Management of advanced
Triple Negative Breast Cancer

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Oncology Department, School Of Medicine
Cairo University
Q# 1 : PARP inhibitors are indicated in patients with advanced triple-negative breast cancer who have

1- Germline BRCA mutation, metastatic disease

2- Germline BRCA mutation but only in previously treated metastatic disease

3- Germline BRCA mutation and platinum resistant metastatic disease

4- Metastatic disease with Any homologous recombination repair defect
Q# 2: Immune therapy-based treatment is indicated in patients with advanced triple-negative breast cancer who have:

1. No Germline BRCA mutation
2. Tumors with High TILs or high mutation burden
3. Previously untreated metastatic disease with high PD-L1 expression in tumor or immune cells
4. Previously untreated metastatic disease with PD-L1 + immune cells, determined only by SP 142 assay
Q# 3: Androgen receptor positive triple-negative breast cancer is expected to be encountered in patients with one of the following features:

a. Old age and morphologically metaplastic tumors

a. Old age and Basal like tumors by PAM50

a. Old age and morphologically apocrine tumors

a. Any age, with high sensitivity to prior chemotherapy
1. Compared to other breast cancer subtypes, TNBC has the worst survival outcome.

2. It is associated with a high rate of early recurrence, with relapses seldom reported after 8 year from diagnosis.

3. High pCR rate ~ 30% using doxo / taxanes chemotherapy
   - Associated with a good prognostic outcome.

Genomic and NGS studies have led to identification of many promising therapeutic targets

- In the clinic, 2 PARP inhibitors and one ICI regimen (Atezo+nab-Pac), have been approved in biomarker selected mTNBC patients

In the adjuvant setting: Outside clinical trials, the standard of care is still chemotherapy.
- This will change during the coming few years.

Cortazar P, et al. SABCS 2012

HR=0.24, p* < 0.001
Case # 1 Lila M 45 ys.. October 2016 : Mild Epigastric, mild low back pain pains / PS0-1 / Normal LFT,KFT& ECHO heart ......[2 years after attaining pCR by neoadjuvant chemo (Anthracycline /taxanes )for her L breast T3/N1 TNBC ]

What is your preferred chemo for the 1st line treatment of a mildly symptomatic mTNBC?

1. Carboplatin + Gemcitabine
2. Paclitaxel + bevacizumab
3. Monotherapy Capecitabine/Paclitaxel / lipo-doxo
4. Clinical trial
Do we have a better chemotherapy in mTNBC?
<table>
<thead>
<tr>
<th>Preferred single agents:</th>
<th>Other single agents:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Pegylated liposomal doxorubicin</td>
<td>Albumin-bound paclitaxel</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Epirubicin</td>
</tr>
<tr>
<td>Anti-metabolites</td>
<td>Ixabepilone</td>
</tr>
<tr>
<td>Capecitabine</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td></td>
</tr>
</tbody>
</table>

Other microtubule inhibitors

Vinorelbine

Eribulin

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page E8.4.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
First-line nab-P/C was active in mTNBC and resulted in a significantly longer PFS and higher ORR versus nab-P/G or G/C.
Chemo ± Bev: Meta-analysis of 3 Randomized Phase III Trials in Previously Untreated HER2-ve MBC

<table>
<thead>
<tr>
<th></th>
<th>E2100</th>
<th>AVADO*</th>
<th>RIBBON-1*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>722</td>
<td>488†</td>
<td>1237</td>
</tr>
<tr>
<td>Geography</td>
<td>US (90%)</td>
<td>Ex-US</td>
<td>US (50%)</td>
</tr>
<tr>
<td>Randomization ratio (BV:PL)</td>
<td>1:1</td>
<td>1:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Paclitaxel weekly</td>
<td>Docetaxel</td>
<td>Capecitabine, Docetaxel/nab-Paclitaxel, Doxorubicin/Epirubicin</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>PFS†</td>
<td>PFS</td>
<td>PFS</td>
</tr>
<tr>
<td>Key Secondary Endpoints</td>
<td>OS, ORR</td>
<td>OS, ORR, 1-yr survival</td>
<td>OS, ORR, 1-yr survival</td>
</tr>
</tbody>
</table>

BV=bevacizumab, PL=placebo, PFS=progression-free survival, ORR=objective response rate, OS=overall survival.
* Permitted continuing on BV or crossing over to BV.
† Analyses based on IRF assessments.
‡ 15 mg/kg cohort.

First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients

D. W. Miles¹*, V. Diéras², J. Cortés³, A.-A. Duenne⁴, J. Yi⁵ & J. O’Shaughnessy⁶

Outcome in TNBC patients # 621 (~25% of all cases)

- PFS: 5.4 vs 8.1
- OS: 17.5 vs 18.9

Miles et al Ann Oncology 2013
Now back to our patient: we discussed these studies with Lila, and she preferred to be treated with Paclitaxel+ Beva.

