Hormono-résistance : nouvelles données biologiques et possibles applications circulantes

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IRON/Inserm U1245

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Disclosure

- Research funding
  - Novartis

- Honoraria
  - Novartis
  - Astra Zeneca
Plan

- Hormone therapy in breast cancer
- Endocrine therapies resistance and associated biomarkers
  - PI3K pathway
  - ESR1 alterations
  - HER2 alterations
  - Cdk4/cdk6 targeting
  - Others pathways
- Take home messages
Early and Metastatic (M+) breast cancer incidence

- Overall breast cancer incidence in France
  - 50 000 cases/year

- Metastatic cases
  - 10% at diagnosis
  - +/- 20% following initially localized stage

  → 15 000 M+ cases/year
  → 10 000 M+ HR+/Her2- cases/year
Hormone receptor positive = luminal breast cancer

HR+ = 70% of breast cancers

CoPath 2014  
Caan Can Ep Bio Prev 2014
Treating breast cancer with endocrine therapies

Adjuvant phase

Diagnosis

5 years
- Aromatase inhibitor
- Tamoxifen

Surgery
Chemotherapy
Radiation therapy
Endocrine therapy
Adjuvant endocrine therapy

25% additional benefit of endocrine therapy

![Graph showing recurrence rates and log-rank analyses for node-negative and node-positive ER-positive women, with chemotherapy and chemotherapy plus tamoxifen comparisons.]

EBCTCG 2011
Treating breast cancer with endocrine therapies

**Adjuvant phase**

- Diagnosis
  - Surgery
  - Chemotherapy
  - Radiation therapy
  - Endocrine therapy

**Metastatic phase**

- Relapse
  - Aromatase inhibitor
  - Tamoxifen
  - Faslodex
1st line M+ (yet...): aromatase-inhibitor

- Letrozole (n = 453), median TTP 9.4 months
- Tamoxifen (n = 454), median TTP 6.0 months

Hazard ratio 0.72, P < .0001

Mouridsen JCO 2001
Metastatic endocrine therapy

Letrozole (n = 453), median TTP 9.4 months
Tamoxifen (n = 454), median TTP 6.0 months
Hazard ratio 0.72, P < .0001

Mouridsen JCO 2001
Endocrine therapies: mechanisms of resistance

Ma, Nat Rev 2015
PI3K pathway

Ma, Nat Rev 2015

Figure 6 | Growth factor receptor signalling, PI3K, MAPK, ER and the p53–RB pathway in ER+ breast cancer.
Figure 6 | Growth factor receptor signalling, PI3K, MAPK, ER and the p53–RB pathway in ER+ breast cancer.
PI3K pathway mutations during cancer evolution

Hortobagyi JCO 2015
Targeting mTOR: everolimus

Bolero 2 Trial
- 724 HR + BC
- Resistance to endocrine therapies

PI3K mutation → better sensitivity?

B Central Assessment

Hazard ratio, 0.36 (95% CI, 0.27–0.47)
P<0.001 by log-rank test

Everolimus plus exemestane
(median PFS, 10.6 mo)

Placebo plus exemestane
(median PFS, 4.1 mo)

No. at Risk
Everolimus 485 385 281 201 132 102 67 43 28 18 9 3 2 0
Placebo 239 168 94 55 33 20 11 11 6 3 3 1 0 0

Figure 1. Kaplan–Meier Plot of Progression-free Survival.

Baselga NEJM 2012
Predictive value of circulating *PIK3CA* mutations

Moynahan BJC 2017
Predictive value of circulating *PIK3CA* mutations

Same outcome whatever the *PIK3CA* status and the treatment arm

No predictive value
**PI3K Inhibitors**

Pan-class I PI3K
- Buparlisib (BKM120)
- Pictilisib (GDC-0941)
- Copanlisib (BAY 80-6946)

**p110α**
- Alpelisib (BYL719)

**p110β**
- GSK2636771
- SAR260301

**p110δ**
- Idelalisib (CAL-101)

**p110α, -γ, -δ**
- Taselisib (GDC-0932)

**AKT**
- MK-2206
- AZD5363
- Ipatasertib (GDC-0068)
- Afuresertib (GSK2110183)
- GSK2141795

**mTORC1**
- Rapamycin (sirolimus)
- Temsirolimus
- Everolimus
- Ridarilimus

**mTORC1/2**
- AZD2014
- CC-223
- MLN0128

**PI3KmTOR**
- BEZ235
- GDC-0980
- SAR245409 (XL765)
Overall buparlisib is effective but too toxic
Overall buparlisib is effective but too toxic

PI3K activation = better outcome?
PI3K « activated » on tumor tissue...

