TRIPLE NEGATIVE BREAST CANCER

Turning disillusion into opportunity

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Istituto Oncologico Veneto IRCCS, Padova, Italy
TNBC: INTRODUCTION

Triple negative breast cancer (TNBC) definition:
- Lack of expression of estrogen receptor and progesterone receptor
- HER2 not overexpressed/amplified

- Higher prevalence in women of Afro–American ethnicity
- More frequently diagnosed in younger women
- Most BRCAmut carriers develop TNBC → BRCA testing has implications for prevention and therapy

High cell proliferation, poor cellular differentiation, many recurrent copy number imbalances, and TP53 mutations

Heterogeneity
- TNBC includes rare histologies: metaplastic, medullary, adenoid cystic carcinoma, secretory
- Molecular heterogeneity

Usually high chemosensitivity
TNBC IS THE MOST LETHAL FORM OF BC

Reproduced from: Bauer KR, et al. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer 2007;109(9):1721–8, by permission of John Wiley and Sons Ltd., Copyright © 2007 American Cancer Society
TNBC SHOWS A HIGHER RISK OF EARLIER RELAPSE…

The estimated hazard curves cross at about 2.5 and 4.5 years for disease progression or death, respectively. The risk of relapse and death is significantly and dramatically higher for TNBC during the first 3 years of follow-up.

Hazard functions for disease progression and death among patients with TNBC (n=255) compared with non-TNBC (n=863)

<table>
<thead>
<tr>
<th>Years after surgery</th>
<th>TNBC</th>
<th>Non-TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.22</td>
<td>0.10</td>
</tr>
<tr>
<td>3</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>5</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.14</td>
<td>0.04</td>
</tr>
<tr>
<td>3</td>
<td>0.07</td>
<td>0.05</td>
</tr>
<tr>
<td>5</td>
<td>0.03</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Kernel estimates of hazard function

...AND HIGHER RISK OF VISCERAL INVOLVEMENT

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Brain</th>
<th>Liver</th>
<th>Lung</th>
<th>Bone</th>
<th>Distant Nodal</th>
<th>Pleural/peritoneal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>458</td>
<td>7.6</td>
<td>28.6</td>
<td>23.8</td>
<td>66.6</td>
<td>15.9</td>
<td>28.2</td>
<td>13.5</td>
</tr>
<tr>
<td>Luminal B</td>
<td>378</td>
<td>10.8</td>
<td>32.4</td>
<td>30.4</td>
<td>71.4</td>
<td>23.3</td>
<td>35.2</td>
<td>19.3</td>
</tr>
<tr>
<td>Luminal/HER2</td>
<td>117</td>
<td>15.4</td>
<td>4.4</td>
<td>36.8</td>
<td>65</td>
<td>22.2</td>
<td>34.2</td>
<td>13.7</td>
</tr>
<tr>
<td>HER2 enriched</td>
<td>136</td>
<td>28.7</td>
<td>45.6</td>
<td>47.1</td>
<td>59.6</td>
<td>25</td>
<td>31.6</td>
<td>16.9</td>
</tr>
<tr>
<td>Basal Like</td>
<td>159</td>
<td>25.2</td>
<td>21.4</td>
<td>42.8</td>
<td>39</td>
<td>39.6</td>
<td>29.6</td>
<td>23.9</td>
</tr>
<tr>
<td>TN non basal</td>
<td>109</td>
<td>22</td>
<td>32.1</td>
<td>35.8</td>
<td>43.1</td>
<td>35.8</td>
<td>28.4</td>
<td>25.7</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.32</td>
<td>0.006</td>
</tr>
</tbody>
</table>

MEDIAN OS FROM THE ONSET OF METASTASIS <18 MONTHS:
No improvement in almost a decade

Grinda T, et al. ESMO Open 2021. Available at: https://www.esmoopen.com/article/S2059-7029(21)00072-7/fulltext under the Creative Commons CC-BY-NC-ND license. © 2021 Published by Elsevier Ltd on behalf of European Society for Medical Oncology
**CUT-OFF FOR ER NEGATIVE: <1% VS <10%**

3055 HER2- BC pts who received NACT (MDACT cohort):
- ER <1% 30.5%
- ER 1-9% 5.6%
- ER ≥10% 63.9%

2765 HER2- BC pts who received NACT (GBG trials):
- ER <1% 32.6%
- ER 1-9% 3.4%
- ER ≥10% 64%

406 HER2- and ER<10% BC pts who received NACT and/or adj therapy (Padova cohort):
- ER <1% 90%
- ER 1-9% 10%

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OESTROGEN AND PROGESTERONE RECEPTOR TESTING IN BREAST CANCER: ASCO/CAP GUIDELINE UPDATE

Steps to consider including in SOP:
- Re-review of controls
- A second reviewer to confirm interpretation
- Validated quantitative digital image analysis to confirm interpretation
- Comparison of result with any prior patient-specific results
- Retesting the same sample if analytic issues suspected (e.g. controls did not work as expected)
- Repeating the test on a different block or subsequent specimen if there are no internal controls, preanalytic issues are suspected, or result is unusual or unexpected

**Step 2: evaluate percentage of cancer cells staining and stain intensity**

- ≤10% of cells staining OR intensity is weak
  - Take steps to confirm/adjudicate result per lab specific SOP and correlate with histology
  - If result considered concordant with histology
    - Report as ER positive

- 10% of cells staining AND intensity is moderate or strong
  - Report as ER positive