Baseline: October 2016

After 4 courses: Feb 2017
- She received a total of 18 weeks and she had to stop treatment because of grade 2-3 neuropathy and fatigue.
A hypothetical question
What if Lila developed mTNBC by the year 2019?
NCCN Guidelines Version 1.2019
Invasive Breast Cancer

RECURRENT/STAGE IV (M1) DISEASE

CLINICAL STAGE

WORKUP

- History and physical exam
- Discuss goals of therapy, adopt shared decision-making, and document course of care
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
- Chest diagnostic CT with contrast
- Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast
- Brain MRI with contrast if suspicious CNS symptoms
- Spine MRI with contrast if back pain or symptoms of cord compression
- Bone scan or sodium fluoride PET/CT (category 2B)
- FDG PET/CT^{1,2} (optional)
- X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- First recurrence of disease should be biopsied
- Determination of tumor ER/PR and HER2 status on metastatic site^{d,zz,aaa}
- For patients with HER2-negative tumors under consideration for chemotherapy, strongly consider germline BRCA1/2 testing.
- For triple-negative breast cancer (TNBC), assess PD-L1 biomarker status on tumor-infiltrating immune cells to identify patients most likely to benefit from atezolizumab plus albumin-bound paclitaxel

See Treatment of Local and Regional Recurrence (BINV-19) and Supportive care^{bbb}

See Systemic Treatment of Recurrent or Stage IV (M1) (BINV-20) and Supportive care^{bbb}
Beyond chemo ± Beva: How to do better in mTNBC?

● Dissecting TNBC molecular subtypes

**Oncogene**

*Original Article | Published: 18 January 2010*

**Integrative molecular profiling of triple negative breast cancers identifies amplicon drivers and potential therapeutic targets**

N Turner$, M B Lambros, H M Horlings, A Pearson, R Sharpe, R Natrajan, P B Geyer, M van Kouwenhove, B Kreike, A Mackay, A Ashworth, M J van de Vijver & J S Reis-Filho

Oncogene 29, 2013–2023(2010) | Cite this article

**Baylor TNBCs gene profiling**

**Comprehensive Genomic Analysis Identifies Novel Subtypes and Targets of Triple-negative Breast Cancer**

Matthew D. Burstein¹, Anna Tseimelzon², Graham M. Poage³, Kyle R. Covington², Alejandro Contreras¹,², Suzanne A.W. Fuqua², Michelle I Savage⁷, C. Kent Osborne², Susan G. Hilsenbeck², Jenny C. Chang⁴, Gordon B. Mills⁶, Ching C. Lau⁵,¹ and Powel H. Brown¹,†

**Vanderbilt (TNBCtype-4)**

**PLOS ONE**

**Reefinement of Triple-Negative Breast Cancer Molecular Subtypes: Implications for Neoadjuvant Chemotherapy Selection**

Brian D. Lehmann¹*, Bojana Jovanović², Xi Chen³,⁴, Monica V. Estrada⁵, Kimberly N. Johnson¹, Yu Shyr⁶, Harold L. Moses⁷, Melinda E. Sanders⁸, Jennifer A. Pietenpol¹,⁷ *
Genomic Heterogeneity Of TNBC and identification of novel targets

BL (70-75%)
More mutation burden

Non-BL (25-30%)
Less mutation burden

Data from Intrinsic subtyping by PAM50 and data from TCGA

High levels of proliferation - related genes

AR (~15%)

Data from Intrinsic subtyping by PAM50 and data from TCGA

Key conclusions from Vanderbilt (TNBC type 4) and Baylor

BL-1 subtype:
• Highest response to chemotherapy
• Enriched for defects in DNA damage response including HRR

BL-2 subtype:
• Poorest response to chemotherapy
• Enriched for genes related to growth factor signaling e.g. EGFR and MET
• Enriched for PIK3CA/PTEN/AKT dysregulations

High TILs
"Immune activated"

M (~25%)
Claudin-low

Modest response to chemotherapy
• Enriched for stem-cell features and epithelial-to-mesenchymal transition markers
• Enriched for PIK3CA/PTEN/AKT dysregulations

Poor response to chemotherapy
• Enriched for genes involved in AR signaling
• Enriched for PI3K mutations
• Not enriched for defects in HRR: not sensitive to platinums

Less proliferative
Least proliferative
Genomic Heterogeneity of TNBC and Identification of Novel Targets

**Data from Intrinsic subtyping by PAM50 and data from TCGA**

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**Non-BL (25-30%)**
- Less mutation burden

**M (~25%)**
- Less proliferative
- Modest response to chemotherapy
- Enriched for stem-cell features and epithelial-to-mesenchymal transition markers
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**AR (~15%)**
- Least proliferative
- Poor response to chemotherapy
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High levels of proliferation-related genes

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Poor response to chemotherapy
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- Enriched for PI3K mutations
- Not enriched for defects in HRR: not sensitive to platinums
Hypothesis: high TMB increases the immunogenicity of tumors, produces more TILs, which is associated with a better outcome of ICIs.