PI3K activation: any PIK3CA mutation or no PTEN expression

Baselga, Lancet Oncol 2017
Circulating *PIK3CA* mutation correlates with outcome

Baselga, Lancet Oncol 2017
Circulating PIK3CA mutation correlates with outcome

Circulating PIK3CA works as a liquid biopsy

Baseline, Lancet Oncol 2017
Assessing circulating PIK3CA mutations

- Recurrent mutations (3 mutations = 80% of all mutations)
- Frequent (50%)
- Not correlated with prognosis
- Correlated with buparlisib (targeting PIK3) response but not with everolimus (targeting mTORC)
- Ongoing trials based on ctDNA detection and PIK3CA and selective PI3K inhibitors
**ESR1 mutations: a late event**

Acquired, activating mutation under AI

Hortobagyi JCO 2015
ESR1 mutations: recurrent mutations

74% of the mutations
Treating breast cancer with endocrine therapies

**Adjuvant phase**
- Diagnosis
- Surgery +/- CT +/- RT
- AI endocrine therapy

**Metastatic phase**
- Relapse
- Progression

- ESR1 mutation
- ESR1 wild-type

Allouchery, ESMO 2017

- 0%
- 5.7%
- 33%
**ESR1 circulating mutation: prognostic value**

**Multivariate analysis**

HR = 1.9 [1.3-3], p=0.002

**Multivariate analysis**

HR = 1.6 [1.3-2], p<0.001

Clatot Oncotarget 2016; Chandarlapaty Jama Oncol 2016
ESR1 mutations: poor outcome under aromatase inhibitors

Fribbens JCO 2016

Centre Henri-Becquerel
**ESR1 mutations: same outcome under fulvestrant + palbociclib**

**ESR1 mutation**

- Fulvestrant + Palbociclib
  - Median PFS, 9.4 months (95% CI, 5.3 to 11.1)
- Fulvestrant + Placebo
  - Median PFS, 3.6 months (95% CI, 2.0 to 5.5)

HR, 0.43 (95% CI, 0.25 to 0.74); P = .002

**ESR1 wild type**

- Fulvestrant + Palbociclib
  - Median PFS, 9.5 months (95% CI, 9.2 to not estimable)
- Fulvestrant + Placebo
  - Median PFS, 5.4 months (95% CI, 3.5 to 7.4)

HR, 0.49 (95% CI, 0.35 to 0.70); P < .001

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Fribbens JCO 2016
Different mutation = different outcome?

Patient with *ESR1* D538G mutation benefit from EVE addition

Chandarlapaty Jama Oncol 2016
Different mutation = different outcome?

Patient with *ESR1* D538G mutation benefit from EVE addition

Patient with *ESR1* Y537S mutation do not benefit from EVE

Chandarlapaty Jama Oncol 2016
Estrogen activation of ESR1 mutants

B

ERE-luciferase

Vehicle
E2

RLU

pcDNA  WT  E360Q  V422del  S432L  S463P  L469V  V534E  L536H  L536P  L536R  Y537C  Y537D  Y537N  Y537S  D538G

Toy Cancer Discov 2017
Estrogen activation of *ESR1* mutants

**B**

ERE-luciferase

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RLU

Centre Henri-Becquerel

Toy Cancer Discov 2017
Estrogen activation of $ESR1$ mutants

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Different mutation = different outcome?

Chandarlapaty Jama Oncol 2016; Toy Cancer Discov 2017
ESR1 mutations: 6 months lead time detection in ctDNA

75% of the cases: detection 3-6 months before clinical progression

Clatot Oncotarget 2016
ESR1 mutations post progression

- Increased amount (n=6) : 100% progressing disease
- Decreased amount (n=26) : 60% stability/PR but 40% PD

Clatot, Oncotarget 2016
Assessing circulating *ESR1* mutations

- Recurrent mutations
- Frequent (30%) in the metastatic setting after AI exposure
- Correlated with prognosis
- Correlated with poor response on AI
- Ongoing trials based on ctDNA detection and early treatment change (PADA-1)
- Differential outcome when considering peculiar mutations
- Next generation endocrine therapies on development
Copy number alterations (CNA) of ESR1 or CYP19A1

- **Comparison tumor/normal tissues**
  - No CNA in primary both for ESR1 or CYP19A1
  - CYP19A1 amplification after treatment
    - 6/37 (16%) after AI exposure
    - 1/30 (3%) after tam exposure
  - ESR1 amplification after treatment
    - 9/37 (24%) after AI exposure
    - 4/30 (13%) after tam exposure
  - Confirmed on validations cohorts (n=19)
    - CYP19A1: 32% amp under AI vs 5% under Tam
    - ESR1: 21% under AI vs 0% under tam

- AI exposure is related to higher acquired CNA of both CYP19A1 and ESR1 than Tam exposure
Impact on PFS of CYP19A1 amp under AI

TTFR

HR = 0.43 (0.22–0.82)

