Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

# Emerging Agents and Combination

Sagar Sardesai MD, MPH
Assistant Professor
The Ohio State University Comprehensive Cancer Center



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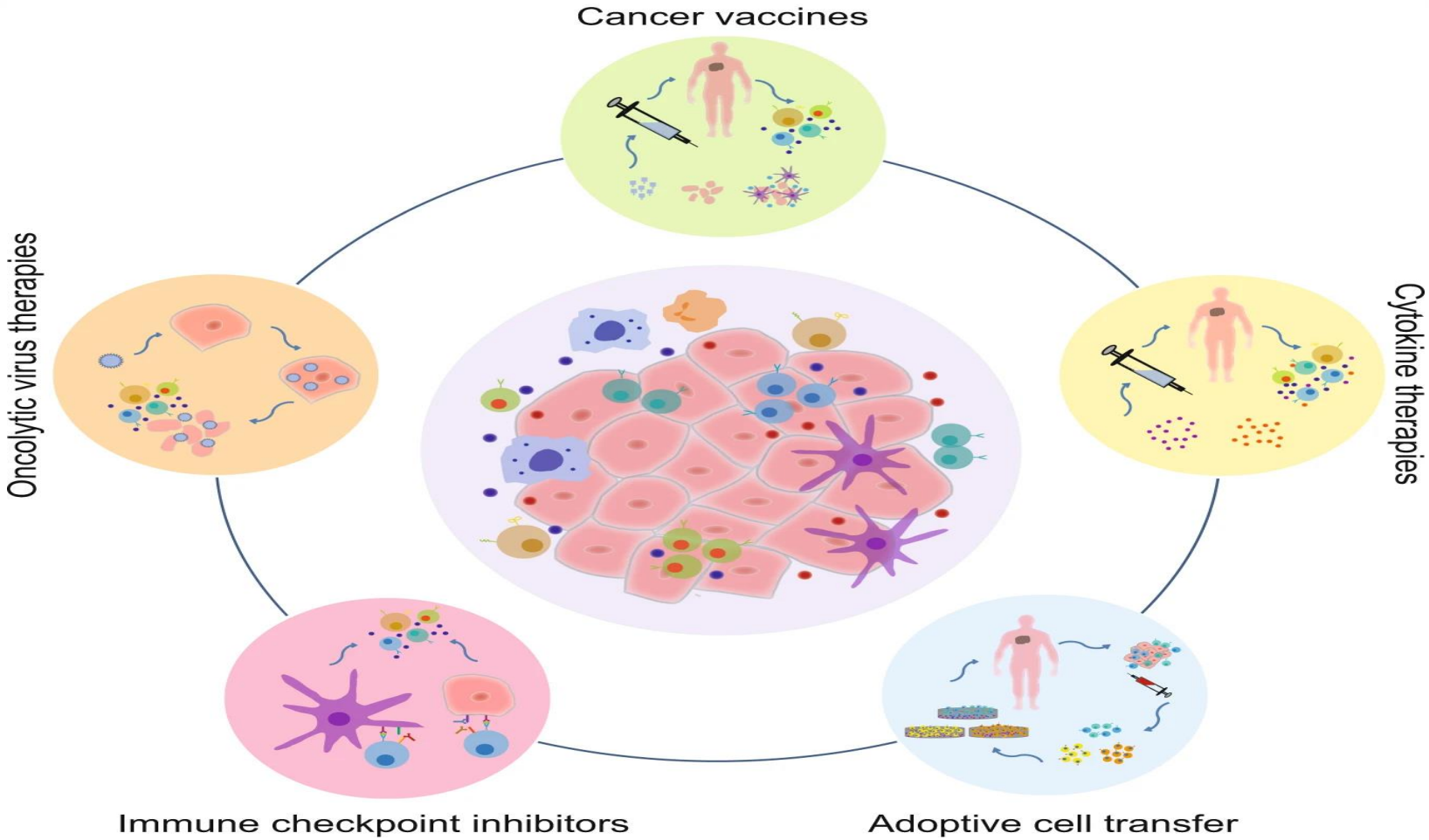
# Disclosures

- Consulting Fees: Novartis, Immunomedics, Gilead, Astrazeneca, Daiichi Sankyo, Biotheranostics
- Contracted Research: Industry funded research
- I will be discussing non-FDA approved indications during my presentation.

# Breast Cancer Immunotherapy

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*Cell & Molecular Immunology volume 17, pages807–821 (2020)*

# Anti PD-1/ PD-L1 combinations

# Anti PD-1/PD-L1 in BC Immunotherapy

- Anti PD-1 / PD-L1 monotherapy is associated with poor response rates in heavily pre-treated MBC.
- However, chemotherapy + ICI combinations demonstrate higher efficacy and offer survival advantage in early high risk TNBC and PD-L1 CPS≥ 10 front line mTNBC
- Other novel combinations?

