

Targeting CDK4/6 in Her2 Positive Breast Cancer Therapeutic Effect, Markers, and Combination Strategies

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Disclosures

Permeon pharmaceuticals 

Consultant, Research Contract 

Elisabell 

Honorarium 

Fluidigm 

Research Contract 

Pfizer 

Advisory Board, Research Contract 

Rationally targeting Her2-positive breast cancer

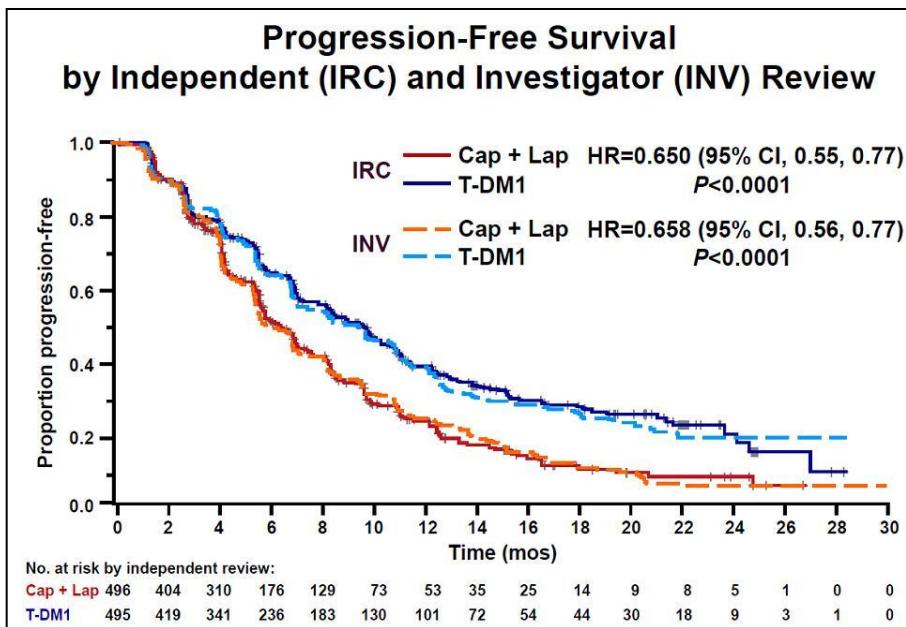
~20% of breast cancer cases are clinically HER2-positive



Targeted Drug
Trastuzamab
Lapatinib
T-DM1

Tumors are treated with HER2 targeted agents

Even with potent targeted therapies **recurrence** and **progression** of disease occur



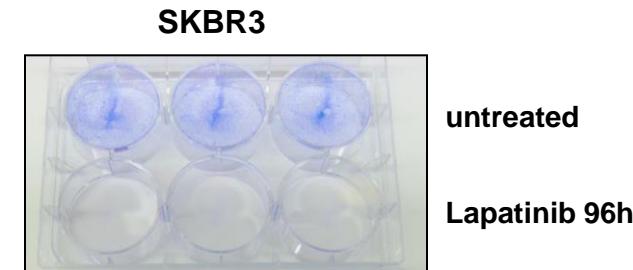
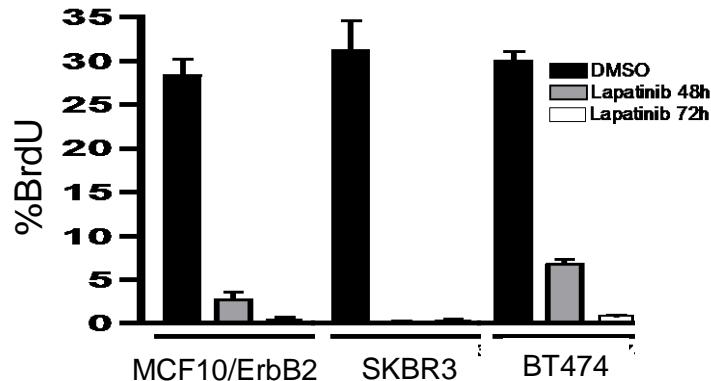
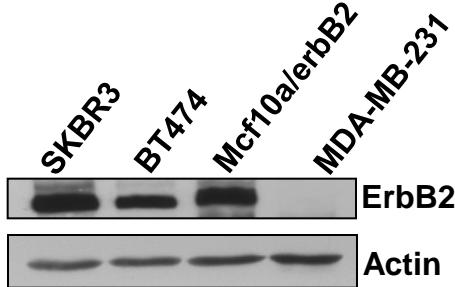
Multiple Mechanisms:

Her2 mutation/loss/masking (e.g. p95)

Alternate receptor signaling (e.g. cMET)

Deregulated intracellular signaling (e.g. PTEN)

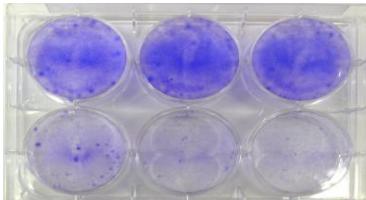
Lapatinib has activity in Her2-positive models



...acquired resistance can readily develop

Sensitive Her2+ model

MCF10A/ErbB2



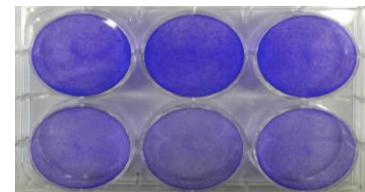
DMSO

Lapatinib 96h

Select low dose drug
3-5 wks

Resistant model

B1-Res

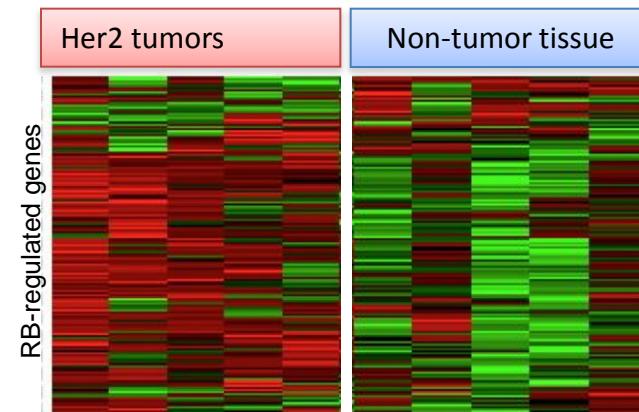
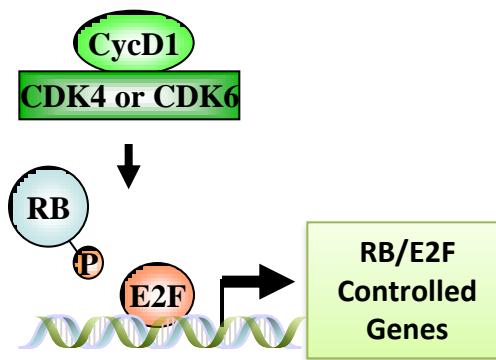
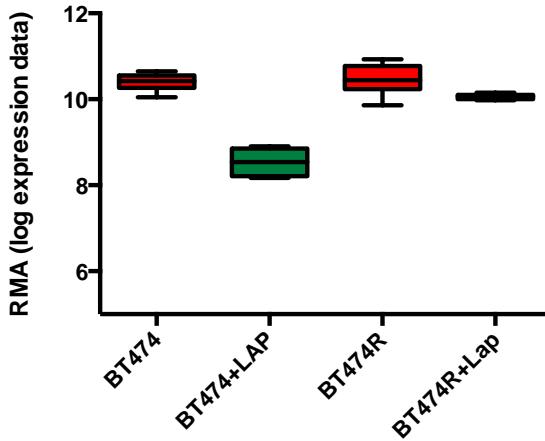


