Tumor Immune Microenvironment: A Holistic Approach Workshop

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UT Southwestern Medical Center

Targeting the Interaction of Oncogenic Signaling with Immunity in Breast Cancer

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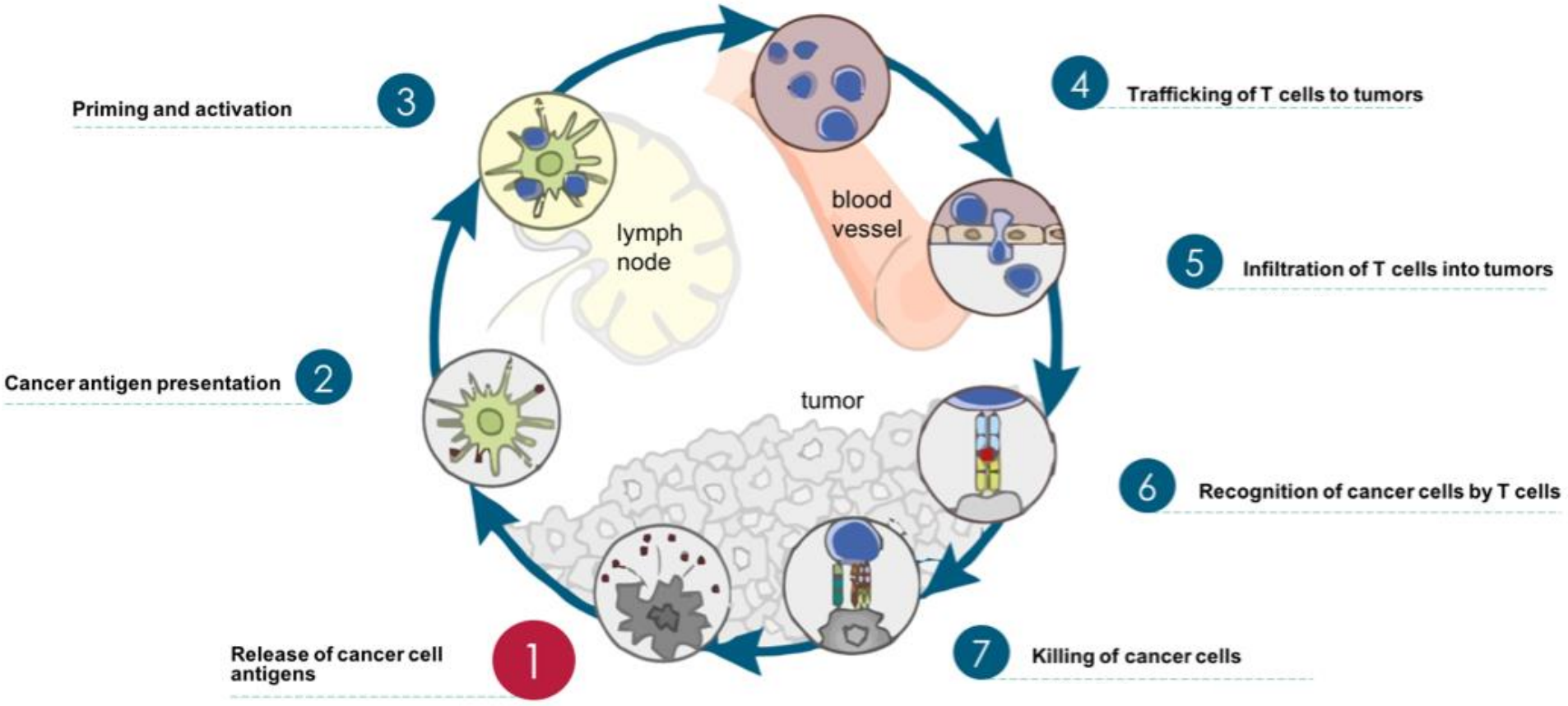
Disclosures

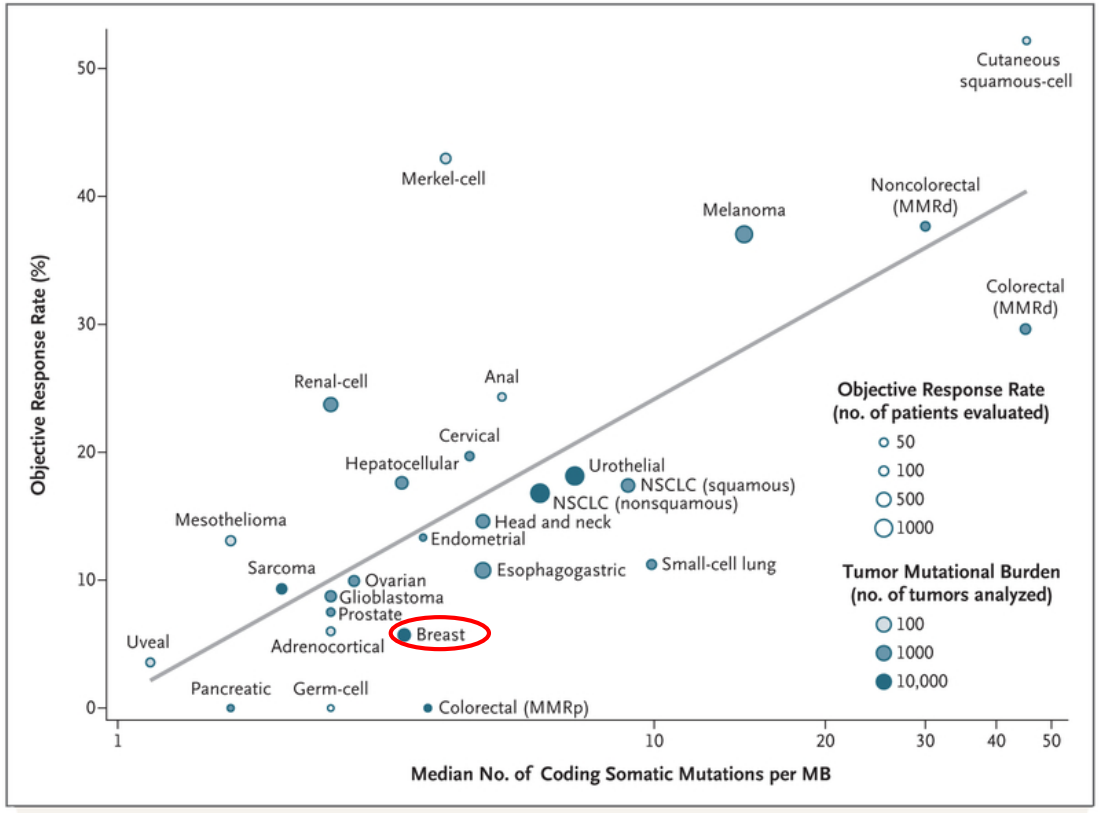
- I have no disclosures.

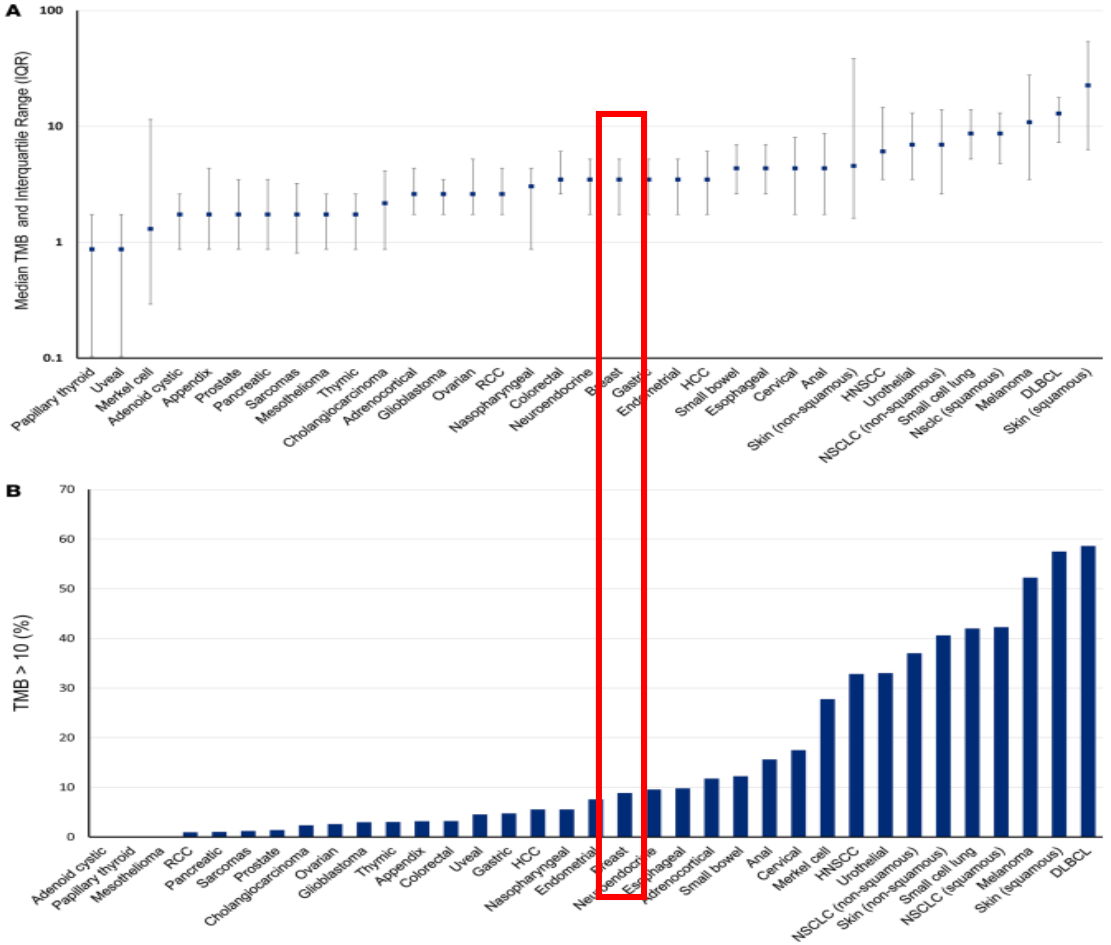
Anti-tumor immunity cycle illustrates multiple steps required for T cell activation against tumor cells.



Chen et al. Immunity 2013.

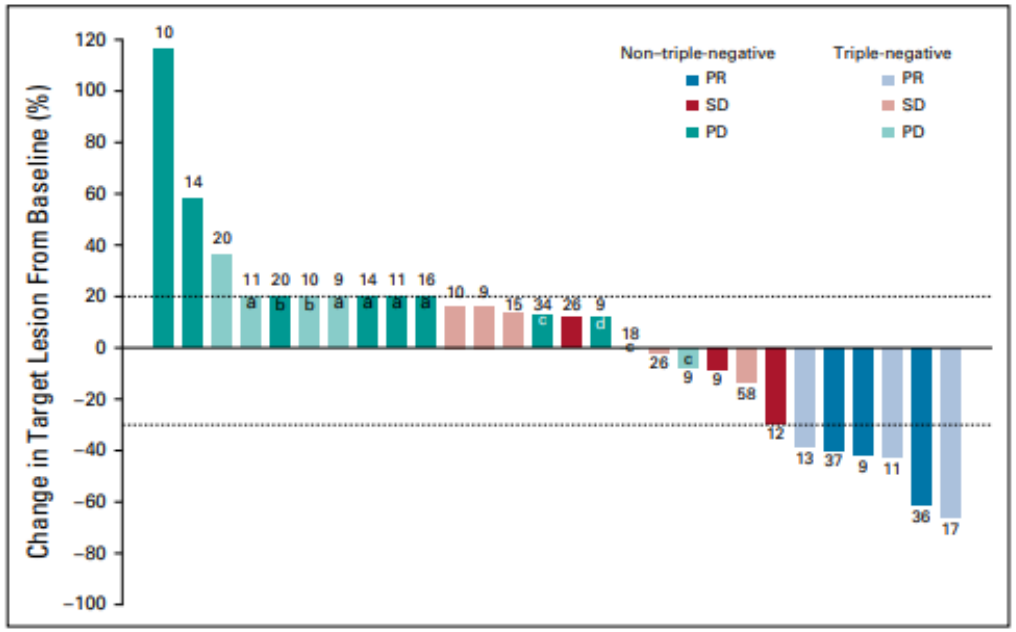
High tumor mutational burden is associated with anti-tumor immune response and immune checkpoint blockade therapy.