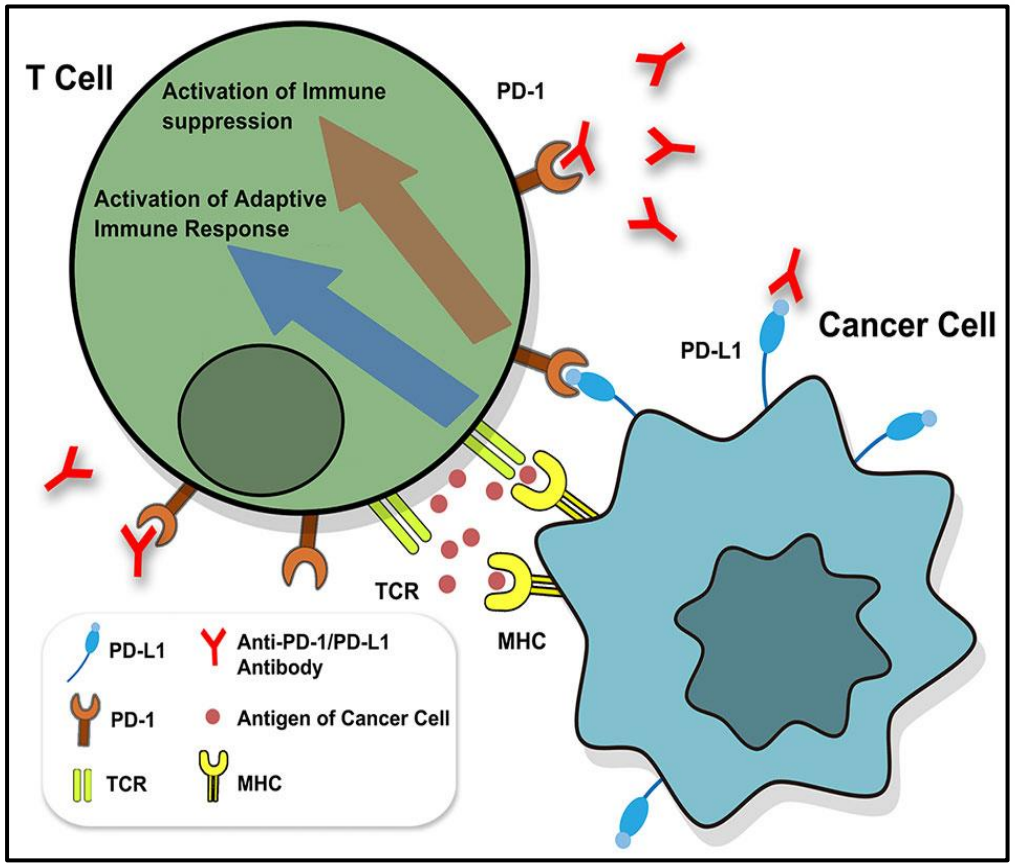


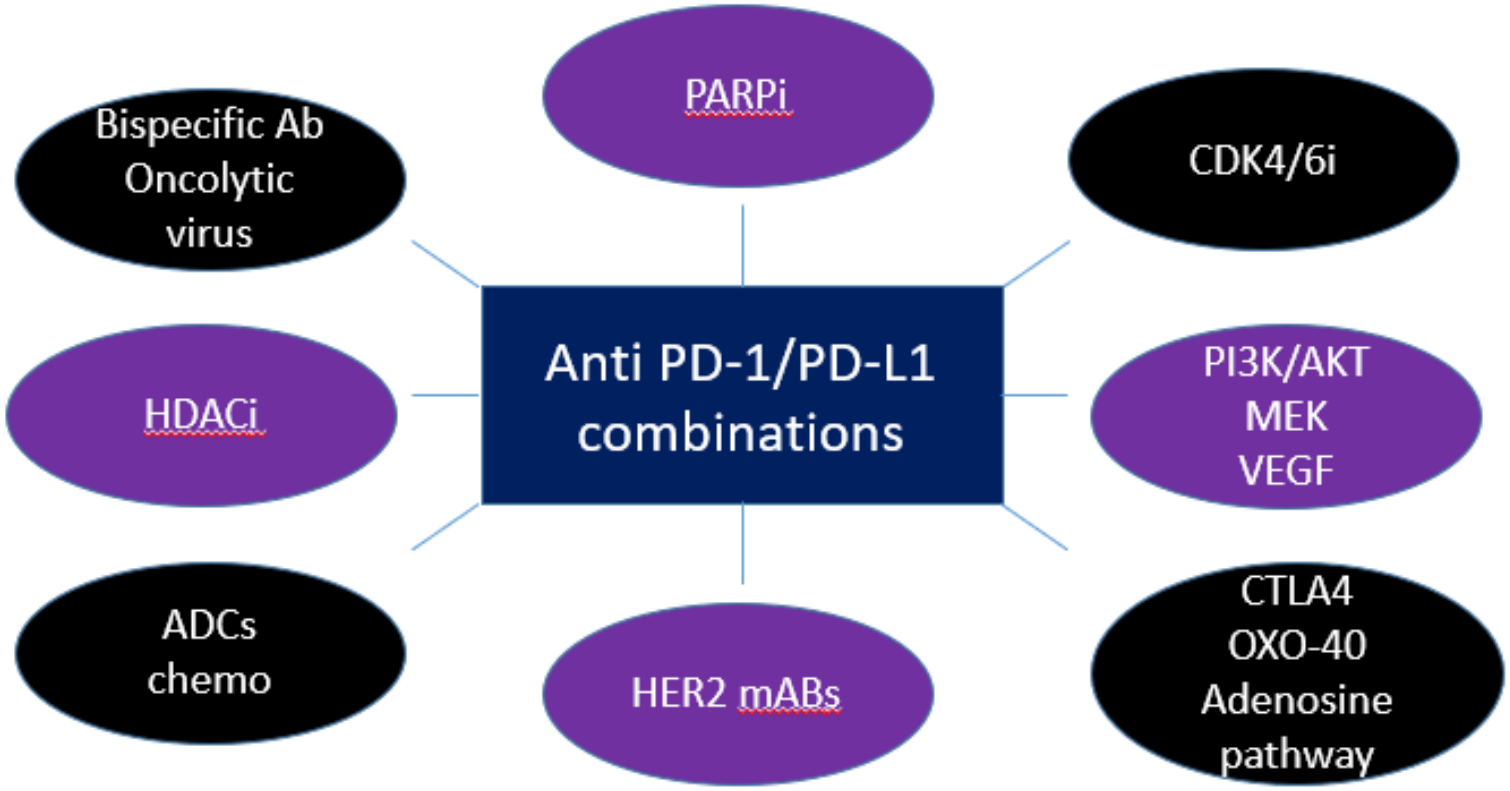

Fig: Mechanism of Action anti PD-1 / PD-L1 checkpoint inhibition




*Front Pharmacol. 2020 May 15;11:722*
Ann Oncol. 2019 Mar 1;30(3):397-404.
Lancet. 2020 Dec 5;396(10265):1817-1828.
N Engl J Med. 2020 Feb 27;382(9):810-821

# Approach to targeted ICI combinations

↑ Antigenicity ↑ Immunogenicity ↓ Immune-suppression

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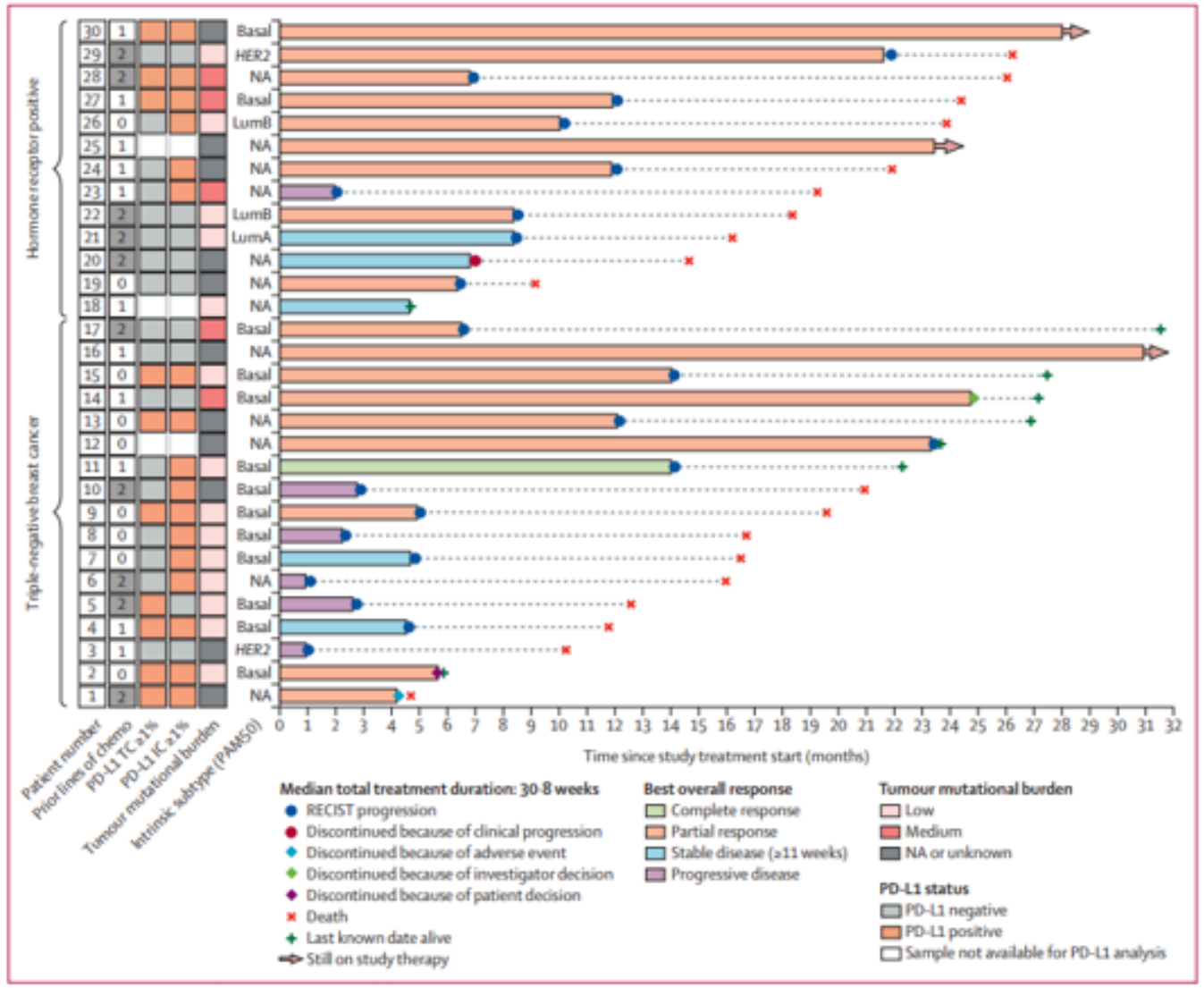
# PARPi combinations

# Phase I/2 MEDIOLA BC – Olaparib + Durvalumab




- ✓ N= 34 w gBRCA1/2,HER 2 neg MBC
- ✓ BRCA1 (16) vs. BRCA2 (18)
- ✓ NO new safety signals
- ✓ **ORR at 12 weeks: 63·3%**
- ✓ **DCR at 28 weeks: 50·0%**
- ✓ NO PD-L1 , TMB, HR & PAM50.
- ✓ Findings c/w Keynote162-TOPACIO

Lancet Oncol. 2020 Sep;21(9):1155-1164

# Dual Blockade (CTLA4 + PD-1/PD-L1)

# Dual CTLA4 + PD-1 blockade

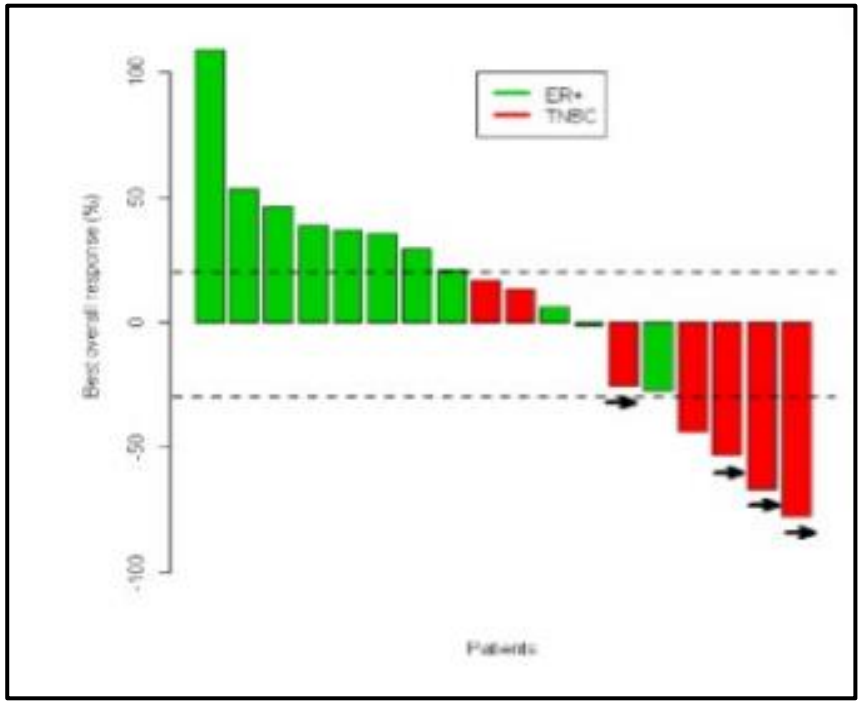



Fig: Waterfall pot showing response rates from Durvalumab + tremelimumab in ER+ & TNBC cohorts