DMSO

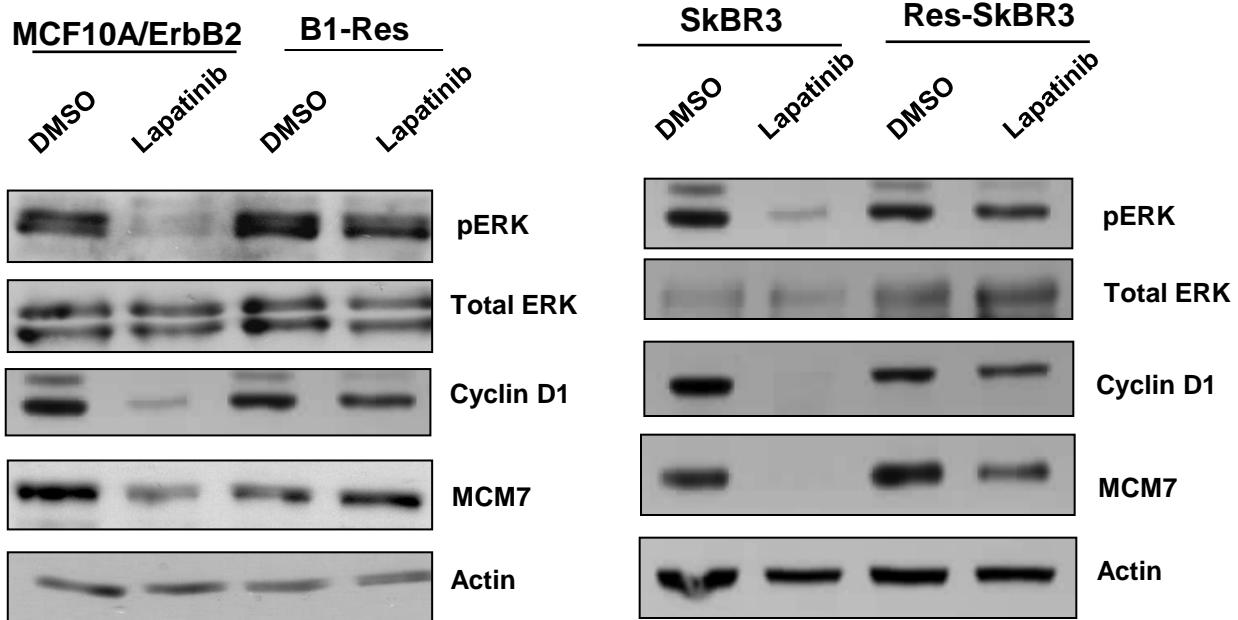
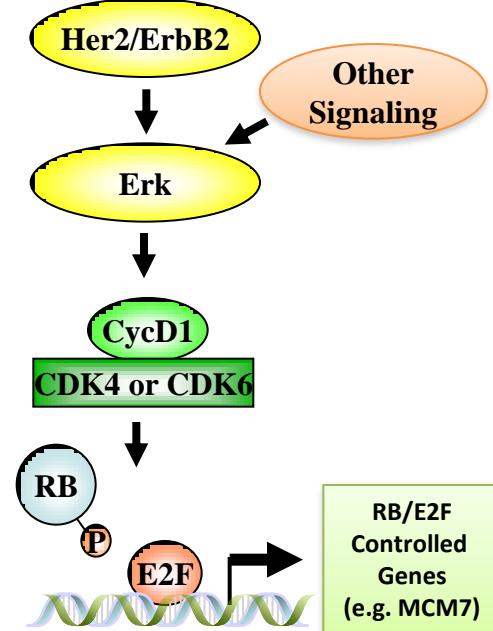
Lapatinib 96h

Her2 signaling impacts the CDK4/RB-pathway

Cyclin D1 Transcript



Resistance and deregulated downstream signaling



Target downstream: CDK4/6 in Her2 positive breast cancer

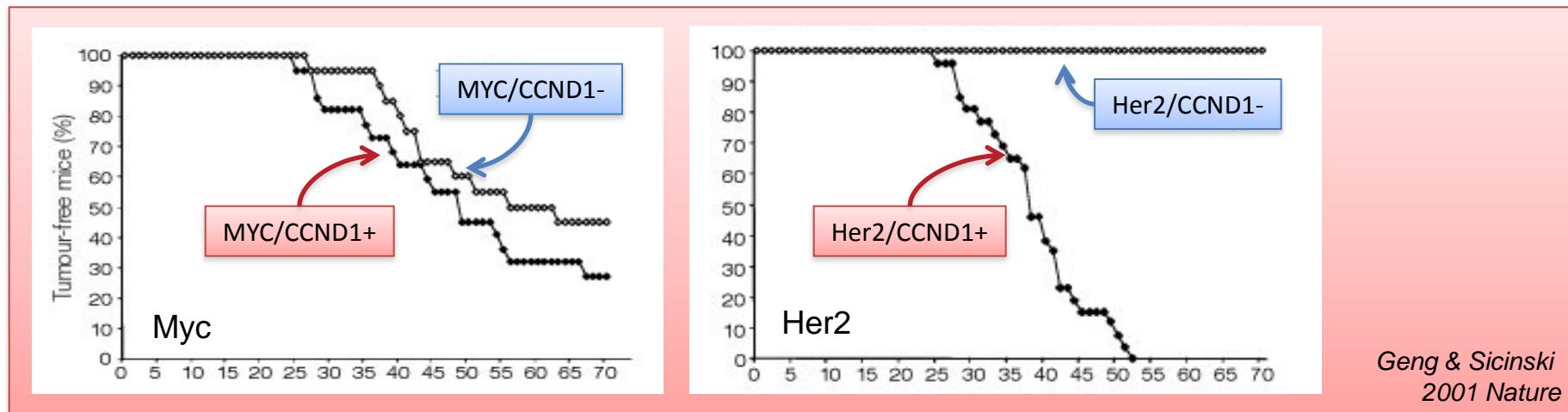
CDK4/6 and Cyclin D1 is downstream of Her2

