Metastatic Triple Negative Breast Cancer: Ongoing Trials

Joan Albanell
Hospital del Mar, Barcelona
Metastatic Triple Negative Breast Cancer Spectrum

Targeting Growth Factor Receptors

Targeting Signaling Transduction Pathways

Targeting The Androgen Receptor

Immune Checkpoint Modulators

Dynamics of mTNBC

Summary
Breast cancer consists of many diseases. This heterogeneity is visible at the histological, clinical, genetic and genomic level. Genomic studies have identified four intrinsic subtypes of breast cancer: basal-like, luminal A and B, and HER2-enriched. The basal-like tumours are identified by high expression of KRT5/6A, ID4, and FOXC1 (basal epithelial-like cluster). The luminal epithelial-like cluster is characterized by high expression of ER, CMA3, XBP1, and FOXA1. Luminal A tumours have the highest expression of luminal epithelial genes when compared with luminal B tumours; luminal A and B tumours show, respectively, low and high proliferation rates. The HER2-enriched subtype, although expressing the luminal-epithelial cluster, is defined by amplification of genes on 17q12 including HER2/ERBB2. Recent studies have described the somatic mutations and DNA copy-number landscapes of breast cancers, showing a good concordance between those genetic alterations and the genetic intrinsic subtypes. Here, we present an overview of the common genetic and genomic events seen in breast tumours.

<table>
<thead>
<tr>
<th>Basal-like</th>
<th>PARP inhibitors</th>
<th>AKT inhibitors</th>
<th>EGFR inhibitors</th>
<th>MEK inhibitors</th>
<th>Sensitivity to chemotherapy</th>
<th>PI3K inhibitors</th>
<th>MET inhibitors</th>
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<tbody>
<tr>
<td>Germline BRCA1/BRCA2 mutation</td>
<td>γ-Secretase inhibitors</td>
<td>AKT inhibitors</td>
<td>EGFR inhibitors</td>
<td>MEK inhibitors</td>
<td>Sensitivity to chemotherapy</td>
<td>PI3K inhibitors</td>
<td>MET inhibitors</td>
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<tr>
<td>NOTCH1/NOTCH3 amplification/mutation</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
<td>Phase I and II trials in other diseases</td>
<td>Retrospective analysis of trials</td>
<td>Preclinical evidence</td>
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<tr>
<td>AKT3 amplification</td>
<td>Preclinical evidence</td>
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<td>Preclinical evidence</td>
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<td>EGFR amplification</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
<td>Phase I and II trials in other diseases</td>
<td>Retrospective analysis of trials</td>
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<td>NF1 deletion, KRAS amplification</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
<td>Phase I and II trials in other diseases</td>
<td>Retrospective analysis of trials</td>
<td>Preclinical evidence</td>
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<td>TP53 mutation</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
<td>Phase I and II trials in other diseases</td>
<td>Retrospective analysis of trials</td>
<td>Preclinical evidence</td>
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</tr>
<tr>
<td>PIK3R1/PTEN/INPP4B mutation/loss</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
<td>Phase I and II trials in other diseases</td>
<td>Retrospective analysis of trials</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
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<tr>
<td>MET amplification/mutation</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
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<td>Preclinical evidence</td>
<td>Preclinical evidence</td>
</tr>
</tbody>
</table>
Potential Therapeutic Implications of TNBC Subtyping

<table>
<thead>
<tr>
<th>TNBCtype Molecular Subtype</th>
<th>Gene Ontology</th>
<th>Therapeutic Targets/Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL1</td>
<td>DNA Damage Response and Cell Proliferation</td>
<td>Cisplatin, PARP inhibitors</td>
</tr>
<tr>
<td>BL2</td>
<td>TP63, EGFR and MET Signaling</td>
<td>mTOR, Growth Factor inhibitors</td>
</tr>
<tr>
<td>IM</td>
<td>Immune Signaling</td>
<td>Cisplatin, PARP inhibitors</td>
</tr>
<tr>
<td>M</td>
<td>EMT, Wnt, TGF(\beta), IG1FR, Notch, Cell Proliferation</td>
<td>mTOR, Growth Factor inhibitors, Src inhibitors</td>
</tr>
<tr>
<td>MSL</td>
<td>EMT, Wnt, TGF(\beta), MAPK, Rac, PI3K, PDGF</td>
<td>mTOR, PI3K, MEK and Growth Factor inhibitors</td>
</tr>
<tr>
<td>LAR</td>
<td>AR signaling, FOXA1 and ERBB4 Signaling</td>
<td>AR antagonists, PI3K inhibitors</td>
</tr>
<tr>
<td>UNC</td>
<td>DNA Damage Response and Cell Proliferation</td>
<td>Cisplatin, PARP inhibitors</td>
</tr>
</tbody>
</table>