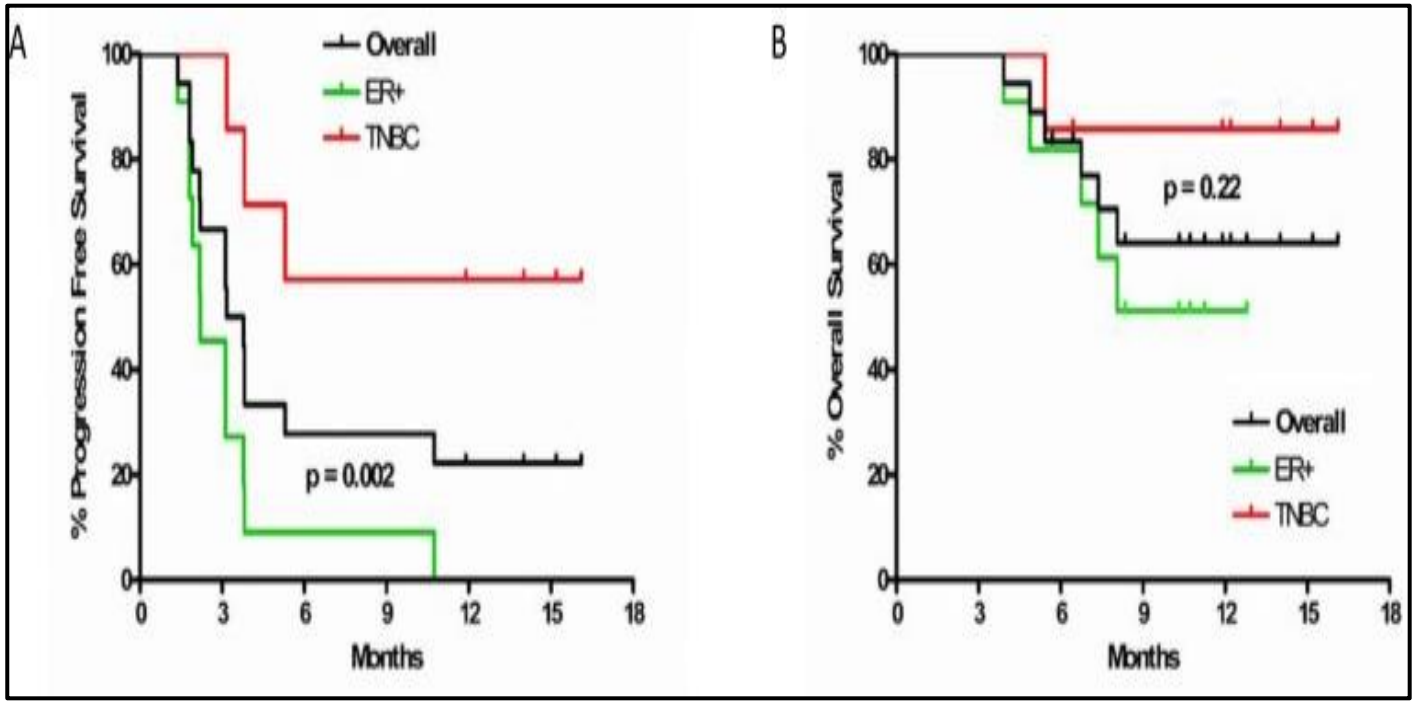



Fig: PFS and OS in n=18 patients receiving Durvalumab + tremelimumab for advanced refractory ER+ & TNBC

A) Upregulation of CD8, granzyme A, perforin gene expression & B) High neoantigen burden and C) TMB associated with improved response

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*Oncotarget. 2018 Apr 10;9(27):18985-18996*

# Dual ICI blockade in Metaplastic Breast Cancer DART (S1609) Cohort 36

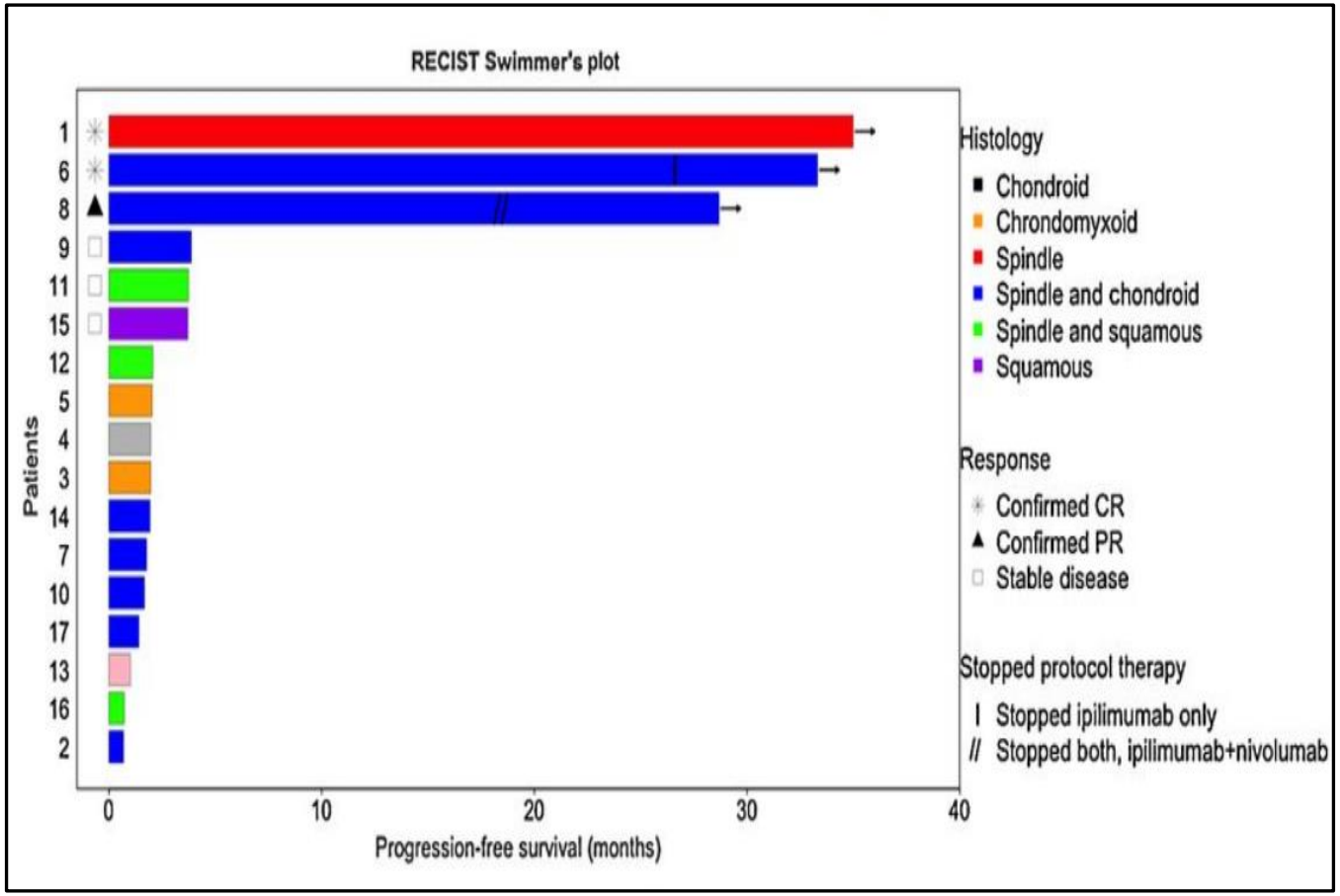


Fig: Swimmer plot depicting responses and PFS seen in n=17 patients with refractory metastatic metaplastic TNBC

- ✓ N =17, All pre-treated & chemo refractory
- ✓ All responses, ongoing > 2years in duration
- ✓ No correlation with TMB , PDL-1 expression
- ✓ Prior PD-1/PDL-1 therapy associated with PD
- ✓ NO new safety signals , but higher toxicity
- ✓ All responders with G3 irAEs

