Evolving Strategies for Enhancing the Impact of Immunotherapy in Breast Cancer

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TILS in Breast Cancer

- High TILS are more frequent in TNBC (30%) > HER2 (19%) > luminal tumors (13%)
- Correlate with grade but not other CP factors
- 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

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Subtype</th>
<th>N</th>
<th>ORR</th>
<th>ORR (PD-L1+)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>TNBC</td>
<td>32</td>
<td>18.5%</td>
<td>18.5%</td>
</tr>
<tr>
<td>• Single agent (Keynote-012)</td>
<td>TNBC</td>
<td>170</td>
<td>5.7% (PD-L1+)</td>
<td>5.7%</td>
</tr>
<tr>
<td>• Single agent (Keynote-028)</td>
<td>ER+</td>
<td>25</td>
<td>12.0%</td>
<td>12.0%</td>
</tr>
<tr>
<td>• Single agent (Keynote-086-A)</td>
<td>TNBC</td>
<td>84</td>
<td>21.4%</td>
<td>21.4%</td>
</tr>
<tr>
<td>• Single agent (Keynote-086-B)</td>
<td>TNBC</td>
<td>58</td>
<td>15.0%</td>
<td></td>
</tr>
<tr>
<td>• Plus trastuzumab (PANACEA)</td>
<td>HER2+</td>
<td>84</td>
<td>25</td>
<td>170</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>TNBC</td>
<td>21</td>
<td>19.0%</td>
<td>19.0%</td>
</tr>
<tr>
<td>• Single agent (expanded)</td>
<td>TNBC</td>
<td>115</td>
<td>10.0%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Avelumab</td>
<td>All</td>
<td>168</td>
<td>4.8%</td>
<td>33.3%</td>
</tr>
<tr>
<td>• Single agent (Javelin)</td>
<td>All</td>
<td>168</td>
<td>4.8%</td>
<td>33.3%</td>
</tr>
<tr>
<td>• Single agent (Javelin)</td>
<td>ER+/HER2-</td>
<td>72</td>
<td>2.8%</td>
<td>NR</td>
</tr>
<tr>
<td>• Single agent (Javelin)</td>
<td>HER2+</td>
<td>38</td>
<td>3.8%</td>
<td>NR</td>
</tr>
<tr>
<td>• Single agent (Javelin)</td>
<td>TNBC</td>
<td>58</td>
<td>8.6%</td>
<td>44.4%</td>
</tr>
</tbody>
</table>


*Studies used different antibodies and cutoffs for PD-L1 positivity*
Immunologic Differences Between Primary and Metastatic Tumor Samples

Percent TIL counts in full sections and TMAs.

Szekely, et al (Pusztai), Ann Oncol 2018
Monotherapy: Overall Survival by RECIST in First-Line Setting

### Atezolizumab

- **N=84**
- Median OS: 17.6 mo

### Pembrolizumab

- **N=116**
- Median OS: 17.6 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 criteriaa:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documentedb
- 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

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

**Atezo + nab-P arm:**
Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle
+ nab-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

**Plac + nab-P arm:**
Placebo IV
- On days 1 and 15 of 28-day cycle
+ nab-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

RECIST v1.1 PD or toxicity

Double blind; no crossover permitted

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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).

PD-L1 IC status by SP142 predicts PFS and OS benefit with atezolizumab + nab-paclitaxel\textsuperscript{1,2} (41% positive by SP142)

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.

Immune-Related Adverse Events

Most Clinically Relevant AESI by Grade

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>34%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16%</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>5%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4%</td>
</tr>
<tr>
<td>Hepatitis (diagnosis)</td>
<td>2%</td>
</tr>
<tr>
<td>Colitis</td>
<td>1%</td>
</tr>
</tbody>
</table>

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 tissues

Efficacy in PD-L1 IC+

<table>
<thead>
<tr>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Metastatic</td>
</tr>
<tr>
<td>HR, 0.61 (95% CI: 0.47, 0.81)</td>
<td>HR, 0.79 (95% CI: 0.57, 1.09)</td>
</tr>
</tbody>
</table>

Median time of sample collection to randomization: 61 days

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).

