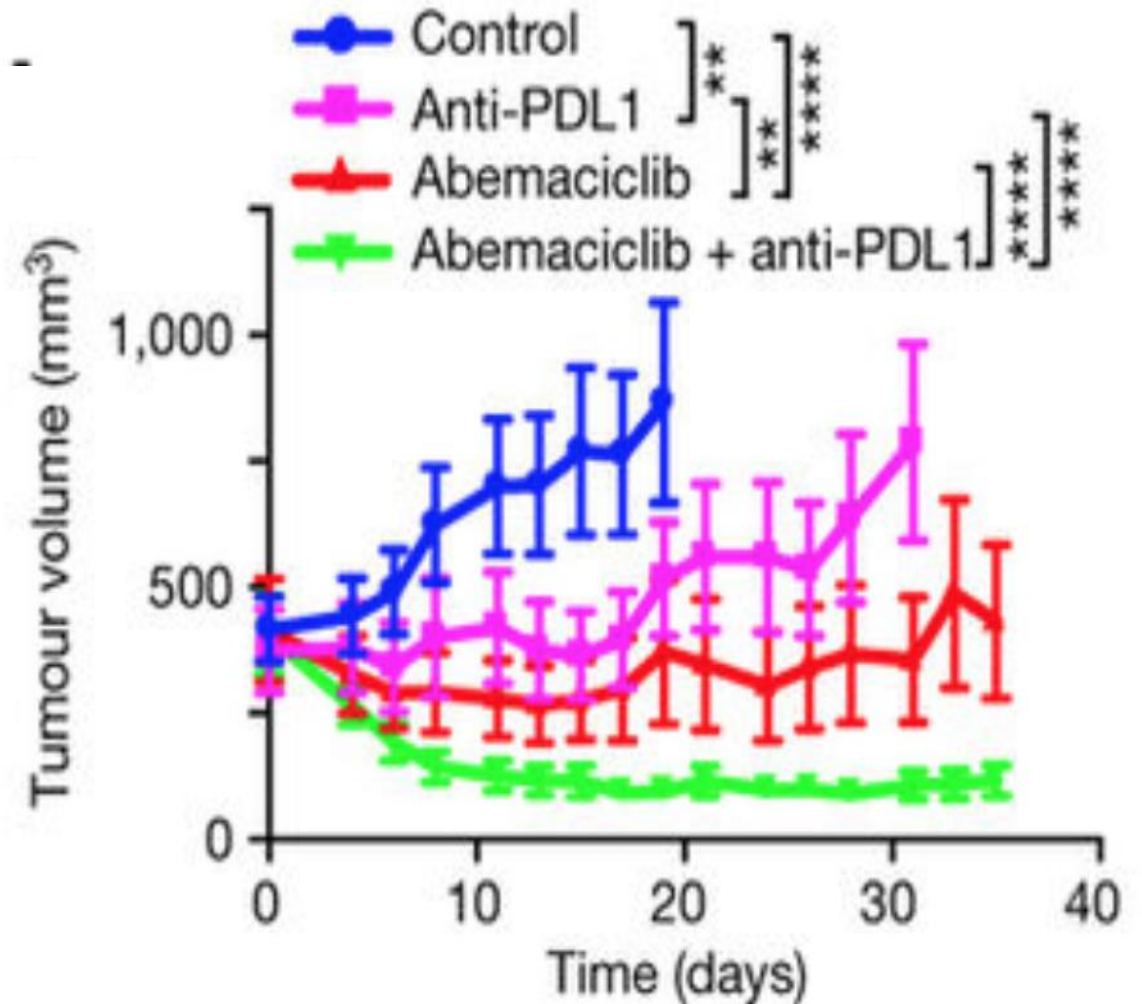
# Palbociclib Preferentially Inhibits Proliferation of Luminal ER+ Human Breast Cancer Cell Lines