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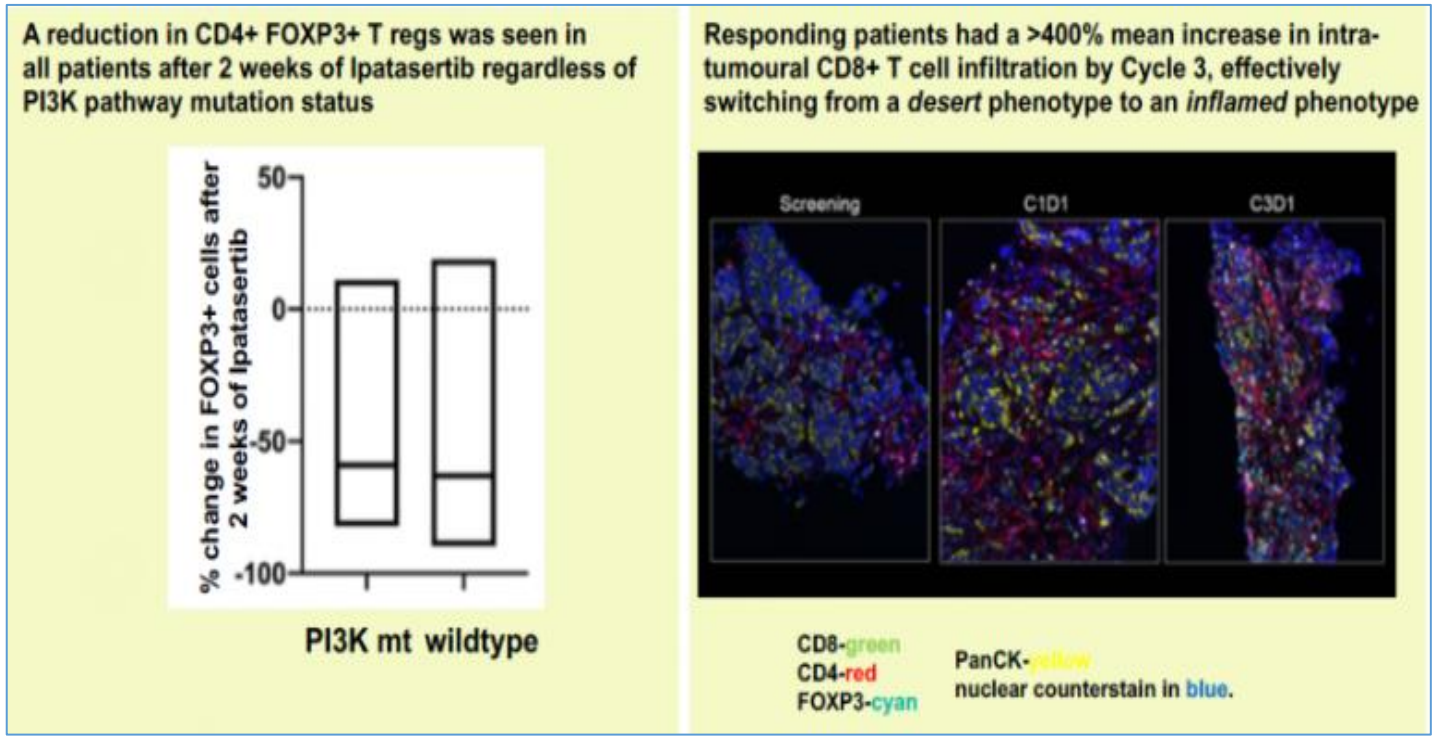
*Clin Cancer Res. 2022 Jan 15;28(2):271-278.*

# PI3K/AKT/PTEN

# Ipatasertib + Atezolizumab shows favorable safety

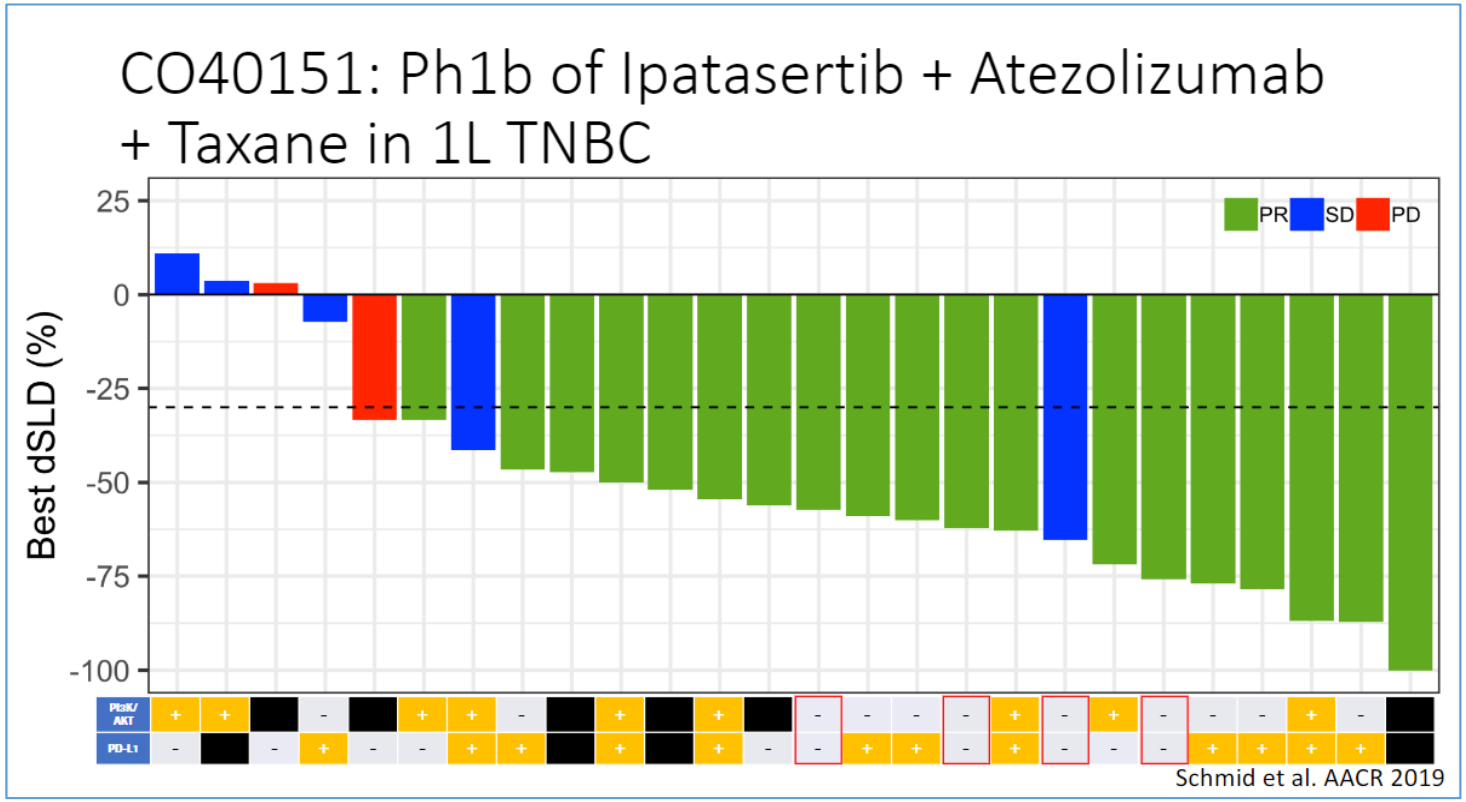
- RP2D of IPAT : 400mg with q3week Atezo
- Ipatasertib + Atezolizumab downregulates stromal T-Regs and upregulates iTILs CD8+ T cells in patients with advanced refractory solid tumors.




Lopez J. et al, Ice- CAP, AACR 2020

# Ipat + Atezo + taxane shows promising efficacy

Triplet shows ORR ~ 70% in front line mTNBC independent of PDL-1 or PI3K pathway alt.