- <1% of cells staining
  - Report as ER Negative (reported data elements should report status of controls)

- 1%–100% of cells staining
  - ER positive

- 1.5%–10% of cells staining
  - Report as ER Low Positive and add recommended comment (reported data elements should include percentage of cells staining, intensity and status of controls)

- >10% of cells staining (but weak)
  - Report as ER Positive (reported data elements should include percentage of cells staining and intensity)
TNBC frequently show intermediate/high TILs
High TILs in TNBC are independently associated with:

- Improved pCR rates after NACT
- Improved survival in pts undergoing NACT (baseline TILs)
- Improved survival in pts with no-pCR after NACT (RD TILs)
- Improved survival in pts undergoing anthra-based adjuvant CT
- Improved survival in pts not receiving adjuvant CT

Routine evaluation of TILs in TNBC because of its prognostic value
Clinical utility (tool to guide treatment choices) still under investigation
ADVANCED TNBC
CLINICAL FEATURES OF METASTATIC TNBC

~30% de novo MBC\(^1\)

Chemotherapy has been the standard for decades

Most patients received A-T as adjuvant/neoadjuvant treatment

Frequent visceral metastases, poor survival from the onset of MBC

High attrition rate from first to subsequent lines\(^2\): a long-term treatment sequence is not possible

Best option first, enrolment in clinical trials

RATIONALE FOR IMMUNOTHERAPY IN TNBC

Mut load across BC subtypes

Number of single nucleotide variants per exome by PAM50 subtype in TCGA breast cancers

TILs across BC subtypes

Prognostic role of TILs in TNBC

CT AS A TRIGGER FOR IMMUNE ACTIVATION

Lessons from pivotal trials
Modest activity as monotherapy
PDL1 status matters
Line of therapy matters

Dieci MV, et al. Multicenter Study Ann Oncol 2014r;25(3):611-618. © 2014 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved
ATEZOLIZUMAB + NABPACLITAXEL AS 1L:
IMPASSION 130

- Metastatic or inoperable locally advanced TNBC
- No prior therapy for advanced TNBC
  - Prior (neo)adjuvant chemo allowed if TFI ≥12 months
- 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: PFS and OS
PFS tested in ITT and PD-L1+ populations
OS tested in ITT and, if significant, in PD-L1+ population

IMPASSION 130: PROGRESSION-FREE SURVIVAL

**ITT population**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Events/ No. of Patients</th>
<th>Median Progression-free Survival (95% CI)</th>
<th>1-Yr Rate of Progression-free Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab+Nab-Paclitaxel</td>
<td>358/451</td>
<td>mo 7.2 (5.6–7.5)</td>
<td>23.7 (19.6–27.9)</td>
</tr>
<tr>
<td>Placebo+Nab-Paclitaxel</td>
<td>378/451</td>
<td>5.5 (5.3–5.6)</td>
<td>17.7 (14.0–21.4)</td>
</tr>
</tbody>
</table>

Stratified hazard ratio for progression or death, 0.80 (95% CI, 0.69–0.92), P=0.0023

**PD-L1 positive subgroup**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Events/ No. of Patients</th>
<th>Median Progression-free Survival (95% CI)</th>
<th>1-Yr Rate of Progression-free Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab+Nab-Paclitaxel</td>
<td>138/185</td>
<td>mo 7.5 (6.7–9.2)</td>
<td>29.1 (22.2–36.1)</td>
</tr>
<tr>
<td>Placebo+Nab-Paclitaxel</td>
<td>157/184</td>
<td>5.0 (3.8–5.6)</td>
<td>16.4 (10.8–22.0)</td>
</tr>
</tbody>
</table>

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

IMPASSION130: OS IN PDL1+ (MFU~19 MONTHS; EVENTS~74%)

Δ mOS = 7.5m

ITT population: 18.7 vs 21.0m; no impact in PD-L1
IMpassion131: 1ST-LINE ATEZOLIZUMAB + PACLITAXEL
Double-blind placebo-controlled randomised Phase 3 trial

- Metastatic or unresectable locally advanced TNBC
- No prior chemotherapy or targeted therapy for advanced TNBC
- Previous eBC treatment completed ≥12 months before randomisation
- Taxane eligible
- Measurable disease
- ECOG PS 0-1

Stratification
- Prior taxane (yes vs no)
- Tumour PD-L1 status (IC <1% vs ≥1%)a
- Liver metastases (yes vs no)
- Geographical region (N America vs Europe/Australia vs E Europe/Asia Pacific vs S America)

Atezolizumab 840 mg d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15
Placebo d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

R 2:1
8-10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

Primary endpoint:
PFS (investigator assessed)

Secondary endpoints include:
- OS, ORR, PFS (IRC assessed)
- PROs
- Safety
- Translational research

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aPD-L1 IC: area of PD-L1-stained tumour-infiltrating Ics as a percentage of tumour area by VENTANA SP142 immunohistochemistry assay. eBC = early breast cancer.
IMpassion131: PRIMARY PFS ANALYSIS

PFS in the PD-L1+ population

PFS in the ITT population

A

B

Miles D, et al. Ann Oncol 2021;32(8):994–1004. © 2021 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.
**IMPASSION131: FINAL OS ANALYSIS**

(mFU~15 months; events~40%)