# CDK4/6 Inhibition + Immune Checkpoint Blocker



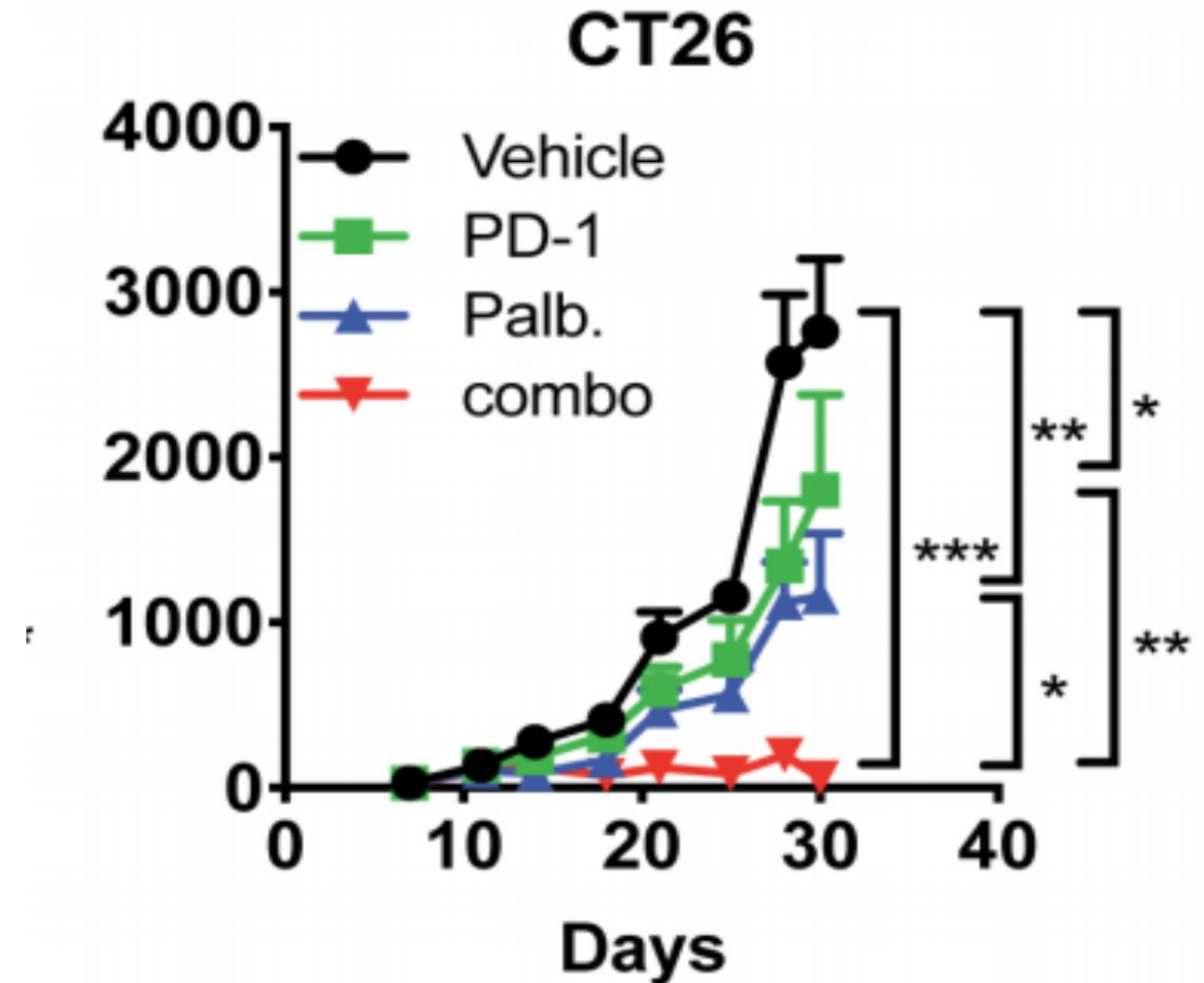
CDK4/6 inhibitors activate tumor cell expression of endogenous retroviral elements, increasing intracellular levels of double-stranded RNA. This induces type III interferons and tumor antigen presentation



