UCSF Helen Diller Family Comprehensive Cancer Center

# Immune Checkpoint Inhibition as a Rational Therapeutic Strategy for Advanced TNBC

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# Disclosures

| | |
|---|---|
| **Contracted Research** | Daiichi Sankyo Inc, Eisai Inc, Genentech, Immunomedics Inc, Lilly, MacroGenics Inc, Merck, Novartis, OBI Pharma Inc, Odonate Therapeutics, Pfizer Inc, Seattle Genetics |
| **Paid Travel** | Amgen Inc, AstraZeneca Pharmaceuticals LP, Lilly, MacroGenics Inc, Merck, Mylan NV, Pfizer Inc, Puma Biotechnology Inc |

# CASE PRESENTATION: DR HAMILTON

A 55-year-old female diagnosed and treated w/ adjuvant chemotherapy by another physician in 2012.

- In 2015 she recurred with lung and abdominal nodal disease, and saw me as a 2nd opinion.
- She was biopsy confirmed triple negative breast cancer.
- She enrolled on the IMpassion130 study and was randomized to *nab*-paclitaxel +/- atezolizumab.

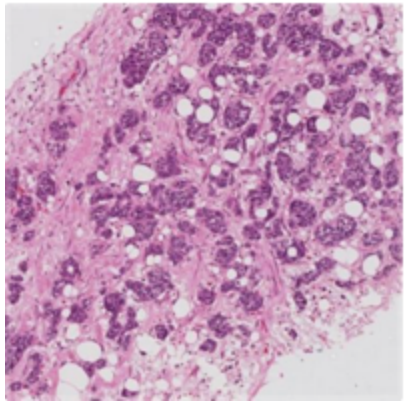
- By cycle 9, she had a CR on scans.
- 20 months into therapy (2016) she had progressive neuropathy and after a long discussion, we discontinued her *nab*-paclitaxel and continued atezolizumab/placebo.
- Scans continued to show CR.
- Ultimately, she was unblinded when the study closed and it was confirmed she was receiving atezolizumab.
- She continues to receive atezolizumab as part of continued study follow up as of December 2019.

Questions for panel:

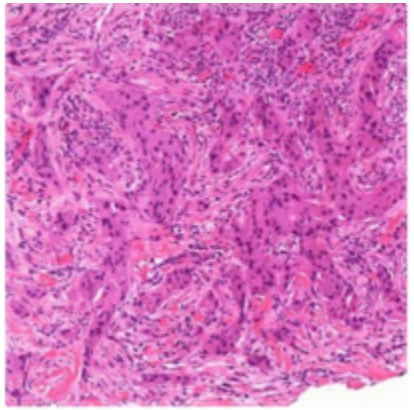
1. Are you reflex testing all your newly diagnosed metastatic TNBC patients for PD-L1 expression? What vendor are you using?
2. Are you profiling your 1st line patients with a broad panel or waiting until later?
3. How would you decide how long to continue chemotherapy? Would you stop atezolizumab?

# TILS in Breast Cancer

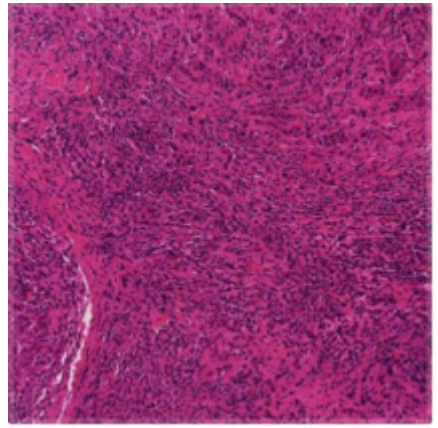
- High TILS are more frequent in TNBC (30%)>HER2 (19%)>luminal tumors (13%)
- High TILS predictive of:
  - DFS and OS in TN early stage breast cancer
  - pCR in TN and HER2+ breast cancer
  - Improved DFS and OS in untreated largely node negative TNBC (>30%)
- International consensus scoring recommendations see www.tilsinbreastcancer.org

0% TILS



30% TILS



80% TILS


Salgado, Denkert et al, 2014 Ann Oncol
Denkert et al 2016 Modern Path
Loi et al, JCO 2019; TILs images from www.tilsinbreastcancer.org
Park et al, Ann Oncol 2019

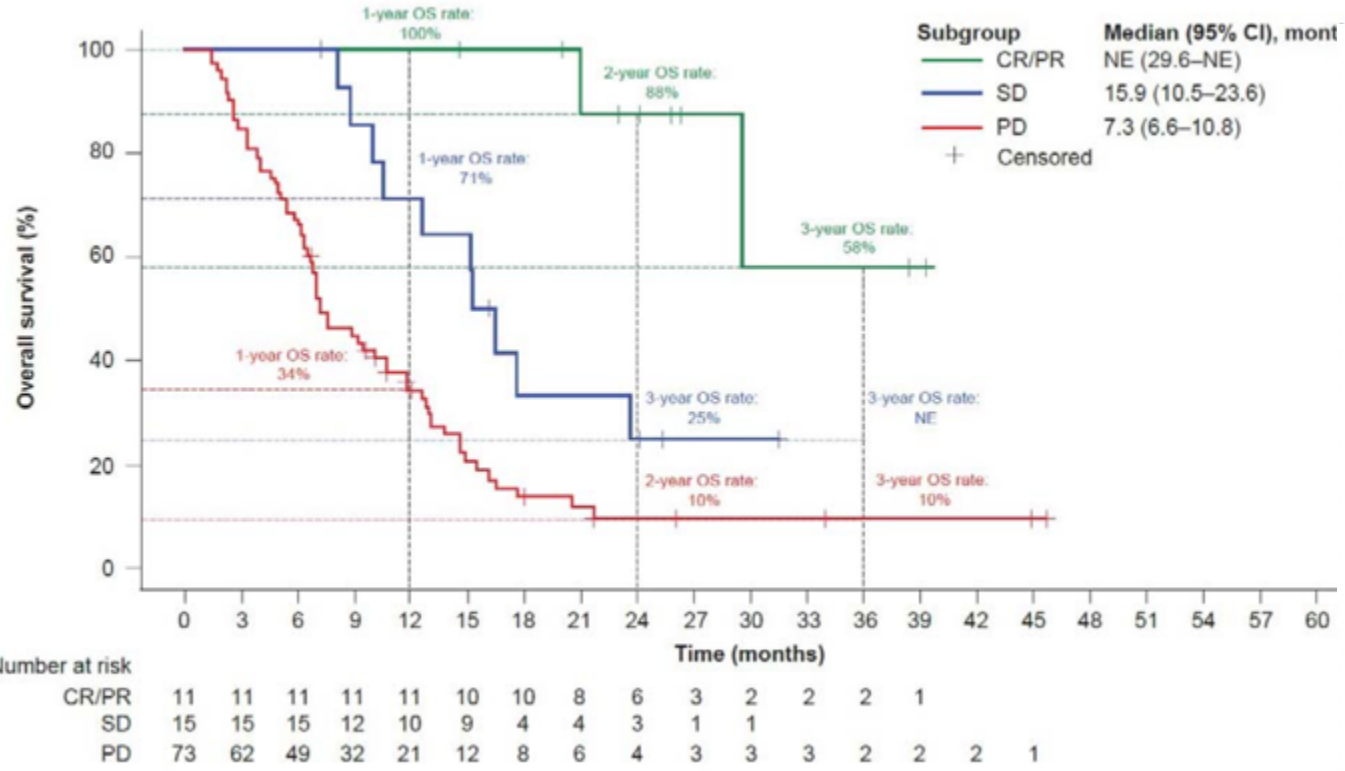
# Checkpoint Inhibitor Monotherapy: Line of Therapy Matters

| Agent | Subtype | N | ORR | ORR (PD-L1+)* |
|---|---|---|---|---|
| Pembrolizumab | | | | |
| • Single agent (KEYNOTE-012) | TNBC | 32 | 18.5% | 18.5% |
| • Single agent (KEYNOTE-028) | ER+ | 25 | 12.0% | 12.0% |
| • Single agent (KEYNOTE-086-A) | TNBC | 170 | 5.7% (PD-L1+) | 5.7% |
| • Single agent (KEYNOTE-086-B) | TNBC | 84 | 21.4% | 21.4% |
| • Plus trastuzumab (PANACEA) | HER2+ | 58 | | 15.0% |
| Atezolizumab | | | | |
| • Single agent | TNBC | 21 | 19.0% | 19.0% |
| • Single agent (expanded) | TNBC | 115 | 10.0%<br>IL (n=21): 26%;<br>≥2L (n=91): 6% | 13.0% |
| Avelumab | | | | |
| • Single agent (JAVELIN) | All | 168 | 4.8% | 33.3% |
| | ER+/HER2- | 72 | 2.8% | NR |
| | HER2+ | 38 | 3.8% | NR |
| | TNBC | 58 | 8.6% | 44.4% |