**PD-L1+**

Paclitaxel/placebo: 28.3 months
Paclitaxel/Atezolizumab: 22.1 months

**ITT**

Paclitaxel/placebo: 22.8 months
Paclitaxel/Atezolizumab: 19.2 months

Miles D, et al. Ann Oncol 2021;32(8):994–1004. © 2021 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.
PROPOSED REASONS FOR DISCREPANT RESULTS IN IMpassion130 AND IMpassion131 TRIALS

Overlapping 95% IC intervals

PD-L1 as a suboptimal predictive biomarker

Surprisingly good performance of paclitaxel alone arm in IMpassion131

Different chemotherapy backbone:

- Paclitaxel requiring steroids premedication
- Different immune effects of paclitaxel vs. nab-paclitaxel
Pembrolizumab 200 mg IV q3w; chemotherapy dosing regimens are as follows: Nab-paclitaxel 100 mg/m² IV on Days 1, 8, and 15 every 28 days; paclitaxel 90 mg/m² IV on Days 1, 8, and 15 every 28 days; gemcitabine 1000 mg/m²/carboplatin AUC 2 on Days 1 and 8 every 21 days; normal saline; treatment may be continued until confirmation of progressive disease.

**KEYNOTE-355:**
**BASELINE PATIENTS’ CHARACTERISTICS**

<table>
<thead>
<tr>
<th></th>
<th>Pembro + CT</th>
<th>Placebo + CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>53 (25-85)</td>
<td>53 (22-77)</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>41%</td>
<td>38%</td>
</tr>
<tr>
<td>PD-L1 CPS ≥10</td>
<td>39%</td>
<td>37%</td>
</tr>
<tr>
<td>PD-L1 CPS ≥1</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Chemotherapy on study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>31%</td>
<td>34%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Carbo-Gem</td>
<td>55%</td>
<td>55%</td>
</tr>
<tr>
<td>Prior same-class chemotherapy</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>DFI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td>≥12 months</td>
<td>48%</td>
<td>52%</td>
</tr>
</tbody>
</table>
KEYNOTE 355: PROGRESSION-FREE SURVIVAL

CPS score ≥10 (38% of patients)

HR 0.65 (95% CI 0.49-0.86)
p=0.0012

CPS score ≥1 (75% of patients)

HR 0.74 (95% CI 0.61-0.90)
p=0.0014

ITT population

HR 0.82 (95% CI 0.69-0.97)

PFS superiority CPS ≥10
boundary α=0.00411

PFS superiority CPS ≥1
boundary α=0.00111 not met

Significance not tested according to hierarchical statistical design

OVERALL SURVIVAL:
PD-L1 CPS ≥10

No significant difference in CPS ≥1 and ITT

*Prespecified P value boundary of 0.0113 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.
OVERALL SURVIVAL IN SUBGROUPS: CPS ≥10

Analysis (HR and 95% CI) in the overall population is based on the stratified Cox regression model; analysis in the subgroups is based on the unstratified Cox model. Data cutoff: June 15, 2021.

Rugo H, ESMO 2021. By permission of Prof Hope S. Rugo.
RANDOMISED CONTROLLED TRIALS OF ICI+CT IN 1ST-LINE MTNBC: PFS AND OS IN PD-L1+

<table>
<thead>
<tr>
<th>Trial</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMpassion130</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SP142 ≥1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nab-paclitaxel + placebo</td>
<td>5</td>
<td>17.9</td>
</tr>
<tr>
<td>Nab-paclitaxel + atezolizumab</td>
<td>7.5</td>
<td>25.4</td>
</tr>
<tr>
<td><strong>IMpassion131</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SP142 ≥1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel + placebo</td>
<td>5.7</td>
<td>22.1</td>
</tr>
<tr>
<td>Paclitaxel + atezolizumab</td>
<td>6</td>
<td>28.3</td>
</tr>
<tr>
<td><strong>Keynote-355</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CPS ≥10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy + placebo</td>
<td>5.6</td>
<td>16.1</td>
</tr>
<tr>
<td>Chemotherapy + pembrolizumab</td>
<td>9.7</td>
<td>23</td>
</tr>
</tbody>
</table>

SAFETY OF IMMUNOTHERAPY + CT FOR PATIENTS WITH METASTATIC TNBC

Incidence of adverse events of special interest (IMpassion130\(^1\) and 131\(^2\) trials) and irAEs (KN-355\(^3\))

<table>
<thead>
<tr>
<th></th>
<th>IMpassion130</th>
<th>IMpassion131</th>
<th>Keynote-355</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICI, any G</td>
<td>59%</td>
<td>62%</td>
<td>26%</td>
</tr>
<tr>
<td>Placebo, any G</td>
<td>43%</td>
<td>53%</td>
<td>6%</td>
</tr>
<tr>
<td>ICI, ≥G3</td>
<td>9%</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Placebo, ≥G3</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

HRQoL in IMpassion130\(^4\)

PD-L1 ASSESSMENT: SOURCES OF VARIABILITY - 1

PD-L1 testing in BC: technical and biological heterogeneity¹

Venn diagram of the overlap between SP142 IC ≥1% and exploratory model-derived optimized cut-off of 22C3 CPS ≥10²

PD-L1 ASSESSMENT: SOURCES OF VARIABILITY - 2

Outcome in PD-L1+

Primary tumour

Metastasis

Emens I, et al. J Natl Cancer Inst 2021;113(8):1005-1016. Available at: https://doi.org/10.1093/jnci/djab004, accessed April 2022. Reproduced under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND; available at: https://creativecommons.org/licenses/by-nc-nd/4.0/; accessed April 2022).
IMMUNOTHERAPY FOR MTNBC:
Anti-PD1/PD-L1 + CT is standard as 1st-line treatment of PD-L1+ mTNBC patients