Abramson et al. Cancer 2015
ClinicalTrials.Gov (Feb 2015)

- Searching term: Triple Negative Metastatic Breast Cancer; Excluding ad hoc trials based on Chemo or PARPinh
- 31 Ongoing Trials (Active, not recruiting; Recruiting; Not yet recruiting) with Targeted Therapy or Immunotherapy
- No trials with mandatory specific mutations/amplifications
- TN Subtypes for Eligibility not Observed
- Lots of biomarker exploratory analysis and planned subsets
ClinicalTrials.Gov (Feb 2015)

• Triple Negative based on traditional ER/PR/HER2 (all comers) (n=23)
  – Growth Factor Receptors: Met (ARQ-197, cabozantinib, onartuzumab (+CT, Beva)); EGFR; Nimotuzumab (+CT), Icotinib; FGFR: Lucitanib
  – PI3K/Akt/mTOR: BKM120, Ipatasertib + paclitaxel, everolimus (+CT), (n=2)
  – MEK: Cometinib + Paclitaxel, Trametinib (andGSK2141795)
  – CDK inhibitor: Dinaciclib
  – Apoptosis: Abraxane + Tigatuzumab (Death Receptor 5)
  – Stemness: CXCR4 POL6326 + ct; Notch/Hedgehog RO4929097 + vismodegiv; LDE225 (+BKM120/CT)
  – Glutaminase Inhibitor: CB-839
  – Angiogenesis: ENMD-2076, Apatinib
  – Immunotherapy (PD-L1+?): Nivolumab + CT; Nivolumab + Ipilimumab, Autologous cMet Redirected T Cells

• Triple Negative and Androgen Receptor Positive (n=5)
  – Bicalutamide (n=2), Enzalutamide, Orterone, 4 OH testosterone

• Triple Negative and Androgen Receptor Negative (n=1)
  – PI3K: GDC-0941 + cisplatin

• Triple Negative EGFR Positive: Gefitinib (n=1)
• Triple Negative gpNMB Positive: Glembatunumab vedotin (n=1)
Comprehensive Genomic Analysis Identifies Novel Subtypes and Targets of Triple-negative Breast Cancer

Matthew D. Burstein, Anna Tsimelzon, Graham M. Poage, et al.

*Clin Cancer Res* Published OnlineFirst September 10, 2014.

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**Figure 4**

<table>
<thead>
<tr>
<th>Subtype 1</th>
<th>Subtype 2</th>
<th>Subtype 3</th>
<th>Subtype 4</th>
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<tbody>
<tr>
<td>Luminal AR (LAR)</td>
<td>Mesenchymal (MES)</td>
<td>Basal-like Immune Suppressed (BLIS)</td>
<td>Basal-like Immune Activated (BLIA)</td>
</tr>
</tbody>
</table>

**Graphs**:

- **Luminal AR (LAR)**
  - % Gains
  - % Losses

- **Mesenchymal (MES)**
  - % Gains
  - % Losses

- **Basal-like Immune Suppressed (BLIS)**
  - % Gains
  - % Losses

- **Basal-like Immune Activated (BLIA)**
  - % Gains
  - % Losses

Chromosome 1 to 22
Heterogeneity in triple negative breast cancer

- **Luminal AR breast cancer distinct subtype of TNBC**
  Separate drivers *PIK3CA* mutations, AR, ?, CDK4/6 etc

- **Lymphocyte predominant TNBC**
  Subset of Basal-like and Mesenchymal Stem-like TNBC
  High pCR rate and good outcome

  Expression PD1 and PD-L1

- **Genetic drivers**
  Diverse requiring deep molecular stratification
  Rare dominant oncogenic drivers
  Complicated by intra-tumoural genetic heterogeneity

San Antonio Breast Cancer Symposium, December 9-13, 2014

From C Turner ES
Metastatic Triple Negative Breast Cancer Spectrum

**Targeting Growth Factor Receptors**

Targeting Signaling Transduction Pathways

Targeting Stemness

Targeting The Androgen Receptor

Immune Checkpoint Modulators

Dynamics of mTNBC

Summary
- EGFR amplification ~5% TNBC
- HER mutation 2–3%
- ERBB3 mutation <2%

- IGF1R amplification <5%

- MET amplification (rare)

- FGFR1 amplification ~10% (enriched luminal B)
- FGFR2 amplification ~2%
- FGFR2/3 translocation (rare)

Pleiotropic receptor tyrosine kinase activation

- PTPN12 mutation ~5% TNBC

PTPN12
Targeting FGFR with Dovitinib (TKI258): Preclinical and Clinical Data in Breast Cancer

Andre et al. CCR 2013
A new breast cancer ‘subtype’?