Nanda et al, JCO 2016; Rugo et al, CCR 2018; Dirix et al, BCRT 2017;
Loi et al, SABCS 2017; Emens et al, JAMA Onc 2019; Adams et al, Ann Onc 2019
*Studies used different antibodies and cutoffs for PD-L1 positivity

# Monotherapy: Overall Survival by RECIST in First-Line Setting

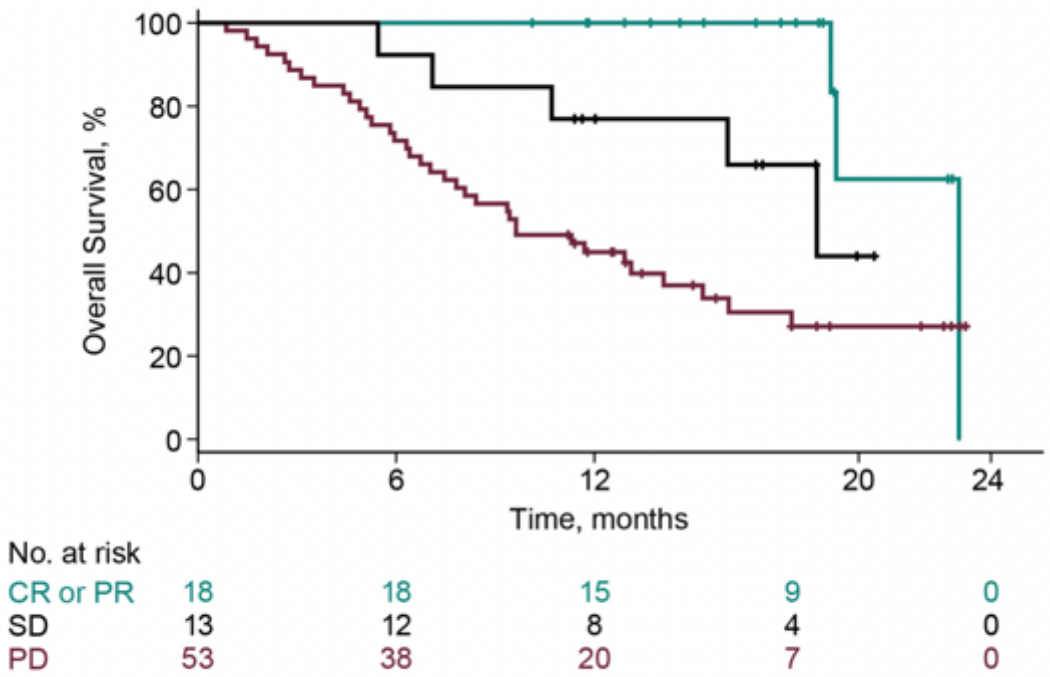
## Atezolizumab




**N=116**

**Median OS: 17.6mo**

## Pembrolizumab

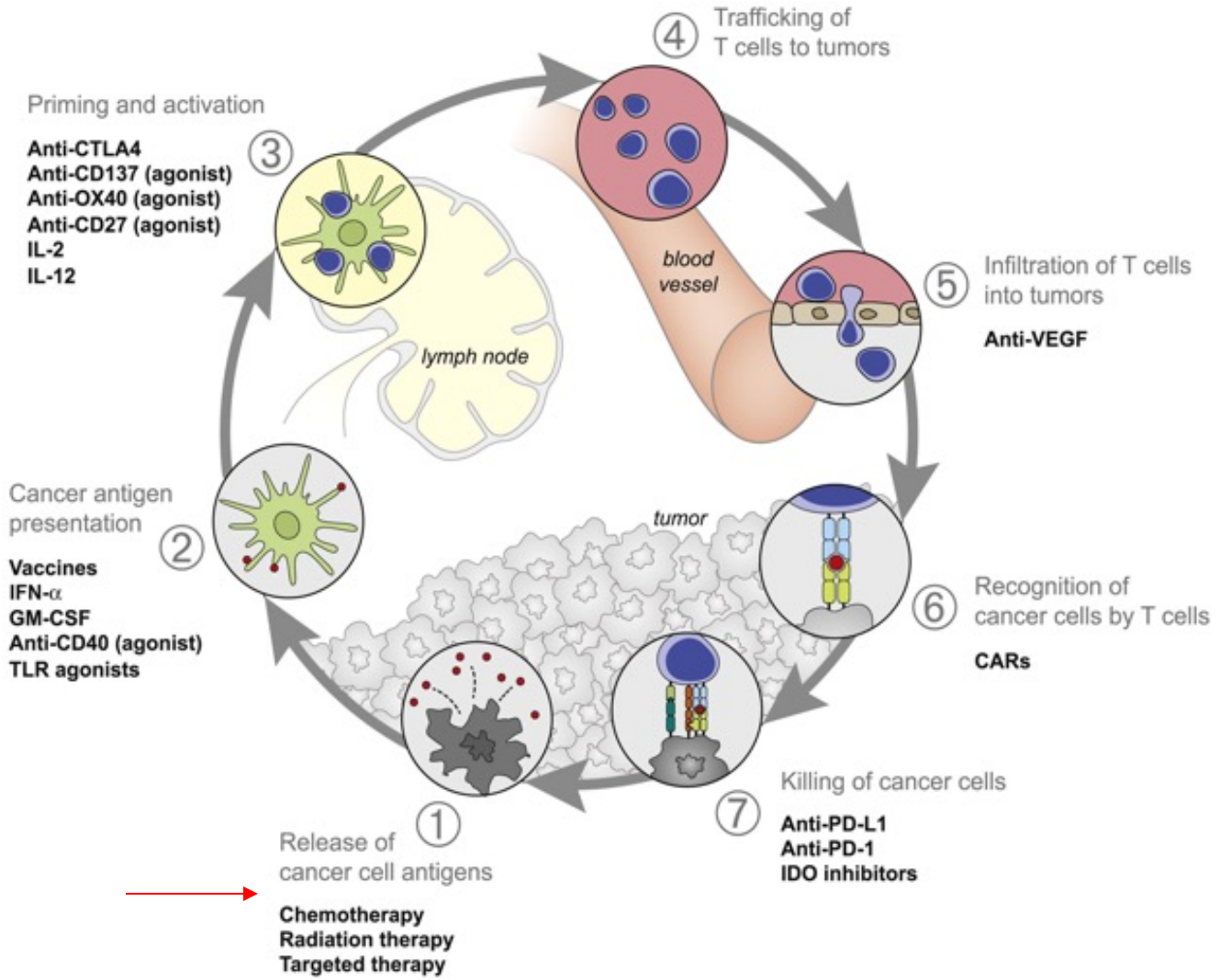



**N=84**

**Median OS: 18 mo**

Adams et al, Ann Onc 2019; Emens et al, Jama Onc 2019

# Augmenting the Cancer Immunity Cycle




Chen DS and Mellman I. *Immunity* 2013;39:1-9

# IMpassion130 study design

**Key IMpassion130 eligibility criteria[a]:**

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

**Stratification factors:**

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

**Atezo + *nab*-P arm:**

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m$^2$ IV
- On days 1, 8 and 15 of 28-day cycle

*Double blind; no crossover permitted*

**Plac + *nab*-P arm:**

Placebo IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m$^2$ IV
- On days 1, 8 and 15 of 28-day cycle