1. Tumors without TILs will not respond to immunotherapy.
2. Cytotoxic T cells are the main effectors in cancer immunotherapy.

- Yong-Chen Lu, Paul F. Robbins, Cancer immunotherapy targeting neoantigens. Seminars in Immunology, 2016
- Spranger et al, PNAS, 2016
Hypothesis: high TMB increases the immunogenicity of tumors, produces more TILs, which is associated with a better outcome of ICIs.
Basal-like cancers have more mutations and more TILs

- Analysis of TCGA data show higher expression of PD-L1 mRNA in TNBC (n=120) vs non-TNBC (n=716), P<0.001
ORR to 1st line mTNBC immune checkpoint inhibitor monotherapy is 23-26%, But quite modest afterwards
Immune checkpoint inhibitor monotherapy in mTNBC: Response in relation to TILs

Pembrolizumab Cohort A:
Beyond 1st line / 60% PD-L1+

Pembrolizumab Cohort B:
1st line  All PD-L1+

#23 patients

Cortes et al ESMO 2019

KN-119

Lori, ESMO 2017

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**KN-119 Cortes et al ESMO 2019**

**Patients**
- Recurrent mTNBC
- 1 or 2 prior systemic treatments for mTNBC
- Documented disease progression on/after most recent therapy
- Previous treatment with an anthracycline and/or a taxane in the neoadjuvant/adjuvant or metastatic setting
- ECOG PS 0-1

**Randomize 1:1 N = 600**

**Pembrolizumab**
- 200 mg Q3W up to 35 cycles

**Follow-up for safety**
- (≤90 days)
**Follow-up for survival**
- (every 3 months)

**Investigator choice**
- Capecitabine
- Eribulin
- Gemcitabine
- Vinorelbine

**Stratification by:**
- PD-L1 tumor status (CPS ≥1 vs CPS <1)
- Prior neoadjuvant/adjuvant therapy vs de novo metastatic disease at initial diagnosis

**Primary**
- OS in patients with PD-L1 positive tumors (CPS ≥10)\(^a\)
- OS in patients with PD-L1 positive tumors (CPS ≥1)\(^a\)
- OS in all patients

**Key Secondary**
- PFS in all patients
- ORR in all patients\(^b\)
- Safety and tolerability

**Additional Secondary**
- DCR and DOR in all patients and patients with PD-L1 positive tumors (CPS ≥1 or CPS ≥10)\(^a\)

**Exploratory**
- OS, PFS, ORR, and DOR in patients with PD-L1 positive tumors using additional CPS cutpoints

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ECOG PS = Eastern Cooperative Oncology Group performance status; mTNBC = metastatic triple-negative breast cancer; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks.

\(^a\) Maximum enrollment cap of 60% of total enrollment for each chemotherapy drug.
KN-119 Cortes et al ESMO 2019

OS by PD-L1 status

**ITT**

- Events: 85.3%
- HR (95% CI): 0.97 (0.82-1.15)
- Median (95% CI): 9.9 mo (8.3-11.4)
- 10.8 mo (9.1-12.6)

**CPS ≥1**

- Events: 84.2%
- HR (95% CI): 0.86 (0.69-1.06)
- Median (95% CI): 10.7 mo (8.3-12.6)
- 10.2 mo (7.9-12.6)

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
Pembrolizumab showed a clear trend in improved efficacy with PD-L1 enrichment
- OS HR: 0.96, 0.86, 0.78, and 0.58 in ITT, CPS ≥1, ≥10, and ≥20, respectively
Important Take Home Messages
Single Agent ICIs in mTNBC : Are we there yet?

• Single agent Pembrolizumab (Pembro) or Atezolizumab (Atezo) produces durable response in a minority of mTNBC patients.. particularly in PD-L1 + tumors during the 1st L setting…… Phase II data

• However, It appears that : the higher the PD-L1 positivity , the higher will be the efficacy of ICIs (KN-119 )
  • This is not yet ready for routine use of ICIs as single agents (validation is still required with pembrolizumab for CPS ≥ 20% in the 2nd line)

• Higher TILs (with no definite cutoff ) was also associated with higher responses in mTNBC, particularly with Pembrolizumab in the first-line setting (phase-II data all cases were PD-L1+ )
  • PD-L1+ tumors with High TILs may emerge as an optimal duet to select patients for an optimal outcome of Pembrolizumab in the first-line setting (validation is required )

• It is clear that as single agents : anti-PD-1/PD-L1 drugs are marginally effective in the overall population of mTNBC ...Novel combinations should be introduced

• Please do not forget that TNBC is not NSCLC, where single agent ICIs have been approved in 1st and 2nd line
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• Please do not forget that TNBC is not NSCLC, where single agent ICIs have been approved in 1st and 2nd line.
**IMpassion130 study design**