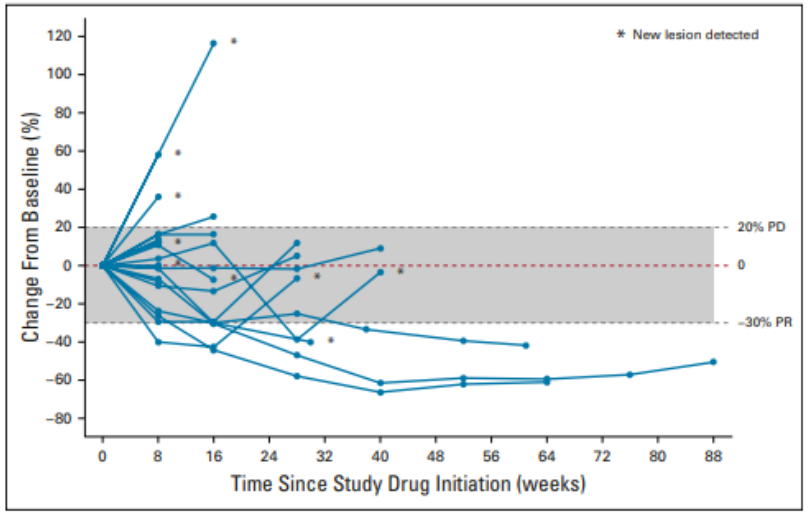


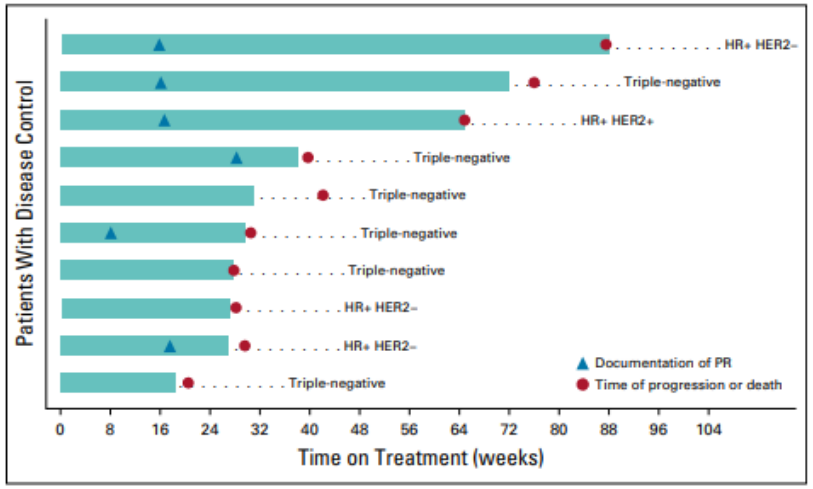


Yarchoan et al. NEJM 2017.

TAPUR (Targeted Agent and Profiling Utilization Registry) MBC cohort of patients (93% received ≥ 3 prior lines) with TMB ≥ 9 confirmed benefit in high TMB cancers.

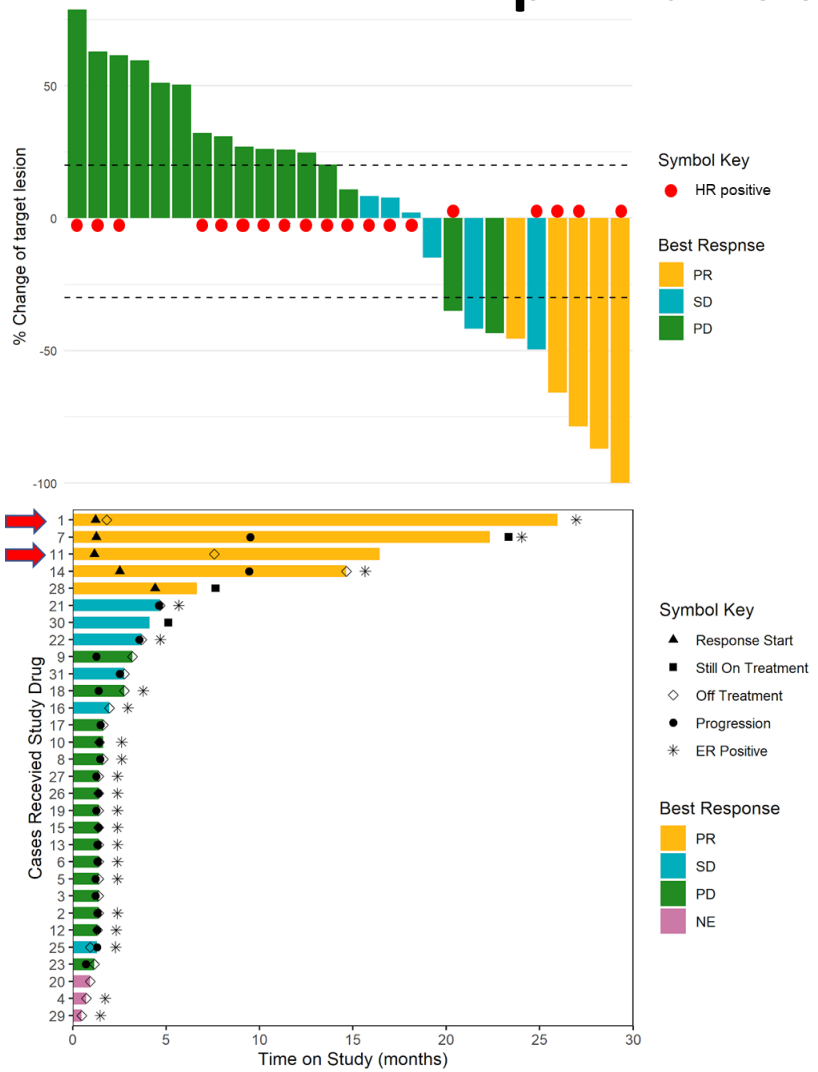




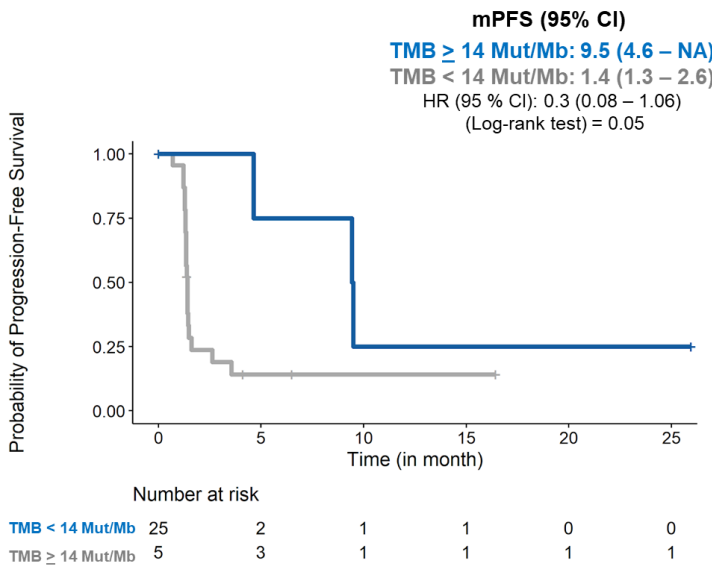


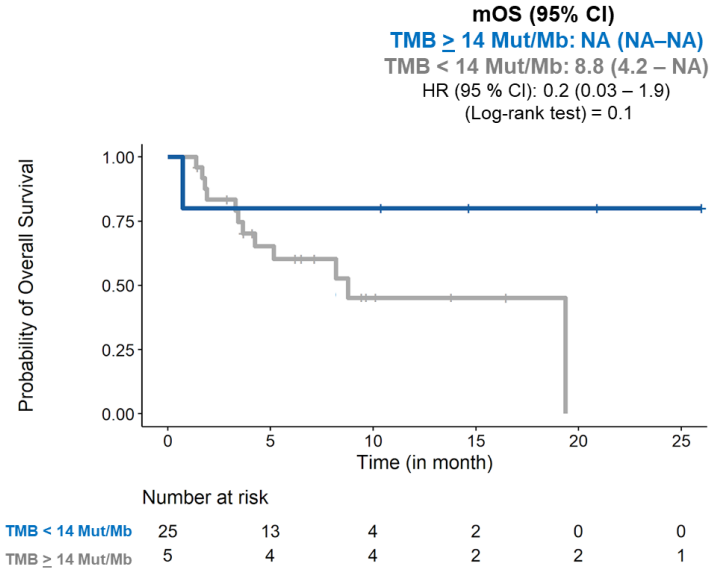
Alva et al. JCO 2021.

NIMBUS clinical trial demonstrated durable responses with ipilimumab + nivolumab in patients with TMB ≥ 9.



TMB	Objective response	No response	Total
<14, n (%)	2 (8)	23 (92)	n = 25
≥14, n (%)	3 (60)	2 (40)	n = 5

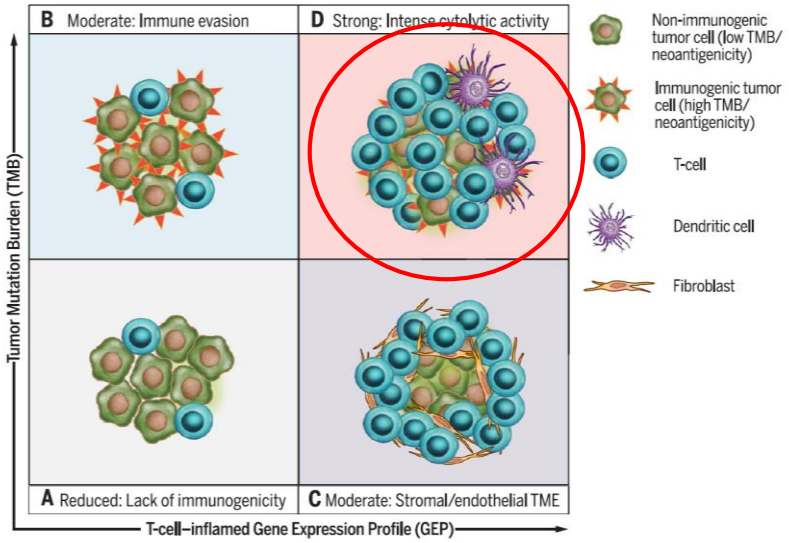


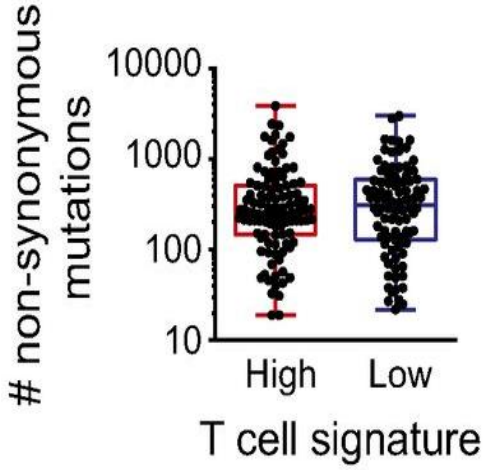


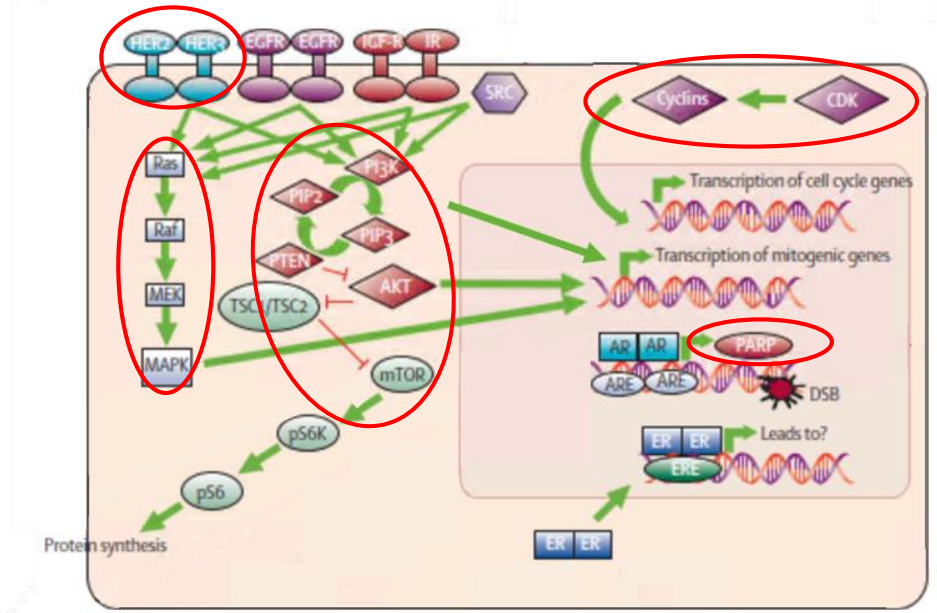
Barroso-Sousa et al. SABCS 2021.