## Resulted Targeted Therapy and Novel Immunotherapy Agent Anti–PD-1/L1 Trials in Metastatic TNBC

| Trial/ ClinicalTrials.gov Identifier | Regimen | Prior Lines[a] | Biomarker | N | ORR, % | Median PFS (95% CI), mo | Median OS (95% CI), mo |
|---|---|---|---|---|---|---|---|
| Targeted therapy combination trials | | | | | | | |
| PARP inhibitors | | | | | | | |
| TOPACIO/ KEYNOTE-162 NCT02657889 | Niraparib + pembrolizumab | 1–3 | PD-L1 + or –, *BRCA*m + or – | 55 | 21 | 2.3 (2.1–3.9) | |
| | | | *BRCA*m + | 15 | 47 | 8.3 (2.1–NR) | |
| | | | *BRCA*m – | 27 | 11 | 2.1 (1.4–2.5) | |
| MEDIOLA NCT02734004 | Olaparib + durvalumab after 4 wk run-in | ≤2 | Germline *BRCA*m | 17 | 58.8 | 4.9 | 20.5 |
| AKT inhibitors | | | | | | | |
| Schmid AACR NCT03800836 | Nab-/paclitaxel + ipatasertib + atezolizumab | 0 (DFS ≥12 mo) | PD-L1 + or – | 26 | 73 | | |
| MEK inhibitors | | | | | | | |
| COLET NCT02322814 | Nab-paclitaxel vs paclitaxel + cobimetinib + atezolizumab | 0 | PD-L1 + or – | 90 | 29.0 vs 34.4 | 7.0 (3.7–12.8) vs 3.8 (3.0–7.4) | NR (10.2–NR) vs 11.0 (9.5–NR) |
| Novel immunotherapy agent trials | | | | | | | |
| IL-2 agonists | | | | | | | |
| PIVOT-02 NCT02983045 | NKTR-214 + nivolumab | 0–2 | PD-L1 + or – | 38 | 13.2 | | |
| CAR T cells | | | | | | | |
| NCT01837602 | Intratumoral c-MET mRNA CAR T cells | Any | PD-L1 + or – | 6 | 0 | | |

Abbreviations: *BRCA*m, *BRCA* mutation; DFS, disease-free survival; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TNBC, triple-negative breast cancer.
[a]Prior lines of systemic therapy for metastatic disease.

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*J Natl Compr Canc Netw. 2020 Apr;18(4):479-489.*

# Ongoing Phase II/III studies with targeted combinations

| Trial/ ClinicalTrials.gov Identifier | Regimen | Lines[a] or Stage | Primary Endpoint | N |
|---|---|---|---|---|
| ETCTN NCT02849496 | Olaparib (PARPi) ± atezolizumab: *BRCA*m-positive | any | PFS | 72 |
| DORA NCT03167619 | Olaparib (PARPi) ± durvalumab: sporadic or germline *BRCA*m | ≤2 including current platinum | PFS | 60 |
| BEGONIA NCT03742102 | Paclitaxel + durvalumab ± capivasertib (AKTi) or danvatirsen (STAT3i) or oleclumab (anti-CD73) | 0 | AE rate | 120 |
| InCITe NCT03971409 | Avelumab + binimetinib (MEKi) or utomilumab (IgG2 antibody) or anti-OX40 antibody | 0–3 | ORR | 150 |




*J Natl Compr Canc Netw. 2020 Apr;18(4):479-489.*

# Emerging Agents – Oncolytic Viruses (OV)

# OVs in MBC

- Oncolytic viruses are derived or engineered from naturally occurring viruses to target and specifically kill cancer cells.

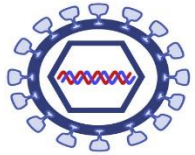
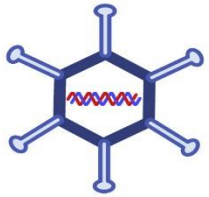
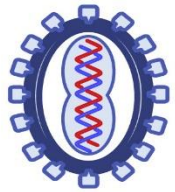
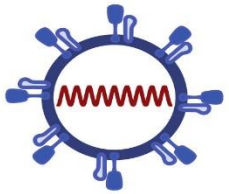
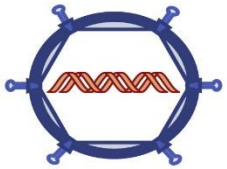
- OVs mediate anti-tumor effects through direct tumor cell lysis and activation of the anti-tumor immune response :
  - ⇧ Tumor-associated antigens (TAAs)
  - ⇩ Immunosuppressive TME.

- OVs have proven safe, with fewer treatment-related severe adverse events (SAEs, grade 3–4), however have shown poor responses as monotherapy in MBC




*O Bryan SM et al. Curr Gene Ther. 2018;18(4):192-205*
*Watanbe N et al, Mol Ther. 2021 Feb 3;29(2):505-520*

# OVs in MBC

| | Herpesvirus | Adenovirus | Vaccinia Virus | Measles Virus | Reovirus |
|---|---|---|---|---|---|
| **Structure** |  |  |  |  |  |
| **Genome** | 152kb dsDNA | 36kb dsDNA | 190kb dsDNA | 16kb ss(-)RNA | 23kb dsRNA |
| **Virion Size** | 200 nm | 70-90 nm | 70-100 nm | 100-200 nm | 75 nm |
| **Receptor** | HVEM, nectin1/2, HSPG | CAR, CD46, DSG-2 | glycosaminoglycans/ laminin, MARCO | CD46 | carbohydrates, JAM-A |
| **Oncolytic Variants** | ICP34.5 &ICP37 deletion (T-VEC), ICP34.5 deletion (HSV1716) | E1B deletion (Onyx-015, H101) Δ24-RGD (DNX-2401), E2F-Δ24-RGD (ICOVIR-5), Ad11/3 chimera (Enadenotucirev) | TK deletion (Pexa-Vec) | Attenuated strains: edmonston-Zagreb (MV-EZ), Edmonston (MV-CEA, MV-NIS) | Wild-type serotype 3 (Reolysin) |
| **Advantages** | High transduction efficiency, broad tumor tropism, large genome, easily manipulated | Extensively studied, ameanable to genetic manipulation, mild/self-limiting disease | Broad tropism with high transduction, large genome, easily manipulated | Extensively studied, easily manipulated, used safely as vaccine | Well understood biology, natural cancer cell selectivity, low pathogenicity |
| **Disadvantages** | pre-existing immunity, major human pathogen | pre-existing immunity, high liver tropism, receptor availability | Rapid neutralization, biology not completely understood | pre-existing immune response due to vaccination | Sensitive to anti-viral responses |

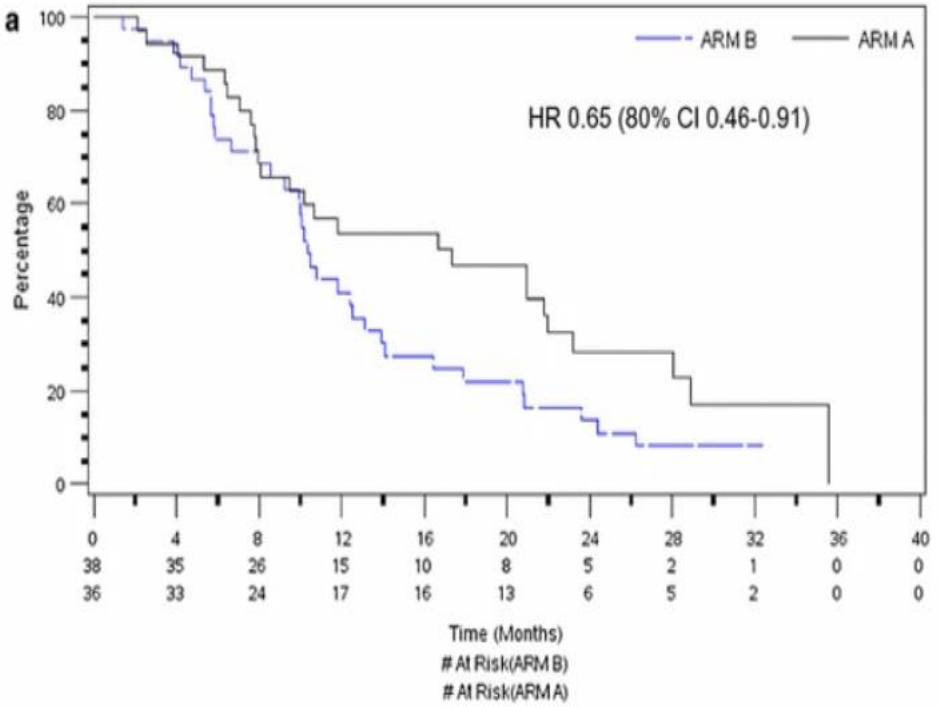
*Watanbe N et al, Mol Ther. 2021 Feb 3;29(2):505-520.*