Key IMpassion130 eligibility criteria:
- Metastatic or inoperable locally advanced TNBC
  - Histologically documented
- 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%])

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

Centrally evaluated on IC per VENTANA SP142 IHC assay (double blinded for PD-L1 status).
A Significant PFS benefit of Atezo in patients with PD-L1 +ve tumors
[IC ≥1%......41% of the total population]

<table>
<thead>
<tr>
<th>Population</th>
<th>PFS HR (95% CI)</th>
<th>Interaction Test (treatment × PD-L1 IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 IC+</td>
<td>0.62 (0.49, 0.78)</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>PD-L1 IC−</td>
<td>0.94 (0.78, 1.13)</td>
<td>0.5152</td>
</tr>
</tbody>
</table>

**PFS in PD-L1-ve population**

- Atezo + nab-P (PD-L1 IC− n = 266)
- Plac + nab-P (PD-L1 IC− n = 267)

**PFS in PD-L1+ population**

- Stratified hazard ratio for progression or death, 0.62 (95% CI, 0.49–0.78)
- P<0.001

- Atezolizumab+nab-paclitaxel

- Placebo+nab-paclitaxel

- 5.6 mo (5.5, 7.3)
- 5.6 mo (5.4, 7.2)
- 5.0 mo (3.8, 5.6)
- 7.5 mo (6.7, 9.2)

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04); Schmid P, et al. ESMO 2018 (LBA1); Schmid P, et al NEJM 2018

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Secondary efficacy endpoints

- Numerically higher and more durable responses were seen in the Atezo + nab-P arm
  - Differences were not significant based on α level = 0.1% (ITT: \( P = 0.0021 \); PD-L1+: \( P = 0.0016 \))
- The CR rate was higher in the Atezo + nab-P arm vs the Plac + nab-P arm
  - ITT population: 7% vs 2%
  - PD-L1+ patients: 10% vs 1%

<table>
<thead>
<tr>
<th></th>
<th>Atezo + nab-P</th>
<th>Plac + nab-P</th>
<th>Atezo + nab-P</th>
<th>Plac + nab-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>56%</td>
<td>46%</td>
<td>59%</td>
<td>43%</td>
</tr>
<tr>
<td>PR:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CR:</td>
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</tr>
<tr>
<td>CR:</td>
<td>7%</td>
<td>2%</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>PR:</td>
<td>49%</td>
<td>44%</td>
<td>49%</td>
<td>42%</td>
</tr>
<tr>
<td>PD-L1+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- DOR, median (95% CI), mo
  - Atezo + nab-P: 7.4 (6.9, 9.0)
  - Plac + nab-P: 5.6 (5.5, 6.9)
  - Atezo + nab-P: 8.5 (7.3, 9.7)
  - Plac + nab-P: 5.5 (3.7, 7.1)

- No. of ongoing responses, n (%)
  - Atezo + nab-P: 78 (31%)
  - Plac + nab-P: 52 (25%)
  - Atezo + nab-P: 39 (36%)
  - Plac + nab-P: 19 (24%)
No benefit at all of Atezolizumab in PFS and OS in PD-L1–ve tumors on IC per VENTANA SP142 IHC assay

- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant.
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + nab-paclitaxel.

Emens LA, et al.. SABCS 2018 (program #GS1-04);
Schmid P, et al. ASCO 2019
**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)

- **Primary Endpoints**
  - pCR (ypT0/Tis ypN0) assessed by local pathologist in ITT population
  - Event-free survival (EFS) assessed by investigator in ITT population

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**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)

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**Neoadjuvant Treatment 1** (cycles 1-4; 12 weeks)
- Carboplatin \(+^b\) Paclitaxel \(+^c\)

**Neoadjuvant Treatment 2** (cycles 5-8; 12 weeks)
- Doxorubicin \(+^d\) Epirubicin \(+^e\) Cyclophosphamide \(+^f\)

**Adjuvant Treatment** (cycles 1-9; 27 weeks)
- Pembrolizumab 200 mg Q3W

**Pembrolizumab 200 mg Q3W**
- Surgery

**Placebo**
- Placebo

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\(^d\) Doxorubicin dose was 60 mg/m\(^2\) Q3W.
\(^e\) Epirubicin dose was 90 mg/m\(^2\) Q3W.
\(^f\) Cyclophosphamide dose was 600 mg/m\(^2\) Q3W.
KN-522: pCR rates

Primary Endpoint: ypT0/Tis ypN0

Δ 13.6 (5.4–21.8)\(^a\)

\[ P = 0.00055 \]

64.8% for Pembro + Chemo

51.2% for Placebo + Chemo

260/401 vs. 103/201

\(^a\)Estimated treatment difference based on Nieltinen & 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 >1. Data cutoff date: September 24, 2018.
KN-522 : EFS (Median follow-up period 15.5 months)