Tumor neoantigen burden and T cell inflamed signature both independently contribute to anti-tumor immune response.

What other tumor intrinsic features may be shaping the tumor immune microenvironment?

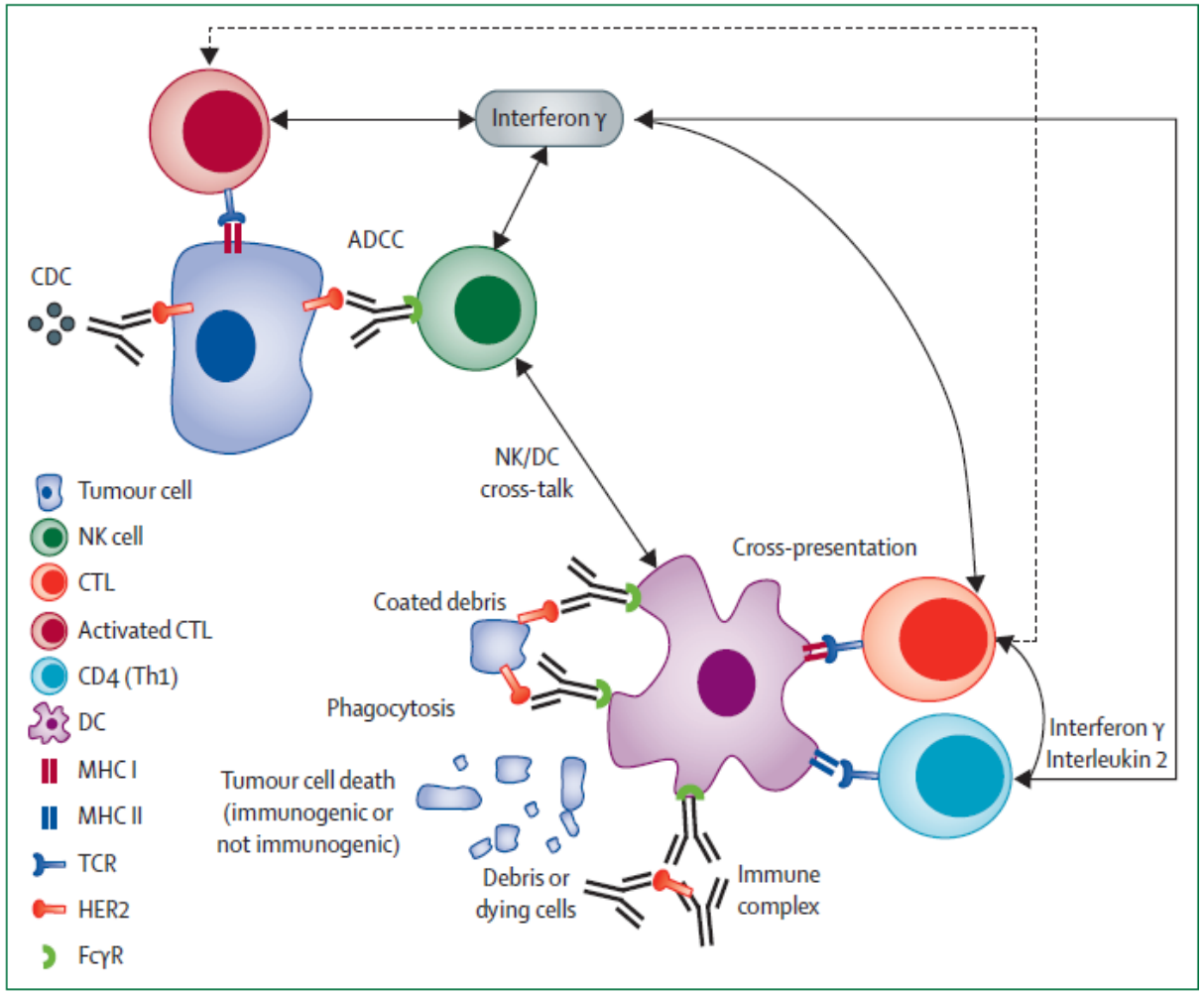






Cristescu et al. Science 2018.
Adapted from Brewster et al. Lancet Oncol 2014.

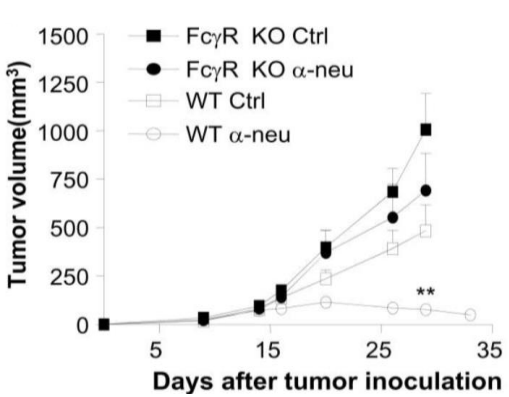
Management of HER2 positive breast cancer is the first successful immunotherapy story in breast cancer.



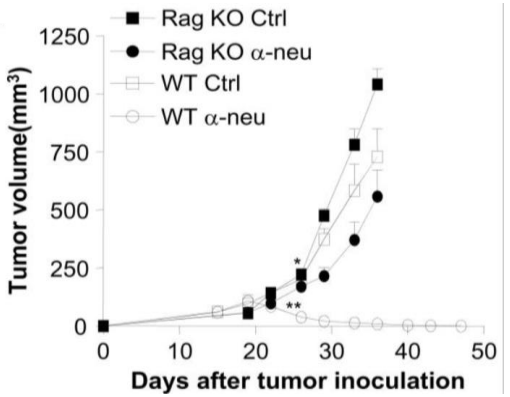
Trastuzumab is IgG1 antibody that promotes:

- Antibody dependent cell mediated toxicity (ADCC)
- Antibody dependent cellular phagocytosis
- Complement dependent cytotoxicity
- Antigen presentation → adaptive immunity
  - Immune complex uptake by antigen presenting cells
  - ↑ HER2 peptide presentation on MHC
  - Induction of type I and II interferons
  - Induction of cross-presentation

Efficacy dependent on BOTH innate and adaptive immunity



Bianchini et al. Lancet Oncol 2014.



Park et al. Cancer Cell 2010.

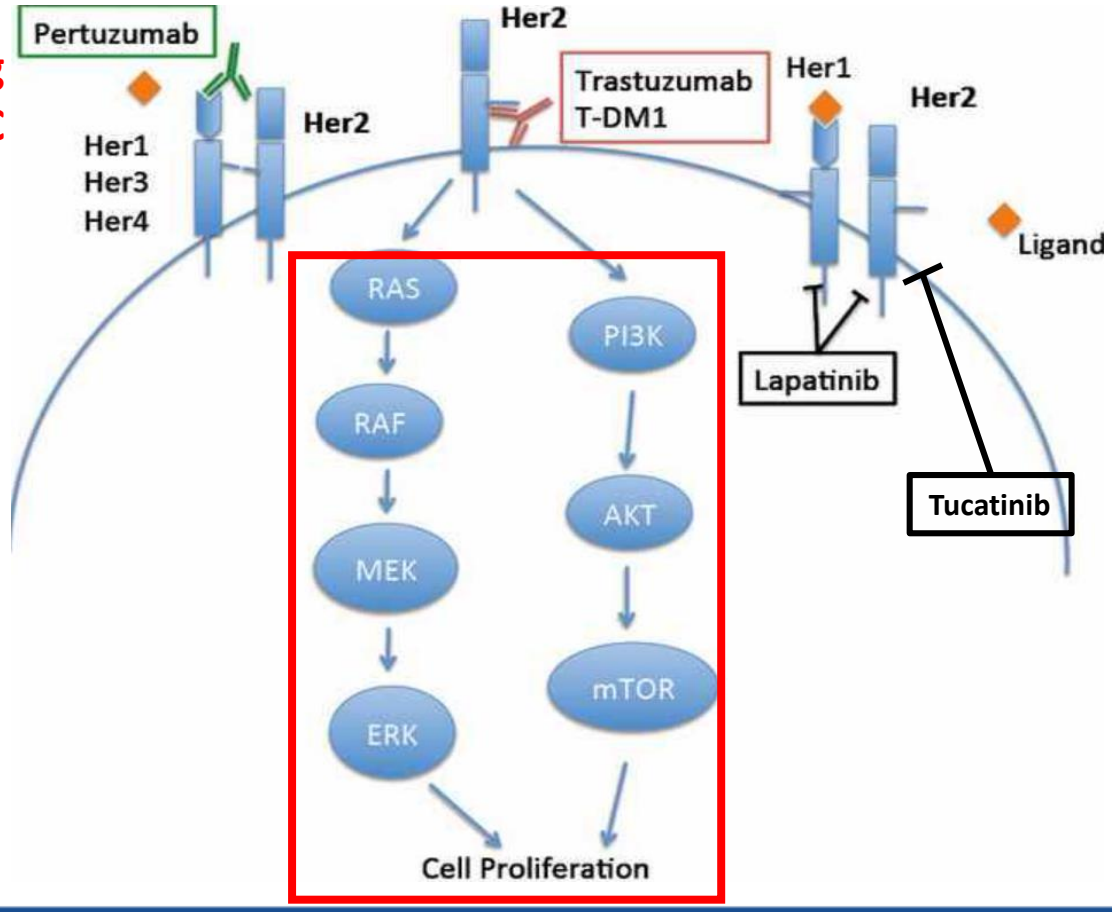
Other HER2 targeting therapies also have immune mechanisms of action.

Pertuzumab:

- **Binding ↑ FcγR binding sites → enhances ADCC**

T-DM1:

- **Induces DC maturation, antigen uptake, migration ↑ effector T cell and NK cell infiltration**