# CDK4/6 Inhibition + ICB



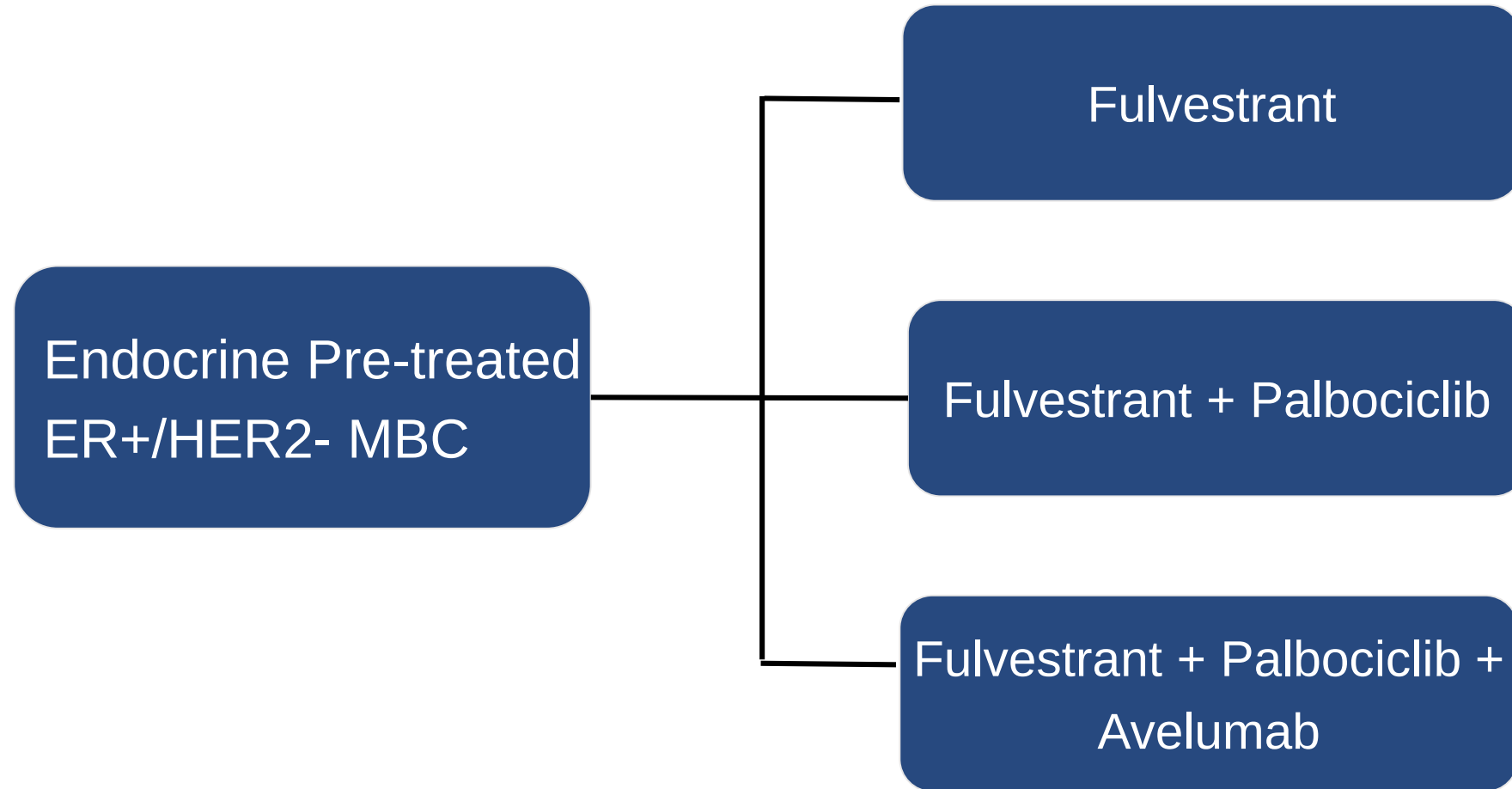
CDK4/6 inhibitors decrease T cell proliferation, but increase tumor T-cell infiltration and activation of effector T cells