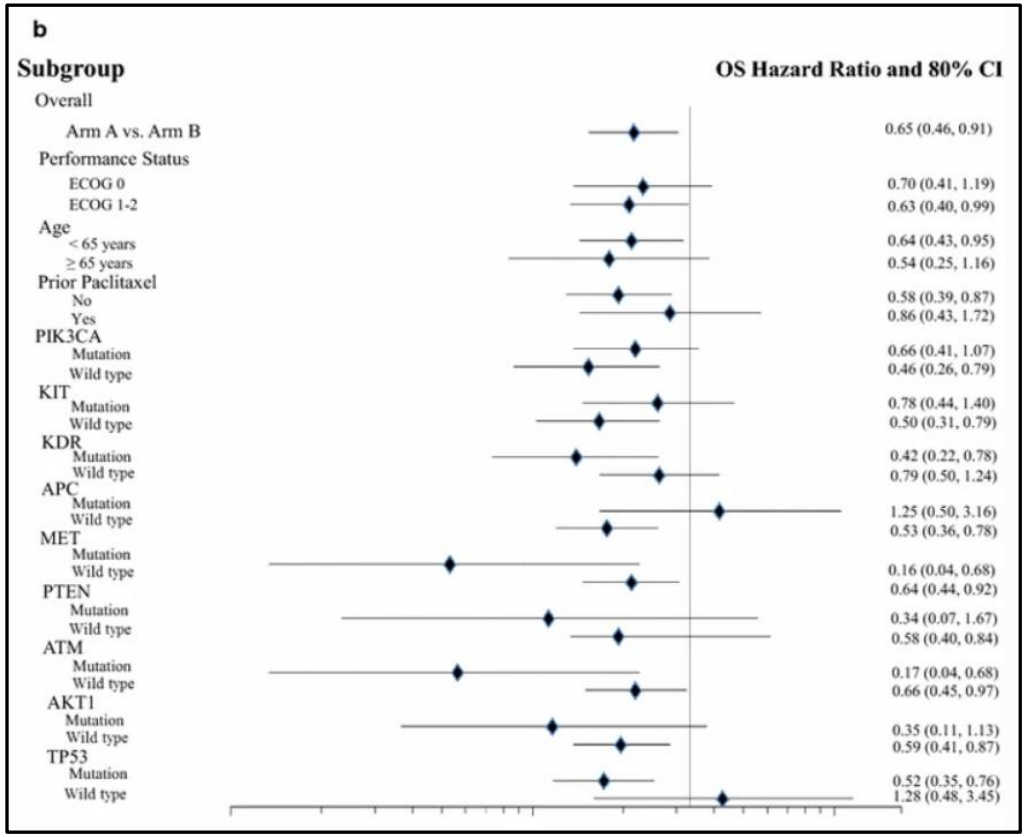
Breast Cancer Res Treat. 2018 Jan;167(2):485-493. doi: 10.1007/s10549-017-4538-4. Epub 2017 Oct 13.

# A randomized phase II study of weekly paclitaxel with or without pelareorep in patients with metastatic breast cancer: final analysis of Canadian Cancer Trials Group IND.213.

Bernstein V[1], Ellard SL[2], Dent SF[3], Tu D[4], Mates M[5], Dhesy-Thind SK[6], Panasci L[7], Gelmon KA[8], Salim M[9], Song X[3], Clemons M[3], Ksienski D[10], Verma S[3], Simmons C[8], Lui H[4], Chi K[8], Feilotter H[11], Hagerman LJ[4], Seymour L[4].

Fig. 3

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# Ongoing trials

| Agents | Trial / Phase | Setting |
|---|---|---|
| Pelareorep, letrozole, atezolizumab, trastuzumab | A Window-of-Opportunity Study of Pelareorep in Early Breast Cancer / Phase 1 | Neoadjuvant |
| Ipilimumab, nivolumab, talimogene, laherparepvec | Ipilimumab, Nivolumab, and Talimogene Laherparepvec before Surgery in Treating Participants with Localized, Triple-Negative or Estrogen Receptor-Positive, HER2-Negative Breast Cancer-Deleted / Phase 1 | Neoadjuvant |
| Paclitaxel, pelareorep, avelumab | A Study to Assess Overall Response Rate by Inducing an Inflammatory Phenotype in Metastatic BReast cAnCEr with the Oncolytic Reovirus PeLareorEp in CombinaTion with Anti-PD-L1 Avelumab and Paclitaxel – BRACELET-1 Study / Phase 2 | Metastatic |
| ADV/HSV-tk, valacyclovir, radiation: SBRT, pembrolizumab | SBRT and Oncolytic Virus Therapy before Pembrolizumab for Metastatic TNBC and NSCLC / Phase 2 | Metastatic |
| PVSRIPO | Examining Bioactivity of PVSRIPO in Invasive Breast Cancer / Phase 1 | Metastatic |
| Pelareorep, retifanlimab | INCMGA00012 and Pelareorep for the Treatment of Metastatic Triple-Negative Breast Cancer, IRENE Study / Phase 2 | Metastatic |
| Cyclophosphamide and JX-594 dose escalation, cyclophosphamide and JX-594, cyclophosphamide | A Study of Metronomic CP and JX-594 in Patients with Advanced Breast Cancer and Advanced Soft-Tissue Sarcoma (METROmaJX) / Phases 1 and 2 | Metastatic |
| TBio-6517, pembrolizumab | Study of TBio-6517, Given Intratumorally, Alone or in Combination with Pembrolizumab, in Solid Tumors / Phases 1 and 2 | Metastatic |
| ONCR-177, pembrolizumab | Study of ONCR-177 Alone and in Combination with PD-1 Blockade in Adult Subjects with Advanced and/or Refractory Cutaneous, Subcutaneous or Metastatic Nodal Solid Tumors / Phase 1 | Metastatic |

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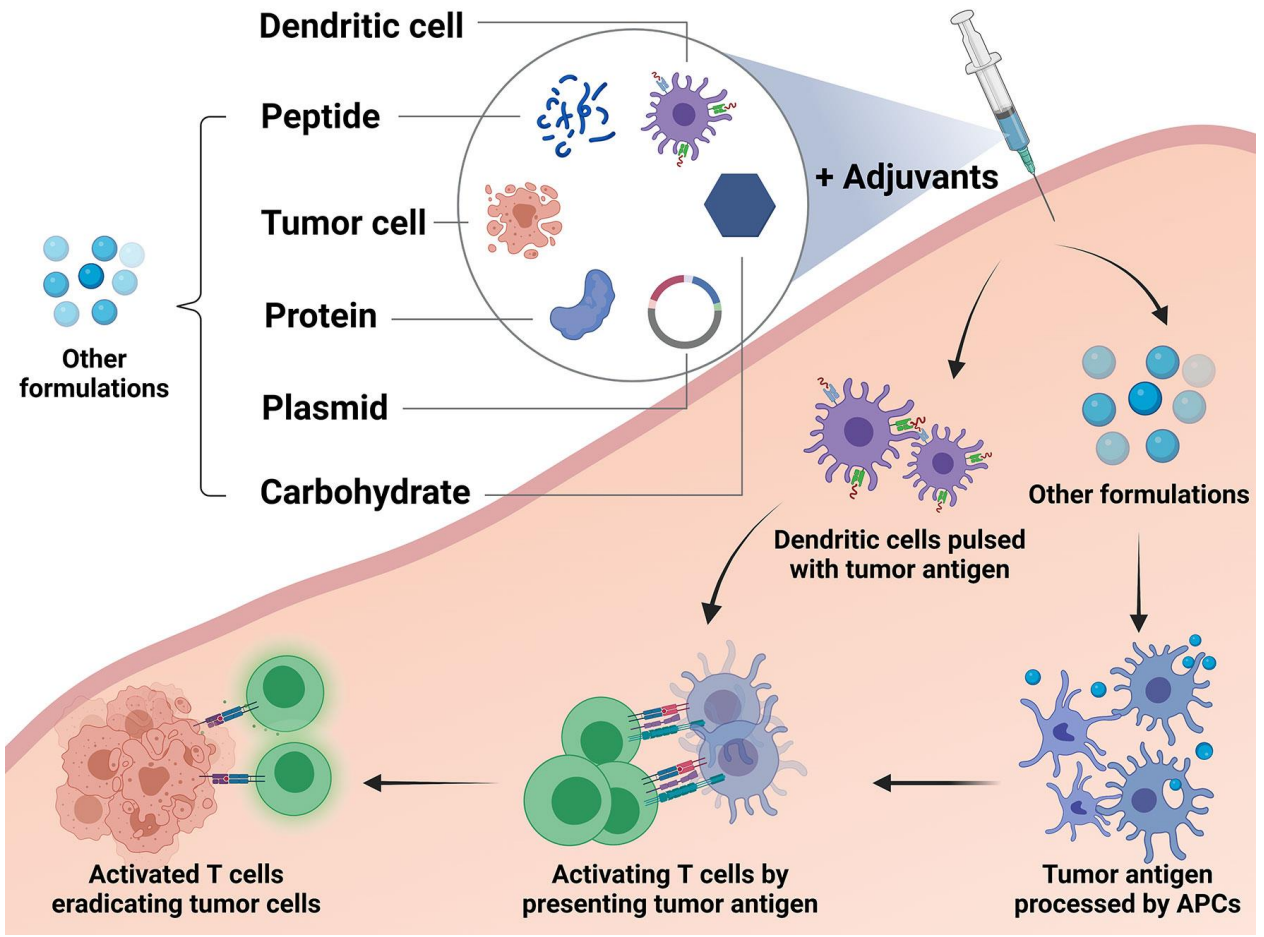
*Radosa JC et al, Breast Care 2020;15:450–469*

# Emerging Agents – Anti tumor vaccines

# Anti Tumor Vaccines in BC

- Breast cancer vaccines can be divided into different types based on platforms and formulations
- They all need to make the targeted antigen recognized by the autologous immune system to induce a therapeutic effect.
- Adjuvant of the vaccine plays a vital role as they are able to enhance antigen immunogenicity and regulate the immune response.
- Administration routes vary depending on vaccine construct (intranodal vs. SQ vs. intradermal)