*Multiple Her2 signaling arms coalesce to control Cyclin D1 accumulation

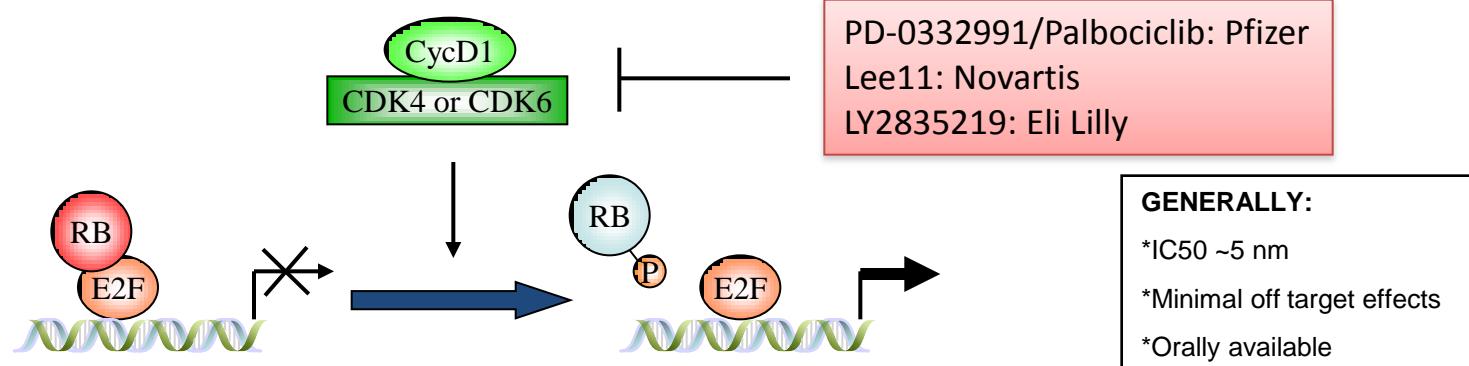
*Deregulation of Cyclin D1 is a common feature of resistance

Cyclin D1 is a unique genetic determinant of Her2 mammary tumors

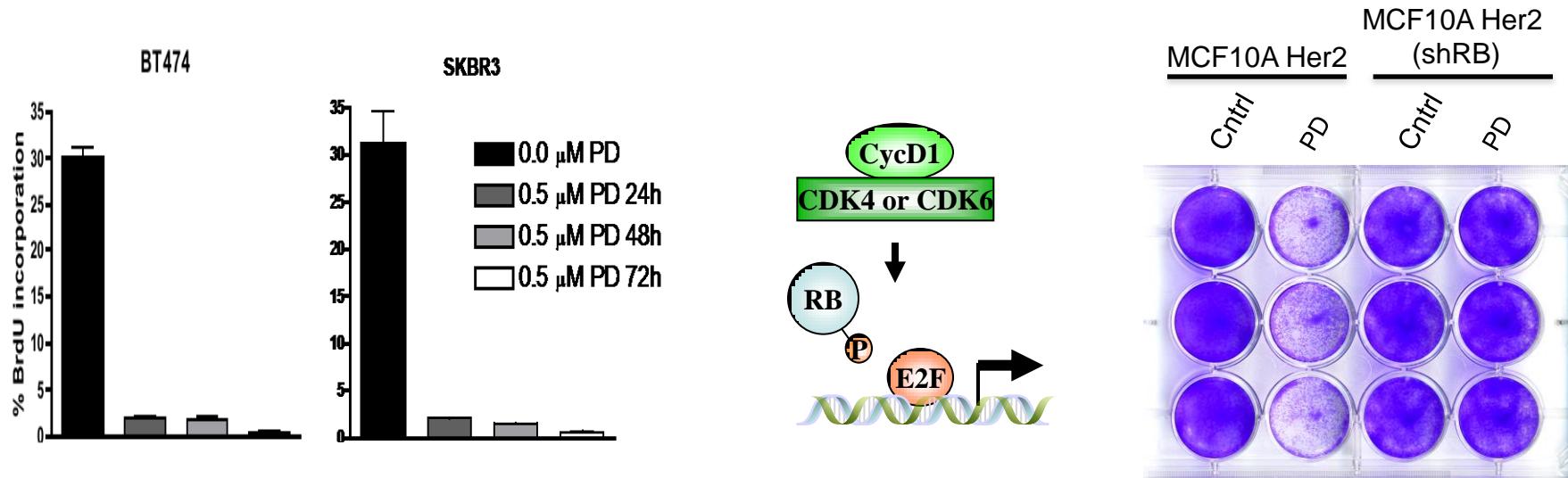
*Deletion of cyclin D1 prevents tumor formation



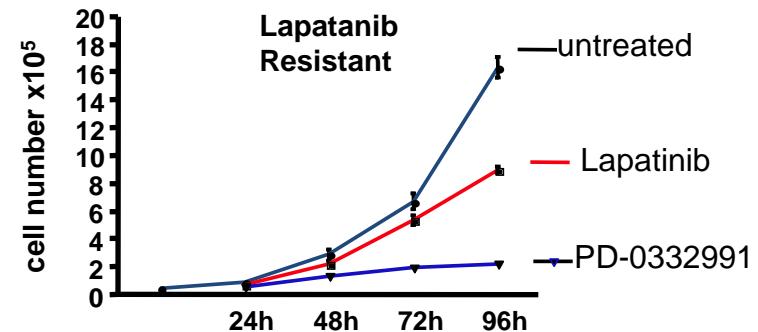
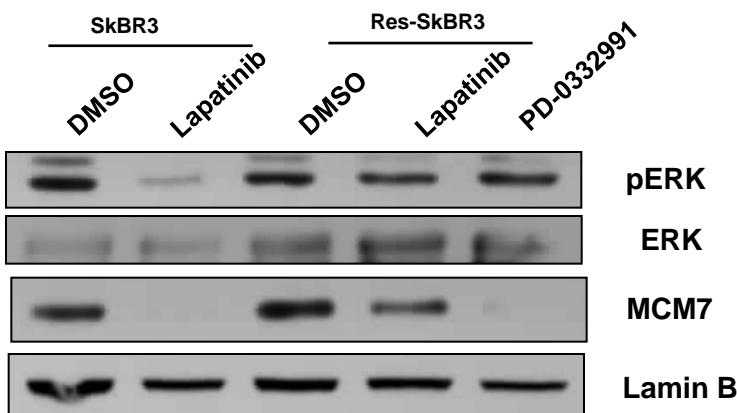
Pharmacological CDK4/6 inhibitors



CDK4/6 inhibition is highly effective in cell models of Her2-positive breast cancer