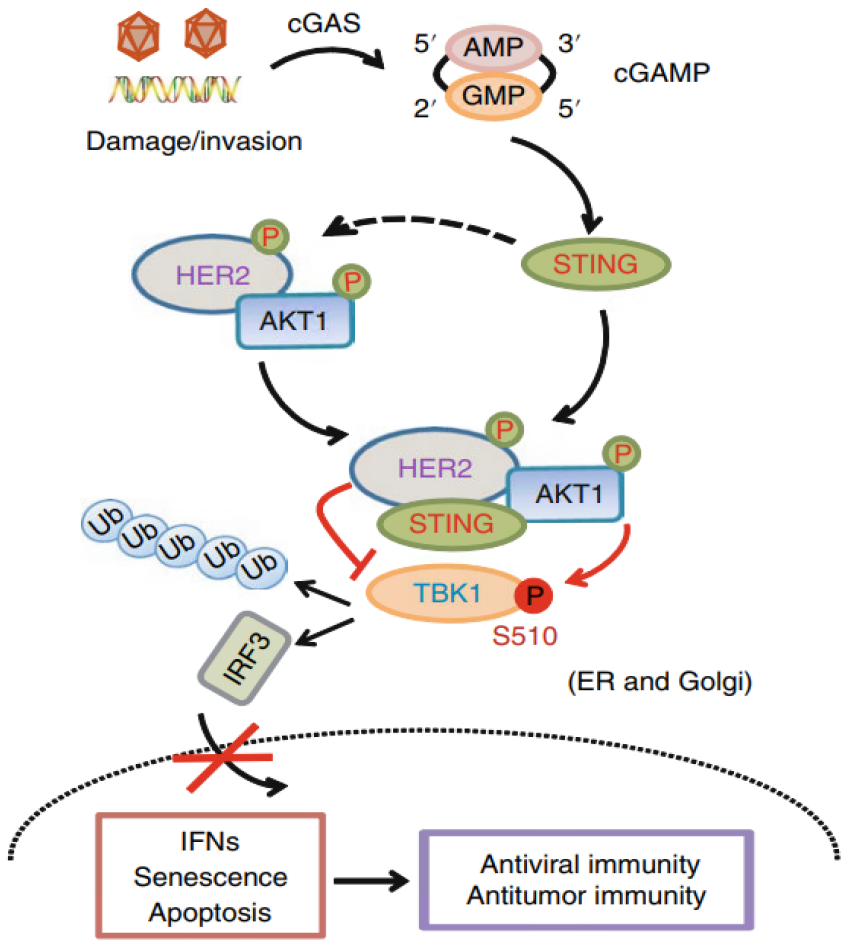


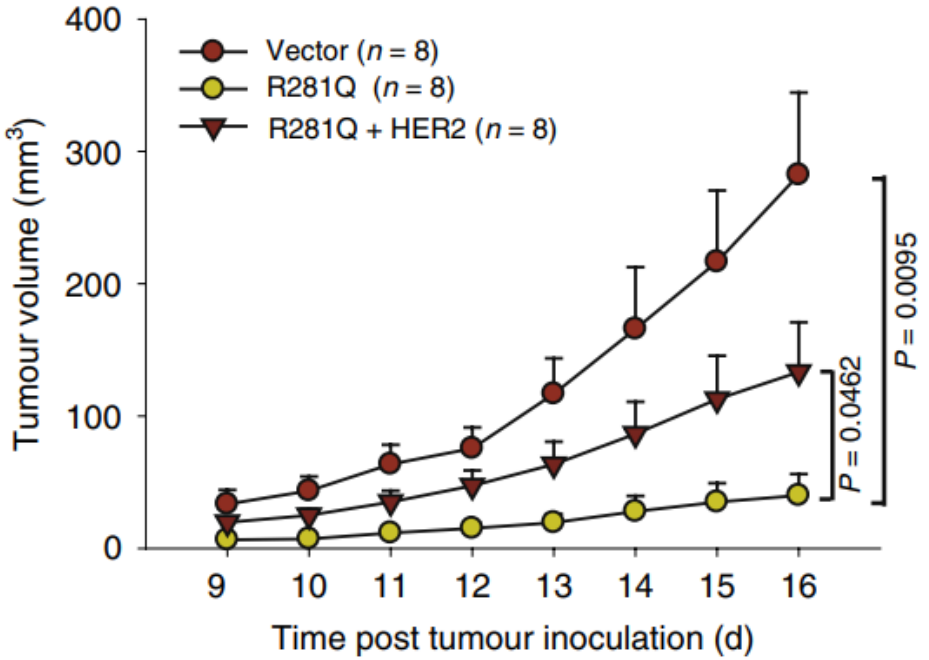
Tucatinib:

- **↑ NK cells, CD4 and CD8 T cell secretion of IFNγ and TNFα, MHC-II DCs and macrophages**
- **↓ neutrophils, MHC-II low macrophages**

Wong et al. Annals of Translational Medicine 2014.

We've also begun to understand tumor intrinsic immune effects of HER2 activation, such as HER2 reducing STING mediated anti-tumor immunity.



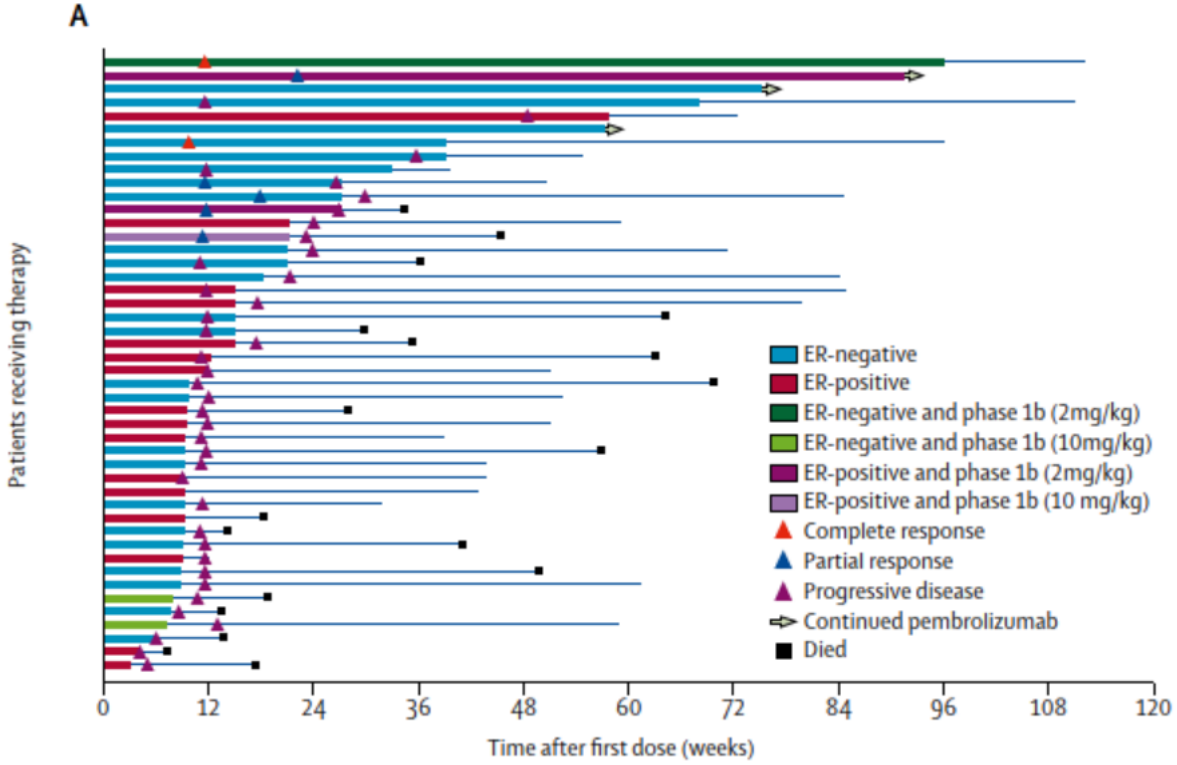


Wu et al. Nat Cell Biology 2019.

Safety and durable responses were seen in PANACEA clinical trial of trastuzumab + pembrolizumab in trastuzumab resistant advanced HER2+ breast cancer.

73% previously received T-DM1, 45% received lapatinib/afatinib/neratinib.

	PD-L1-negative, phase 2 (n=12)	PD-L1-positive, phase Ib (n=6)	PD-L1-positive, phase 2 (n=40)	All PD-L1-positive patients, phase 1b–2 (n=46)
Objective response	0 (0%; 0–18)	1 (17%; 1–58)	6 (15%; 7–29)	7 (15%; 7–27)
Disease control*	0 (0%; 0–18)	1 (17%; 1–58)	10 (25%; 14–39)	11 (24%; 14–36)
Best overall response				
Complete response	0	1 (17%)	1 (3%)	2 (4%)
Partial response	0	0	5 (13%)	5 (11%)
Stable disease	2 (17%)	0	7 (18%)	7 (15%)
Progressive disease	9 (75%)	5 (83%)	25 (63%)	30 (65%)
Not evaluable	1 (8%)	0	2 (5%)	2 (4%)



No new safety signals seen.

→ **Further study warranted in earlier line, PD-L1+ disease**

Loi et al. Lancet Oncol 2019.

KATE-2 studied combination atezolizumab with T-DM1 and showed signal in PD-L1+ tumors, though small numbers limit definitive conclusions.

Progressi

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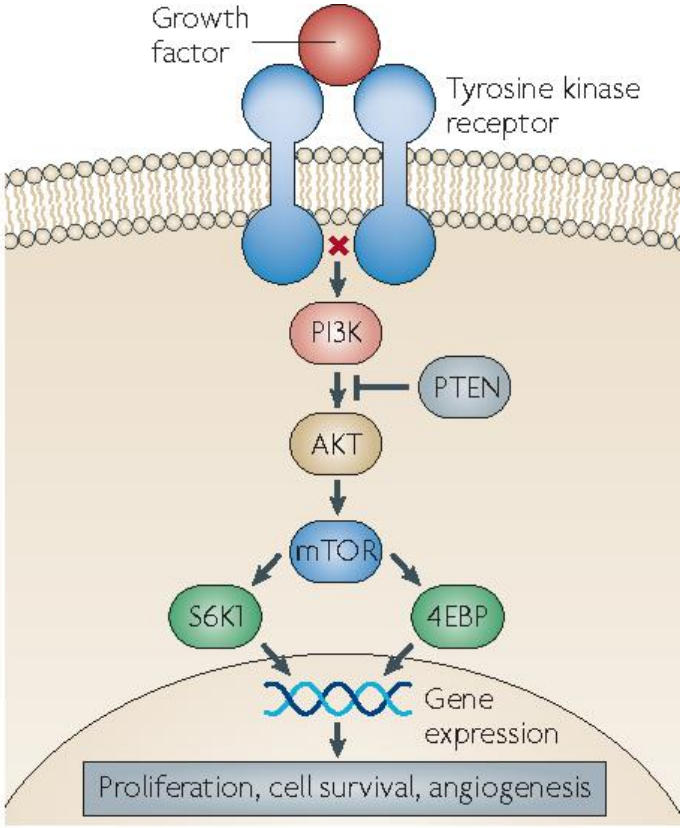
Other Immune Targeted Strategies Are Under Investigation:

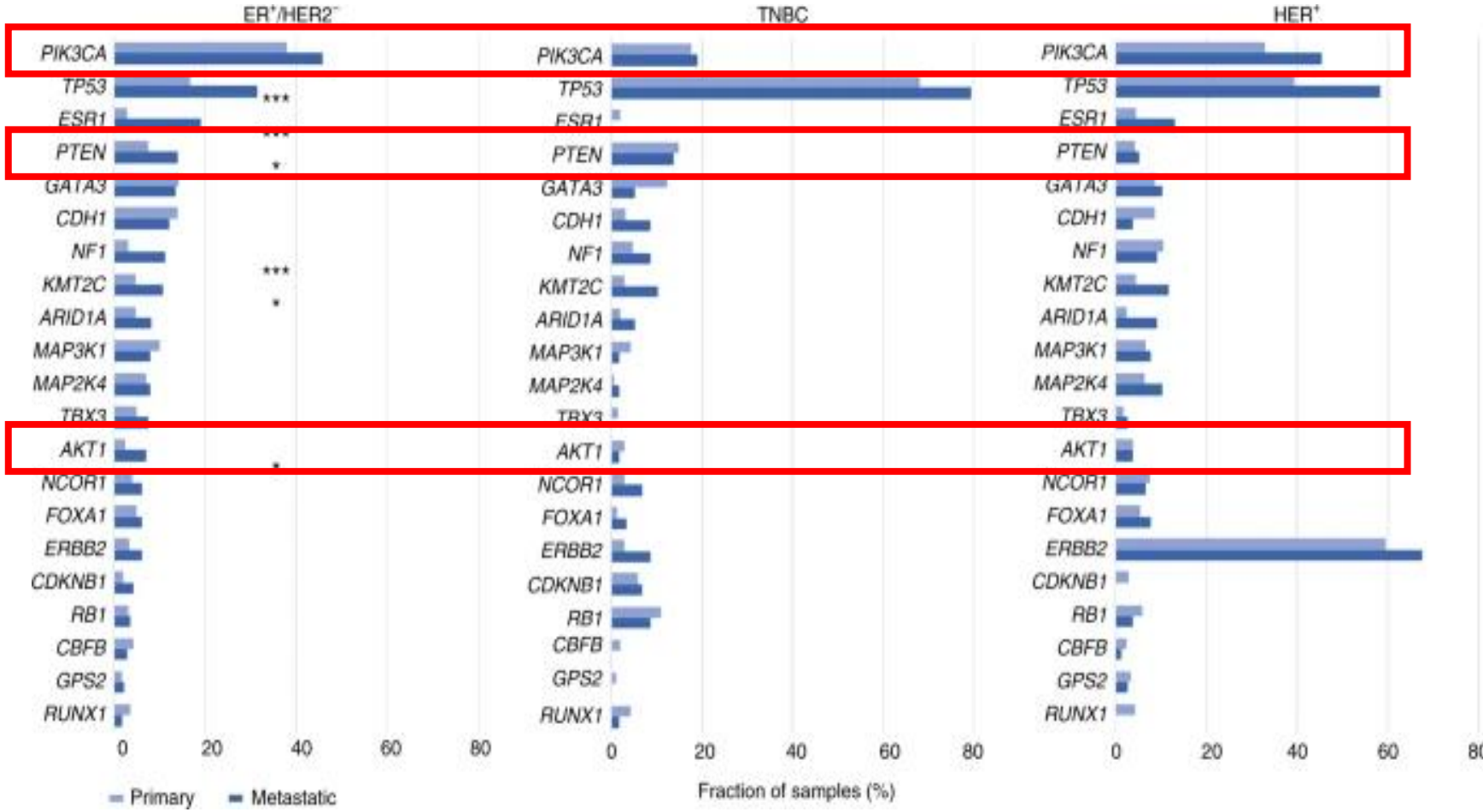
- Fc receptor immune optimized anti-HER2 antibodies
- Vaccine studies
- Bispecific antibodies against HER2 and CD3
- Antibody-adjuvant conjugates
- Cytokine Treatment (IFN-ɣ)
- Cellular immunotherapy
  - **CAR-T cells against HER2**
  - **NK cell therapy**

➔ **Ongoing evaluation of ICB in 1st line metastatic** (NCT03125928) **and neoadjuvant** (NCT03726879) **setting.**

Emens et al. ESMO 2019.