- HER2 Negative (1+ or 2+; FISH negative)
- HER3 Positive

- ER + or -
RG7116, a Therapeutic Antibody That Binds the Inactive HER3 Receptor and Is Optimized for Immune Effector Activation

Christian Mischberger¹, Christian B. Schiller², Michael Schramm², Nikolaos Dimoudis³, Thomas Friess¹, Christian A. Gerdes⁴, Ulrike Reiff¹, Valeria Lifs⁵, Gabriele Hoetzkammer⁵, Irene Kolm⁵, Karl-Peter Hopfner³, Gerhard Niederfellner¹, and Birgit Bossenmaier¹
Phase I Pharmacodynamic and Antitumor Data with RG7116

Figure 2: Representative example of HER3 staining in a FFPET tumor sample of a CRC patient in the 800-mg cohort at screening (A) and at Day 14 of Cycle 1 (B).

Figure 3: Immunoreactive scores of membranous HER3 protein in FFPET skin samples at baseline and Day 14 of Cycle 1 displayed for the individual patients of the dosing cohorts. BSL = baseline; OT = on treatment.

Figure 5: CT scan of a BC patient in the 1600 mg cohort at screening (A) and at Day 14 of Cycle 4 (B). Non-target lesions (anterior thorax soft tissue and subcutaneous metastases and mediastinal adenopathies) show significant decrease in size. In addition, the pleural effusion on the right side almost vanished without drainage.

Figure 6: PET/CT and PET images of the BC patient in the 1600 mg cohort showing SUV_{max} decrease in the target chondroecternal bone lesion (red arrow) after one cycle of therapy. The patient had PMR with 70% reduction in the SUV_{max} of the target lesion at Day 14 of Cycle 1.

Proc ASCO 2013
RT7160 (anti-HER3) Combined with Anti-EGFR or Pertuzumab

Anti-EGFR + anti-HER3

Pertuzumab + anti-HER3

HER2 1+/2+ and FISH- / HER3+ trial

Mirschberger et al. Cancer Res 2013
Metastatic Triple Negative Breast Cancer Spectrum

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Summary
PIK3CA Mutations in Basal-like Cancer and by Lehmann’s Subtypes
PI3K Inhibitors in Development

• Three generations of PI3K inhibitors have now been developed\(^1\)\(^–\)\(^3\)

**First-generation**

Pan-PI3K class I inhibitors
- Inhibit all four isoforms of class I PI3K (α, β, γ, δ) and provide the broadest inhibition of PI3K\(^3\),\(^6\)
- May be better suited to combination therapy and in tumour types lacking PIK3CA mutations\(^4\)

**Second-generation**

Isoform specific inhibitors
- Characterised by greater and PI3K isoform-specific activity\(^3\)
- Provide the potential to completely block a specific target while limiting toxicities associated with a broader inhibition\(^5\)

**Third-generation**

Dual PI3K/mTOR inhibitors
- Target homologous regions in the catalytic sites of PI3K and downstream components mTORC1 and mTORC2\(^3\),\(^6\)
- Targeting two levels of the pathway may provide the potential advantage of stronger inhibition\(^3\),\(^6\)

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Taselisib, a Selective Inhibitor of PI3Kα and Mutant Variants, Was More Active in PIK3CA-Mutant Breast Cancer

In this Phase Ib study PMT4979g, heavily pretreated patients (>4L) with either wild-type or PIK3CA-mutant BC responded to single-agent taselisib.
Phase II trial of Everolimus and Carboplatin in TNBC (Sing et al. BCRT 2014)

- Majority of patients had prior chemo, including carboplatin
- 1 CR, 6 PR, 7 SD
- Clinical Benefit 36% (21-57%)

Akt upregulation is a mechanism of resistance to mTOR inhibition.

Preclinical evidence supporting a dual mTOR/Akt inhibition for basal like BC in patient derived xenograft models.

E.g. Ridaforolimus + MK2206 Combination
MEK Inhibitor Trametinib and Akt Inhibitor GSK2141795 in Treating Patients With Metastatic Triple-Negative Breast Cancer

PART 1: Patients receive trametinib PO QD on days 1-28. Patients who experience disease progression continue to Part 2.