P = 0.0112

CYP19A1<sup>amp</sup>

CYP19A1<sup>WT</sup>

Percent relapse-free

Time (months)
**HER2 mutations**

- **Activating mutations**
- **Rare**
  - 3% in 12,905 BC cases
  - Detectable in ctDNA in 84% of the cases
  - L755S, V777L and D769H/Y = 53% of the mutations
- **Neratinib effect**
  - Heavily preteated patients
  - 16 weeks PFS (n=16)

Ma CCR 2017, Petrelli BCRT 2017
Next standard of care: cdk4/6

- PALOMA 2: Létrozole +/- palbociclib, Phase 3, n=666
- MONALEESA 2: Letrozole +/- ribociclib, Phase 3, n=668
- MONARCH 3: Letrozole or anastrozole +/- abemaciclib, Phase 3, n=493
Mutations in cell cycle pathway
Cell cycle regulation

Garrido Castro Cur Breast Rep 2017
Theoretical biomarkers of cdk4/6 inhibition response

Cyclin D1 amplification → higher impact of cdk4/6 inhibition

Garrido Castro Cur Breast Rep 2017
Theoretical biomarkers of cdk4/6 inhibition response

Cyclin D1 amplification → higher impact of cdk4/6 inhibition

High p16 expression → no impact of cdk4/6 inhibition

Garrido Castro Cur Breast Rep 2017
Theoretical biomarkers of cdk4/6 inhibition response

- Cyclin D1 amplification → higher impact of cdk4/6 inhibition
- High p16 expression → no impact of cdk4/6 inhibition
- Rb loss → no impact of cdk4/6 inhibition

Garrido Castro Cur Breast Rep 2017
Theoretical biomarkers of cdk4/6 inhibition response

- Cyclin D1 amplification → higher impact of cdk4/6 inhibition
- High p16 expression → no impact of cdk4/6 inhibition
- Rb loss → no impact of cdk4/6 inhibition
- No proliferation → no impact of cdk4/6 inhibition
Real life (phase 2: n=37 and 165, phase 3: n=666)

- Cyclin D1 amplification
  - No impact
- p16 expression
  - No impact
- Rb loss
  - No impact
- Proliferation
  - No impact

DeMichele CCR 2015; Finn Ann Oncol 2016
FGFR amplification

- Frequent among luminal B tumors
- Correlated with PFS
- Possible efficacy of dovitinib (FGFR1,2,3 inhibitor)?
  - Expression assessed by qPCR

Phase II ended 2 years ago: Fulvestrant +/- Dovitinib, n=97, resistant to endocrine therapy.

Andre CCR 2013
Musolino et al. BCR 2017

![Graph showing PFS percentages over time for patients with FGF Pathway Amplification.](image)

<table>
<thead>
<tr>
<th>Patients With FGF Pathway Amplification</th>
<th>Median PFS (95% CI), months</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dovitinib + fulvestrant (n = 15)</td>
<td>10.5 (3.5-16.5)</td>
<td>0.64 (0.22-1.86)</td>
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<tr>
<td>Placebo + fulvestrant (n = 16)</td>
<td>5.5 (3.5-16.4)</td>
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**Number of patients still at risk**

- Dovitinib + fulvestrant: 15, 13, 9, 9, 6, 5, 5, 5, 4, 4, 4, 3, 3, 2, 2, 2, 1, 1, 1, 1, 1, 1
- Placebo + fulvestrant: 16, 14, 11, 11, 8, 7, 5, 5, 3, 3, 2, 2, 1, 1, 1, 1, 0, 0, 0, 0
Pan-HER blockade: MINT study

- Phase II randomized study (n=359)
- AZD8931: EGFR+HER2+HER3 inhibitor
- Obj I: PFS

Endocrine naive HR+ MBC

- Anastrozole + placebo
- Anastrozole + AZD8931 20mg
- Anastrozole + AZD8931 40mg
MINT study

No benefit of AZD8931
Increased toxicity

![Graph showing proportion of patients progression-free over time from randomization (months)].

Number of patients at risk:
- AZD8931 40 mg: 120 113 72 42 40 28 24 17 16 7 5 4 2 0
- AZD8931 20 mg: 118 110 69 39 37 26 19 10 10 3 1 1 0 0
- Placebo: 121 114 76 53 51 37 29 20 17 7 5 4 0 0

Johnston BCRT 2016
Take home messages

- BC cancer and endocrine therapies resistance
  - Major problem of metastatic BC cancer
- CtDNA potential to date: in the metastatic setting
  - Screening patients before PIK3 inhibition
  - Patient monitoring for early AI failure
  - Screening patients with \( ESR1 \) mutants for new endocrine therapies
- Cdk4/6 inhibitor
  - « First line » intuitive biomarkers failed
  - Signatures ongoing (Rbsig)
Treating breast cancer with endocrine therapies

Adjuvant phase

Metastatic phase

Diagnosis

Relapse

Progression

Surgery +/- CT +/- RT

AI endocrine therapy

ESR1 mutation

ESR1 wild-type

5.7%

0%

33%