Natural history and clinical characteristics of ERBB2 mutant hormone receptor-positive breast cancers: Results from the AACR Project GENIE Registry

Disclosures

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Background

• Activating ERBB2 mutations have been identified in around 1-2% of breast cancers\(^1,2\)
• They have been reported to be oncogenic and resistant to some anti-HER2 therapies\(^1\) put potentially sensitive to the irreversible TKI neratinib
• Due to the rarity of ERBB2 mutations, evaluation of the natural history of ERBB2 mutant breast cancer requires a large, multi-center series
• The AACR-GENIE consortium database includes information from > 60,000 de-identified genomic records from different types of cancer including nearly 8,700 patients with breast cancer

Methodology

• Multi-center, retrospective, case-controlled study

• We interrogated the AACR-GENIE database to identify HR+/HER2- MBC cases with ERBB2 mutation until end of December 2016

• The objective was to describe the clinicopathological features, response to standard therapies and outcome in the HR+HER2- MBC population harboring an ERBB2 mutation
Methodology

- Eligibility:
  - Patients metastatic invasive breast carcinoma
  - HR-positive, HER2-negative in at least one biopsy sample
  - Known ERBB2 mutation:

- Matching control cases (2:1) were identified from the database with known ERBB2-WT and they were matched to the ERBB2mut cases on race, gender, birth year, and age at sequencing at this order
Study Objectives

• Primary Endpoint: Overall Survival from date of metastatic relapse

• Secondary Endpoints:
  • Differences clinical and pathological characteristics
  • OS from diagnostic of primary disease and from date of second line of treatment metastatic setting
  • For each line of therapy:
    • Duration of therapy
    • Time to next therapy
    • Time to progression
    • Objective Response Rate
Statistical methods

• For single time-point data, the paired t-test or Wilcoxon signed-rank test or McNemar’s Chi-square

• Between-group comparisons assessed using either analysis of variance (ANOVA) with adjusted least squares means or Fisher’s exact test

• Survival outcome and time-to-event data evaluated by constructing Kaplan-Meier curves and compared between ERBB2-mut and ERBB2-wt patient groups by log-rank tests

• The Cox proportional hazards model for adjusted tests of significance and estimates of hazard ratios
Results

68 ERBB2mut

46 eligible

45 data

26 (58%) deceased
19 (42%) alive

22 non-eligible
4 Non-metastatic
9 HR-negative
10 HER2-amplification
3 Disallowed ERBB2 mutation

155 ERBB2wt

109 eligible

90 data

46 (51%) deceased
44 (49%) alive

40 non-eligible
8 Non-metastatic
23 HR-negative
17 HER2-amplification
Sample Characteristics

12 patients had more than one sample sequenced (6 ERBB2mut, 6 ERBB2wt)

Sequencing in ERBB2mut cases was more frequently conducted on recurrent/metastatic samples than in ERBB2wt (70% vs 51%)
Clinical characteristics at diagnoses between ERBB2mut vs ERBB2wt

No significant differences in major clinicopathological features between ERBB2mut vs ERBB2wt
Clinical characteristics at relapse between ERBB2mut vs ERBB2wt

Overall no differences frequency visceral metastases (64% vs 53%, p=0.37 ERBB2mut vs ERBB2wt, respectively)

ERBB2mut vs ERBB2wt:
- Higher frequency liver metastases (53% vs 38%, p=0.006)
- Bone metastases (76% vs 64%, p=0.019)
- Lower frequency lung metastases (11% vs 23%, p=0.028)
OS analyses

OS from metastatic relapse

Median OS: 55.1mo ERBB2wt

Median OS: 50.6mo ERBB2mut

p = 0.3856

OS from date of primary diagnoses

Median OS: 134mo ERBB2wt

Median OS: 128mo ERBB2mut

p = 0.7828
ERBB2 mutation and benefit from treatment

Median of lines treatment in the metastatic setting was 5.0 for both ERBB2mut and ERBB2wt (P=0.67)