RECIST v1.1
PD or toxicity

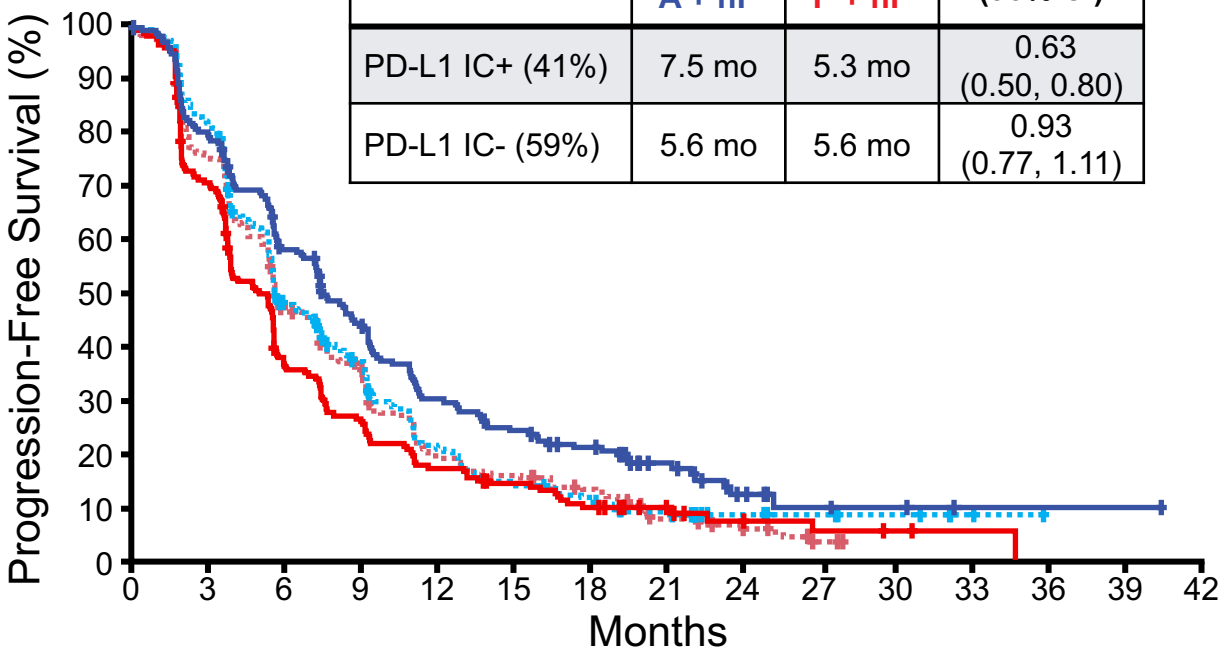
- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

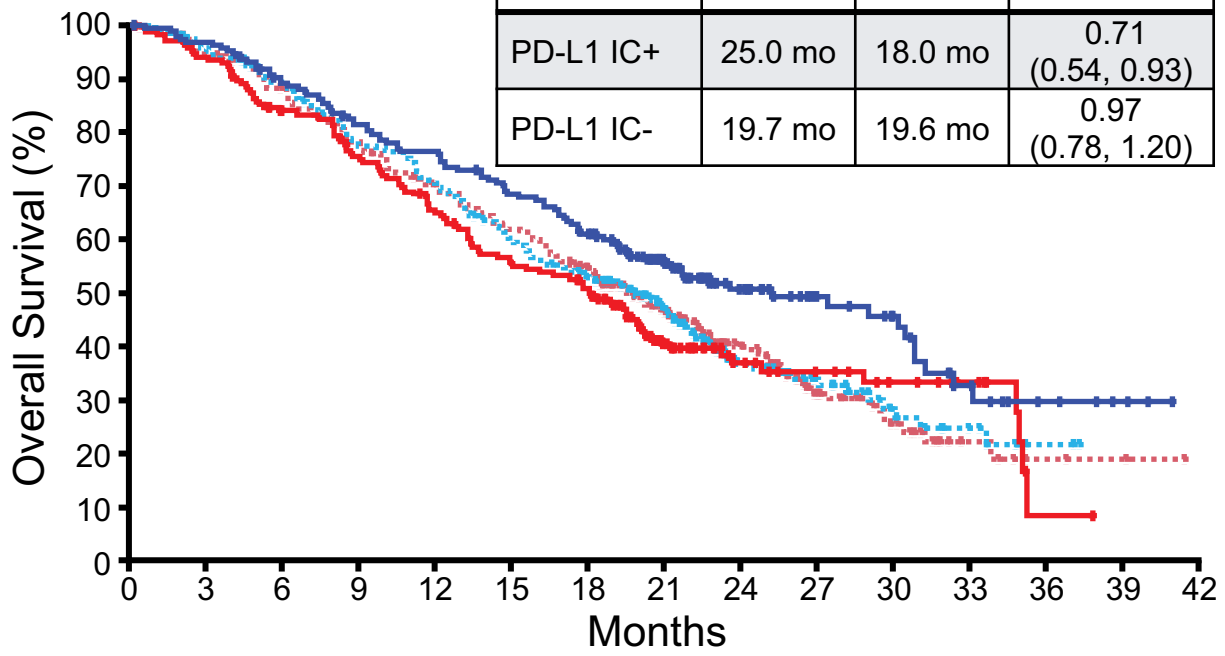
Schmid P, et al. NEJM 2018, ASCO 2019

# PD-L1 IC status by SP142 predicts PFS and OS benefit with atezolizumab + *nab*-paclitaxel[1,2]
## (41% positive by SP142)

| Population | Median PFS | | HR (95% CI) |
|---|---|---|---|
| | A + nP | P + nP | |
| PD-L1 IC+ (41%) | 7.5 mo | 5.3 mo | 0.63 (0.50, 0.80) |
| PD-L1 IC- (59%) | 5.6 mo | 5.6 mo | 0.93 (0.77, 1.11) |




| Population | Median OS | | HR (95% CI) |
|---|---|---|---|
| | A + nP | P + nP | |
| PD-L1 IC+ | 25.0 mo | 18.0 mo | 0.71 (0.54, 0.93) |
| PD-L1 IC- | 19.7 mo | 19.6 mo | 0.97 (0.78, 1.20) |



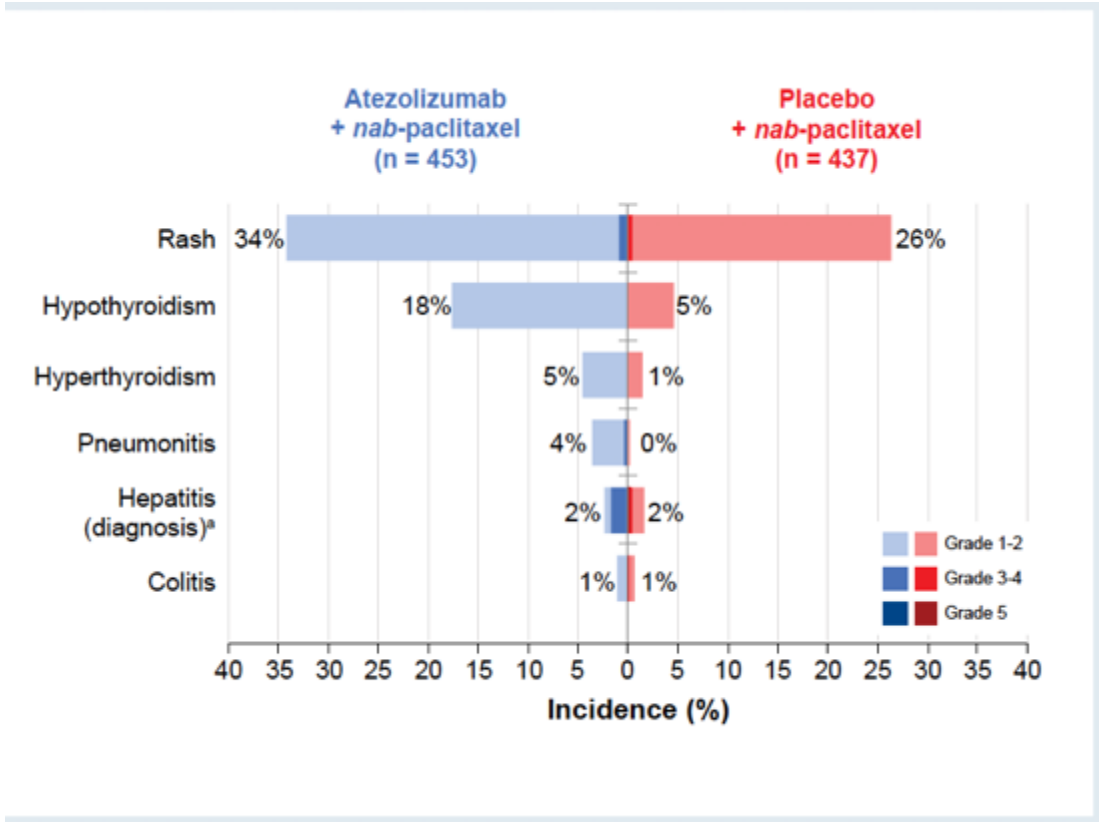

A + nP (IC+, n = 185)
P + nP (IC+, n = 184)
A + nP (IC-, n = 266)
P + nP (IC-, n = 267)