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Should we apply the KN-522 results at the present time? "as off label use"

- Classically: Not yet... till more mature EFS data is required
- But Maybe YES in selected patients with good PS / locally advanced TNBC: The pCR results of the KN-522 trial are unprecedented especially in N+ disease (pCR 64.8% with pembro+ chemo vs 44.1% with chemo alone)
- Do forget the higher rate of adverse events

- Should we use other ICIs with other chemo assuming a class effect of these agents?
- The NeoTRIPaPDL1 Michelangelo: 280 patients; 87% LN+ / 50% T3 and T4, which are more advanced than those included in the KN-522 study
  - Neoadjuvant chemotherapy (carboplatin AUC 2 and nab-P 125 mg/m2 on days 1 and 8), with or without atezolizumab 1200 mg on day 1
Targeting defects in DNA damage response “HRD” in TNBC
Mechanisms of DNA damage response: DNA Repair Vs. cell death

Any DNA injury
Spontaneous DNA damage events occur in the range of thousands per day

DNA DAMAGE

Cell death

Or DNA REPAIR PATHWAYS

Cell Survival

Single strand breaks
Base excision repair
• PARP1/2

Double strand breaks
HRR: Error free repair
• BRCA1/BRCA2

Unrepaired SSB
In BRCA1/2 defective cancer cells: both PARPi and platins will increase DNA SSBs, which are converted during replication to non-reparable toxic DNA DSBs.

Platinums and PARP inhibition both cause replication fork arrest and DSBs.

When SSBs are encountered by replication forks, they generate DSBs that need to be repaired by HRR.

NHEJ depends on PARP activity.
• TNT: A randomized phase III trial of carboplatin compared with docetaxel for patients with mTNBC or BRCA1/2 breast cancer

• The TNT Trial provides no evidence of superior response to carboplatin compared to docetaxel in unselected mTNBC

• Patients with BRCA1 or BRCA2 germ-line mutations and those who have tumor BRCA1 or BRCA2 mutations experience significantly greater response and PFS with carboplatin than docetaxel
  – This would strongly suggest a genotype-specific nature of platinums cytotoxicity in BRCA-mutant breast cancer
  – The TNT Trial supports BRCA1/2 genotyping to inform therapy choice in metastatic TNBC and familial breast cancer

Tutt et al, SABCS 2014.
BRCA Deficient BC Cells Are Highly Sensitive To PARP Inhibition in vitro

BRCA1/2 dysfunction profoundly sensitizes cells to the inhibition of PARP enzymatic activity, resulting in cell cycle arrest and subsequent apoptosis “genotype-specific anti-cancer agents” PARPi are do not affect normal BRCA-expressing cells.
The pivotal phase III studies of PARPi in gBRCA mutation MBC patients: 
Both Olaparib and Talazoparib demonstrated remarkable efficacy outcomes.

### Response Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (BICR), %</td>
<td>60</td>
<td>29</td>
</tr>
<tr>
<td>▪ CR</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Median TTR, days</td>
<td>47</td>
<td>45</td>
</tr>
</tbody>
</table>

**EMBRACA: PFS**

**Blinded Independent Central Review**

<table>
<thead>
<tr>
<th></th>
<th>TALA (n=287)</th>
<th>Overall PCT (n=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, no. (%)</td>
<td>186 (65)</td>
<td>83 (58)</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>8.6 (7.2–9.3)</td>
<td>5.6 (4.2–6.7)</td>
</tr>
<tr>
<td>Hazard ratio, 0.54, 95% CI: 0.41–0.71</td>
<td></td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>ORR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>62.6</td>
</tr>
<tr>
<td></td>
<td>(55.8–69.0)</td>
</tr>
<tr>
<td></td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td>(19.3–36.3)</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>(2.9–8.8)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## OlympiAD: Olaparib Response rates according to receptor subtype

<table>
<thead>
<tr>
<th></th>
<th>TNBC</th>
<th>HR+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Olaparib (n=86) %</td>
<td>TPC (n=33) %</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>54.7</td>
<td>21.2</td>
</tr>
<tr>
<td>SD ≥ 6 ms (%)</td>
<td>9.3</td>
<td>3.0</td>
</tr>
<tr>
<td>CBR %</td>
<td>64%</td>
<td></td>
</tr>
</tbody>
</table>

EMBRACA: Investigator-Assessed Unconfirmed ORR* – Stratified Subgroup Analysis (ITT Population with Measurable Disease)†

<table>
<thead>
<tr>
<th>TNBC</th>
<th>Talazoparib Group n=102</th>
<th>Chemo group n=48</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>61.8 (51.6–71.2)</td>
<td>12.5 (4.7–25.3)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>11.89 (4.54–41.37)</td>
<td></td>
</tr>
</tbody>
</table>


Rugo et al, 15th HOPA, April 2019

Do not duplicate or distribute without permission of ESO and the author.
Platinum or PARP inhibitors in BRCA mutant breast cancers

• Please note that ORR and PFS with carboplatin was very much similar to PARPi in MBC patients with BRCA mutant tumors

• Caveats:
  • TNT Trial (1st line)
  • PARPi (majority beyond 1st line)
Olaparib antitumor activity in BRCA1/2 mutation ovarian cancer, is determined by prior platinum sensitivity.