PD-L1 status by anatomical location

- Breast (64%)
- Lymph node (12%)
- Lung (6%)
- Liver (5%)
- Soft tissue (4%)
- Skin (2%)
- Other (6%)

PD-L1 status by primary vs metastatic tissue

- Primary tissue (62%) 44% (P = 0.014)
- Metastatic tissue (38%) 36%

PD-L1 IC+

- Primary tissue (62%)
- Metastatic tissue (38%)

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.
Comparison of PD-L1 Assays: Exploratory post hoc IMpassion130 substudy

- Intensity of PD-L1 staining did not impact clinical outcome (1 – 3+) (Emens et al, SABCS2018)
- Central testing of VENTANA PD-L1 SP142, DAKO 22C3 and VENTANA PD-L1 SP263 IHC assays performed according to the respective package inserts
- PD-L1 IC algorithm (SP142 and SP263)
  - Presence of discernible PD-L1 staining of any intensity in IC covering ≥ 1% of tumour area occupied by TC, associated intratumoural and continuous peritumoural stroma
- PD-L1 CPS algorithm (22C3)
  - Number of PD-L1–stained cells (TC, lymphocytes and macrophages) divided by the total number of viable TC, multiplied by 100
- BEP population: 614 patients (68% of ITT) with samples tested with the 3 PD-L1 assays
  - Prevalence of PD-L1 IC+ status according to SP142 was higher in the BEP (46%) than the ITT (41%). All other evaluated baseline characteristics were balanced between BEP and ITT
  - PFS outcome with A+nP in the BEP slightly overperformed compared with PFS outcome in the ITT
PD-L1 IHC assays: prevalence and analytical concordance

NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement.

- > 97% of SP142+ samples included in 22C3+ or SP263+ samples.
- ≥ 90% OPA, PPA and NPA required for analytical concordance.
Clinical outcomes in BEP subpopulations defined by SP142 (IC 1%) and 22C3 (CPS 1)

<table>
<thead>
<tr>
<th>Population</th>
<th>Median PFS, mo</th>
<th>HR (95% CI)</th>
<th>Median OS, mo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP142+ 22C3+</td>
<td>8.3</td>
<td>3.9</td>
<td>4.4</td>
<td>27.3</td>
</tr>
<tr>
<td>(45%; 279/614)</td>
<td>0.60 (0.46, 0.78)</td>
<td>0.71 (0.52, 0.98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP142- 22C3+</td>
<td>7.3</td>
<td>5.6</td>
<td>1.7</td>
<td>21.3</td>
</tr>
<tr>
<td>(36%; 218/614)</td>
<td>0.81 (0.61, 1.09)</td>
<td>0.92 (0.64, 1.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP142- 22C3-</td>
<td>5.5</td>
<td>5.6</td>
<td>−0.1</td>
<td>14.7</td>
</tr>
<tr>
<td>(18%, 111/614)</td>
<td>1.00 (0.66, 1.51)</td>
<td>1.08 (0.67, 1.76)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Double positive: SP142 IC ≥ 1%, 22C3 CPS ≥ 1; single positive: SP142 IC < 1%, 22C3 CPS ≥ 1; double negative: SP142 IC < 1%, 22C3 CPS < 1.

HR adjusted for prior taxanes, presence of liver metastases, age and ECOG PS.
Conclusions

In this post hoc exploratory biomarker sub-study of the IMpassion130 trial

- Clinical activity was observed in the SP142 PD-L1 IC+ subgroup, regardless of whether the sample was from the primary tumour or metastatic tissue

- With overall percentage agreements of 64% (22C3) and 69% (SP263), the analytical concordance was subpar (<90%) and the assays are not equivalent
  - 22C3 (CPS ≥ 1) and SP263 (IC ≥ 1%) PD-L1 assays identified a larger patient population of which SP142+ (IC ≥ 1%) is a subgroup

- The clinical benefit in 22C3+ and SP263+ subgroups was driven by the SP142+ subgroup
  - The SP142 assay identified patients with the smallest HR point estimates and longest median PFS and OS from atezolizumab + nab-paclitaxel