A + nP, atezolizumab + *nab*-paclitaxel; HR, hazard ratio; ITT, intention to treat; OS, overall survival; P + nP, placebo + *nab*-paclitaxel; PFS, progression-free survival.
PD-L1 IC+: PD-L1 in ≥ 1% of IC as percentage of tumour area assessed with the VENTANA SP142 assay.
NCT02425891. Stratification factors: prior taxane use, liver metastases and PD-L1 IC status. Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS.
Clinical cutoff date: 2 January 2019.
1. Schmid, ASCO 2019. 2. Schmid et al., submitted.

Rugo et al. Abstract 6571
IMpassion130 PD-L1 IHC
https://bit.ly/30OmOqz

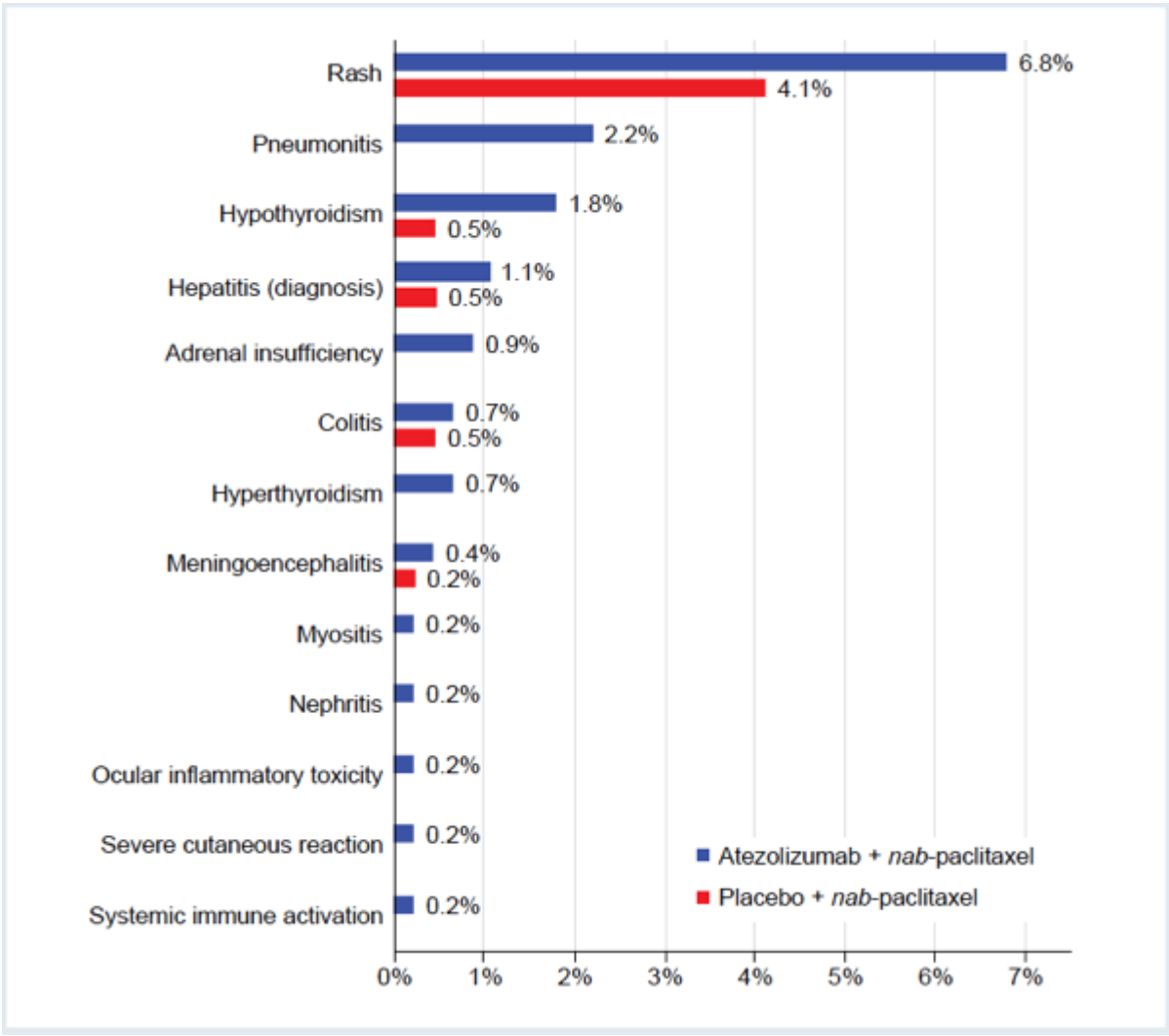
# Immune-Related Adverse Events

## Most Clinically Relevant AESI by Grade




AESI = adverse event of special interest

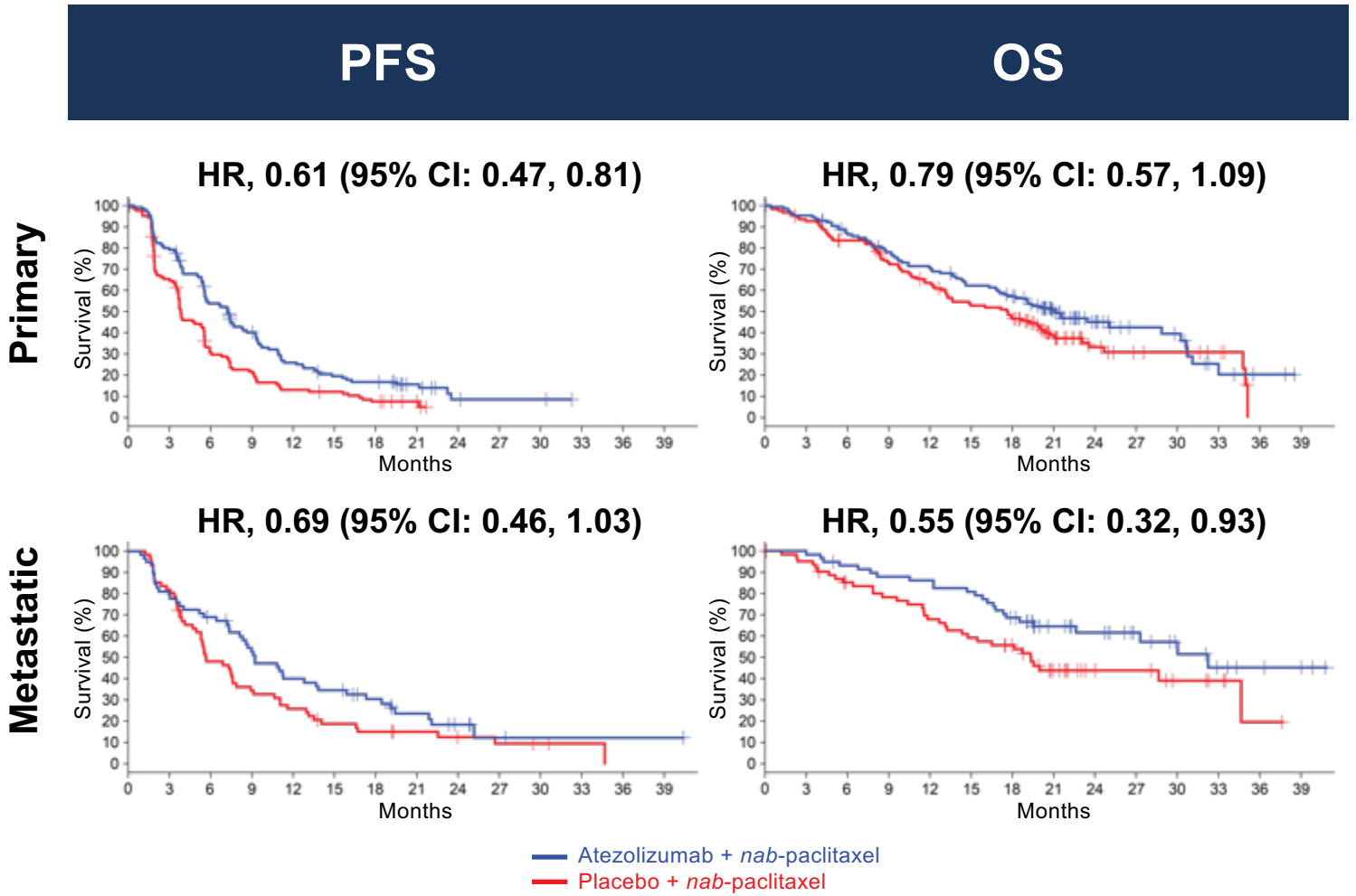
## Immune-Mediated AESI Requiring Systemic Corticosteroids