Early relapsers need more effective options
KN-355 data are reassuring about the possibility to combine ICI with paclitaxel and carbo-gem

PD-L1: what, when, how?
In perspective:

- Further predictors beyond PD-L1 have been proposed: TILs, basal-like immune-activated, immune phenotype, CD8+, angiogenesis pathway, CD274 gain/amplification
- Many of these biomarkers are correlated with each other
  - How to integrate?
- Timing of chemotherapy, combinations with PARPi

**OLYMPIAD AND EMBRACA PHASE 3 TRIALS**

OlympiAD trial – Olaparib

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
  - Deleterious or suspected deleterious gBRCAm
  - Prior anthracycline and taxane
  - ≤2 prior chemotherapy lines in metastatic setting
  - HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

- Olaparib 300 mg tablets bd

- Chemotherapy treatment of physician’s choice (TPC)
  - Capecitabine
  - Eribulin
  - Vinorelbine

- R 2:1

EMBRACA trial – Talazoparib

- Patients with locally advanced or metastatic HER2 negative BC and a germline BRCA1/2 mutation

**Stratification factors**

- Number of prior CT regimens (0 or ≥1)
- TNBC or HR+
- History of CNS mets or no CNS mets

- Talazoparib 1 mg PO daily

- Treatment (21-day cycles) continues until progression or unacceptable toxicity

- Physicians choice of therapy (PCT):
  - capecitabine, eribulin, gemcitabine or vinorelbine

OLYMPIAD AND EMBRACA: PFS RESULTS

OLYMPIAD¹
50% TN; A/T pretreated; 71% prior CT for MBC; TN: non-platinum resistant

Median PFS 7.0 vs 4.8 months
HR 0.58, 95% CI: 0.43, 0.80; P<0.001
TNBC: HR 0.43, 95% CI: 0.29, 0.63

EMBRACA²
44% TN; A/T pretreated; 62% prior CT for MBC; TN: non-platinum resistant

Median PFS 8.6 vs 5.6 months
HR 0.54, 95% CI: 0.41, 0.71; P<0.001
TNBC: HR 0.60, 95% CI: 0.41, 0.87

OLYMPIAD AND EMBRACA: OS RESULTS

**OLYMPIAD**
- HR: 0.90 (95% CI: 0.66, 1.23; P=0.513)
- 1st line HR: 0.51 (95% CI: 0.29, 0.90; P=0.02)

**EMBRACA**
- HR: 0.848 (95% CI: 0.670, 1.073; P=0.17)
- 33% of patients in CT arm received subsequent PARPi
  - Adjusted HR: 0.756 (95% CI: 0.503, 1.029)
OlympiAD1

<table>
<thead>
<tr>
<th>Olaparib 300 mg bid</th>
<th>Chemotherapy TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=201)</td>
<td>(n=93)</td>
</tr>
<tr>
<td>Deterioration, n (%)</td>
<td>49 (24)</td>
</tr>
<tr>
<td></td>
<td>25 (27)</td>
</tr>
<tr>
<td>Not Changing (NC)</td>
<td>15.3</td>
</tr>
</tbody>
</table>

HR 0.44
95% CI 0.25, 0.77; P=0.0043

EMBRACA2

A


PARP INHIBITORS IN MTNBC: SUMMARY

PARP inhibitors are a standard option for gBRCA mut HR– patients

- Highest priority in TNBC

Positioning in TNBC treatment algorithm according to PD-L1 status (speaker’s view):

- Preferrable over CT as first-line option in PD-L1- (especially if non carboplatin-resistant)
- ICI + CT preferrable over PARPi as first line option in PD-L1+

Future perspective: expanding HRD criteria to select patients for PARPi
(i.e. somatic BRCA mut or germline PALB2 mut\(^1\))

SACITUZUMAB GOVITECAN

- Humanised anti-TROP2 antibody
- TROP2: epithelial antigen highly expressed on most epithelial cancers, including TNBC; minimal expression in normal tissues
- Hydrolysable linker for payload release
- High drug-to-antibody ratio (7.6:1)

- Payload: SN-38, topoisomerase I inhibitor (active metabolite of irinotecan; 100–1000-fold more potent)
- Sacituzumab govitecan delivers SN-38 to tumour cells at a much higher level than irinotecan

ANTI TROP2 ADC SACITUZUMAB GOVITECAN IN PRETREATED TNBC

ASCENT trial

TN at diagnosis 70%
Previous anticancer regimes: Median 4 (2-17)
Previous PD-1 or PD-L1 inhibitors 26-29%
# ASCENT STUDY: SAFETY

Summary of treatment-related adverse events in the safety population

<table>
<thead>
<tr>
<th></th>
<th>Sacituzumab-govitecan</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any G</td>
<td>G3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>63%</td>
<td>34%</td>
</tr>
<tr>
<td>Anemia</td>
<td>34%</td>
<td>8%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>16%</td>
<td>9%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>59%</td>
<td>10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>57%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29%</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45%</td>
<td>3%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>46%</td>
<td>0</td>
</tr>
</tbody>
</table>

EMA indication: two or more prior systemic therapies, including at least one of them for advanced disease.
TRASTUZUMAB-DXD VS TPC IN HER2 LOW MBC: EXPLORATORY RESULTS OF DESTINY-BREAST04 IN HR-

30-50% of patients with metastatic TNBC develop brain metastases, typically early since diagnosis of MBC.