Response measured according to RECIST and/or GCIG criteria

- MBC Patients with highly sensitive disease to prior platinum (durable responses), make most benefit of PARP inhibitors
- ORR: 0% with interval <8 weeks; and 47% ORR with interval >6 months
- Platinum and PARPi appear to have cross resistance

Platinum-Free Interval in Cohort 1

# 47 patients

Median time from last platinum dose to progression was 4.0 months (range, 0.03–49.15)
PARP inhibitors in the clinic: Challenges and remaining questions

- Should PARP inhibitors used in combination with chemotherapy?

Primarily due to some overlapping toxicities (anemia and GIT), the combination of PARP inhibitors in therapeutic doses with chemotherapy has been difficult.

The results of Olympia study is awaited.
BROCADE3 : Veliparib + Carboplatin/Paclitaxel for HER2- ABC With gBRCA1/2 Mutations (A double-blind Phase III Study)

- Fixed-sequence testing procedure with $\alpha = 0.05$ in ITT population (defined as all randomized patients with centrally confirmed gBRCA1/2 mutation)
  - Primary endpoint: investigator-assessed PFS (RECIST v1.1)
  - Followed by prespecified interim and final analysis of OS; CBR at 24 wks; investigator-assessed ORR (RECIST v1.1); PFS2 (defined as time from randomization until PD on subsequent therapy or death)

Patients with germline $BRCA1/2$ mutation–positive, HER2-negative advanced BC; ≤ 2 previous lines of cytotoxic therapy for metastatic disease; ≤ 1 previous line of platinum without progression in ≤ 12 mos after completing ($N = 509$)

- Veliparib* 120 mg PO BID on Days -2 to 5 + Carboplatin AUC 6 on Day 1 + Paclitaxel 80 mg/m$^2$ on Days 1, 8, 15 in 21-day cycles ($n = 337$)

- Placebo* 120 mg PO BID on Days -2 to 5 + Carboplatin AUC 6 on Days 1 + Paclitaxel 80 mg/m$^2$ on Days 1, 8, 15 in 21-day cycles ($n = 172$)

Stratified by HR expression, prior platinum, CNS mets

Until PD; crossover to veliparib permitted

*If patient discontinued C/P before PD, veliparib or placebo dosing increased to 300 mg BID continuous and then 400 mg BID as tolerated.
BROCADE3: Investigator-Assessed PFS (Primary Endpoint)

- Primary endpoint met with investigator-assessed PFS significantly improved with veliparib vs placebo ($P = .002$).
- PFS assessed by independent central review also significantly improved with veliparib vs placebo (median PFS: 19.3 vs 13.5 mos, respectively; HR: 0.695; 95% CI: 0.537-0.899; $P = .005$).

Comparison between the three phase III studies using PAPRi in the treatment of mBC patients with gBRCA mutations [OlympiAD , EMBRACA and BROCADE-3 ]

<table>
<thead>
<tr>
<th>Trial</th>
<th>Olympiad</th>
<th>EMBRACA (42)</th>
<th>BROCADE 3 (48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Olaparib vs TPC (2:1)</td>
<td>Talazoparib vs TPC (2:1)</td>
<td>VCP vs Pla-CP (2:1)</td>
</tr>
<tr>
<td></td>
<td>(N = 302)</td>
<td>(N = 431)</td>
<td>(N= 512)</td>
</tr>
<tr>
<td>Prior Rx for mBC</td>
<td>70%</td>
<td>62%</td>
<td>19%</td>
</tr>
<tr>
<td>- TNBC population</td>
<td>50%</td>
<td>45%</td>
<td>48%</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>PFS</td>
<td>PFS</td>
<td>PFS</td>
</tr>
<tr>
<td></td>
<td>7.0 mos vs 4.2 mos HR 0.58 (95% CI 0.43-0.80) p&lt;0.001</td>
<td>8.6 mos vs 5.6 mos HR 0.54 (95% CI 0.41-0.71) p&lt;0.001</td>
<td>14.5 mos vs 12.6 mos HR 0.71 (95% CI 0.57, 0.88) p=0.002</td>
</tr>
<tr>
<td>- PFS (prior platinum)</td>
<td>HR 0.67 (95% CI 0.41-1.14)</td>
<td>HR 0.76 (95% CI 0.4-1.45)</td>
<td>mPFS2: 21.3 mos vs 17.4 mos HR 0.76 (95% CI 0.60, 0.96)</td>
</tr>
<tr>
<td>- PFS (no prior platinum)</td>
<td>HR 0.60 (95% CI 0.43-0.84)</td>
<td>HR 0.52 (95% CI 0.39-0.71)</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>19.3 mos vs 17.1 mos HR 0.90 (95% CI 0.66-1.23) p = .513</td>
<td>22.3 mos vs 19.5 mos HR 0.76 (95% CI 0.55-1.06) p=0.105</td>
<td>33.5 mos vs 28.2 mos HR 0.95(95% CI 0.73, 1.2) P=0.67</td>
</tr>
<tr>
<td>ORR (ITT)</td>
<td>59.9% vs 28.8% [OR and p value NR]</td>
<td>62.6% vs 27.2% OR 5 (95% CI 2.9–8.8) p&lt;0.001</td>
<td>75.8% Vs 74 % CBR at 24 wks : 90.7% vs 93.2%</td>
</tr>
<tr>
<td>- ORR (prior platinum)</td>
<td>46.0% vs 26.7%</td>
<td>50% vs 24% [OR 3.16 ( 0.88, 15.67)]</td>
<td>NR</td>
</tr>
<tr>
<td>- ORR (no prior platinum)</td>
<td>65.8% vs 29.4%</td>
<td>65.2% vs 28.1% [OR5.36 (2.89, 9.89)]</td>
<td>NR</td>
</tr>
</tbody>
</table>