Schneeweiss, Rugo et al, ASCO 2019

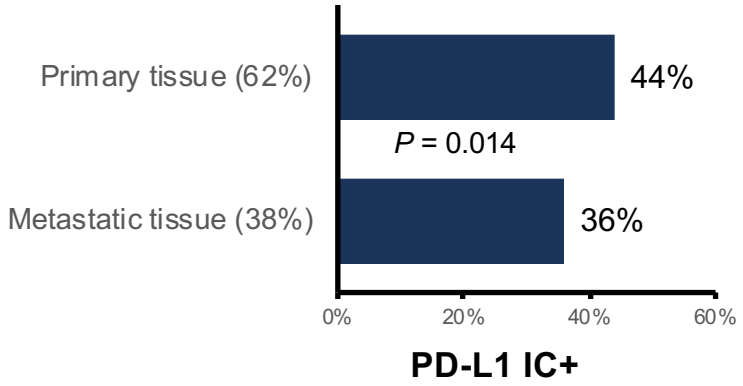
# PD-L1 status in primary vs metastatic tissue

## Efficacy in PD-L1 IC+

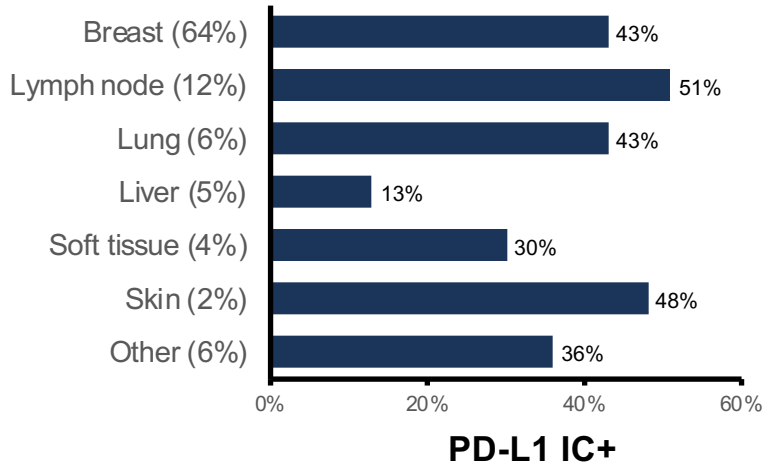



- Median time of sample collection to randomization: 61 days

## PD-L1 status by primary vs metastatic tissue[a]




## PD-L1 status by anatomical location[a]

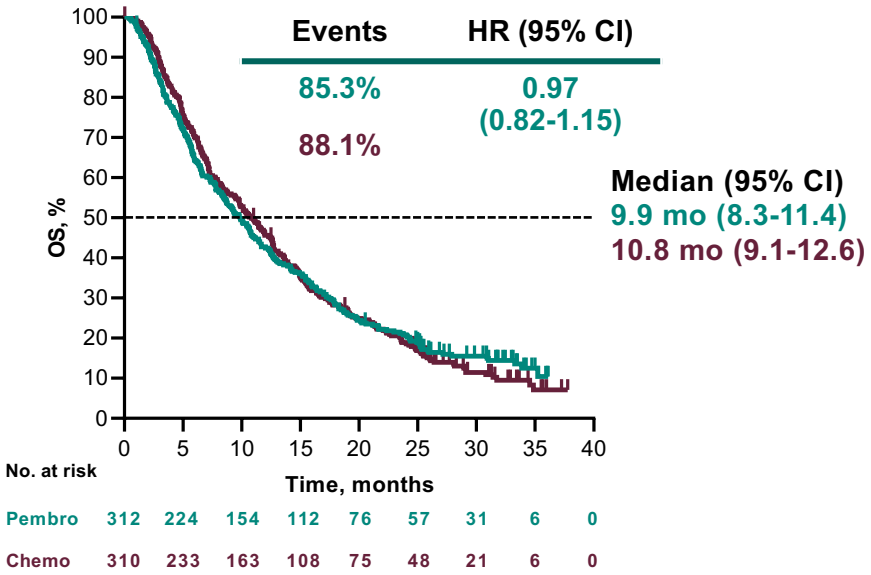



[a] Evaluable population (n = 901). PD-L1 IC+: PD-L1 in ≥ 1% of IC as percentage of tumour area assessed with the VENTANA SP142 assay.
HRs adjusted for prior taxanes, presence of liver metastases, age and ECOG PS. No major differences were observed for clinical benefit in samples collected within 61 days of randomization or beyond that period (Emens, et al, manuscript in preparation).