CDK4/6 inhibition is effective in models resistant to Her2-targeted agents



Efficacy of CDK4/6 inhibition in Her2 positive tumor models

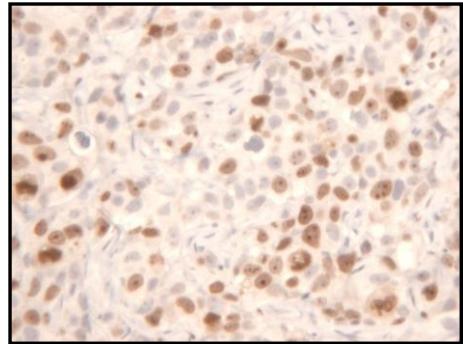
Tumor Lines
or
GEMMs



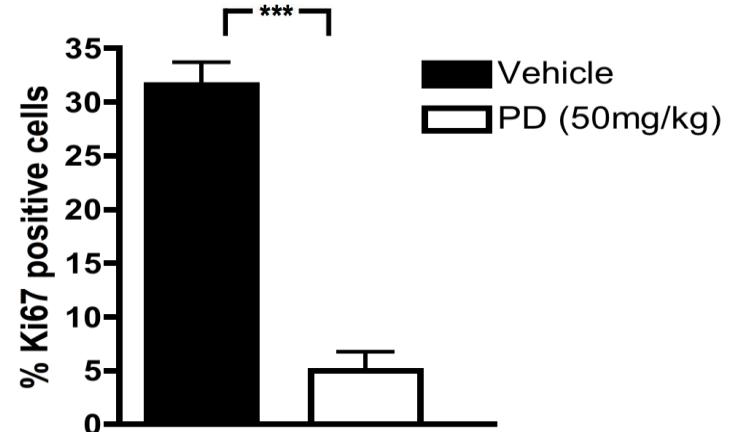
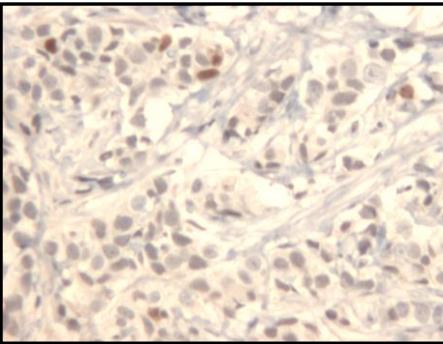
Treat with
PD-0332991
Orally

BT474 Xenografts

Vehicle

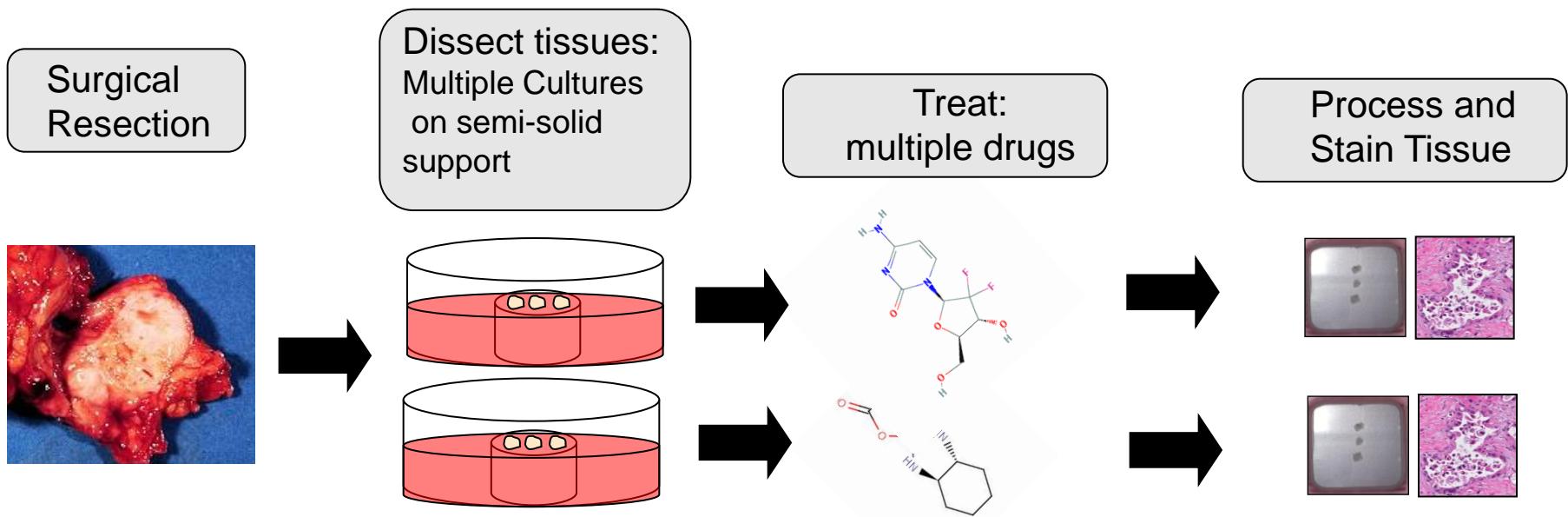


PD (50mg/kg)