PART 2: Patients receive trametinib as in Part 1 and also receive Akt inhibitor GSK2141795 PO QD on days 1-28.
HER3 Phosphorylation in TNBC cells in Response to Cetuximab plus Akt or PI3K inhibition (Tao et al. Sci Signal 2015)
Metastatic Triple Negative Breast Cancer Spectrum

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Dynamics of mTNBC

Summary
### Gamma-Secretase Inhibitor (PF-03084014) Clinical Trials

<table>
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<tr>
<th>Title</th>
<th>Phase</th>
<th>Status</th>
<th>ID Number</th>
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<tr>
<td>A Phase 1 Trial of PF-03084014 in patients with advanced solid tumor malignancy and T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma</td>
<td>1</td>
<td>Closed</td>
<td>NCT00878189 A8641014</td>
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<tr>
<td>Phase 1b study of docetaxel + PF-03084014 in metastatic or locally recurrent/advanced triple negative breast cancer</td>
<td>1b</td>
<td>Open for recruitment</td>
<td>NCT01876251 A8641016</td>
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Phase I Trial Results with the Gamma-Secretase Inhibitor PF-03084014 (Messersmith et al. CCR 2014)
PF-03084014 + Docetaxel Leads to Enhanced Effect in Triple Negative Breast Cancer Models in Part via CSC Inhibition

HCC1599 treated tumors

HCC1599 cell line xenograft

CXCR1 blockade selectively targets human breast cancer stem cells in vitro and in xenografts.

A phase 1b study of the CXCR1/2 inhibitor reparixin in combination with weekly paclitaxel in metastatic HER2 negative breast cancer – First Analysis

Anne F. Schott, MD1, Max S. Wicha, MD1, Raymond P. Perez, MD2, Giraldo Kato, MD2, Tiffany Avery, MD2, Massimo Cristofanilli, MD4, James M. Reuben, PhD MBA5, Katherine Alpaugh, PhD5, Susan Mc Canna, BSc5, Pier Adelchi Ruffini, MD6, Lori J. Goldstein, MD6

1Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI, USA 48109; 2University of Kansas Medical Research Center, Fairway, KS, USA 66205; 3Pitman Oncology Hematology, Scottsdale, AZ, USA 85258; 4Thomas Jefferson University, Philadelphia, PA, USA 19107; 5MD Anderson Cancer Center, Houston, TX, USA; 6Fox Chase Cancer Center, Philadelphia, PA, USA 19111; 7Dompé spa, Milano, Italy, 20122;

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
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<tr>
<td>ORR%</td>
<td>33</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0</td>
<td>5 (+1 uPR)</td>
</tr>
<tr>
<td>SD≥16 weeks</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>median TTP (days)</td>
<td>45</td>
<td>67</td>
<td>128</td>
</tr>
<tr>
<td>6 month PFS%</td>
<td>33</td>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>
Breast Cancer
TN, no more than 3 previous QT treatment lines.

Docetaxel IV C3s
LDE225 Oral daily
Design 3+3

ND1 (3-6 patients)
Docetaxel 75 mg/m²
LDE225 400 mg

ND2 (3-6 patients)
Docetaxel 75 mg/m²
LDE225 400 mg
LDE225 400 mg

ND3 (3-6 patients)
Docetaxel 75 mg/m²
LDE225 400 mg
LDE225 400 mg

TLD window 42 days (2 cycles)
Treatment till progression, unacceptable toxicity or ICF withdraw

Phase Ib Dose Escalation, Open Label, Multicenter Study Evaluating the Hedgehog Inhibitor LDE225 in Combination With Docetaxel in Triple Negative (TN) Advanced Breast Cancer (ABC) Patients.

GEICAM/2012-12 “EDALINE”

Martín M, et al. ESMO 2014
Metastatic Triple Negative Breast Cancer Spectrum

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Targeting Stemness

**Targeting The Androgen Receptor**

Immune Checkpoint Modulators

Dynamics of mTNBC

Summary
Phase II Trial of Bicalutamide in Patients with Androgen Receptor–Positive, Estrogen Receptor–Negative Metastatic Breast Cancer

- Consented for AR testing ($n=452$)
- Screened for AR expression ($n=424$)
- AR(+) ($n=51$)
- On study ($n=28$)

*N = 26 (PFS events = 23)
Median PFS: 12 wks, 95% CI: (11–22)*

Gucalp et al. CCR 2013
PIK3CA Mutations in AR-Positive TNBC Confers Sensitivity to Combined PI3K and AR Inhibitors (Lehmann et al. BCR 2014)

Table 1. PIK3CA mutations in AR expressing TNBC

<table>
<thead>
<tr>
<th>TNBC</th>
<th>N= 25</th>
</tr>
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<tbody>
<tr>
<td>AR+</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>AR-</td>
<td>1 (4%)</td>
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</table>

Figure 1 Identification of PIK3CA mutations in androgen receptor (AR) + triple-negative breast cancer (TNBC) cell lines and tumors.