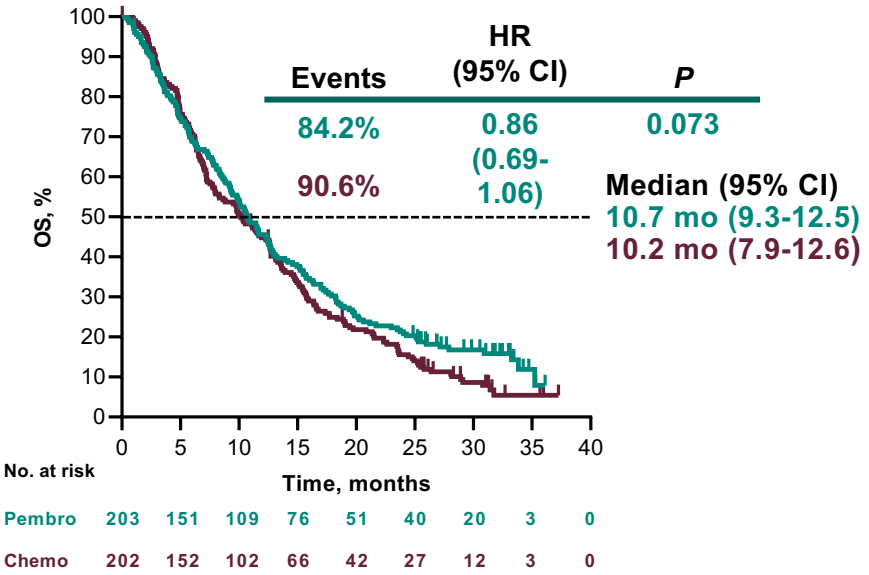
Rugo H et al, ESMO 2019

# KEYNOTE 119: Phase III Pembrolizumab vs. Chemo in 2L/3L TNBC: OS by PD-L1 CPS

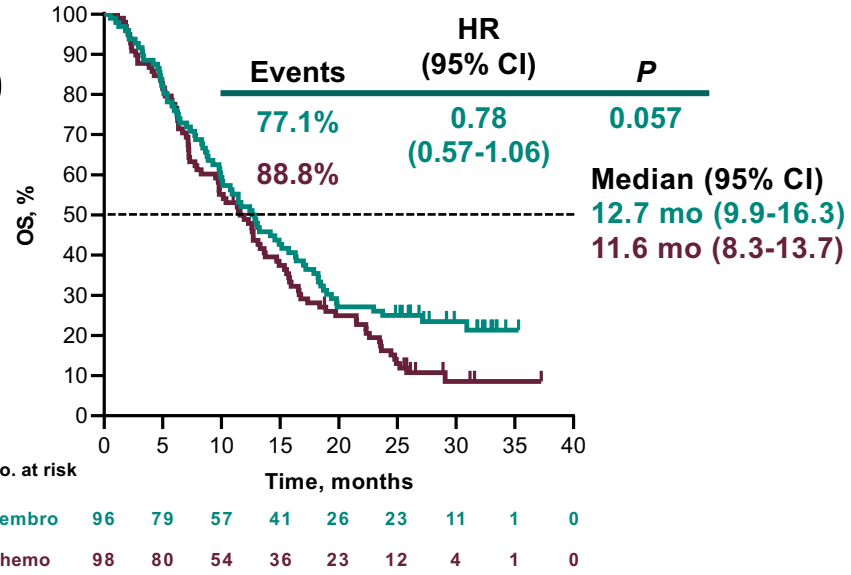
**ITT**
**N=622**



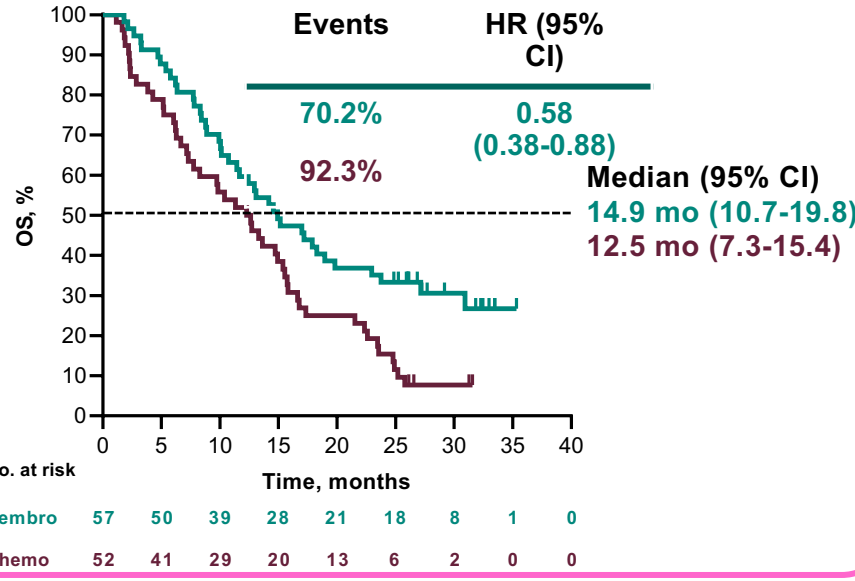

**CPS ≥1**
65%




**CPS ≥10**
31%




**CPS ≥20**
18.5%

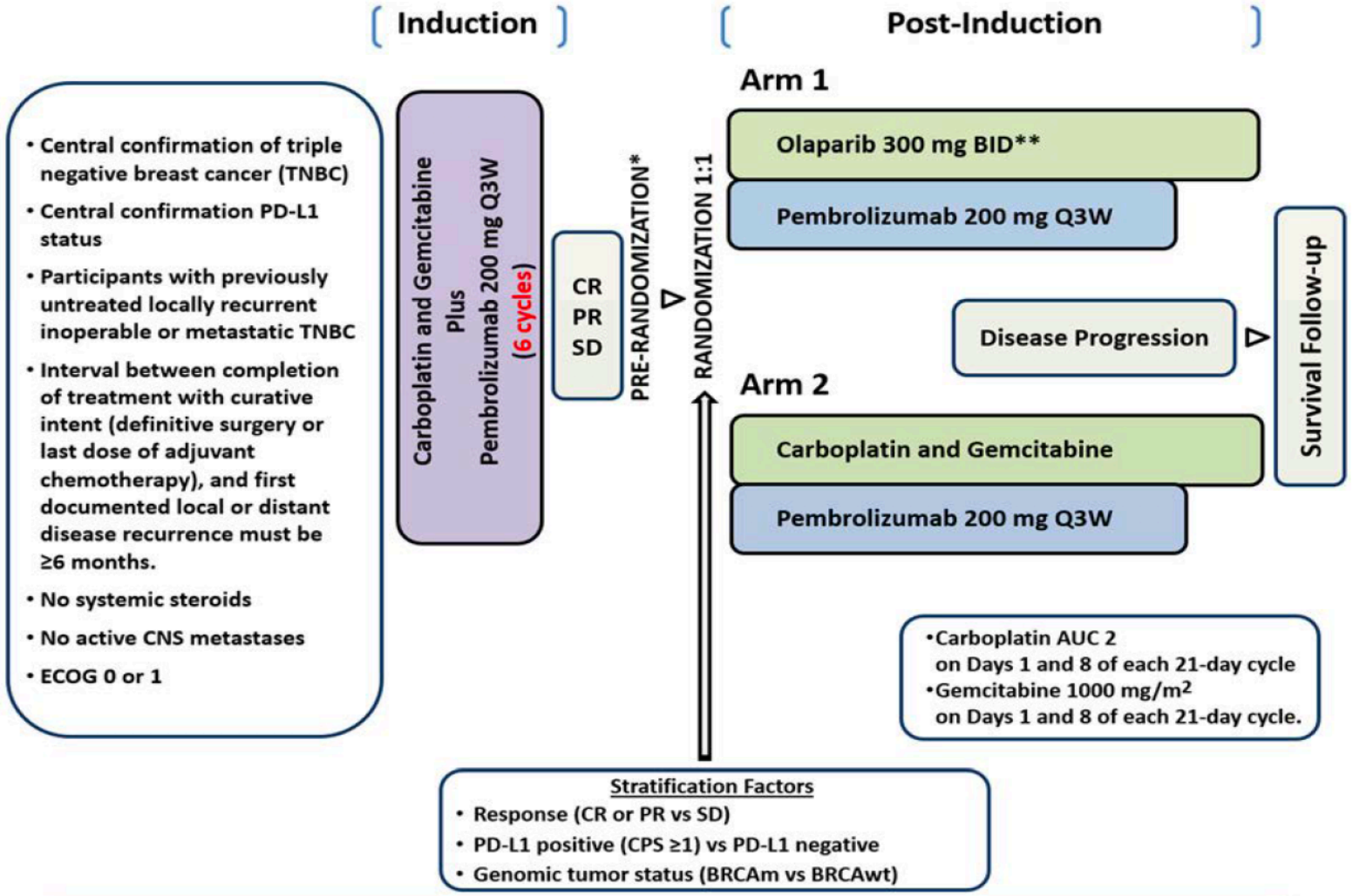


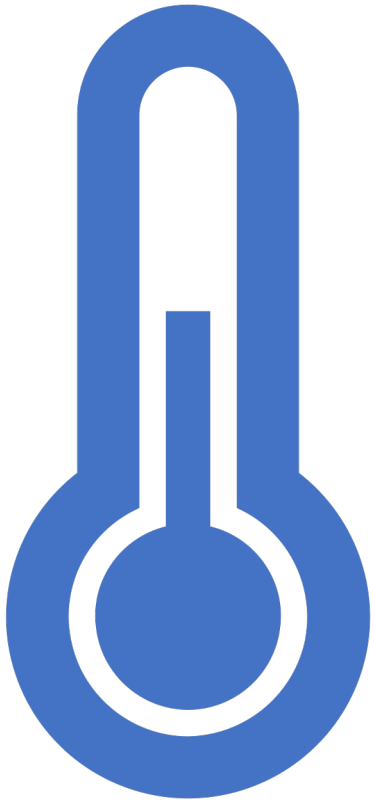

OS in the ITT, CPS ≥1 and CPS ≥10 populations were primary endpoints; OS in the CPS ≥20 population was an exploratory endpoint. Data cutoff date: April 11, 2019