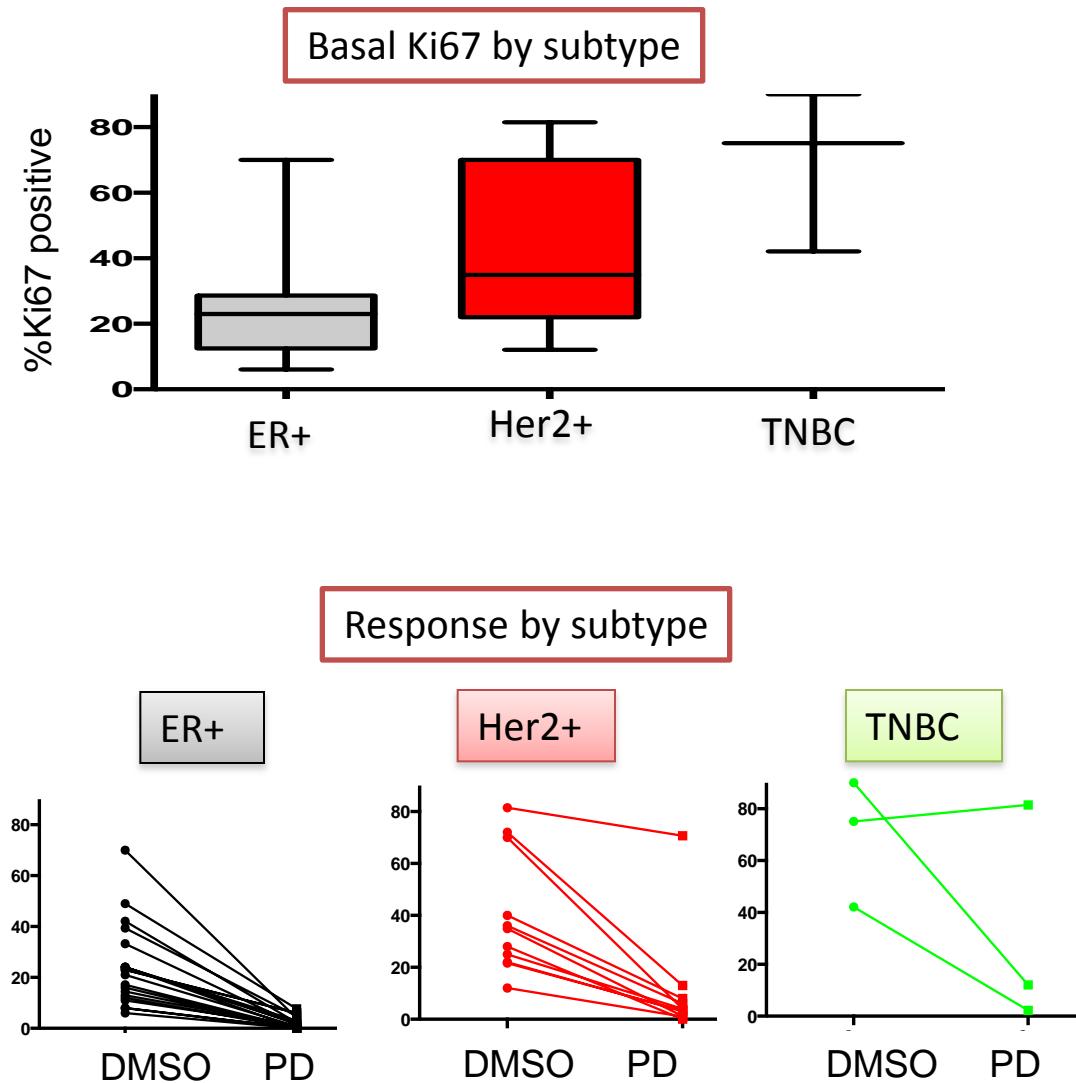
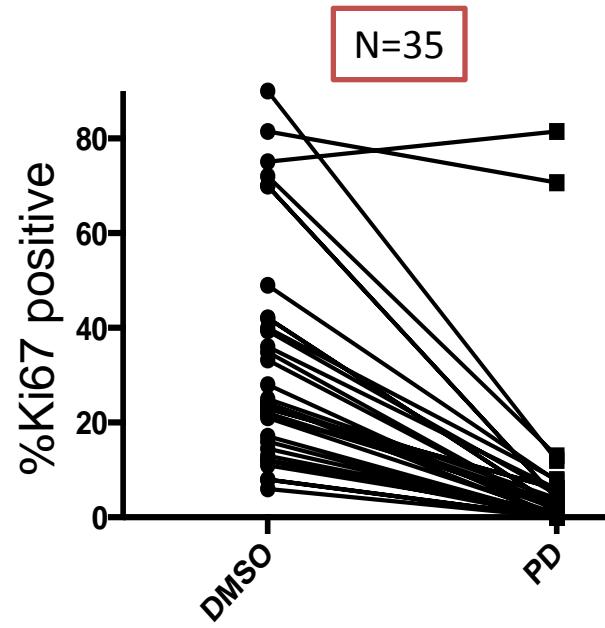
Reflect the heterogeneity of breast cancer
as seen in the clinic?

Bringing the clinic to the lab: tumor explants

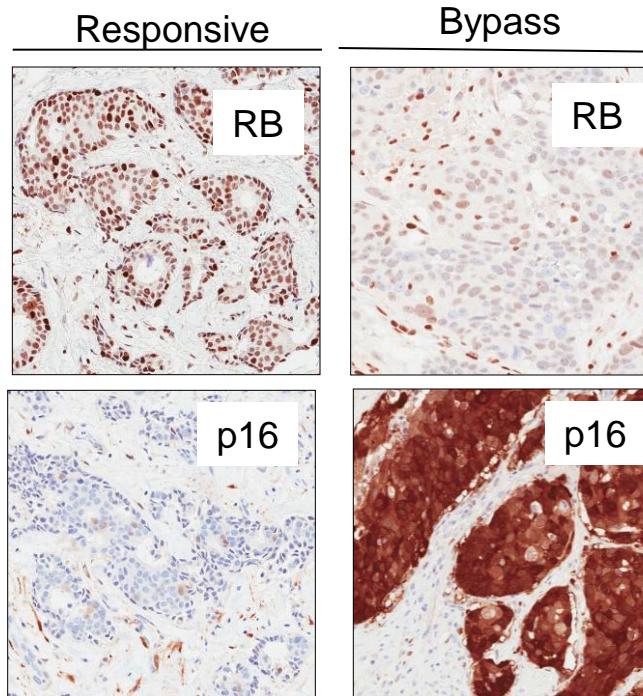
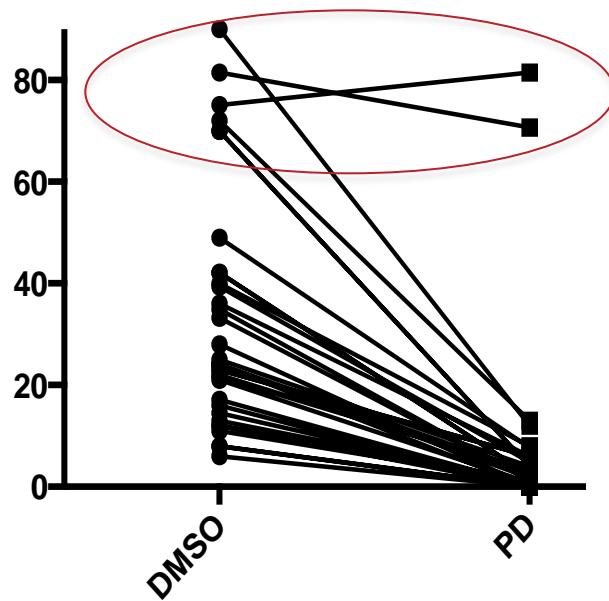


- 1. Unselected cases (higher volume disease)**
- 2. Multiple therapy relevant drugs**
- 3. Evaluation of response/markers**

Subtypes specific response to CDK4/6 inhibition ex vivo



Predicting response of tumors to CDK4/6 inhibition *ex vivo*



Primary human tumors provide

*Frequency of response (33/35->90%)