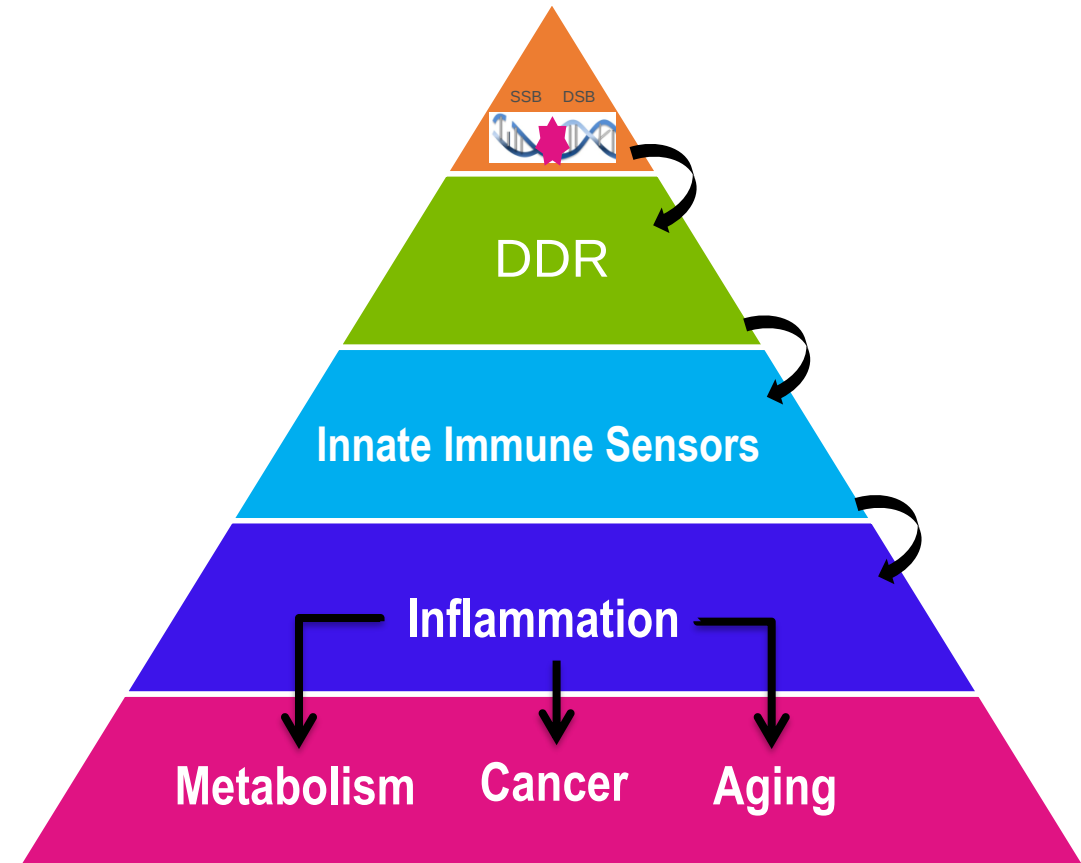
# Randomized Experience to Test Preclinical Hypothesis