PI3K/PTEN/AKT/mTOR activation leads to resistance to CD8 T cell killing, constitutive PD-L1 expression, increase in immunosuppressive cells, and poor memory T cell formation.





Holmes et al. Nat Rev Drug Discov 2011.
Angus et al. Nat Genetics 2019.

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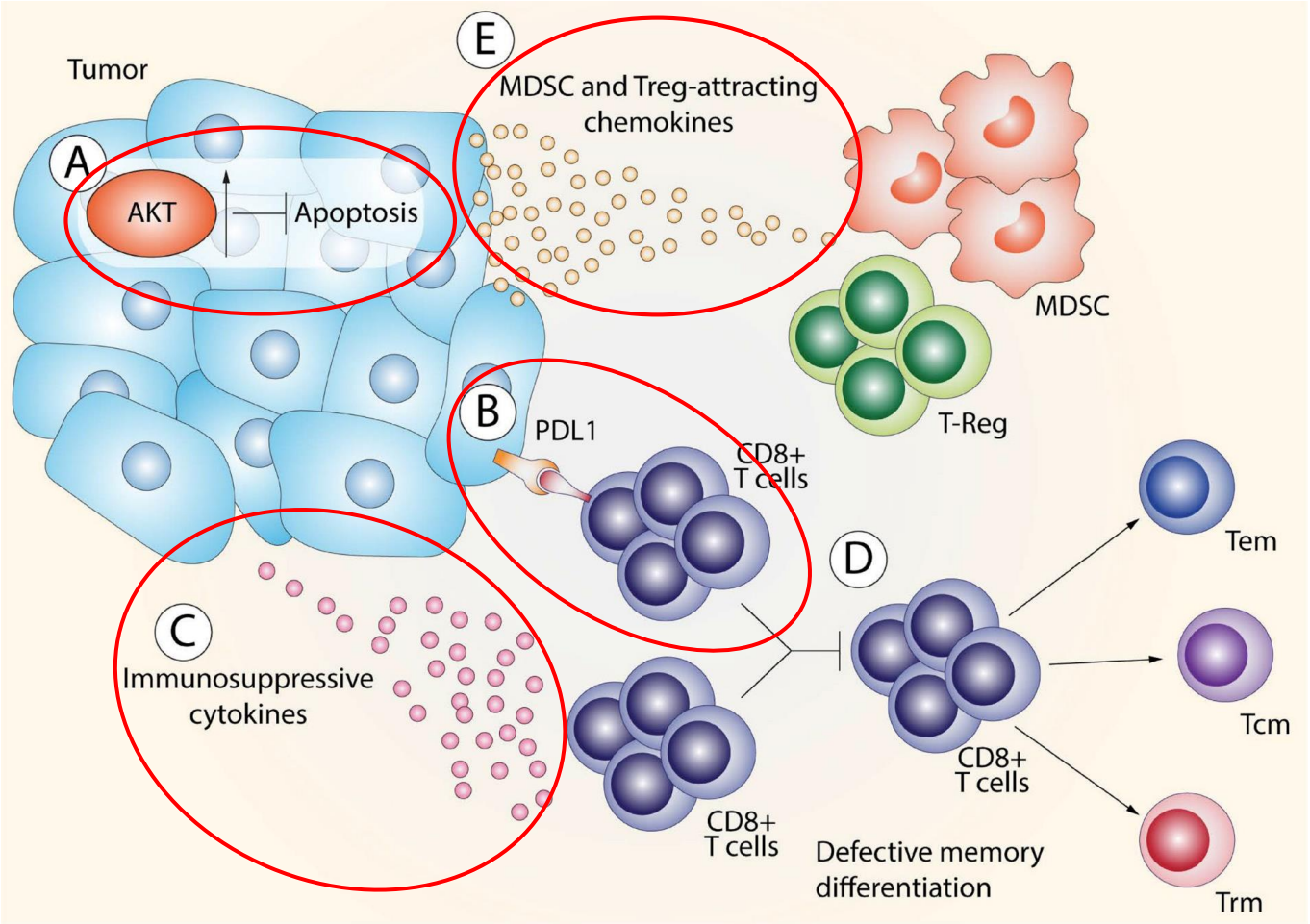
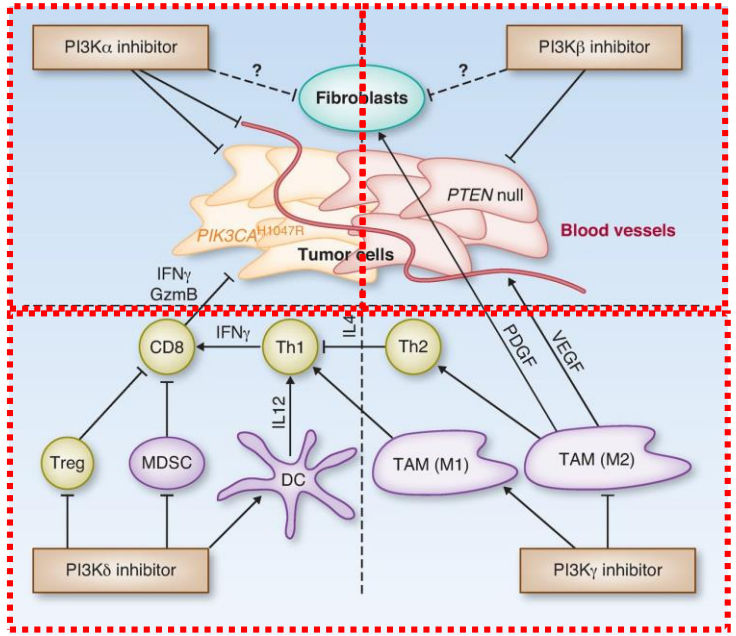


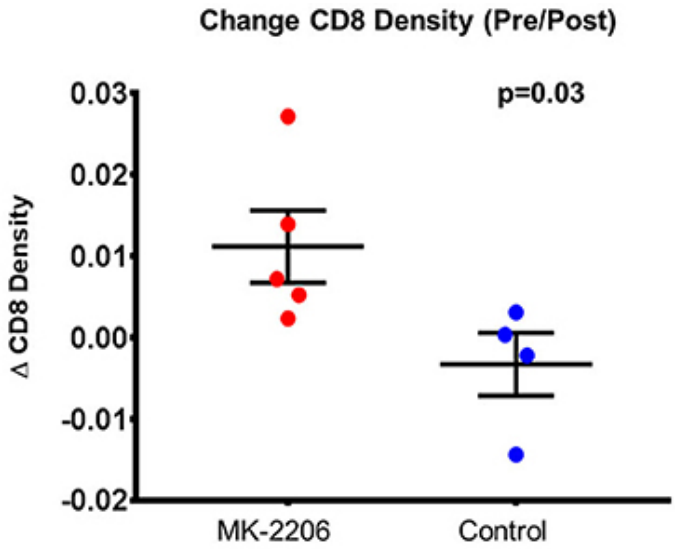
O'Donnell et al. Semin Cancer Biol 2018.

These changes may be reversed with PI3K (isoform specific) and AKT inhibition.

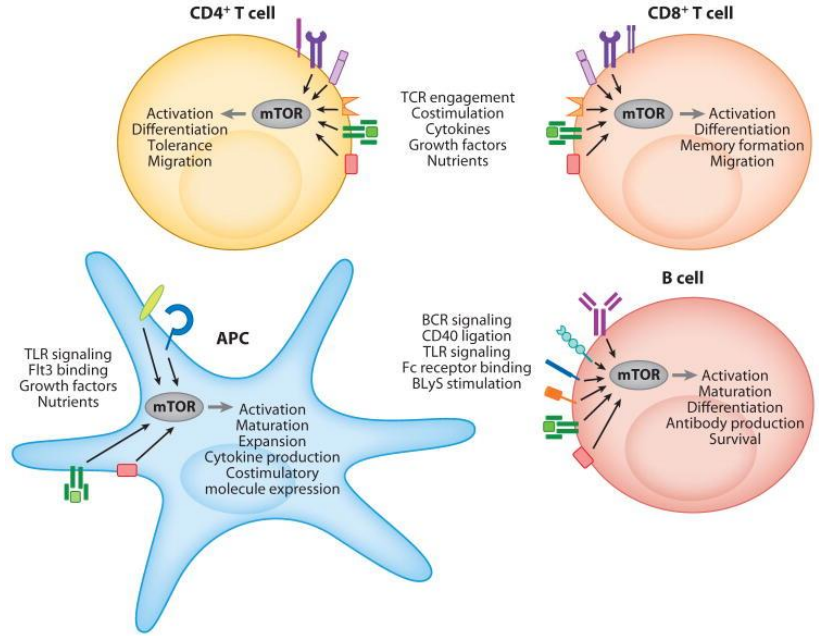
PI3 kinase inhibitors have isoform specific activities



Akt inhibitors increase # of CD8 T cells and memory, stem like phenotype



mTOR is important for growth, proliferation, and activation of multiple immune cells, and inhibitors are immunosuppressive



Okkenhaug et al. Cancer Discovery 2016.
Powell et al. Annu Rev Immunol 2013.
Crompton et al. Oncoimmunology 2016.

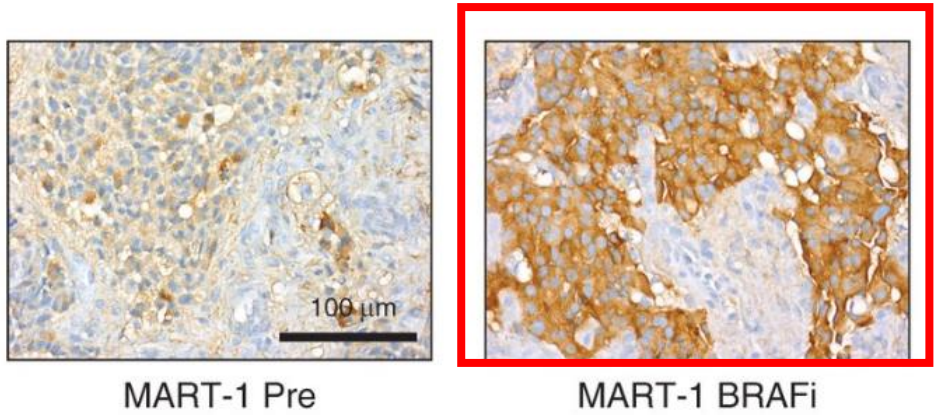
Multiple trials are investigating PI3 kinase isoform specific and Akt inhibitors in combination with immunotherapy in breast cancer.