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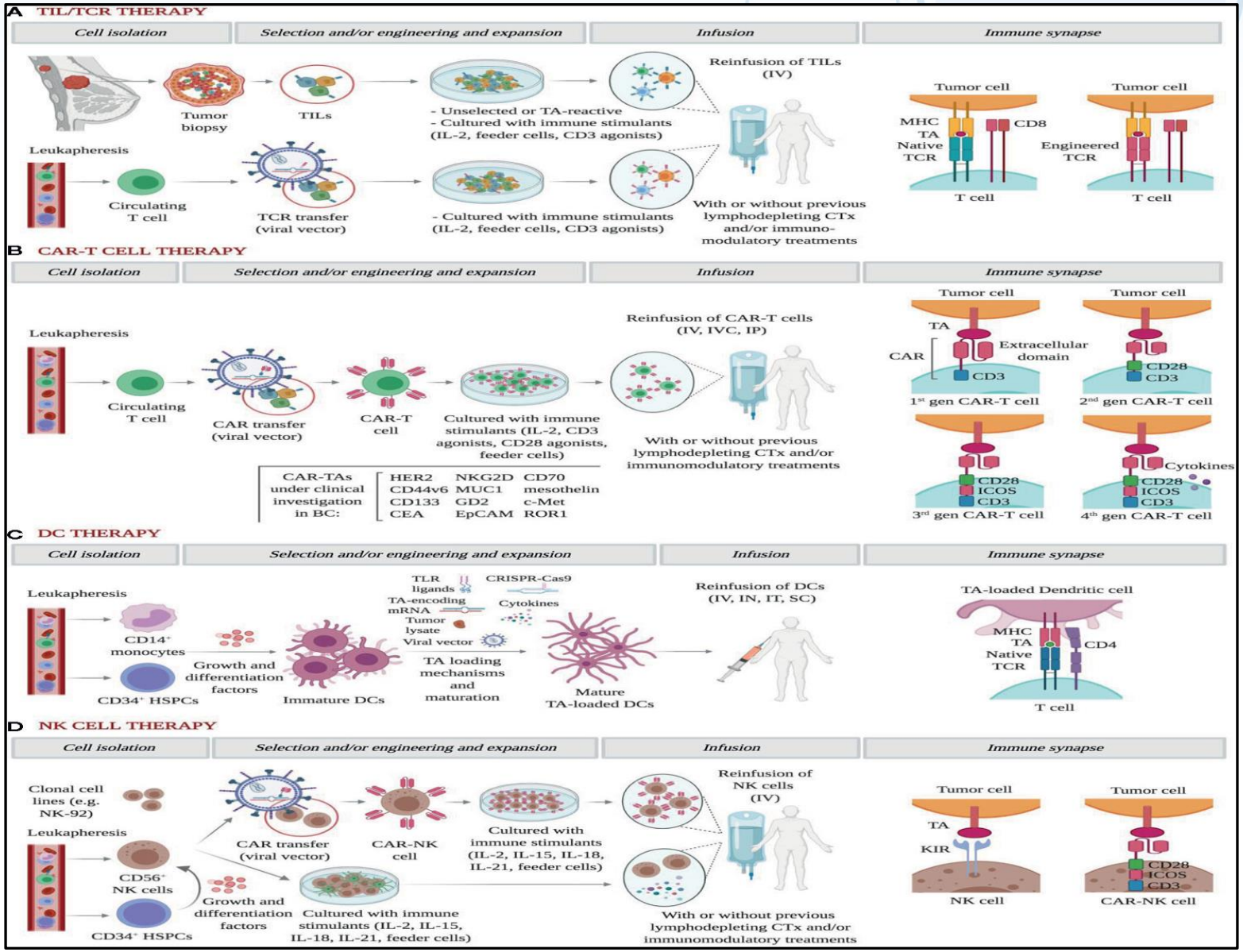
*Front Immunol. 2022 Jan 28;13:828386.*

| Clinical Trial Reference | Trial Phase | Setting | Targeted Tumor Antigen | Design and Arms | Breast Cancer Subtype | Primary Objectives | Outcomes |
|---|---|---|---|---|---|---|---|
| PRESENT Trial<br><br>NCT01479244 | III | Adjuvant | HER2-derived peptide E75 | Vaccination Arm: E75 + GM-CSF (N=376)<br>Control Arm: Placebo + GM-CSF (N=382) | HLA-A2/A3+, HER2 low-expressing (IHC 1/2+), node-positive | DFS | RR at 16.8 months interim analysis: 9.8% (vaccinated group) versus 6.3% (control group) (P = 0.07). Based on these data, the study was terminated for futility. |
| US Military Cancer Institute Clinical Trials Group Study I-01 and I-02 | I/II | Adjuvant | HER2-derived peptide E75 | Vaccination Arm: E75 + GM-CSF of different doses (N=108)<br>Control Arm: Observation (N=79) | HLA-A2/A3+, HER2-expressing, node-positive or high-risk node-negative | Safety, optimal dosing of immune response | Five-year DFS: 89.7% (vaccinated group) versus 80.2% (control group) (P = 0.08). Toxicities were minimal. |
| NCT01570036 | II | Adjuvant | HER2-derived peptide E75 | Vaccination Arm: E75 + GM-CSF + trastuzumab (N=136)<br>Control Arm: Placebo + GM-CSF + trastuzumab (N=139) | HLA-A2/A3+, HER2 low-expressing (IHC 1/2+), node-positive | DFS | The estimated 24-month DFS: 89.8% (vaccinated group) versus 83.8% (control group) (P= 0.18). |
| NCT00524277 | II | Adjuvant | HER2-derived peptide GP2 | Vaccination Arm: GP2 + GM-CSF (N=89)<br>Control Arm: GM-CSF alone (N=91) | HLA-A2+, HER2-expressing, node-positive or high-risk node-negative | DFS, RR | The estimated 5-year DFS: 88% (vaccinated group) versus 81% (control group) (P = 0.43); 100% (HER2 3+ vaccinated patients) versus 89% (HER2 3+ placebo patients) (P=0.03). |
| US Military Cancer Institute Clinical Trials Group Study I-04 | I | Adjuvant | HER2-derived peptide GP2 | Single arm: GP2 + GM-CSF of different doses (N=18) | HLA-A2+, HER2-expressing, node-negative | Safety, immune response | Immune response was induced in all the enrolled patients. Toxicities were minimal. |
| NCT00524277 | II | Adjuvant | HER2-derived peptide AE37 | Vaccination Arm: AE37 + GM-CSF (N=153)<br>Control Arm: GM-CSF alone (N=145) | HLA-A2+, HER2-expressing, node-positive or high-risk node-negative | RR | RR at 25-month median follow-up: 12.4% (vaccinated group) versus 13.8% (control group) (P=0.70). |
| US Military Cancer Institute Clinical Trials Group Study I-03 | I | Adjuvant | HER2-derived peptide AE37 | Single arm: AE37 + GM-CSF of different doses (N=15) | HLA-A2+, HER2-expressing, node-negative | Safety, immune response | Immune response was induced in all the enrolled patients. Toxicities were minimal. |
| NCT00399529 | II | Metastatic | HER2 | Single arm: HER2 GM-CSF-secreting tumor cell vaccine + cyclophosphamide + trastuzumab (N=20) | Stage IV, HER2-expressing | Safety, CBR | CBR at 6 months and 1 year was 55% and 40%, respectively. Toxicities were minimal. |
| NCT00140738 | I/II | Metastatic | HER2 | Single arm: recombinant HER2 protein + AS15 (N=40) | Stage IV, HER2-expressing | Safety, CBR | Clinical activity was observed with 2/40 objective responses and prolonged stable disease for 10/40 patients. Immunization was associated with minimal toxicity. |
| NCT02061332 | II | Neoadjuvant | HER2 | Single arm: HER2 dendritic cell vaccine with different routes (N=27) | HER2-expressing DCIS or early invasive breast cancer | Safety, immune and clinical response | Vaccination by all injection routes was well tolerated. There was no significant difference in immune response rates by vaccination route. |

*CBR, clinical benefit rate; DCIS, ductal carcinoma in situ; DFS, disease-free survival; GM-CSF, granulocyte-macrophage colony-stimulating factor; HER2, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; IHC, immunohistochemistry; RR, recurrence rate.*

# Emerging Agents – Adoptive Cell Therapy

# ACT Approach







*Front Oncol. 2020 Oct 27;10:605633*

# CAR-T cell therapy in MBC

## Safety and Efficacy of Intratumoral Injections of Chimeric Antigen Receptor (CAR) T Cells in Metastatic Breast Cancer

Julia Tchou [1 2], Yangbing Zhao [3 4], Bruce L Levine [3 4], Paul J Zhang [3], Megan M Davis [4], Jan Joseph Melenhorst [3 4], Irina Kulikovskaya [4], Andrea L Brennan [4], Xiaojun Liu [4], Simon F Lacey [4], Avery D Posey Jr [5 3 4], Austin D Williams [5 2], Alycia So [5 2], Jose R Conejo-Garcia [6], Gabriela Plesa [4], Regina M Young [4], Shannon McGettigan [4], Jean Campbell [7], Robert H Pierce [7], Jennifer M Matro [5 8], Angela M DeMichele [5 8], Amy S Clark [5 8], Laurence J Cooper [9], Lynn M Schuchter [5 8], Robert H Vonderheide [5 8], Carl H June [1 3 4]

## Phase I study of immunotherapy for advanced ROR1+ malignancies with autologous ROR1-specific chimeric antigen receptor-modified (CAR)-T cells.