## Palbociclib After CDK and Endocrine Therapy (PACE) Phase 2 Study



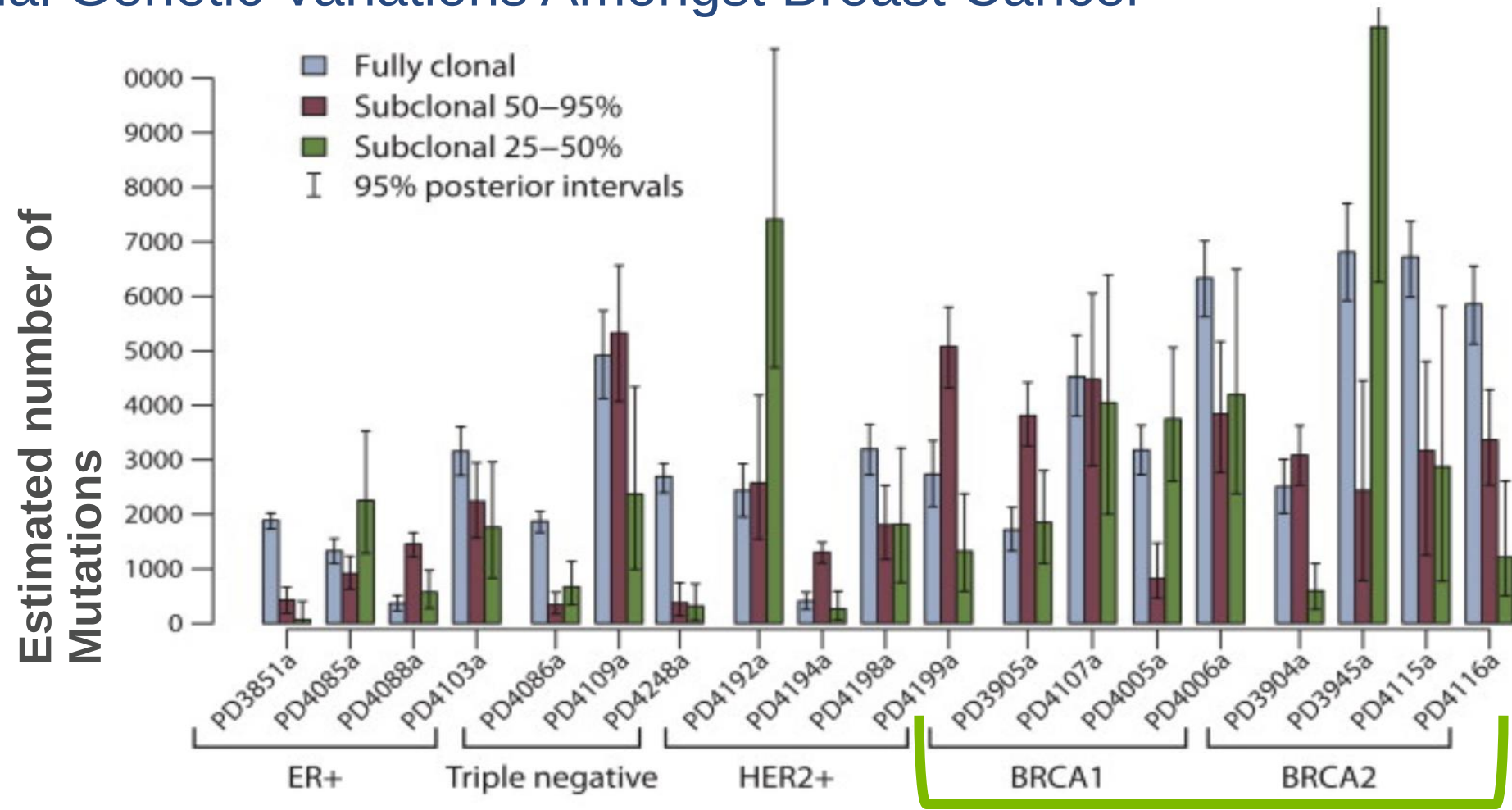
- ◆ DNA damage accumulates with age, leading to the persistent activation of DNA damage sensors and the DDR
- ◆ Chronic activation of DDR triggers inflammatory responses leading to age-related pathologies including cancer
- ◆ DDR defects are present in 2-30% of all cancers and could indicate sensitivity to PARP inhibitors or other DNA repair targeted therapies