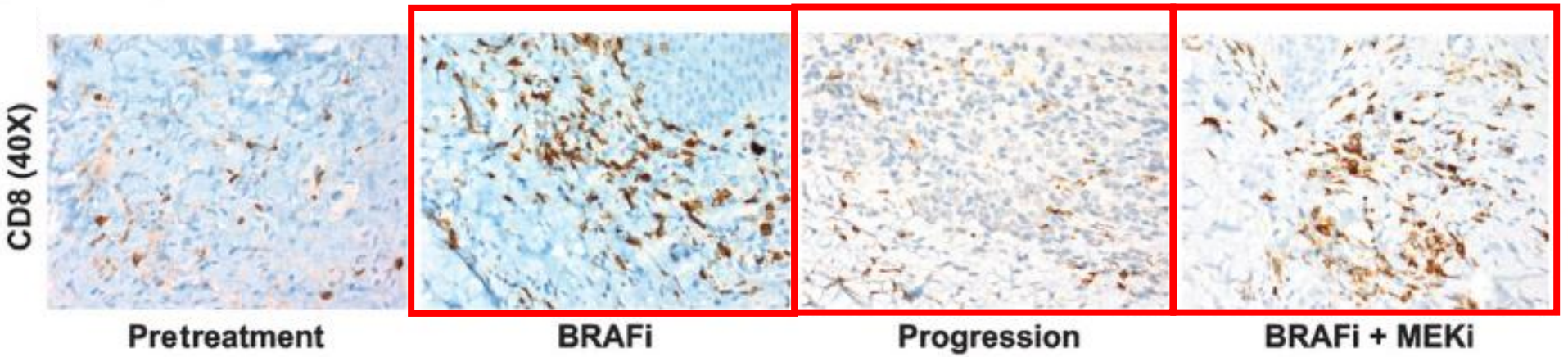
Trials with Immunotherapy + PI3 Kinase Pathway Inhibition in Breast Cancer	
A Study to Evaluate Safety/Tolerability of Immunotherapy Combinations in Participants With TNBC or Gynecologic Malignancies (PI3Kɣ inhibitor + Doxil + adenosine receptor antagonist)	NCT03719326
Pembrolizumab Combined With Itacitinib (INCB039110) and/or Pembrolizumab Combined With INCB050465 in Advanced Solid Tumors (PI3Kδ inhibitor)	NCT02646748
Evaluation of IPI-549 Combined With Front-line Treatments in Pts. With Triple-Negative Breast Cancer or Renal Cell Carcinoma (MARIO-3) (PI3Kɣ inhibitor + PD-L1 ab + Abraxane)	NCT03961698
Pre-operative Immunotherapy Combination Strategies in ER+ Breast Cancer (ECLIPSE): Atezolizumab + Ipatasertib (Akt inhibitor)	NCT03395899
Ipatasertib + Atezolizumab to Prevent Recurrence in TNBC (Akt inhibitor)	NCT04434040
A Study Of Ipatasertib in Combination With Atezolizumab and Paclitaxel as a Treatment for Participants With Locally Advanced or Metastatic Triple-Negative Breast Cancer (Akt inhibitor).	NCT04177108
A Study of Novel Anti-cancer Agents in Patients With Metastatic Triple Negative Breast Cancer (BEGONIA) (capivasertib AKT inhibitor + PD-L1 + Paclitaxel)	NCT03742102

MAPK pathway in melanoma provides another example of how oncogenic pathway creates an immunosuppressive TME, and importantly how targeting it therapeutically can reverse this until development of resistance mechanisms.

- MAP kinase pathway activation causes immunosuppression.

- MAP kinase pathway inhibition leads to
  - ↑ melanoma antigen expression
  - ↑ activated CD8 T cells, dendritic cells, NK cells
  - ↑ PD-L1 leading to resistance





Frederick et al. Clin Cancer Res 2013.

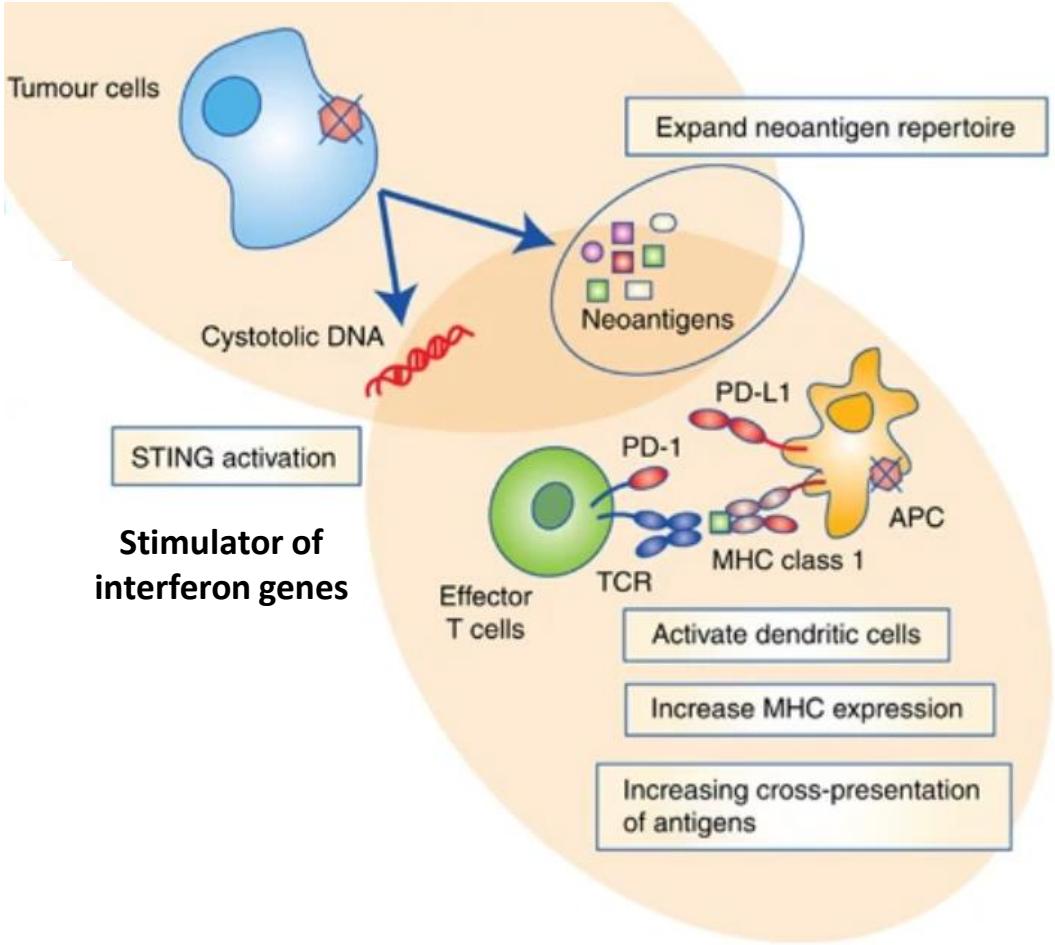
In breast cancer, MEK inhibition is under investigation in combination with immunotherapy +/- chemotherapy.

- **Pre-clinical data suggest that MEKi increases immunogenicity of breast cancers (increasing surface MHC) but with increased PD-L1 and detrimental effects on T cell function that are reversed with immunotherapies such as immune checkpoint blockade or T cell agonists (4-1BB and OX-40 agonists).**

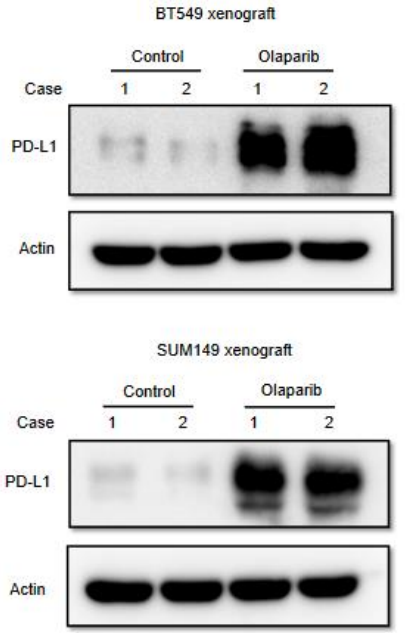
Trials with Immunotherapy + MEK inhibitors in Breast Cancer	
A Study of Cobimetinib Plus Paclitaxel, Cobimetinib Plus Atezolizumab Plus Paclitaxel, or Cobimetinib Plus Atezolizumab Plus Nab-Paclitaxel as Initial Treatment for Participants With TNBC That Has Spread	NCT02322814
Atezolizumab and Cobimetinib or Idasanutlin in Participants With Stage IV or Unresectable Recurrent Estrogen Receptor Positive Breast Cancer	NCT03566485
Pembrolizumab and Binimetinib in Treating Patients With Locally Advanced or Metastatic TNBC	NCT03106415
Pre-operative Immunotherapy Combination Strategies in ER+ Breast Cancer (ECLIPSE). (1) Atezolizumab + Cobimetinib, (2) Atezolizumab + Ipatasertib, (3) Atezolizumab + Cobimetinib + Bevacizumab, (4) Atezolizumab alone.	NCT03395899
Avelumab With Binimetinib, Utomilumab, or Anti-OX40 Antibody PF-04518600 in Treating Triple Negative Breast Cancer (InCITe)	NCT03971409
Atezolizumab, Cobimetinib, and Eribulin in Treating Patients With Chemotherapy Resistant Metastatic Inflammatory Breast Cancer	NCT03202316

Loi et al. Clin Cancer Res 2019.
Dushyanthen et al. Nat Commun 2017.

PARP inhibition can enhance antigen presentation through activation of STING pathway, increase PD-L1 expression, and may increase neoantigen burden.



Stimulator of interferon genes



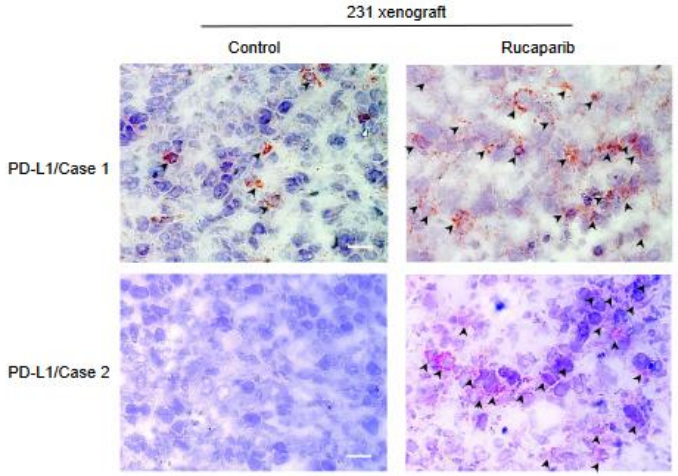
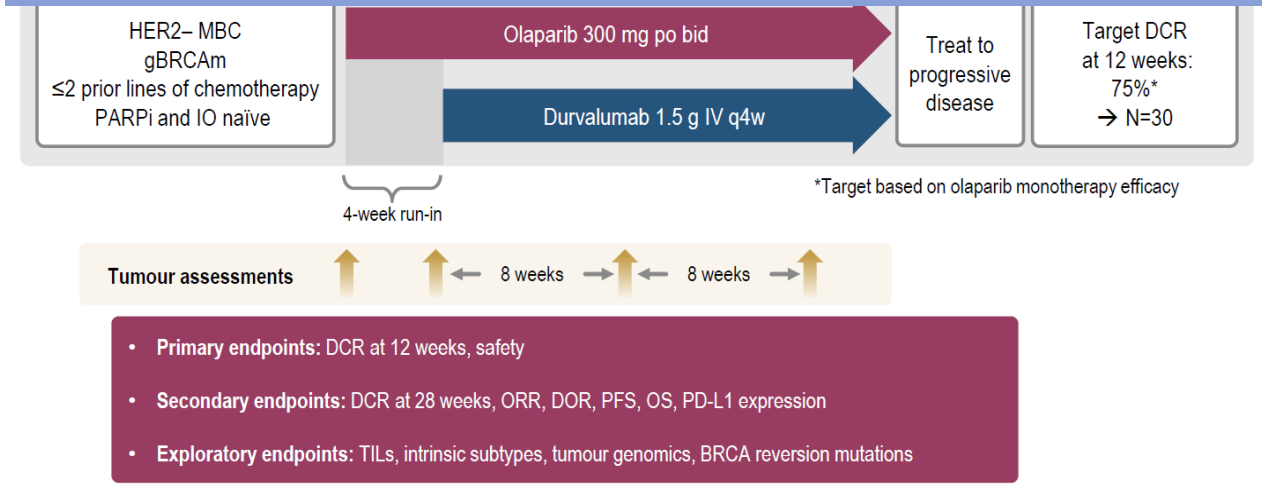
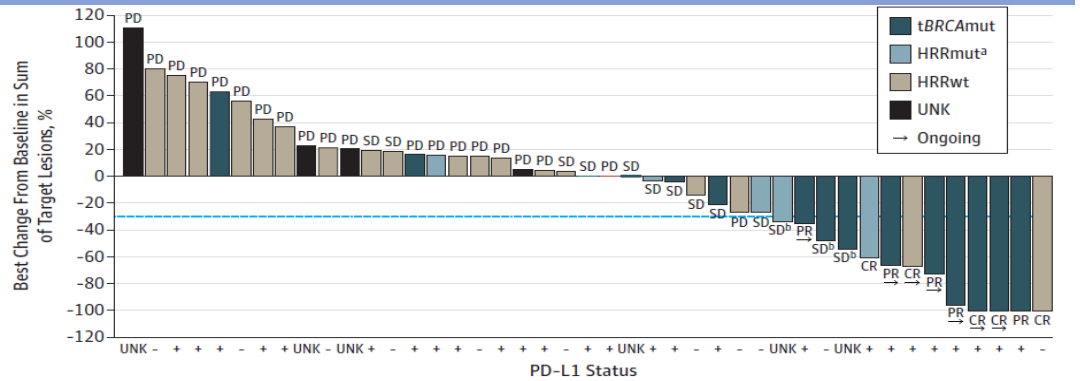