TNBC patients with BM experience a dismal prognosis.

The presence of BMs should be explored by neuroimaging in all patients with clinical symptoms or signs.

Current EANO/ESMO guidelines open to the possibility of screening for BM patients with metastatic TN and HER2+ BC in the absence of symptoms.

Management of BM in TNBC should follow EANO/ESMO guidelines.

Systemic therapies with improved intracranial activity are urgently needed for these patients.
Patients with TNBC should receive ChT [I, A]

Sequential anthracycline/taxane-based regimen is the standard for the majority of patients [I, A]

…with the possible exception of low-risk ‘special histological subtypes’ such as secretory or, adenoid cystic carcinomas or very early (T1aN0) tumours
PROGRESS IN ADJUVANT CT

Anthraclyline vs. no CT

- **2076 women, ER-poor (73% N+)**
- **Control 41.9%**
- **Anth. 34.8%**
- **RR 0.80 (0.69–0.93)**
- **Logrank 2p = 0.003**
- **10-y gain 7.1% (se 2.3)**

Anthra+Tax vs. no Tax

- **11258 women, ER-poor (81% N+)**
- **Control 27.7%**
- **Tax + anth 24.0%**
- **RR 0.86 (0.79–0.94)**
- **Logrank 2p = 0.0005**
- **8-y gain 3.7% (se 1.1)**

Peto R, et al. Republished with permission of Elsevier Science & Technology Journals, from The Lancet, EBCTCG, 379(9814), 2012; permission conveyed through Copyright Clearance Center, Inc.
### OPTIMISING THE STANDARD: TIMING

**MD Anderson Cancer Center, The University of Texas OS¹**

<table>
<thead>
<tr>
<th>TTC (days)</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-60 vs ≤30</td>
<td>1.05</td>
<td>0.94 to 1.18</td>
<td>0.39</td>
</tr>
<tr>
<td>≥61 vs ≤30</td>
<td>1.19</td>
<td>1.02 to 1.38</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Stage I</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-60 vs ≤30</td>
<td>0.85</td>
<td>0.64 to 1.12</td>
<td>0.25</td>
</tr>
<tr>
<td>≥61 vs ≤30</td>
<td>0.80</td>
<td>0.54 to 1.18</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-60 vs ≤30</td>
<td>1.13</td>
<td>0.97 to 1.31</td>
<td>0.12</td>
</tr>
<tr>
<td>≥61 vs ≤30</td>
<td>1.17</td>
<td>0.96 to 1.42</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-60 vs ≤30</td>
<td>1.14</td>
<td>0.88 to 1.48</td>
<td>0.33</td>
</tr>
<tr>
<td>≥61 vs ≤30</td>
<td>1.76</td>
<td>1.26 to 2.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hormone receptor-positive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-60 vs ≤30</td>
<td>1.14</td>
<td>0.95 to 1.36</td>
<td>0.16</td>
</tr>
<tr>
<td>≥61 vs ≤30</td>
<td>1.29</td>
<td>1.02 to 1.64</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>HER2-positive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-60 vs ≤30</td>
<td>0.92</td>
<td>0.69 to 1.22</td>
<td>0.54</td>
</tr>
<tr>
<td>≥61 vs ≤30</td>
<td>1.16</td>
<td>0.82 to 1.63</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Triple negative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31-60 vs ≤30</td>
<td>1.74</td>
<td>1.32 to 2.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥61 vs ≤30</td>
<td>1.54</td>
<td>1.09 to 2.18</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**The Royal Marsden, NHS Foundation Trust²**

![Kaplan-Meier survival estimates graph]

**5-year OS:**
- Early chemo: 89.8%
- Delayed chemo: 90.7%
- HR 1.21 (0.89-1.46), p=0.23

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>5-year OS Early chemo</th>
<th>5-year OS Late chemo</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC (n=550)</td>
<td>89%</td>
<td>77%</td>
<td>2.18 (1.11-4.30)</td>
<td>0.024</td>
</tr>
</tbody>
</table>
OPTIMISING THE STANDARD: SCHEDULE

E1199 Phase 3 trial, TNBC patients subgroup:
Weekly paclitaxel is the best taxane schedule
OPTIMISING THE STANDARD: DOSE-DENSE

Breast cancer mortality, ER-negative (10,900 women)

Breast cancer mortality, ER-positive (25,029 women)

EBCTCG, Lancet 2019,393(10179):1440-1452. Reproduced under the terms of an Attribution-NonCommercial-NoDerivatives 4.0 Unported License. Available at: visit http://creativecommons.org/licenses/by-nc-nd/4.0/ Accessed April 2022.
THRESHOLD FOR SYSTEMIC THERAPY IN TNBC

St Gallen 2019 International Consensus Guidelines:
Threshold for initiating systemic therapy (either as neo- or adjuvant) according to BC subtype
NEOADJUVANT APPROACH AS A PLATFORM FOR TREATMENT PERSONALISATION IN TNBC

Pathologic response as a surrogate endpoint

Strongest prognostic value when defined as ypT0/is/N0

Increase the comprehensiveness of residual disease evaluation

Residual disease

H&E
RCB
TILs

IHC
Ki67
HER2 protein overexpression loss

FISH
HER2 gene amplification loss

LIQUID BIOPSY
WGS/NGS

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CREATE-X

NAC | Surgery
Pathology: Non-pCR or node +

**Control: Standard**

R 2:1
N=900

**Capecitabine 2500 mg/m²/ day 1-14**
**6–8 cycles**

**Stratification factors**
- ER, age, NAC, ypN, 5FU and institution

**Standard therapy**
- HR+: Hormone therapy
- HR-: No further systemic treatment

- Possible pharmacogenomic effect
- Amount of NACT received not specified
- Capecitabine use in adjuvant setting is off-label

**ESMO 2019:** Although more data are necessary in non-Asian patients, this option may be offered to TN patients who do not achieve a pCR after optimal neoadjuvant ChT [I, B]

---

Lower capecitabine dose may be effective (data from Asian patients)*: 2000 mg/m²/day 1-14 commonly used in US and EU.