ER+:100%

Her2+:90%

TNBC: 75%

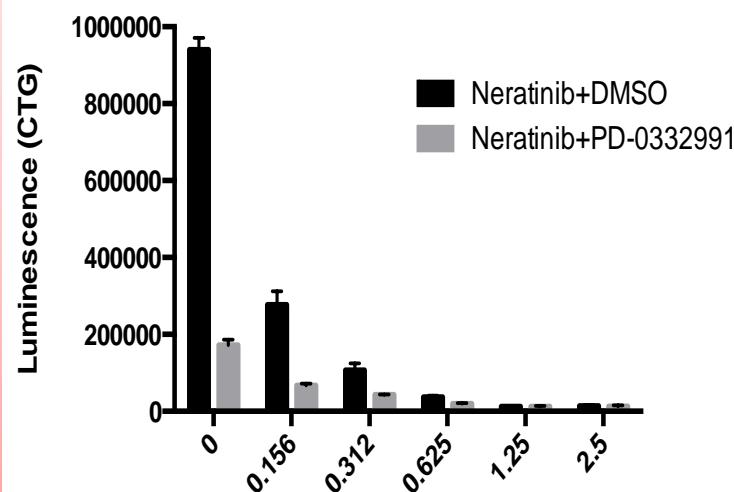
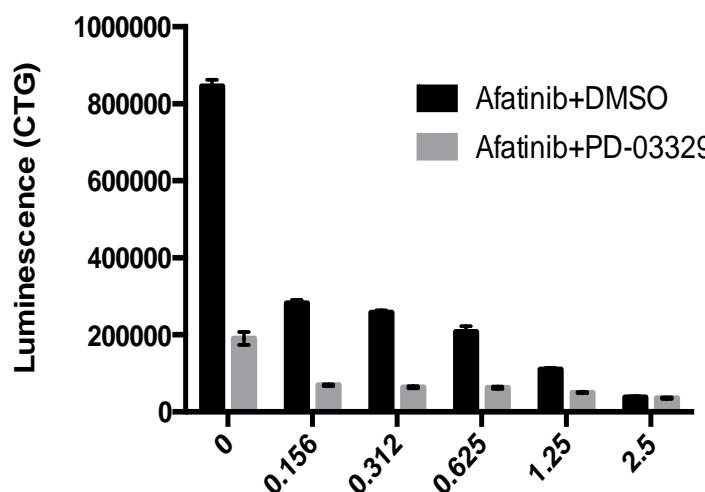
*Biomarkers of response (RB/p16)

Applying CDK4/6 inhibition in Her2-positive breast cancer

Combine with the Her2-targeted therapy for advanced disease

Screening for cooperation with Her2-targeted small molecules

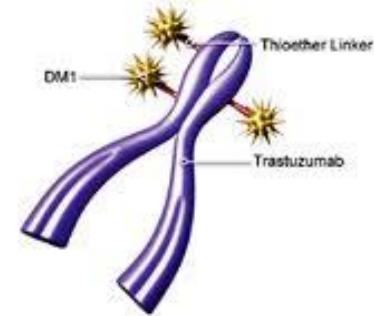
Generally Additive effects



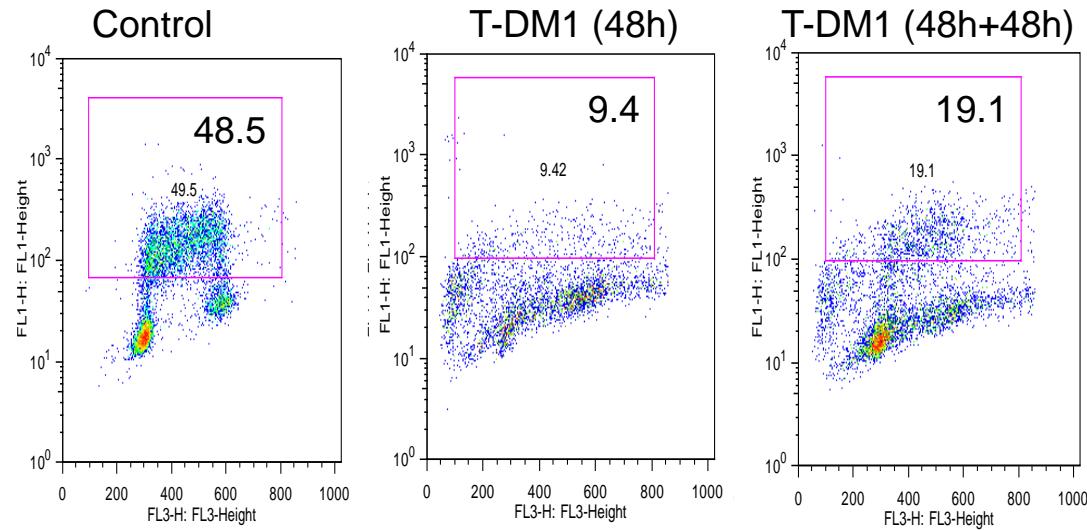
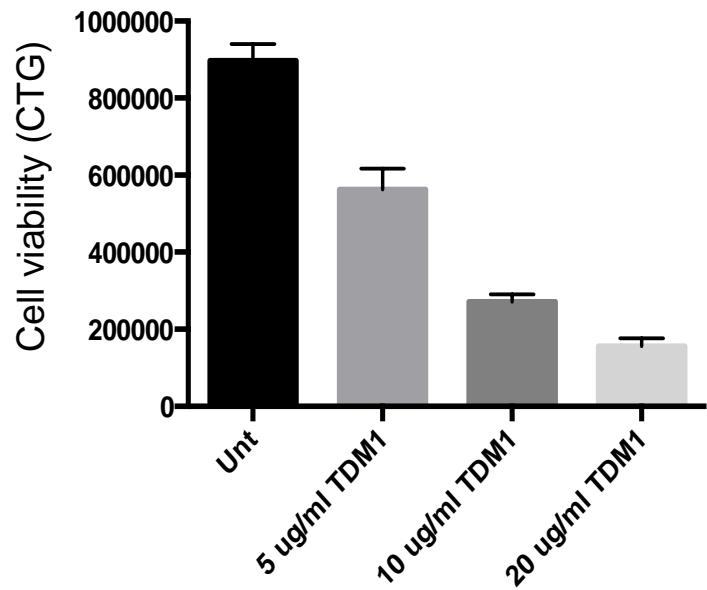
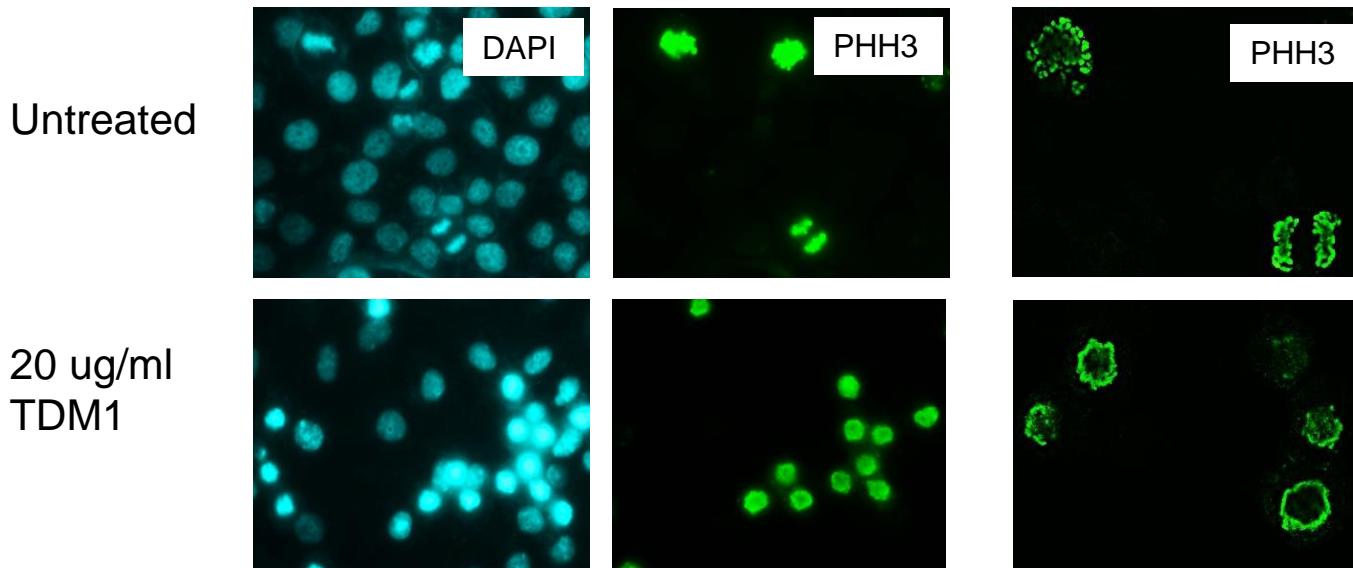
Interaction with T-DM1