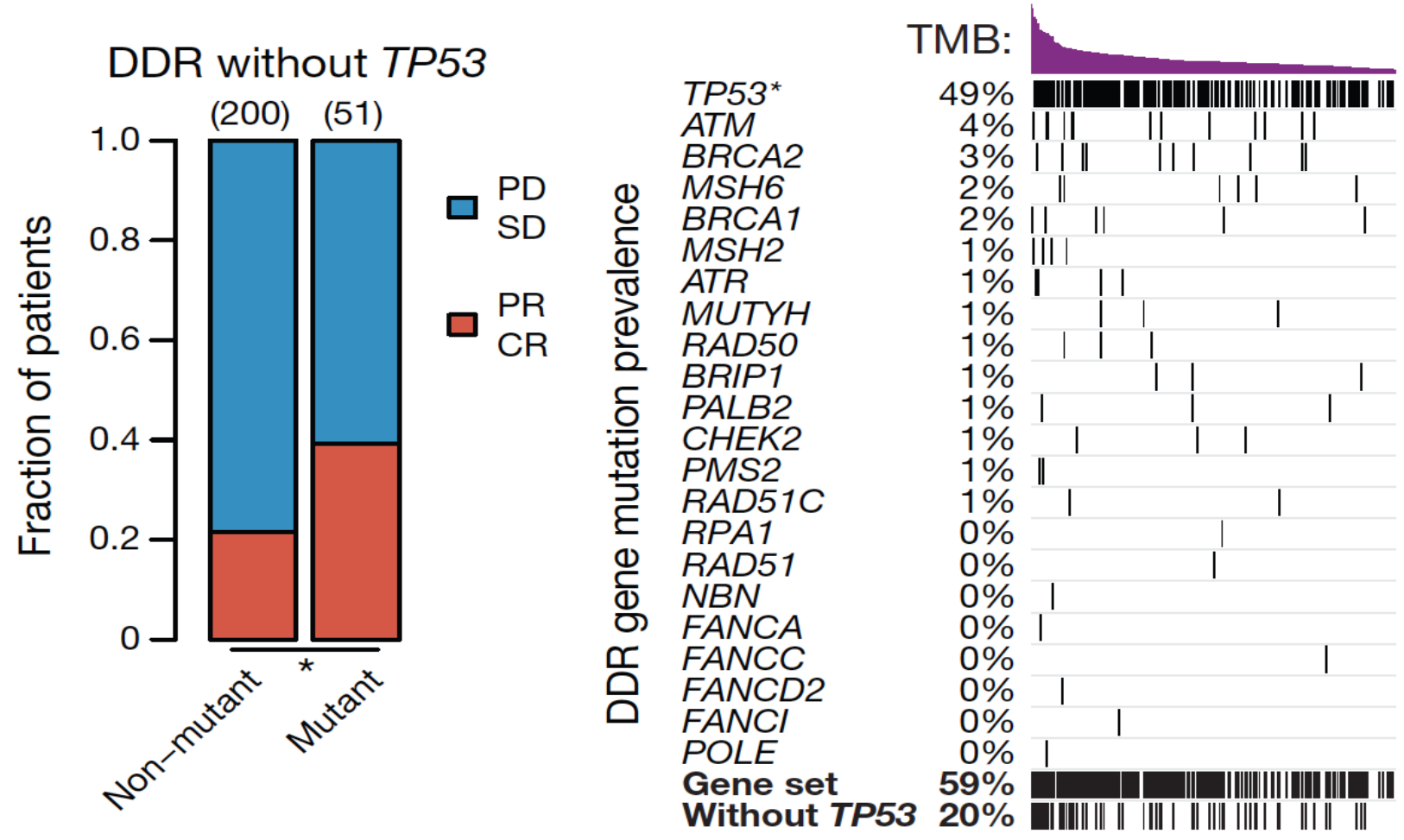
DDR = **D**NA **D**amage **R**esponse



## Subclonal Genetic Variations Amongst Breast Cancer



# Association Between DDR Status & Responses to Atezolizumab in UCC



| NSCLC   |          |
|---------|----------|
| Variant | Mean TMB |
| EGFR    | 4.5      |
| ALK     | 2.8      |
| ROS1    | 3.9      |
| BRAF    | 9.7      |
| KRAS    | 10.3     |
| BRCA1   | 19.2     |
| BRCA2   | 13.8     |
| POLE    | 25.1     |