Hamdy Azim et al TBJ Dec 2019

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luminal AR TNBC?

1. Have a GEP that closely resembles that of ER+ breast cancers: hormonal driven pathways
2. Express androgen receptors/PIK3CA mutations
3. Around 15-20% of all TNBCs
4. Less grade 3 tumors compared to the other TNBC subtypes
5. Apocrine features
6. More seen in elderly but rarely in patients with BRCA mutations
7. Chemotherapy modest sensitivity

Enzalutamide and Bicalutamide inhibits the growth of AR+ TNBC *in vitro* and *in vivo*, supporting the hypothesis that anti-androgens may be useful targeted therapies for such tumors.
Targeting AR in TNBC: Results of Enzalutamide pilot study

**PFS median 12.6 weeks**
95% CI: 8.1, 15.7

- **CR or PR**
- ITT = 6%
- Evaluable = 8%
Focus on the truly AR driven TNBC
( PREDICT AR : AR gene signature)

Progression-Free Survival in TNBC Patients on Enzalutamide and According to PREDICT AR Status

ITT (n = 118)

PREDICT AR+ mPFS 16.1 weeks
(95% CI: 13.3, 27.4)

PREDICT AR- mPFS 8.1 weeks
(95% CI: 7.4, 12.6)

Patients at risk:
PREDICT AR+: 51
PREDICT AR-: 67

PREDICT AR+ mPFS 3.7 months
PREDICT AR- mPFS 1.8 months

ITT = AR IHC > 0% by central assessment and received ≥ 1 dose of enzalutamide.
Case discussion

• A 48 y old male patient presented in June 2008 by right breast mass and axillary LN enlargement

• Biopsy revealed IDC grade II, Triple negative

• MRM and adjuvant FEC 100 and PO Rx

• From November 2009 to October 2014, he suffered from 4 local recurrence events (with no evidence of distant metastases) that were all treated by complete excision. All resected specimens were of TNBC phenotype. The patient received one course of pseudo-adjuvant chemotherapy (capecitabine) in 2013.

• In October 2015, he presented with minimally symptomatic bone metastases (FDG avid in PET CT scan) and rising tumor markers (CA15.3 = 252). He received w-paclitaxel x 24 weeks (+ZA/4 ws) with good response (CA15.3 = 69), and complete pain alleviation (grade II sensory neuropathy). He was kept under follow up.
3 months later, he complained of progressive generalized bone pains, with chest wall skin nodules (CA15.5 = 430): PET/CT showed disease progression in bone lesions with multiple right chest wall nodules.

Given the indolent nature of such disease, LAR subtype was suspected.

- A new biopsy from a skin lesion showed the disease to be of TNBC phenotype with a Ki-67 of 17%.
- The tumor cells were shown to be strongly positive for AR by IHC (in 100% of the malignant cells).