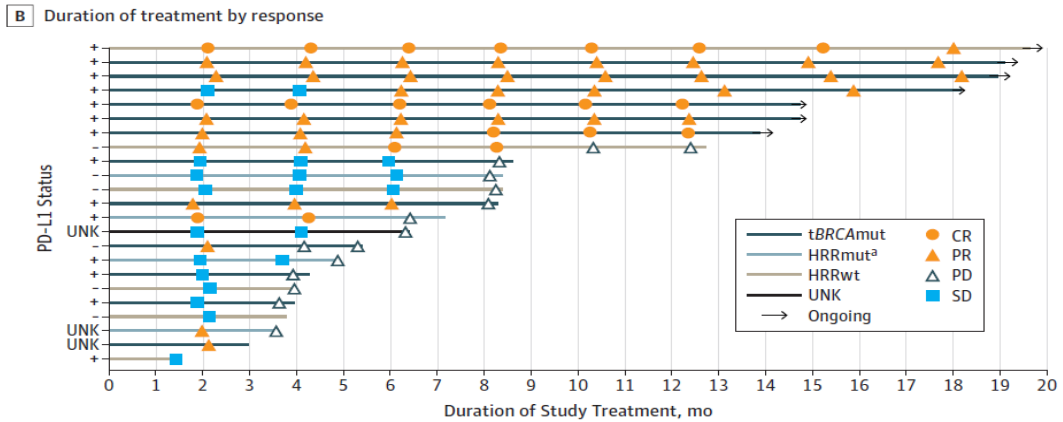
Figure adapted from Brown et al. BJC 2018.
Jiao et al. CCR 2019.

Combination PARPi + IO in metastatic setting have demonstrated safety but unclear efficacy signal given single arm, non-randomized studies.

→ Additional combination trials of PARPi and checkpoint blockade are underway in breast cancer, including <u>randomized trials</u> which will be highly informative.



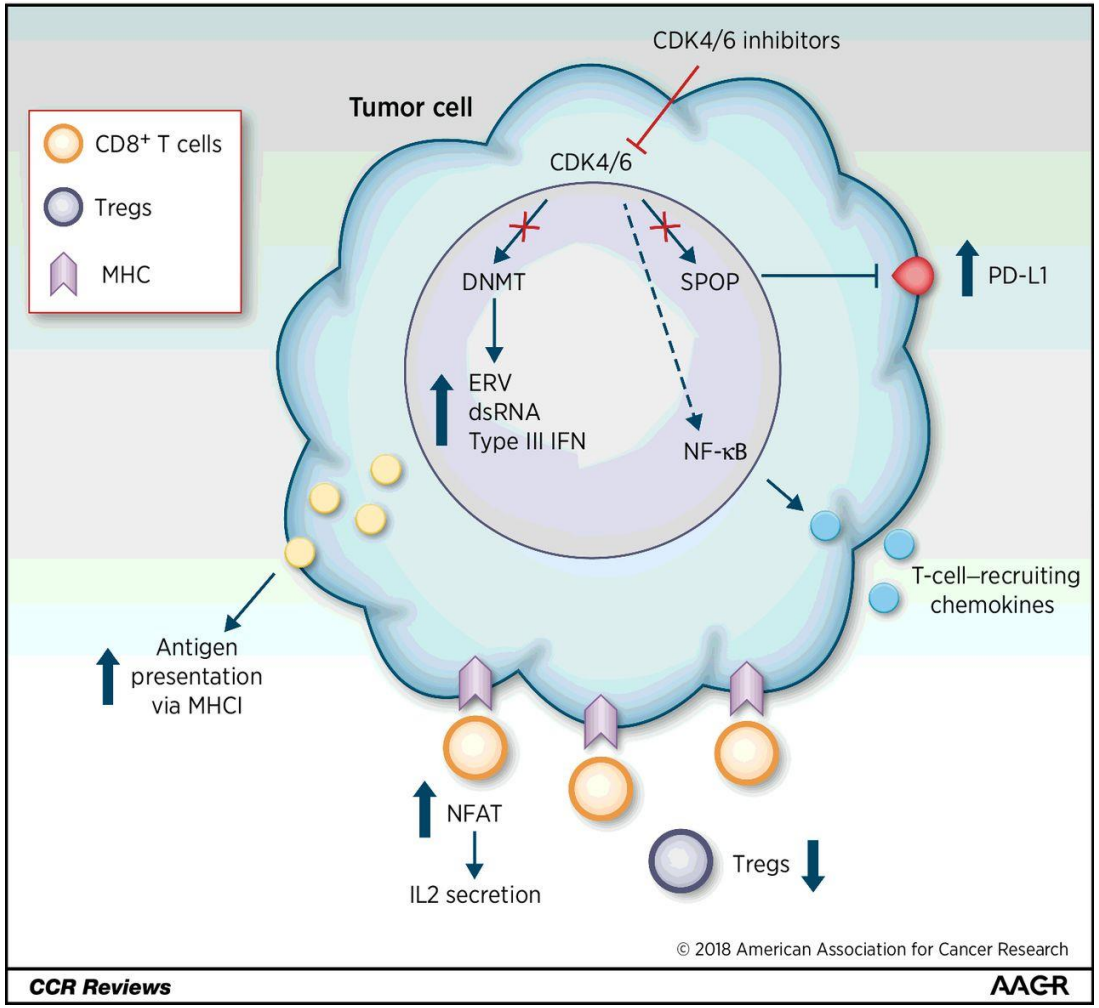




Responses seen in MEDIOLA	
ORR	63% (vs 60% in Olympiad)
DOR	9.2 mo (vs 6.4 mo in Olympiad)
PFS	8.2 mo (vs 7.0 mo in Olympiad)
OS	21.5 mo (vs 19.3 mo in Olympiad)

Domchek et al. ESMO 2019.
Vinayak et al. JAMA Oncol 2019.

CKD4/6 inhibitors have been shown to increase antigen presentation by tumor cells and also directly have favorable effects on T cells.



CDK4/6i →

↓ DNA methyltransferase 1 (E2F target)

→ ↑type III interferons

→ ↑ antigen presentation machinery

→ ↑ antigen presentation by tumor cells

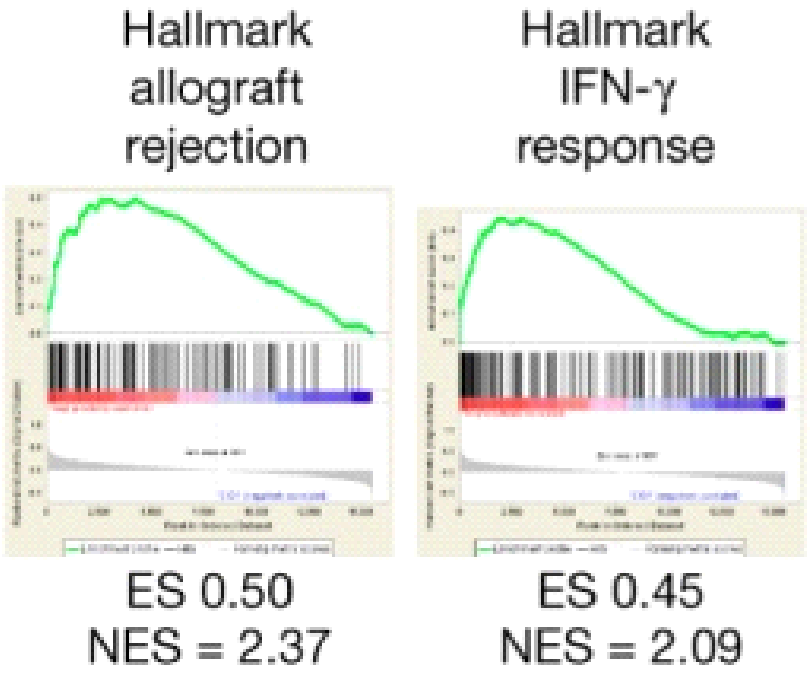
Direct effects on immune cells

- **↓ T cell antigen-induced apoptosis**
- **↑ T cell differentiation to memory cells**
- **↓ T regulatory cells**

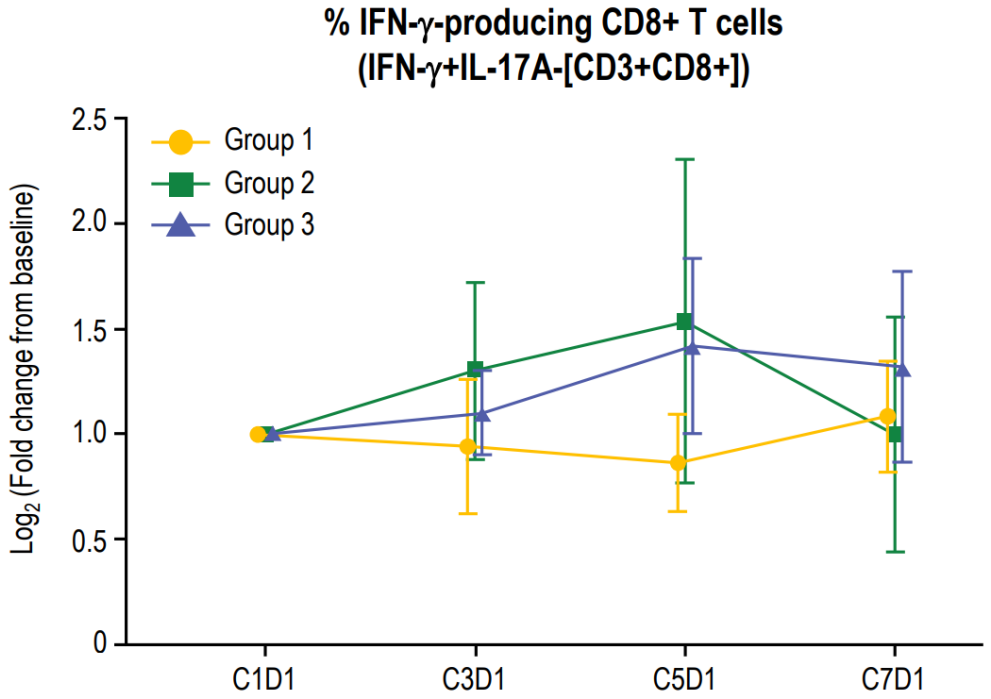
Teh et al. Clin Cancer Res 2019.
Goel et al. Nature 2017.

Clinical trials have supported what has been seen pre-clinically with increased T cell activation and antigen presentation signaling seen in patient samples.