No differences in terms of ORR ascertained by clinical notes between ERBB2mut vs ERBB2wt
ERBB2 mutation and benefit from treatment

• No differences in TTP between ERBB2-mut vs ERBB2wt in first-line endocrine therapy (p= 0.4969)

• No differences in TTP between ERBB2-mut vs ERBB2wt in first-line treatment (p= 0.8597)

• Similarly in second-line (p = 0.9226)
Co-Mutations (46 common genes)

No statistically significant differences in most frequent molecular alterations PIK3CA (48% vs. 43%), TP53 (18% vs. 30%) and CDH1 mutations (28% vs. 10%)
CDH1 mutation enriched in ERBB2mut (28%) vs ERBB2wt (10%) (p=0.07)
ERBB2 mutant population

<table>
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<th>ERBB2_variant</th>
<th>N=45</th>
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<tr>
<td>L755S</td>
<td>38% (17)</td>
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<tr>
<td>V777L</td>
<td>25% (11)</td>
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<tr>
<td>D769Y/H</td>
<td>15% (7)</td>
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<tr>
<td>S310F/Y</td>
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<tr>
<td>L869R</td>
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<tr>
<td>P780_Y781insGSP</td>
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</tbody>
</table>

6 ERBB2mut cases were sequenced more than once
3 showed differences:
- Two gain ERBB2 mutation at distant metastases
- One lost ERBB2 mutation in later metastatic setting (untreated with anti-HER2 therapy)

ERBB2 mutant population

- A total of 19 patients with ERBB2mut were treated with anti-HER2 therapy
- Of those, 14 received neratinib, 3 received lapatinib, and 2 received an undisclosed HER2 TKI
- Neratinib has shown efficacy in ERBB2-mutated tumors including breast cancer¹

No differences in OS between ERBB2mut and ERBB2wt when excluding neratinib-treated patients

Effect neratinib treatment in ERBB2mut patients

- Median duration on neratinib treatment was 148 days and median line treatment administration neratinib in the metastatic setting was 6.0
- Neratinib ORR (CR+PR) = 5.9% with CBR (CR+PR+SD>24 weeks) = 53%
- There seems to be a trend towards improved OS in neratinib treated patients vs no treated although not significant
Conclusions (I)

• Limitations of this study:
  • Retrospective series with low number of cases
  • Patients with already distant metastases; no information about negative impact ERBB2mut in DDFS or RFS as other publications¹-³
  • ERBB2 mutation status categorically classified as present or absent and type without information allele frequency and multiple platforms

• Strengths:
  • Largest series so far to describe HR-positive, ERBB2-mutant population in BC
  • Data had been compared to matched cases
  • CLIA-/ISO-certified genomic data

2. Wang et al, Cancer Science 2017; 108:671
Conclusions (II)

• No significant differences in clinicopathological features between ERBB2mut and ERBB2wt tumors except higher rates of bone and liver metastases in ERBB2mut cases and lung metastases in ERBB2wt.

• No significant differences observed in OS from diagnostic of distant metastasis between ERBB2mut and ERBB2wt.

• ORR and TTP first and second line of treatment did not differ between ERBB2mut vs ERBB2wt irrespective of the type of therapy.

• Although some numerical variations, no significant differences in mutation rates in PIK3CA, TP53, CDH1 or CCND1 Amplification between cases and controls although CDH1 mutation enriched in ERBB2mut (28%) vs ERBB2wt (10%) (p=0.07) and no ESR1mut observed in ERBB2mut.
Conclusions (III)

- Frequency type of ERBB2-mutation according to previously published
- The presence of ERBB2 mutation might evolve over time
- Subgroup analyses patients treated with neratinib we observed a non-significant trend on OS for neratinib treatment although study not designed to answer this question (SUMMIT Trial, NCT01953926)
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