Hamdy Azim et al Breast Cancer Journal. 2019
AR+ / TNBC : Case discussion

August 2016

Goserelin started

November 2016

November 2017

Hamdy Azim et al Breast Cancer Journal . 2019
Luminal AR is the most clinically well identified TNBC subtype
- AR+ TNBCs are more seen in those patients with lower grade, apocrine features, old age and non g-BRCA, rather indolent natural history
- Clinically responsive to AR antagonists

No gold standard for AR IHC expression in breast cancer
- An AR genomic signature independent of AR expression level may better identify patients
- Improving learning curve on how to select best responders

Management of mTNBC in 2020 (Hamdy Azim et al TBJ Dec 2019)

**Essential Biomarkers:**
- Confirm the TNBC phenotype
- PD-L1 expression on tumour-infiltrating immune cell per VENTANA SP142 IHC assay
- Germline BRCA mutations (gBRCA): using one of the approved assay e.g. BRACAnalysis CDx
- Tumor BRCA mutations (tBRCA): using NGS-based in vitro diagnostic device for qualitative detection of BRCA1 and BRCA2 alterations in FFPE tumor tissue. e.g. FoundationFocus CDx BRCA
Q# 1: PARP inhibitors are indicated in patients with advanced triple-negative breast cancer who have

1- Germline BRCA mutation, metastatic disease

2- Germline BRCA mutation but only in previously treated metastatic disease

3- Germline BRCA mutation and platinum resistant metastatic disease

4- Metastatic disease with Any homologous recombination repair defect
Q# 2 : Immune therapy-based treatment is indicated in patients with advanced triple-negative breast cancer who have

1- No Germline BRCA mutation

2- Tumors with High TILs or high mutation burden

3- Previously untreated metastatic disease with high PD-L1 expression in tumor or immune cells

4- Previously untreated metastatic disease with PD-L1 + immune cells, determined only by SP 142 assay
Q# 3 : Androgen receptor positive triple-negative breast cancer is expected to be encountered in patients with one of the following features:

a. Old age and morphologically metaplastic tumors

a. Old age and Basal like tumors by PAM50

a. Old age and morphologically apocrine tumors

a. Any age, with high sensitivity to prior chemotherapy
• Backup
Targeting PI3K/AKT/mTOR pathway

- According to TCGA, the incidence of PI3K/AKT/mTOR pathway aberrations is quite high in BL tumors. Intriguingly, these aberrations are infrequently related to PIK3CA mutations (7%), but they are more commonly attributed to loss of function in two negative regulators of this pathway; namely PTEN (mutation or loss, 35%) and INPP4B, (loss 30%)

- Since all of the above molecular abnormalities would result in AKT hyperactivation, hence the interest in selective AKT inhibitors to treat these tumors. Preclinical studies have further shown that taxane treatment can induce an immediate AKT hyperactivation, that was associated with resistance to these agents. Interestingly, in these models co-administration of AKT inhibitors and taxanes resulted in increased tumor cell death compared to their monotherapy use

Targeting PI3K/AKT/mTOR pathway

Primary analysis: IPAT effect on PFS enhanced in PIK3CA/AKT1/PTEN-altered subgroup (Foundation Medicine®)

- PBO + PAC
- IPAT + PAC

ITT population (n=124)
Stratified HR: 0.60 (95% CI 0.37 - 0.98)
Unstratified HR: 0.44 (95% CI 0.20 - 0.99)

PFS by tumour PIK3CA/ AKT1/PTEN status

LOTUS Study Dent et al ASCO 2018

PACT Study Schmid at al ASCO 2018
Among all breast cancer subtypes: TNBC has the highest TMB, TILs and PD-L1 expression. These data suggest a potential role of anti-PD-1/PD-L1 agents in TNBC.

The Cancer Genome Atlas

Mittendorf et al, Cancer Immunol Res April 2014 2; 361
10 most immune-infiltrated tumors in decreasing order.

The head and neck cancer immune landscape and its immunotherapeutic implications

Rajarsi Mandal,1,2,3 Yasin Şenbabaoğlu,4 Alexis Desrichard,1,3 Jonathan J. Havel,1,3 Martin G. Dalin,1,3 Nadeem Riaz,3,5 Ken-Wing Lee,1,3 Ian Ganly,2 A. Ari Hakimi,6 Timothy A. Chan,1,3,5 and Luc G.T. Morris1,2,3

TNBC: What do we know in 2020?

1. Compared to other breast cancer subtypes, TNBC has the worst survival outcome.
2. It is associated with a high rate of early recurrence, with relapses seldom reported after 8 years from diagnosis.
Targeting surface receptors outside the genomic landscape

• Sacituzumab govitecan is ADC, composed of SN-38 - a potent active metabolite of irinotecan- conjugated to a humanized monoclonal antibody against Trop-2, which is a transmembrane calcium signal transducer, implicated in tumor progression, that is expressed in ≥ 50% of all TNBCs

• In the initial IMMU-132-01 phase I/II study, 69 heavily pretreated mTNBC patients (median of 5 prior therapies; range, 1 - 12), were treated by SG at a dose of 10 mg/kg on days 1 and 8 of 21-day repeated cycles

• The ORR and the CBR were 30% and 46% respectively, while the median response duration was 8.9 months and the mOS was 16.6 months
  • The drug was well tolerated with diarrhea (13%); anemia (14%), and febrile neutropenia (7%) as the main grade ≥ 3 adverse events

• Based on these impressive results, SG was granted a breakthrough therapy designation from the FDA for mTNBC, who have received at least two previous lines of treatment.