Jennifer M Specht, Sylvia Lee, Cameron Turtle, Carolina Berger, Josh Veatch, Ted Gooley, Erin Mullane, Colette Chaney, Stanley Riddell, David G. Maloney

University of Washington, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; Fred Hutchinson Cancer Research, Seattle, WA; Seattle Cancer Care Alliance, Seattle, WA




Cancer Res (2019) 79 (4_Supplement): P2-09-13.

*Cancer Immunol Res. 2017 Dec;5(12):1152-1161*

# Ongoing trials / CAR T cell targets

| CAR-T cell target | Clinical Trials.gov identifier | Clinical trial phase |
|---|---|---|
| Mesothelin | NCT02580747 | Phase I |
| Mesothelin | NCT02792114 | Phase I |
| cMet | NCT01837602 | Phase I |
| MUC1 | NCT02587689 | Phase I/II |
| TnMUC1 | NCT04025216 | Phase I |
| MUC1* | NCT04020575 | Phase I |
| NKG2D Ligand | NCT04107142 | Phase I |
| ROR1 | NCT02706392 | Phase I |

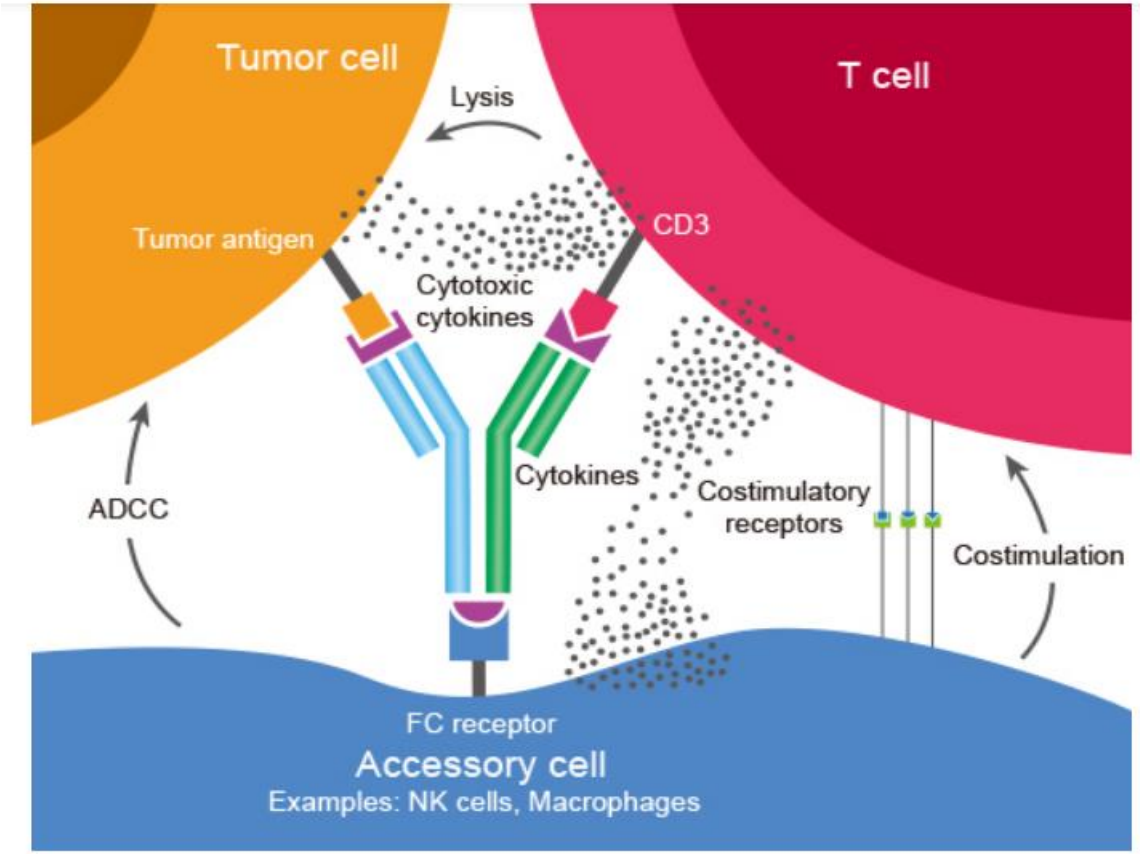



Mol Cancer Ther (2020) 19 (12): 2409–2421.

# Bispecific Antibodies

# BsAbs- Mechanism of Action

- Bispecific Antibodies (BsAbs) are recombinant protein constructs that can simultaneously bind two separate and unique antigens (usually on effector and tumor cell)
- This cross-linking of tumor and effector cells increases their proximity while simultaneously triggering T cell activation through ADCC







*Trends Cancer. 2021 Feb;7(2):162-173.*
*Clin Cancer Res. 2015 May 15;21(10):2305-14*

# BsABs under current investigation

**HER 2 Targeting**

| Listings | N | Phase | Target |
|---|---|---|---|
| NCT04276493<br>NCT02892123 | 50<br>234 | Ib/2 | 2 distinct sites on HER2 |
| NCT03821233 | 174 | 1 | 2 sites on HER2 (plus ADC delivery) |
| (5 studies) | 187 | 1 & 2 | Biparatropic HER2 |
| NCT03321981<br>NCT02912949 | 101<br>250 | 1<br>1/2 | HER2 and HER3 |
| NCT03983395 | 158 | | |
| NCT03272334<br>NCT03661424 | 33<br>16 | | |
| NCT01022138 | 32 | 2 | HER2/CD3 (ER/PR+/HER2 Neg) |
| NCT03842085 | 34 | 1 | 2 sites on HER2, afucosylated |
| NCT04501770 | 32 | 1 | HER2 and CD3 |
| NCT03912441 | 15 | 1 | 2 sites on HER2 |
| NCT04143711 | 220 | 1/2 | HER2 and undisclosed NK engager |
| NCT03448042 | 449 | 1/2 | HER2 and CD3 |
| NCT04162327 | 191 | 1a/1b | HER2 and PD-L1 |

**Non- HER 2 Targeting**

| NCT number | N | Phase | Status | Targets |
|---|---|---|---|---|
| NCT03524261 | 90 | 2 | Recruiting | CD3 and MUC1 |
| NCT01730612 | 23 | 1 | Not recruiting | |
| NCT03927573 | 24 | 1 | Recruiting | PSCA |
| | | | | CD3 and 5T4 |
| | | | | PDL1 and CD27 |
| NCT04224272 | 86 | 2a | Recruiting | 2 distinct sites on HER2 |
| NCT03849469 | 242 | 1 | Recruiting | CTLA4 and LAG3 |
| NCT04429542 | 292 | 1/1b | Recruiting | EGFR and TGFβ |
| NCT03752398 | 164 | 1 | Recruiting | PD1 and ICOS |
| NCT03620201 | 20 | 1 | Recruiting | TGFb and PD-L1 |

**WATCH FOR CRS!**

#Learn



*Clin Cancer Res. 2015 May 15;21(10):2305-14*

# Summary

- Rapidly evolving IO landscape with several novel agents and combinations in clinical development.
- Current strategies aim to improve antigenicity & immunogenicity while decreasing immune-tolerance in conventionally 'cold' breast tumors
- ICI's have entered routine clinical practice; several ICI combinations show promising efficacy and are in later stages of clinical development with potential practice changing implications for appropriate candidates.
- Similarly, ADCs undergoing prolific expansion in low HER 2(T-Dxd, ARX-788) and TNBC (SG, Dato-DXD, SGN- LIV1a); Ph II/III monotherapy and combination trials are currently underway with potential to change practice soon.

# Summary

- Novel checkpoint targets,  vaccines, cytokines, oncolytic viruses, ACT and BsABS all emerging in early development- some show promise, however, Its too soon to tell , how this will impact practice.
- Toxicity! IO is certainly not without risks and novel combinations face challenges in terms of safety (on-target/on tumor & on-target/off tumor effects) and scalability in the community ( eg: CAR-T and BsABs)
- Biomarkers are key in predicting benefit , identifying populations more likely to benefit  and potential mechanisms of resistance. PD-L1 , MSI and TMB are now considered standard practice to determine IO benefit in advanced breast cancer.

# Thank you