- At the present time, the SP142 assay at IC ≥1% cutoff is the approved diagnostic test used to identify patients with mTNBC most likely to benefit from the addition of atezolizumab to nab-paclitaxel
KEYNOTE 119: Phase III Pembrolizumab vs. Chemo in 2L/3L TNBC: OS by PD-L1 CPS

**ITT N=622**

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>85.3%</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>88.1%</td>
<td>(0.82-1.15)</td>
<td></td>
</tr>
</tbody>
</table>

**CPS ≥1**

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>84.2%</td>
<td>0.86</td>
<td>0.073</td>
</tr>
<tr>
<td>90.6%</td>
<td>(0.69-1.06)</td>
<td></td>
</tr>
</tbody>
</table>

**CPS ≥10**

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>77.1%</td>
<td>0.78</td>
<td>0.057</td>
</tr>
<tr>
<td>88.8%</td>
<td>(0.57-1.06)</td>
<td></td>
</tr>
</tbody>
</table>

**CPS ≥20**

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70.2%</td>
<td>0.58</td>
</tr>
<tr>
<td>92.3%</td>
<td>(0.38-0.88)</td>
</tr>
</tbody>
</table>

Median (95% CI)

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
OS by PD-L1 CPS: Role of high score?

Data cutoff date: April 11, 2019.

Cortes et al, ESMO 2019
pCR is a highly significant predictor of EFS and DRFS

Yee et al SABCS 2018
Event Free Survival by pCR & non-pCR by Subtype

pCR is a Great Early Endpoint
I-SPY2: Pembrolizumab Graduated for Efficacy in HER2-Negative Cohorts

Current I-SPY2 Immunotherapy Arms:
- Pembolizumab x 8, extended through AC
- Olaparib/Durvalumab/Pac -> AC
- SD101/paclitaxel/pembrolizumab -> AC

Nanda et al, ASCO 2017
KEYNOTE-522 Study Design (NCT03036488)

Key Eligibility Criteria
- Age ≥18 years
- Newly diagnosed TNBC of either T1c N1-2 or T2-4 N0-2
- ECOG PS 0-1
- Tissue sample for PD-L1 assessment

Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

PD-L1 + defined by CPS ≥1

aMust consist of at least 2 separate tumor cores from the primary tumor.
bCarboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
cPaclitaxel dose was 80 mg/m² QW.
dDoxorubicin dose was 60 mg/m² Q3W.
eEpirubicin dose was 90 mg/m² Q3W.
fCyclophosphamide dose was 600 mg/m² Q3W.

Schmid et al, ESMO 2019
Pathological Complete Response at IA1
Total N=1174; pCR in 1st 602 pts, P value boundary for significance 0.003

Primary Endpoint: ypT0/Tis ypN0

By PD-L1 Status\(^b\): ypT0/Tis ypN0

\(^a\)Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. \(^b\)PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells \(x 100\)); PD-L1–positive = CPS \(\geq 1\). Data cutoff date: September 24, 2018 – after last patient enrolled.
Event-Free Survival at IA2: 1\textsuperscript{st} Interim Analysis

P value boundary for significance 0.000051 (HR<0.4)

Prespecified P value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS).

If pCR hypothesis successful at IA1, pCR will not be formally tested at IA2.

HR (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by randomization stratification factors.

Data cutoff April 24, 2019; 24 mo after last pt enrolled

Immune related AEs:
- 14.1 vs 2.1% grade 3-5

Discontinuation of any drug:
- 9.5 vs 2.6%

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo/Pembro</td>
<td>7.4%</td>
</tr>
<tr>
<td>Placebo + Chemo/Placebo</td>
<td>11.8%</td>
</tr>
</tbody>
</table>

9% events with median FU 15.5 months

*Prespecified P value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS). IA2: If pCR hypothesis successful at IA1, pCR will not be formally tested at IA2. HR (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by randomization stratification factors. Data cutoff April 24, 2019; 24 mo after last pt enrolled.*
Immune-Mediated AEs and Infusion Reactions in Combined Phases: IA2

<table>
<thead>
<tr>
<th></th>
<th>Pembro Arm (N = 781)</th>
<th>Placebo Arm (N = 389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>42.3%</td>
<td>21.3%</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>14.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Led to death</td>
<td>0.1%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Led to discontinuation of any drug</td>
<td>9.5%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

<sup>a</sup>1 patient from pneumonitis.

Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: April 24, 2019.
GeparNUEVO Study Design

N = 174
TNBC

Stratum: TILs (low/med/high)

Window of opportunity until amendment

Nab-Pac + Durvalumab

N = 174
TNBC

Stratum: TILs (low/med/high)

Nab-Pac + Placebo

Clinical response

ECx4 + Placebo

Surgery

Core biopsy

R

Durvalumab

Placebo

2 weeks

12 weeks

8 weeks

Durvalumab (0.75g) 1.5g d1q28

Nab-Paclitaxel 125mg/m² weekly

Epirubicin 90mg/m²; Cyclophosphamide 600mg/m² d1q14

* Tissue: FFPE, fresh frozen; Liquid biopsies: full blood; plasma, serum;

Loibl et al, Ann Oncol 2019
Subgroup Analysis of the Window Cohort
(Overall pCR 52.4% vs 44.2%; Adjusted OR 1.53, p 0.182)

Window (N=117)

- Durvalumab: 61.0% (P=0.052)
- Placebo: 41.4%

No window (N=57)

- Durvalumab: 37.9%
- Placebo: 50.0% (P=0.515)
## pCR Rates Across IO Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>pCR + carbo/pac</th>
<th>pCR + pac</th>
<th>pCR + IO carbo/pac</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis</td>
<td>52.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poggio et al 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KN522</td>
<td>51.2%</td>
<td></td>
<td>ITT 64.8% (pembro)</td>
<td>13.6%</td>
</tr>
<tr>
<td>N=1174</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISPY2</td>
<td>20%</td>
<td>60% (pembro/no carbo)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>GeparNeuvo ITT</td>
<td>44.2%</td>
<td>53.4% (durva/no carbo/nab-pac)</td>
<td>9.2%</td>
<td></td>
</tr>
<tr>
<td>N=174</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GeparNeuvo window</td>
<td>ITT 41.4%</td>
<td>ITT 61%</td>
<td></td>
<td>19.6%</td>
</tr>
<tr>
<td>N=117</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KN173 N=80 window</td>
<td>Single arm</td>
<td>ITT 60% (pembro)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Window</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of Sherene Loi; adapted
Do All Patients with Early Stage TNBC Need Immunotherapy?

*N=2210 early stage TNBC patients treated with AC-T;*

Stage I/II high TIL/PD-L1 patients do very well
Should we personalize treatment based on TILS?

Loi et al, JCO 2019
Ongoing Phase III Trials with IO in TNBC

<table>
<thead>
<tr>
<th>Neoadjuvant/adjuvant</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Atezolizumab</td>
<td>• Atezolizumab</td>
</tr>
<tr>
<td>• Impassion 31 (n=204)</td>
<td>• Impassion 30 (n=2300)</td>
</tr>
<tr>
<td>• Nab-pac → AC or EC</td>
<td>• Pac → AC/EC</td>
</tr>
<tr>
<td>• NeoTRIPaPDL1 (n=272)</td>
<td>• Avelumab</td>
</tr>
<tr>
<td>• Nab-pac/Carbo (no post-op IO)</td>
<td>• A-Brave (n=335)</td>
</tr>
<tr>
<td>• NSABP B59/GeparDouze (n=1520)</td>
<td>• Adjuvant and post NAC high risk:</td>
</tr>
<tr>
<td>• Pac/carbo → AC/EC</td>
<td>avelumab alone</td>
</tr>
<tr>
<td>• Pembrolizumab</td>
<td>• Pembrolizumab</td>
</tr>
<tr>
<td>• EFS Keynote 522</td>
<td>• SWOG S1418/NRG BR006 (n=1000)</td>
</tr>
<tr>
<td></td>
<td>• Post NAC: Pembro vs Obs x 1 yr</td>
</tr>
</tbody>
</table>

**Metastatic:**
- Keynote 355: Pembro + gem/carbo or paclitaxel/nab-P
- Impassion 131: Atezo + paclitaxel
- Impassion 132: Atezo + gem or carbo or capecitabine
Improving the response to immunotherapy