*Trastuzumab drug conjugate and considered the most potent agent:

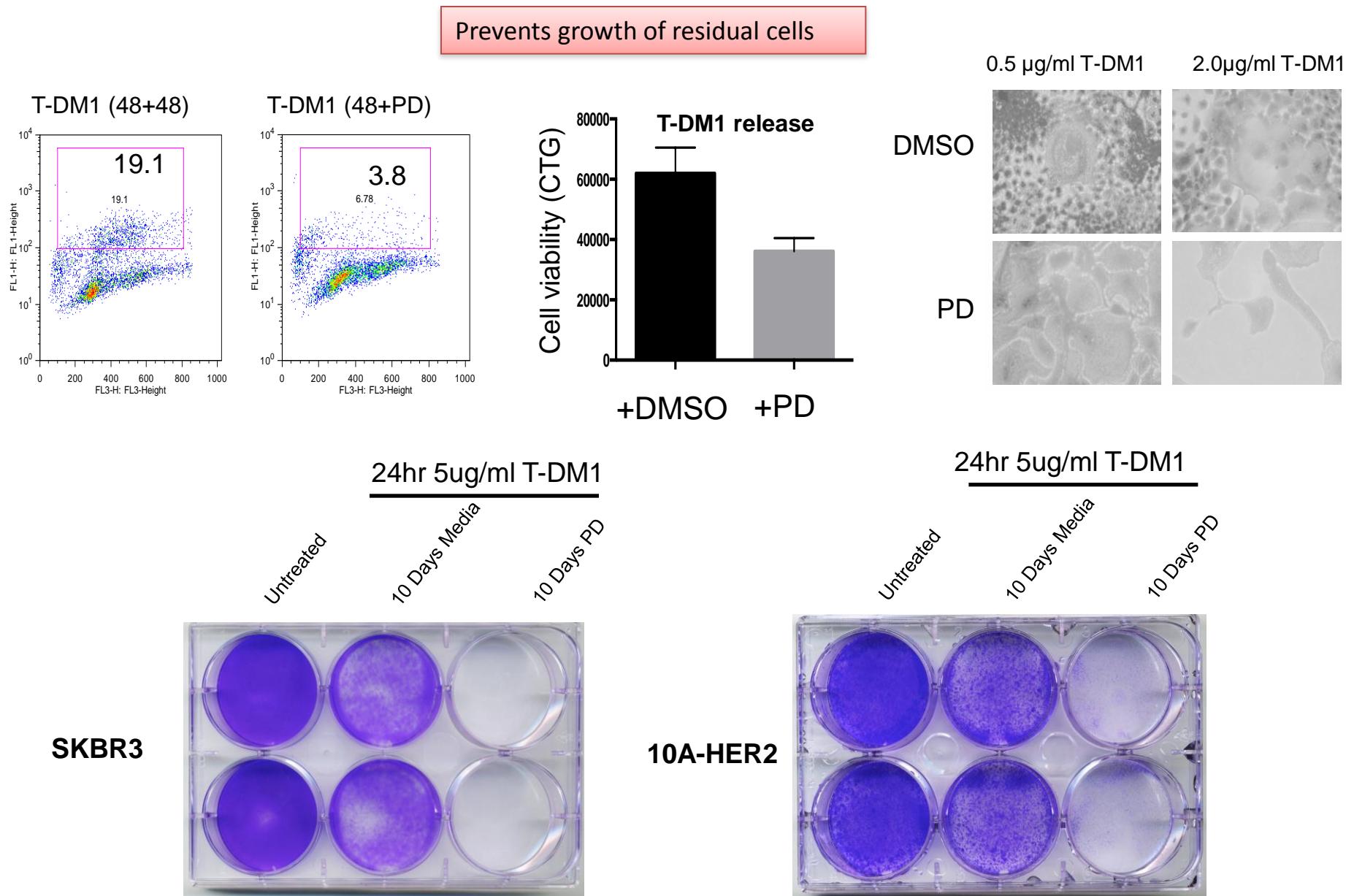
*Functions of Trastuzumab and Her2 targeted microtubule poison



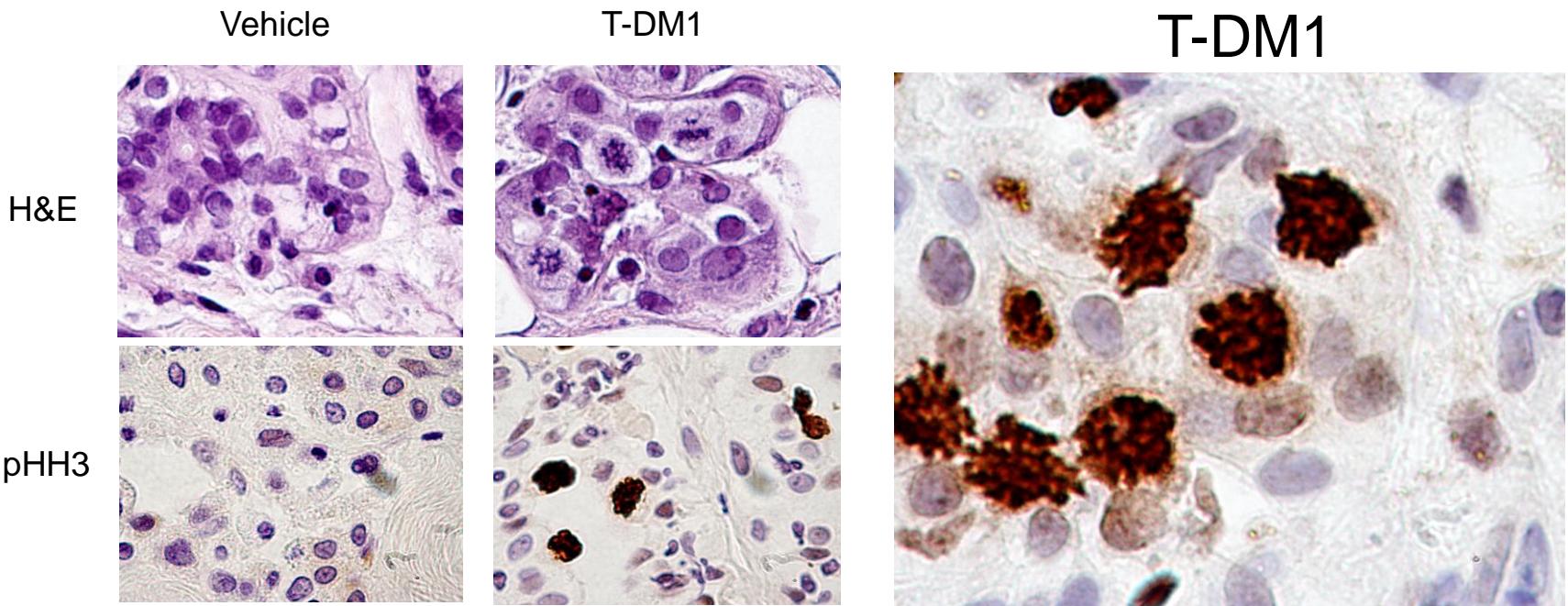
T-DM1 induces mitotic catastrophe residual tumor cells survive