Pan-PI3kinh Dual PI3K/mTOR
Metastatic Triple Negative Breast Cancer Spectrum

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Summary
KEYNOTE-012: Triple-Negative Breast Cancer Cohort

- Recurrent or metastatic ER- /PR- /HER2- breast cancer
- ECOG PS 0-1
- PD-L1+ tumor
- No systemic steroid therapy
- No autoimmune disease (active or history of)
- No active brain metastases

Pembro 10 mg/kg Q2W

- Complete Response: Discontinuation Permitted
- Partial Response or Stable Disease: Treat for 24 months or until progression or intolerable toxicity
- Confirmed Progressive Disease: Discontinue

- PD-L1 positivity: 58% of all patients screened had PD-L1-positive tumors
- Treatment: 10 mg/kg IV Q2W
- Response assessment: Performed every 8 weeks per RECIST v1.1

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aPD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells were eligible for enrollment.

bIf clinically stable, patients are permitted to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. If progressive disease is confirmed, pembrolizumab is discontinued. An exception may be granted for patients with clinical stability or improvement after consultation with the sponsor.
Maximum Percentage Change From Baseline in Target Lesions (RECIST v1.1, Central Review)\textsuperscript{a,b}

\textsuperscript{a}5 patients were excluded from the analysis because they did not have measurable disease at baseline per RECIST v1.1 by central review.

\textsuperscript{b}Only patients with evaluable tumor measurements by central review at baseline and \textgeq 1 post-baseline assessment are included.

Analysis cut-off date: November 10, 2014.

This presentation is the intellectual property of the presenter, Rita Nanda. Contact rnanda@medicine.bsd.uchicago.edu for permission to reprint and/or distribute.
Time to and Durability of Response  
(RECIST v1.1, Central Review)

- Median follow-up duration: 9.9 months (range, 0.4-15.1)
- Median time to response: 18 weeks (range, 7-32)
- Median duration of response*: not reached (range, 15 to 40+ weeks)

*Kaplan-Meier estimate.  
Analysis cut-off date: November 10, 2014.

This presentation is the intellectual property of the presenter, Rita Nanda. Contact rnanda@medicine.bsd.uchicago.edu for permission to reprint and/or distribute.
Inhibition of PD-L1 by MPDL3280A leads to clinical responses in patients with metastatic triple-negative breast cancer

Figure 3. Tumor Burden Over Time in Patients With TNBC
Metastatic Triple Negative Breast Cancer Spectrum

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Summary
Newly diagnosed or 1st Line MBC Patients

N=1,300

‘Actionable’ Mutation(s) (n=300)

‘Non-Actionable’ Mutations (n=700)

Downstream Targeted Clinical Trials as first or second line

Standard of Care

Clinical Outliers (Exceptional Responders and Rapid Progressors) to be subjected to WES

Timeline
- Entry in DCT
- Cycle 1
- Cycle 2
- Cycle 3
- Cycle X
- Continue until disease progression
- Disease Progression

Metastatic Lesion
- Biopsy – TGS (real time) and RNAseq (on batches)

Primary Tumour
- Archival – TGS (real time) and RNAseq (on batches)

Blood
- TGS (real time)

Plasma/Serum
- Collection every 6 months – up to 10 years

Clinical Outcome Information
- Collection every 6 months – up to 10 years
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Summary
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1. The majority of trials select patients based on traditional triple negative status.

2. The majority of trials included biomarker endpoints or enrichment of subsets.

3. Androgen receptor is the main biomarker used for subtyping TNBC for anti-androgen trials.

4. Increasing preclinical evidence and the limited activity of single agent data with signal transduction inhibitor point to drug combinations and biologically-driven patients selection as an attractive strategy.

5. Targeting stem-like/EMT ongoing. Role of Mesenchymal subtype tbd.

6. Immune checkpoint modulators are promising. Role of Basal/Immune subtype and PD1/PD-L1 tbd.

7. Tackling the dynamics of TNBC biology in sequential patient specimens is necessary to better understand this aggressive disease. Aurora as a big effort.