NeoPalAna



Trilaciclib (with chemotherapy) in TNBC

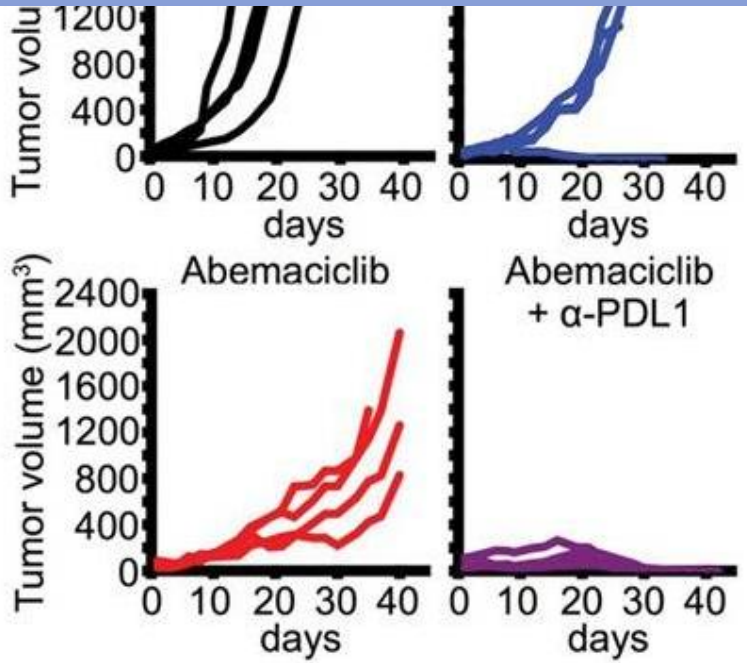


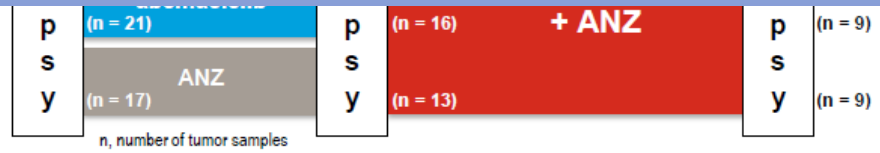
Goel et al. Nature 2017.
Tan et al. Lancet Oncol 2019.

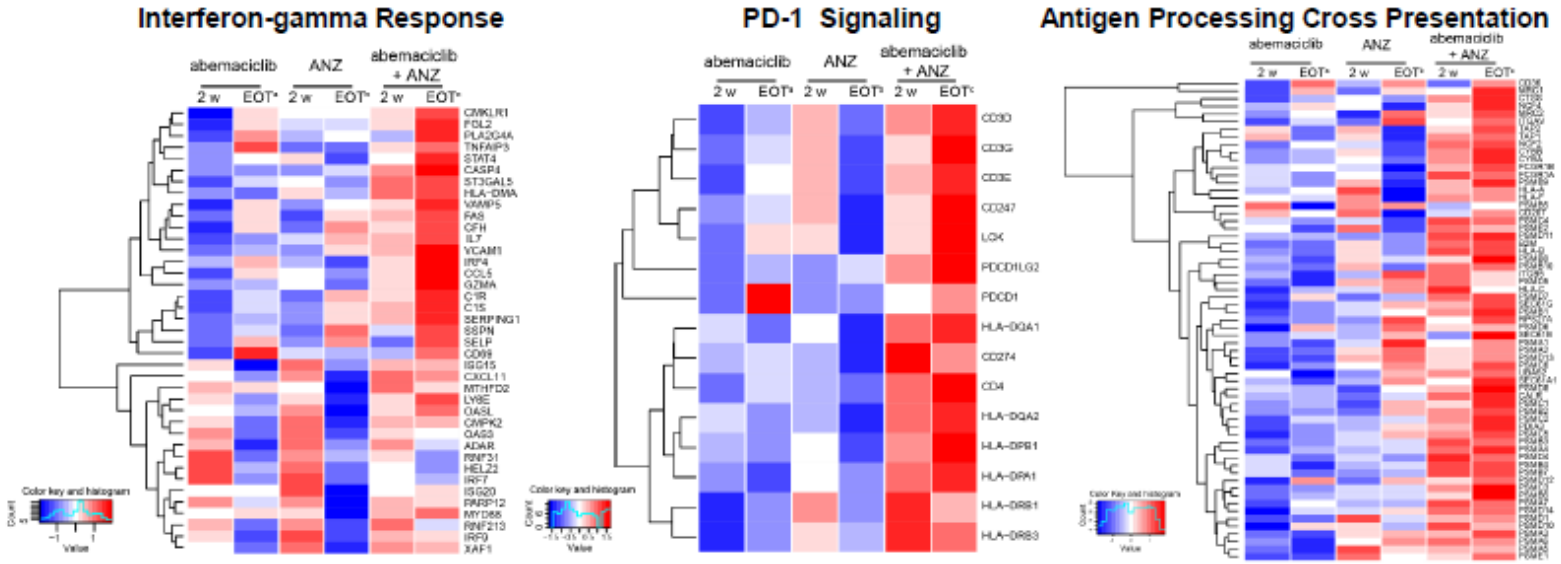
Pre-clinical and initial clinical data initially supported combination with PD-1/PD-L1 immune checkpoint blockade

Unfortunately, clinical trials have not demonstrated this significant benefit and also showed some concerning toxicity signals (pneumonitis, hepatitis).

How to identify other suitable targets?



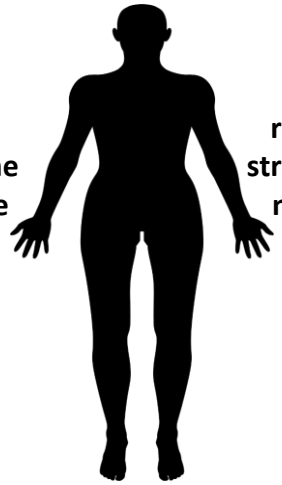




Goel et al. Nature 2017.
Hurvitz et al. SABCS 2018.

We are conducting a window trial of abemaciclib + letrozole to study impact on immune cells and cancer cells in humans and identify targets for combination immunotherapy trials.

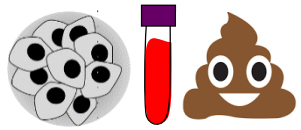
Breast cancer patients with localized hormone receptor positive breast cancer



4:1 randomization, stratified by lymph node positivity (n=60)

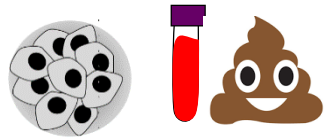
Arm A: Abemaciclib + letrozole (2 weeks)

Arm B: Letrozole (2 weeks)



-Multiplex immunohistochemistry
-Single cell RNA sequencing of tumor and immune microenvironment cells

Surgery or Repeat biopsy (followed by planned systemic neoadjuvant therapy) Measure Ki-67 for complete cell cycle arrest (≤2.7%)



-Multiplex immunohistochemistry
-Single cell RNA sequencing of tumor and immune microenvironment cells

Endpoints:

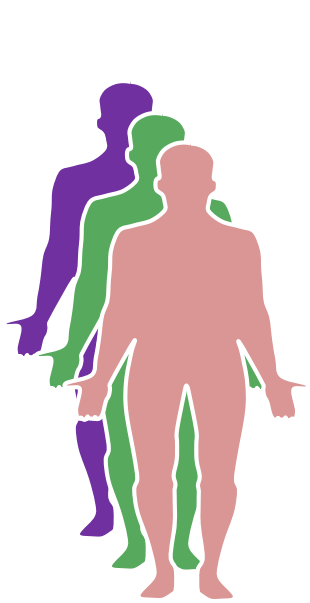
Primary:

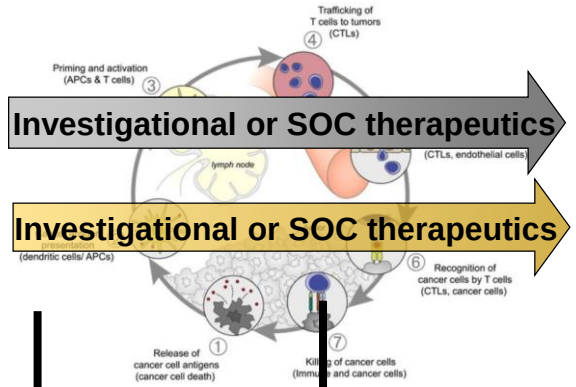
1) Change in T cell activation in responders to abemaciclib + letrozole (response defined as Ki-67 ≤2.7%).

Secondary:

1) Pharmacodynamic single cell changes associated with treatment and response.
2) Pre-treatment and post-treatment single cell phenotypes associated with treatment and response.
3) Comparison of single cell phenotypes seen with abemaciclib and letrozole compared to letrozole alone.

A bi-directional immunology approach is needed to identify clinically relevant approaches, including how to target oncogenic and traditional immune pathways.





Investigational or SOC therapeutics

Investigational or SOC therapeutics

Responder

Non-responder

Progression

- Biomarkers
- Pharmacodynamics
- New hypotheses for novel combinations, dosing, sequencing, patient selection

- Immune phenotyping
  - scRNAseq
  - Singlet + multiplex IHC
  - Functional studies
  - TCR sequencing
  - Flow cytometry, +/- CyTOF

- Humanized PDXs
- Molecular profiling
- Microbiome
- Immuno-PET

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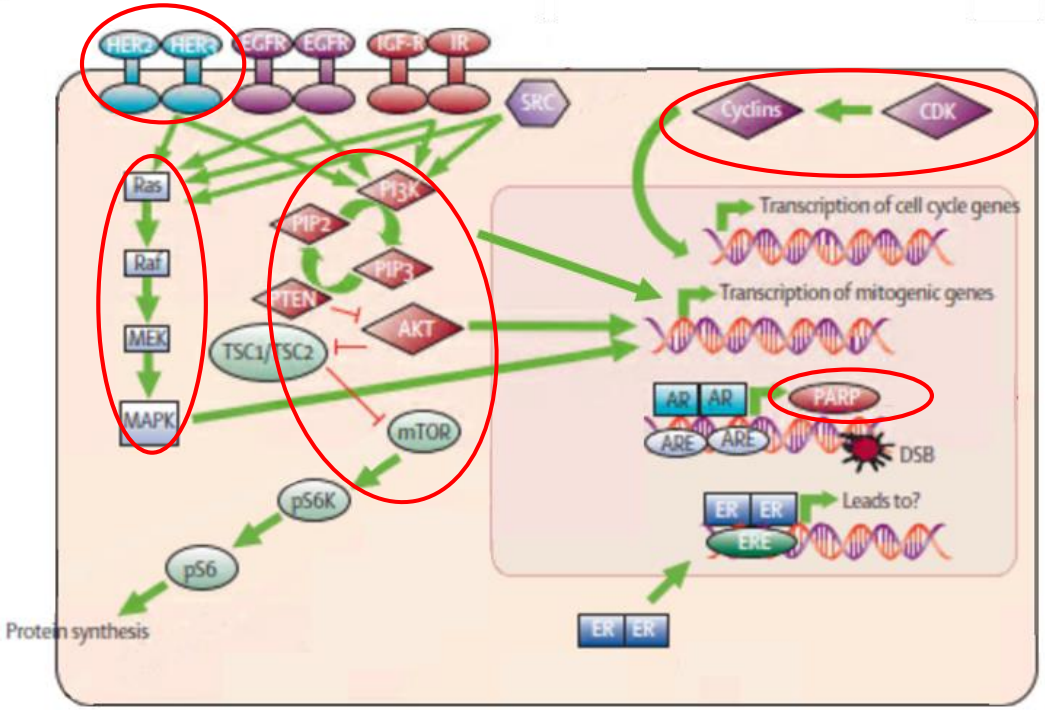
Concluding Remarks



- Oncogenic signaling pathways are interconnected and can impact the immune microenvironment (TME) by altering:
  - Antigen presentation machinery
  - Chemokine/cytokine secretion
  - Inhibitory ligand expression
- Targeted therapies impact tumor effects on TME but also can directly impact immune cell proliferation and differentiation.
- Increased toxicity signals can be seen, so trials will need to carefully assess safety prior to larger or earlier line studies.
- Continued translational research will be critical to understanding how these different therapies interact and identify resistance mechanisms.