EA1131: CAPECITABINE VS CARBOPLATIN IN NO-PCR TNBC PATIENTS

Kaplan-Meier estimates of invasive disease-free survival (iDFS)¹
- Median follow-up of 20 months and 120 iDFS events
- Three-year iDFS in patients with basal subtype TNBC were similar across both treatment arms

<table>
<thead>
<tr>
<th></th>
<th>Platinuma (n=148)</th>
<th>Capecitabineb (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year iDFS, % (95% CI)</td>
<td>42 (30, 53)</td>
<td>49 (39, 59)</td>
</tr>
<tr>
<td>HR (95% RCI)</td>
<td>1.06 (0.62, 1.81)</td>
<td></td>
</tr>
</tbody>
</table>

a carboplatin or cisplatin once every 3 weeks for four cycles
b capecitabine 14 out of 21 days every 3 weeks for six cycles
RCI, repeated CI

N=308 clinical stage II or III basal-like TNBC with ≥1 cm RD in the breast post NACT²
100% taxane; 86% anthra; 40% other
~50% ypN+
~60% ≥ypT2
(ITT CREATE-X 60% ypN+, 42% marked treatment responses to NAC)

Outcome was worse than expected
Capecitabine role in non-basal?

Threshold for recommending neoadjuvant chemotherapy in TNBC

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESMO 2019</td>
<td>N+ and/or T&gt;2cm</td>
</tr>
<tr>
<td>St. Gallen 2021</td>
<td>N+ and/or T&gt;2cm</td>
</tr>
<tr>
<td>ASCO</td>
<td>N+ and/or T&gt;1cm</td>
</tr>
</tbody>
</table>

St Gallen 2019 International Consensus Guidelines: Threshold for initiating systemic therapy (either as neo- or adjuvant) according to BC subtype

Burstein HJ, et al. Ann Oncol 2021;32(10):1216-1235. © 2021 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved;
IMPROVING BEYOND THE STANDARD

Neoadjuvant platinum salts

Immunotherapy

Olaparib in high-risk BRCA$_{\text{mut}}$
pCR RATES (ypT0/IS/ypN0) IN TNBC WITH CARBOPLATIN-CONTAINING CT

Effect of platinum on pCR irrespectively from BRCA status

Increased G3/4 haematological AEs

No effect on EFS (contrasting data from GeparSixto and CALGB 40603)
**Summary of EFS events**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Paclitaxel + carboplatin + veliparib (n=316)</th>
<th>Paclitaxel + carboplatin (n=160)</th>
<th>Paclitaxel (n=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with EFS event</td>
<td>65 (21)</td>
<td>30 (19)</td>
<td>47 (30)</td>
</tr>
<tr>
<td>PD before surgery</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Any recurrence or new malignancy</td>
<td>50 (16)</td>
<td>26 (16)</td>
<td>35 (22)</td>
</tr>
<tr>
<td>Distant</td>
<td>22 (7)</td>
<td>12 (8)</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Local</td>
<td>16 (5)</td>
<td>10 (6)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Ipsilateral breast</td>
<td>6 (2)</td>
<td>4 (3)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Regional</td>
<td>4 (1)</td>
<td>3 (2)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>AML/MDS</td>
<td>4 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>New malignancy other than breast cancer or AML/MDS</td>
<td>10 (3)</td>
<td>1 (1)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Death as first event</td>
<td>13 (4)</td>
<td>3 (2)</td>
<td>6 (4)</td>
</tr>
</tbody>
</table>

*a* EFS events summarized by types of events reported as documented on date of first event(s). Patients may have had multiple types of EFS events reported on the same day. Major EFS categories were: (i) PD before surgery; (ii) any recurrence or new malignancy; and (iii) death as first event. Patients might have had more than one type of EFS event documented at the time of their first event(s). Post-analysis adjudication of second malignancies identified a second malignancy reported in three patients on the paclitaxel plus carboplatin arm (squamous skin cancer, AML, and colon cancer) who had not been reported with a prior EFS event and were not classified as an EFS event.