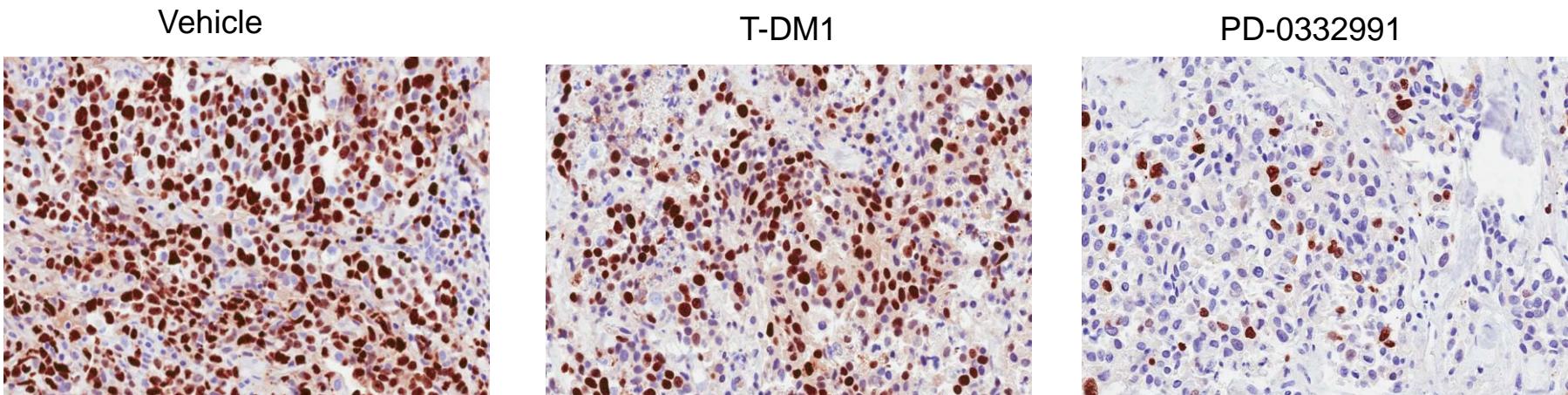
CDK4/6 inhibition can augment T-DM1 activity



In Her2+ tumors (3+) T-DM1 induces mitotic catastrophe



Minimal effect of T-DM1 on Ki67, but CDK4/6 inhibition is effective



Summary:

Mechanisms of bypass of Her2-targeted agents are complex

- *Aberrant cellular proliferation in the presence of agents
- *Common deregulated signaling that feeds into CDK4/6

CDK4/6 inhibition has activity against Her2-positive models

- *Cell Culture models, xenografts, GEMMS, tumor explants
- *Markers of resistance (p16 and RB) can be identified in clinical specimens

CDK4/6 inhibitors cooperate with Her2-targeted agents

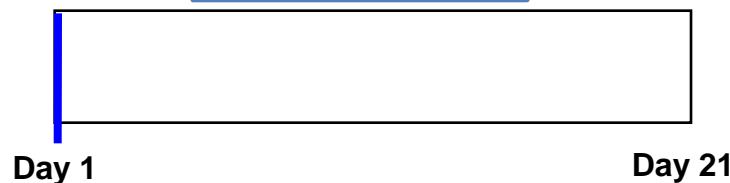
- *Cooperation with multiple small molecules in Her2-positive models
- *Cooperation with T-DM1 to prevent growth of residual clones

Clinical Delivery of T-DM1

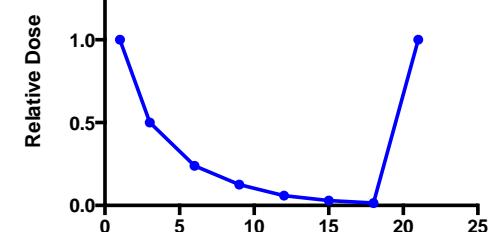
Standard of Care T-DM1

Adv. Her2+ Disease Failed prior therapy

3.6 mg/kg T-DM1
IV every 21 days



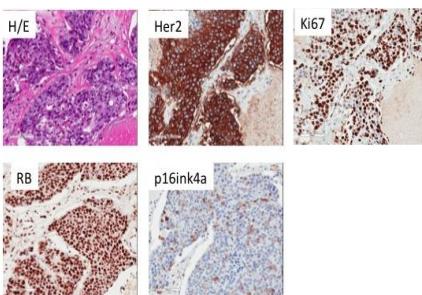
T-DM1 T_{1/2} ~3.5 days



Phase IB: T-DM1+PD-0332991 (NCT01976169)

T-DM1+PD-0332991

Adv. Her2+ Disease
Failed prior therapy
RB-proficient Tumor

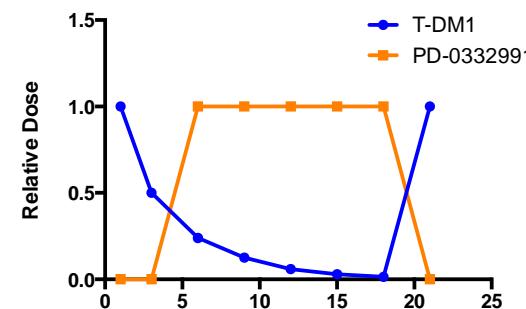


3.6 mg/kg T-DM1
IV every 21 days

PD-03322991-5012
Oral Days 5-18



PD-0332991 T1/2 ~1day



Endpoints:

Safety

Progression free survival

Markers of response

*pre/post treatment

*Ki67,p27,CCNE, etc.