Cortes et al, ESMO 2019

# Ongoing and Planned Phase III Trials with IO in Metastatic TNBC

- KEYNOTE 355: Pembro + gem/carbo or paclitaxel/*nab*-P
- IMpassion 131: Atezo + paclitaxel
- IMpassion 132: Atezo + gem/carbo or capecitabine
- New!
  - KEYLYNK-009: PARP as maintenance therapy



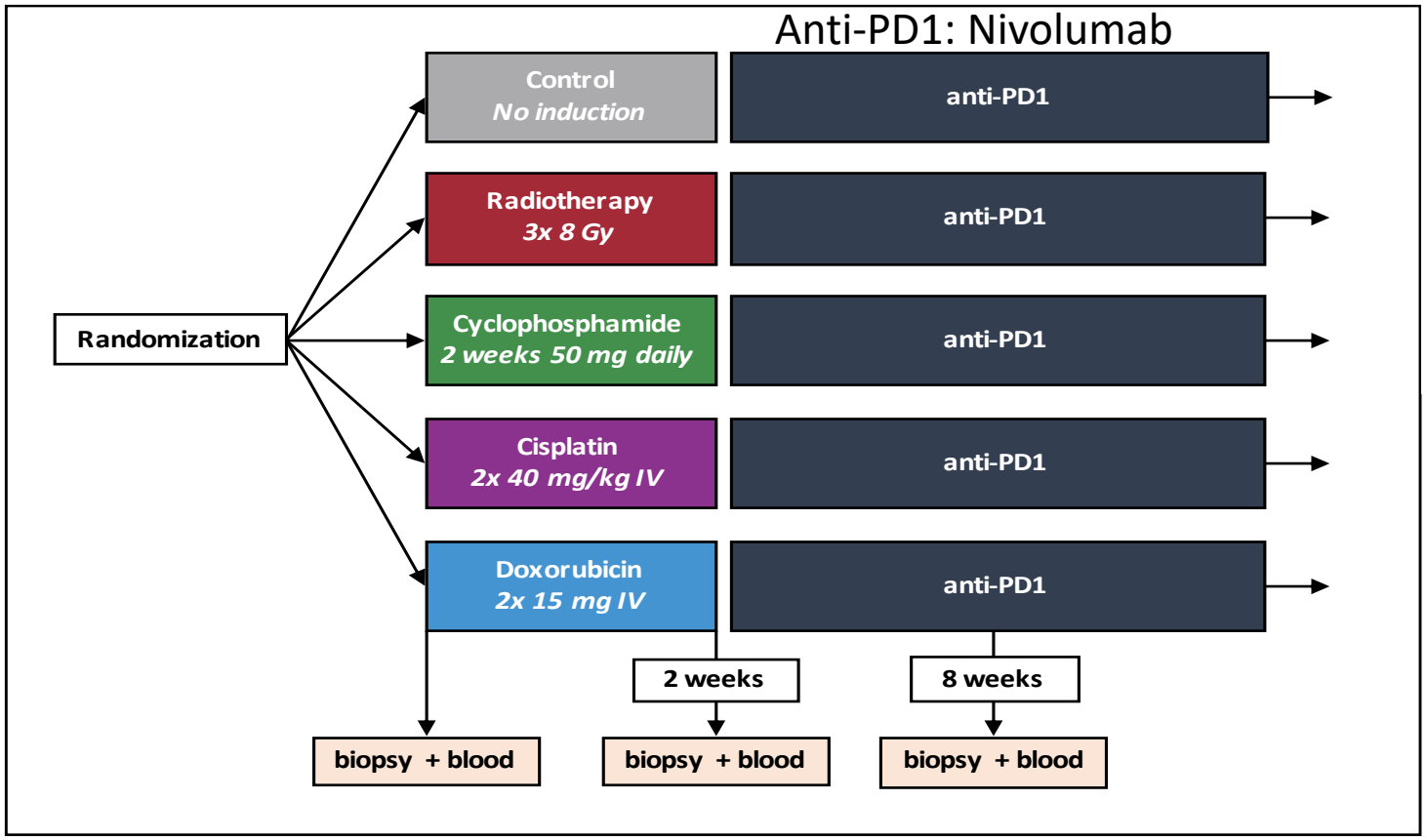


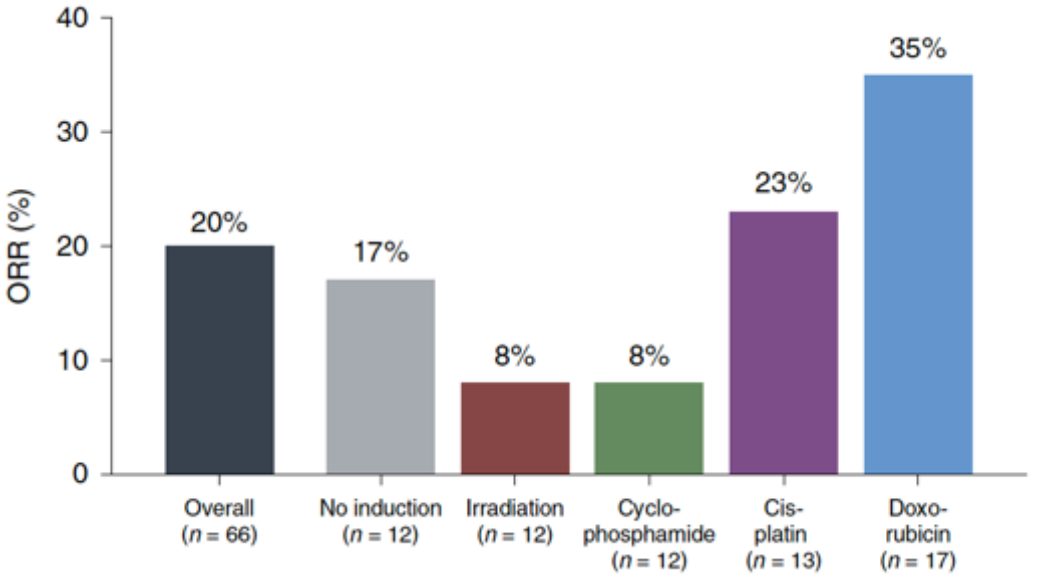
# Improving the response to immunotherapy

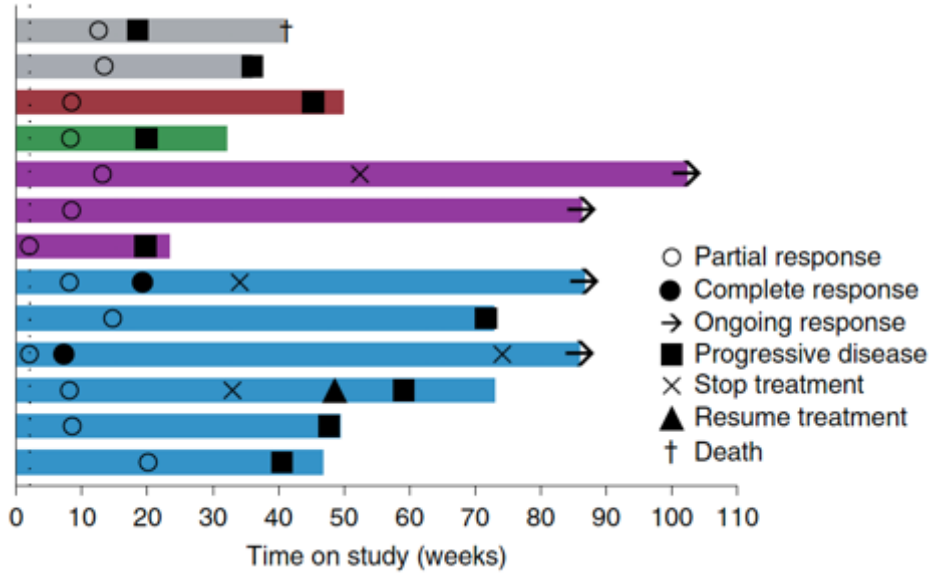
Turning cold tumors hot

- Targeted agents
- Immune agonists
- Priming
- Radiation therapy
- ?Vaccines?