Turning cold tumors hot
TTONIC Trial

Randomization

- Control
  - No induction
  - Anti-PD1

- Radiotherapy
  - 3x 8 Gy
  - Anti-PD1

- Cyclophosphamide
  - 2 weeks 50 mg daily
  - Anti-PD1

- Cisplatin
  - 2x 40 mg/kg IV
  - Anti-PD1

- Doxorubicin
  - 2x 15 mg IV
  - Anti-PD1

2 weeks 50 mg daily
biopsy + blood

8 weeks
biopsy + blood

Voorwerk et al, Nat Medicine 2019

7 patients who died within 6 weeks of nivolumab are not included
Biomarkers in the TONIC Trial

TONIC stage II: randomized to doxorubicin lead-in or no lead-in
InCITe: Innovative Combination Immunotherapy for Metastatic Triple Negative BC TBCRC 047

Metastatic TNBC
- Measurable disease
- No more than 3 prior metastatic lines of chemotherapy
- Known PD-L1 status
- Prior IO allowed

REGISTER

Randomize

Binimetinib
Binimetinib + Avelumab

Utomilumab
Utomilumab + Avelumab

PF04518600
PF04518600 + Avelumab

Novel agent 1: Binimetinib, a MEK inhibitor
Novel agent 2: Utomilumab, a 4-1BB agonist
Novel agent 3: PF04518600, an OX40 agonist

15 day lead-in

1 Cycle=4 weeks
Tumor assessments & PRO q 8 wks

Tumor biopsy
Blood collection

Tumor biopsy
Blood collection

Blood collection (at 8 weeks and at PD)

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)
DORA Study: A Randomized Phase 2 Maintenance study of PARP Inhibition alone vs PARP Inhibition + Anti-PD-L1 therapy

Randomised, non-comparator, international, AZ Investigator Initiated Trial
And Duke-Singapore/Duke-USA Collaborative Grant for Translational Studies

Eligibility:
- Mets TNBC
- Response after 4 cycles of platinum chemo as 1st or 2nd line therapy

Olaparib 300mg bid daily

1st Endpoint = PFS

Durvalumab 1500mg q 4 weekly

PI: Domchek, OT3-5-03, SABCS 2018

R Dent, T Tan, SB Kim, T Traina, H McArthur, YH Im, S Sammons, K Blackwell
Singapore, Korea, USA collaboration
Enhancing Efficacy of Immunotherapy: Paclitaxel/Atezolizumab plus Ipatasertib

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
Enhancing the Efficacy of Immunotherapy

• Most studies in breast are studying CPI; a small number of trials are evaluating vaccines and adoptive T-cell therapy

Adams et al, JAMA Onc 2019
Immune-Related AEs

Awareness, provider and patient education, early intervention is critical

Postow et al: NEJM. 2018
Cancer Treatment Reviews 45 (2016) 7–18
Case History

• 40 year old woman
  • Stage II TNBC treated with AC/T and radiation
  • No germline mutation
• 1.5 years later routine CXR picks up nodular density
  • CT: multiple pulmonary nodules
  • FNA+ TNBC
• Treatment
  • Capecitabine: stabilization then increase in one nodule at 10 weeks
  • Pembrolizumab on single agent >2nd line trial
Outcome

• CT scans: reduction in lung nodules
• After a trip to Mexico 3 months after starting pembrolizumab, developed diarrhea that improved then worsened after a brief antibiotic course
  • Colonoscopy with blind biopsy revealed inflammatory changes consistent with immune colitis
  • With loperamide, up to 3 loose stools/day
  • Treated with oral budesonide with complete resolution of symptoms
• CT scan at 8 months: one residual 1 cm nodule RUL, no FDG avidity
  • SBRT to single nodule
• 4.5 years after starting pembrolizumab, remains NED on occasional budesonide
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
    • Keynote 522: success in treating earlier line independent of PD-L1 positivity?
      • Await EFS results next year
  • Novel combination strategies offer great promise
  • Role in HER2+ and ER+ disease also being actively explored
The Dawn of Immunotherapy for Breast Cancer!

Thank you!