Spigel, et al. ASCO, 2017

# Avelumab (anti-PD-L1) + talazoparib (PARPi) Somatic BRCA1 Mutant Ovarian Cancer



25.9mm x 20.3mm  
Oct 2017

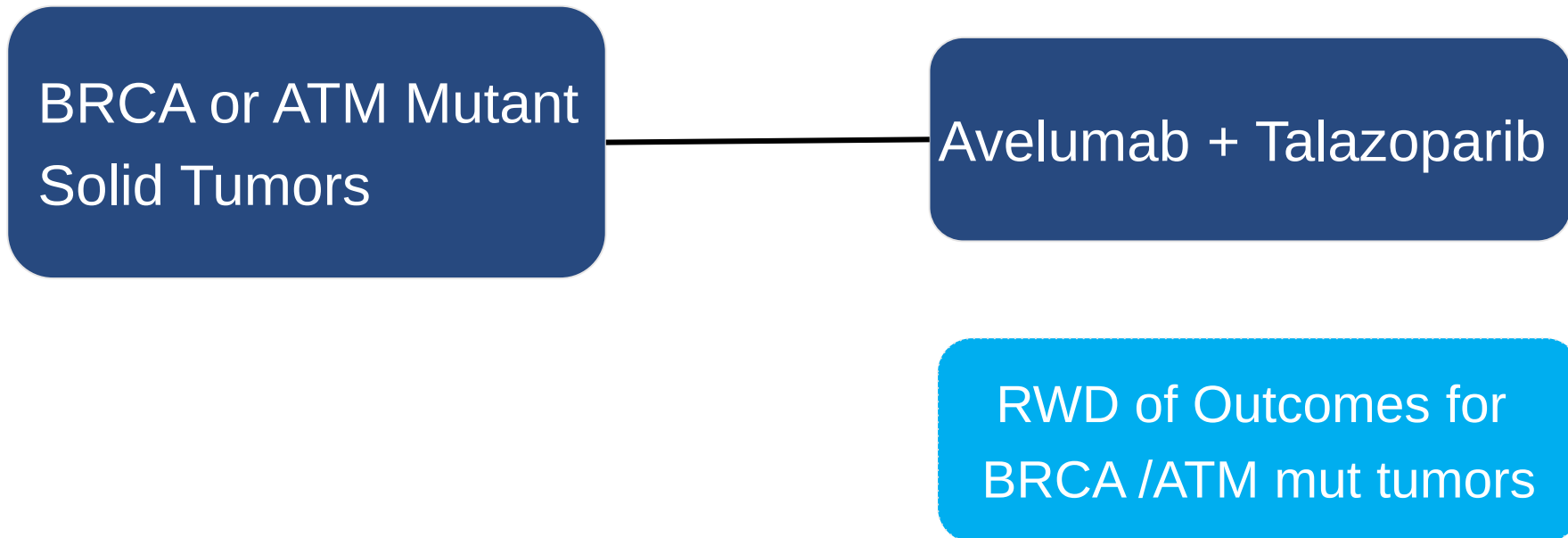


7.8mm x 6.3mm  
Apr 2018

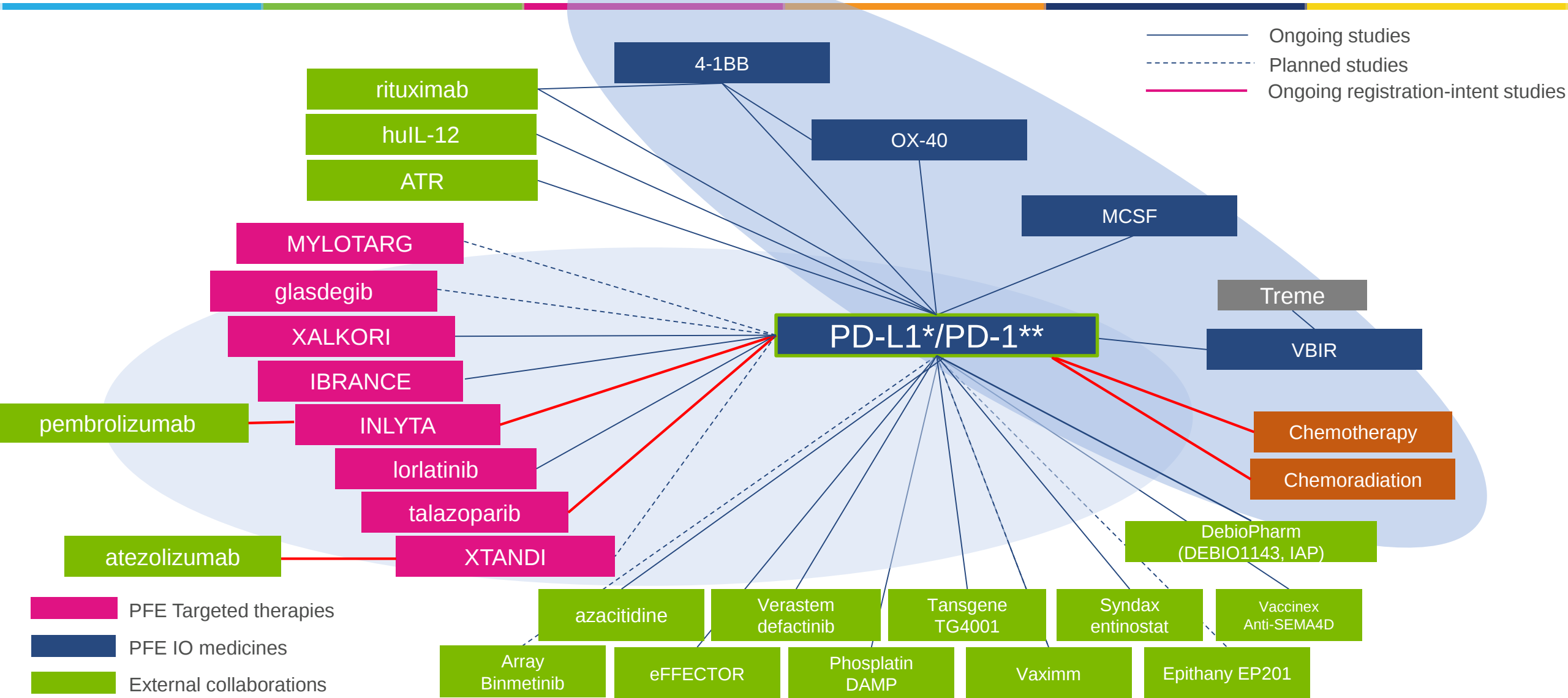


58% RECIST PR (ongoing)

## Javelin BRCA/ATM: Phase 2



# Ongoing and Planned Combinations



\*Avelumab/Bavencio, co-development and co-commercialization with Merck KGaA

\*\*Subcutaneous 4 weekly anti-PD-1, RN888/PF-06801591



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# Thank You