# TONIC Trial



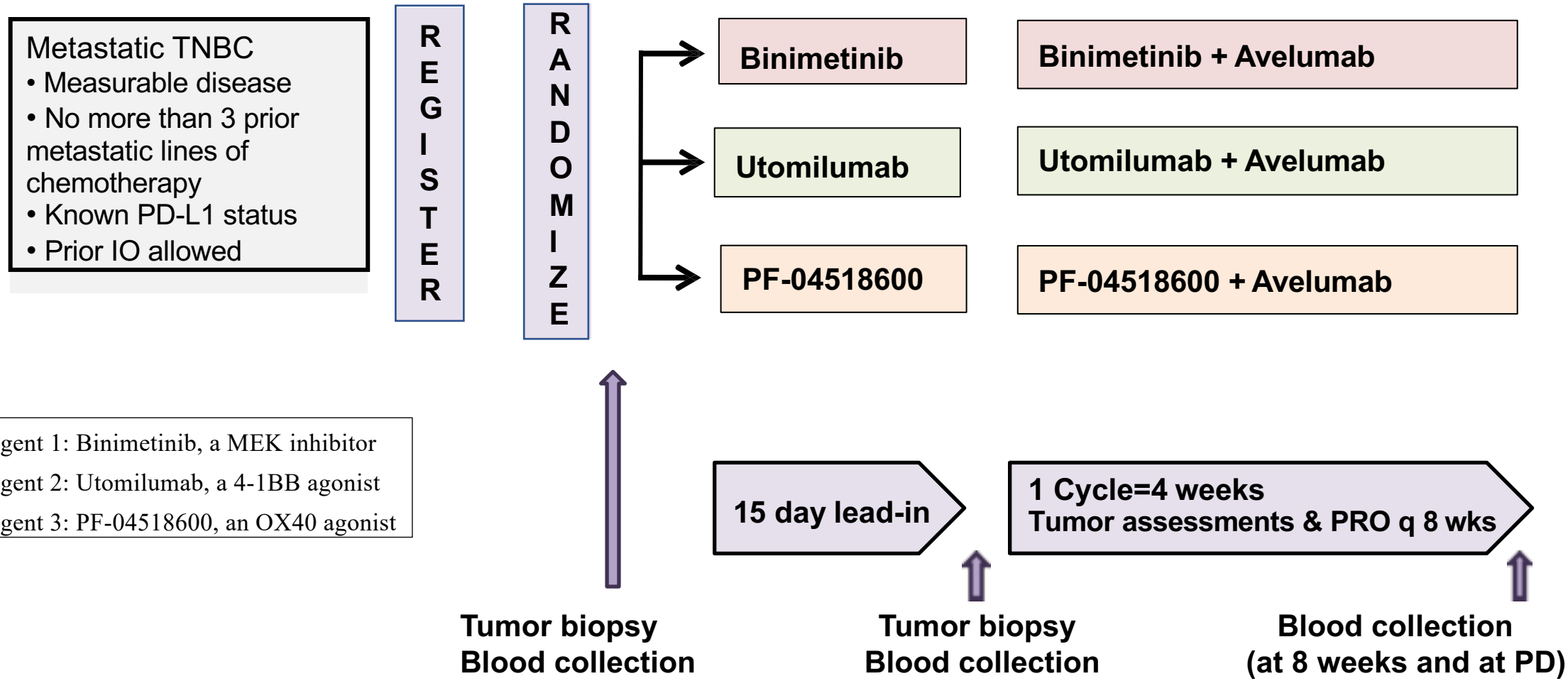




Voorwerk et al, Nat Medicine 2019

7 patients who died within 6 weeks of nivolumab are not included

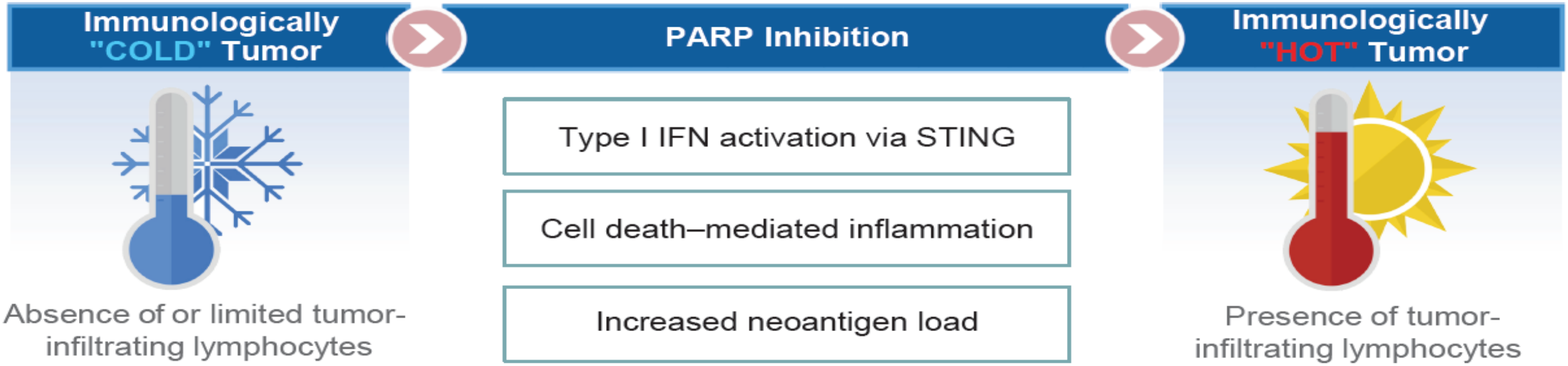
# InCITe: Innovative Combination Immunotherapy for Metastatic Triple Negative BC
# TBCRC 047




**A multicenter, multi-arm TBCRC study funded by the Breast Cancer Research Foundation**

**PI: Hope S. Rugo; Co-PI: Ingrid Mayer**

# PARP Inhibition May Enhance Immune Surveillance Through Multiple Mechanisms




TOPACIO and MEDIOLA trials indicate safety combining PARPi with IO: subset analysis unclear (Domchek, Vinayak, SABCS 2018)

# Enhancing Efficacy of Immunotherapy: Paclitaxel/Atezolizumab plus Ipatasertib

**Arm A**: Oral ipatasertib 400 mg/day, days 1–21 + IV atezolizumab 840 mg on days 1 & 15 + IV PAC 80 mg/m$^2$ on days 1, 8, & 15 (n=6)

**Arm B**: Oral ipatasertib 400 mg/day, days 1–21 + IV atezolizumab 840 mg on days 1 & 15 + IV nab-PAC 100 mg/m$^2$ on days 1, 8, & 15 (n=6)

**ORR 73% (95% CI = 53, 88)**
- **PD-L1+: 82%**
- **PD-L1–: 75%**
- ***PIK3CA/AKT*+: 71%**
- ***PIK3CA/AKT*–: 82%**


The combination of *(nab-)*paclitaxel, ipatasertib and atezolizumab not approved for triple-negative breast cancer, investigational use.
AKT, protein kinase B; CI, confidence interval; IV, intravenous; ORR, objective response rate;
PD, progressive disease; PD-L1, programmed death-ligand 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha;
PR, partial response; SD, stable disease; SLD, sum of longest diameters; TNBC, triple-negative breast cancer.

A phase III trial is planned

Schmid P, *et al*. AACR 2019 (Abstract CT049).

# Conclusions

- Immunotherapy comes of age in breast cancer!
  - Checkpoint blockade + chemotherapy
    - IMpassion130: Defining a subset of patients with mTNBC who benefit!
      - Regulatory approval for atezolizumab + *nab*-paclitaxel as first line therapy for PD-L1+ (IC) mTNBC
      - Survival benefit > PFS benefit suggests change in tumor microenvironment and host response
  - Novel combination strategies offer great promise
  - Role in HER2+ and ER+ disease also being actively explored