*Stratified by BRCA status, lymph node status, and planned doxorubicin/cyclophosphamide dose intensity. C, carboplatin; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; P, paclitaxel; V, veliparib.*

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Geyer CE, et al. Ann Oncol 2022;33(4):384-394. © 2022 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.
PLATINUM-BASED NEOADJUVANT CHEMOTHERAPY IN TNBC
Systematic review and meta-analysis
IMPROVING BEYOND THE STANDARD

Neoadjuvant platinum salts

Immunotherapy

Olaparib in high-risk BRCA_{mut}
NEOADJUVANT IMMUNOTHERAPY + CT IN TNBC

Pathologic complete response (%)

- I-SPY2
- GEPARNuevo
- KEYNOTE-522
- NeoTRiP
- IMPASSION031

**ITT**

- CT
- CT+
- Placebo Durva
- Placebo Durva
- Placebo Durbo
- ITT
- PD-L1+

**Placebo**

- Durva
- Durva

**Pembro**

- CT
- CT+

**PD-L1+ (IC IHC SP142 >0):** 47%

**PD-L1+ (TC or IC IHC SP263 ≥1%):** 87%

**PD-L1+(CPS IHC 22C3 ≥1):** 83%

*Estimated probabilities of pCR.


a. Pac →DC; b. Nab-Pac→ EC(dd); c. Carboplatin+Pac → EC/DC; d. Carboplatin+Nab-Pac (anthra given after surgery); e. Nab-Pac→ DC(dd)
KEYNOTE-522: STUDY DESIGN

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)

IA1: Primary pCR analysis to test primary hypothesis of pCR based on prespecified first 602 subjects (pre-calculated P-value boundary for significance of 0.003

IA2: If pCR hypothesis successful at IA1 (thus definitive), pCR will not be formally tested at IA2
Median FU 39.1 months

EFS 36 months: 84.5% vs 76.8%
HR 0.63 (95%CI 0.48-0.82)
P<0.001

Major reduction in distant recurrences with pembrolizumab (7.7% vs 13.1%)

KEYNOTE-522: EFS ACCORDING TO PCR

## SUMMARY OF AESI/IRAES IN NEOADJUVANT TRIALS OF IMMUNOTHERAPY FOR TNBC

<table>
<thead>
<tr>
<th></th>
<th>GeparNUEVO</th>
<th>KEYNOTE-522</th>
<th>NeoTRIP</th>
<th>Impassion 031</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Durva</td>
<td>Placebo</td>
<td>Pembro</td>
</tr>
<tr>
<td>Hypothyroidism G1/2</td>
<td>2.4%</td>
<td>7.6%</td>
<td>3.3%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Hypothyroidism G ≥3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.4%</td>
</tr>
<tr>
<td>Hyperthyroidism G1/2</td>
<td>1.2%</td>
<td>9.8%</td>
<td>1.0%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Hyperthyroidism G ≥3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0</td>
<td>1.1%</td>
<td>0.3%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>2.3%</td>
</tr>
<tr>
<td>Colitis (all G)</td>
<td>-</td>
<td>-</td>
<td>0.8%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Severe skin reaction</td>
<td>1.2%</td>
<td>2.2%</td>
<td>1.0%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Pancreatitis G ≥3</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0.5%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0</td>
<td>1.1%</td>
<td>0.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Serious AESI</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

# Ongoing Adjuvant Trials with Immunotherapy

## In TNBC

<table>
<thead>
<tr>
<th>Trial Code</th>
<th>n</th>
<th>Treatment</th>
<th>Setting</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-BRAVE</td>
<td>474</td>
<td>Avelumab x 1-yr vs observation</td>
<td>Stratum A: high risk primary surgery (after standard CT) Stratum B: no-pCR after NACT</td>
<td>DFS in all patients; DFS in post-NACT patients</td>
</tr>
<tr>
<td>SWOG S1218/NRG BR006</td>
<td>1000</td>
<td>Pembrolizumab x 1-yr vs observation</td>
<td>No pCR after NACT</td>
<td>iDFS in all patients; iDFS in PD-L1+</td>
</tr>
<tr>
<td>Impassion030</td>
<td>2300</td>
<td>P→AC/EC + Atezolizumab* vs P→AC/EC</td>
<td>Stage II-III primary surgery</td>
<td>iDFS</td>
</tr>
</tbody>
</table>

*Concomitant and up to 1 yr
IMPROVING BEYOND THE STANDARD

Neoadjuvant platinum salts
Immunotherapy
Olaparib in high-risk BRCA_{mut}
Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥1%). Triple negative defined as ER and PgR negative (IHC staining <1%).


Neoadjuvant Group
- TNBC: non-pCR
- Hormone receptor-positive: non-pCR and CPS+EG score ≥ 3
- ≥ 6 cycles

Neoadjuvant → Surgery → +/- Radiotherapy chemotherapy

Adjuvant Group
- TNBC: ≥pT2 or ≥pN1
- Hormone receptor-positive ≥4 positive lymph nodes
- Surgery → ≥6 cycles adjuvant chemotherapy → +/- Radiotherapy

Randomisation N=1836

1:1

Olaparib
300 mg twice daily for 1 year

Placebo
Twice daily for 1 year

Primary Endpoint
- Invasive disease-free survival (IDFS) by STEEP System

Secondary Endpoints
- Distant disease-free survival (DDFS)
- Overall Survival (OS)
- BRCA 1/2 associated cancers
- Symptom/Health related QoL
- Safety

Adjuvant Group
- TNBC: ≥pT2 or ≥pN1
- Hormone receptor-positive
- ≥4 positive lymph nodes
- Surgery → ≥6 cycles adjuvant chemotherapy → +/- Radiotherapy

Concurrent adjuvant therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

Stratification factors
- Hormone receptor-positive vs TNBC
- Neoadjuvant vs adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Neoadjuvant Group
- TNBC: non-pCR
- Hormone receptor-positive: non-pCR and CPS+EG score ≥ 3
- ≥ 6 cycles

Neoadjuvant → Surgery → +/- Radiotherapy chemotherapy

Stratification factors
- Hormone receptor-positive vs TNBC
- Neoadjuvant vs adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Local genetic testing or on-study central screening (Myriad genetics Inc.)

Germline pathogenic or likely pathogenic BRCA 1/2 mutation

HER2-negative (hormone receptor-positive or TNBC)

Stage II-III Breast Cancer or lack of PathCR to NACT

Local genetic testing or on-study central screening (Myriad genetics Inc.)

Germline pathogenic or likely pathogenic BRCA 1/2 mutation

HER2-negative (hormone receptor-positive or TNBC)

Stage II-III Breast Cancer or lack of PathCR to NACT
OLYMPIA: PRIMARY IDFS ANALYSIS

mFU 2.5 years, 165 iDFS events

Invasive disease-free survival

Between-group difference in 3-yr invasive disease–free survival, 8.8 percentage points (95% CI, 4.5–13.0)
Stratified hazard ratio for invasive disease or death, 0.58 (99.5% CI, 0.41–0.82)
P < 0.001

OLYMPIA: SECOND OS INTERIM ANALYSIS
mFU 3.5 years, 341 iDFS events, 184 deaths

98.5% confidence intervals are shown for the hazard ratio because P<0.015 is required for statistical significance.

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OLYMPIA: IDFS AT SECOND OS INTERIM ANALYSIS

Difference: 3 Yr. IDFS rate 8.8% (95% CI: 5.0%, 12.6%)  
Difference: 4 Yr. IDFS rate 7.3% (95% CI: 3.0%, 11.5%)  

Stratified hazard ratio 0.63 (95% CI: 0.50, 0.78)
OLYMPIA: DDFS AT SECOND OS INTERIM ANALYSIS

Difference: 3 Yr. DDFS rate 7.0% (95% CI: 3.5%, 10.6%)

Difference: 4 Yr. DDFS rate 7.4% (95% CI: 3.6%, 11.3%)

Stratified hazard ratio 0.61 (95% CI: 0.48, 0.77)

No. at risk:
- Olaparib: 921, 828, 784, 746, 698, 609, 501, 391, 302, 209
- Placebo: 915, 818, 777, 728, 670, 582, 471, 379, 300, 193

Time since randomisation (months):
- Olaparib: 18, 24, 30, 36, 42, 48, 54
- Placebo: 18, 24, 30, 36, 42, 48, 54

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OLYMPIA: IDFS AND OS SUBGROUP ANALYSES

Tutt ANJ, ESMO Virtual Plenary 2022. By permission of Prof A. Tutt
## OLYMPIA: SUMMARY OF ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Event</th>
<th>Olaparib (n=911)</th>
<th>Placebo (n=904)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>836 (91.8%)</td>
<td>758 (83.8%)</td>
</tr>
<tr>
<td>Serious adverse event (SAE)</td>
<td>79 (8.7%)</td>
<td>78 (8.6%)</td>
</tr>
<tr>
<td>Adverse event of special interest*</td>
<td>31 (3.4%)</td>
<td>51 (5.6%)</td>
</tr>
<tr>
<td>MDS/AML</td>
<td>2 (0.2%)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>9 (1.0%)</td>
<td>12 (1.3%)</td>
</tr>
<tr>
<td>New primary malignancy</td>
<td>21 (2.3%)</td>
<td>36 (4.0%)</td>
</tr>
<tr>
<td>Grade ≥3 adverse event</td>
<td>223 (24.5%)</td>
<td>102 (11.3%)</td>
</tr>
<tr>
<td>Grade 4 adverse event</td>
<td>17 (1.9%)</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td>Adverse event leading to permanent discontinuation of treatment†</td>
<td>98 (10.8%)</td>
<td>42 (4.6%)</td>
</tr>
<tr>
<td>Adverse event leading to death‡</td>
<td>1 (0.1%)</td>
<td>2 (0.2%)</td>
</tr>
</tbody>
</table>

*One patient has both pneumonitis and a new primary malignancy and is counted in both categories. † Adverse events leading to permanent discontinuation of treatment in the olaparib group occurring in > 1% of patients were: nausea, anaemia and fatigue. ‡ Adverse events leading to death were: cardiac arrest (olaparib, n = 1), AML (placebo, n = 1) and ovarian cancer (placebo, n = 1)
Sequential anthra-taxanes (including cyclophosphamide) is standard → schedule and timing matter!

- Is it too early de-escalate systemic regimens for low-risk patients?
  - Risk stratification is key: Histotype, Stage, TILs

The neoadjuvant approach enhances personalised treatment opportunities and should be standard for the majority of TNBC

Adding carboplatin to A-T as neoadjuvant therapy increases pCR rate independently of BRCA status and improves EFS

- However: higher risk of haematologic toxicity and lack of OS advantage

Immunotherapy improves pCR rate (and EFS in Keynote-522), but additive side effects (early and late)

- Pending data from post-NACT trials

Adjuvant olaparib for high-risk, gBRCA\textsubscript{mut} HR- almost halves the risk of relapse
ALGORITHM PROPOSAL FOR >T1CN0 TNBC

**T1c N0**
- **NACT**

**T ≥2 cm, any N**
- **T/AC**
- **TCa/AC + Pembrolizumab**

**SURGERY**

- **No pCR**
  - **pCR**
  - **No pCR**

- **pCR**

**No further Tx**

- **Is pembrolizumab up to 1 year needed?**
  - **gBRCA wt: Pembrolizumab**
  - **gBRCA mut: Olaparib**
  - **Clinical trials (i.e., SASCIA)**

Based on speaker's opinion
THANK YOU!