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PROJECT GENIE
Genomics Evidence Neoplasia Information Exchange

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

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Disclosures

- Honoraria from Novartis, Astra Zeneca, PUMA, Pfizer and Seattle Genetics
- Research grant from Pfizer and Eli Lilly
- Travel expenses from Astra Zeneca, Pfizer and Roche
- My institution has received funding for clinical research from Daichii, Novartis, Roche, Eli Lilly, Pfizer, Merus, MSD, Astra Zeneca

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

1. Bose, R. et al. Cancer Discov. 2013; 3: 224–37
2. Ross, J. S. et al. Cancer 2016; 122: 2654–2662

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:
    - S310F, S310Y, L755S, L755P, D769H, D769Y, D769N, A775_G776insYVMA, G776delinsVC (G776VinsC), V777L, G778_S779insCPG, P780_Y781insGSP (G778_P780dup), V842I, and L869R

- 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

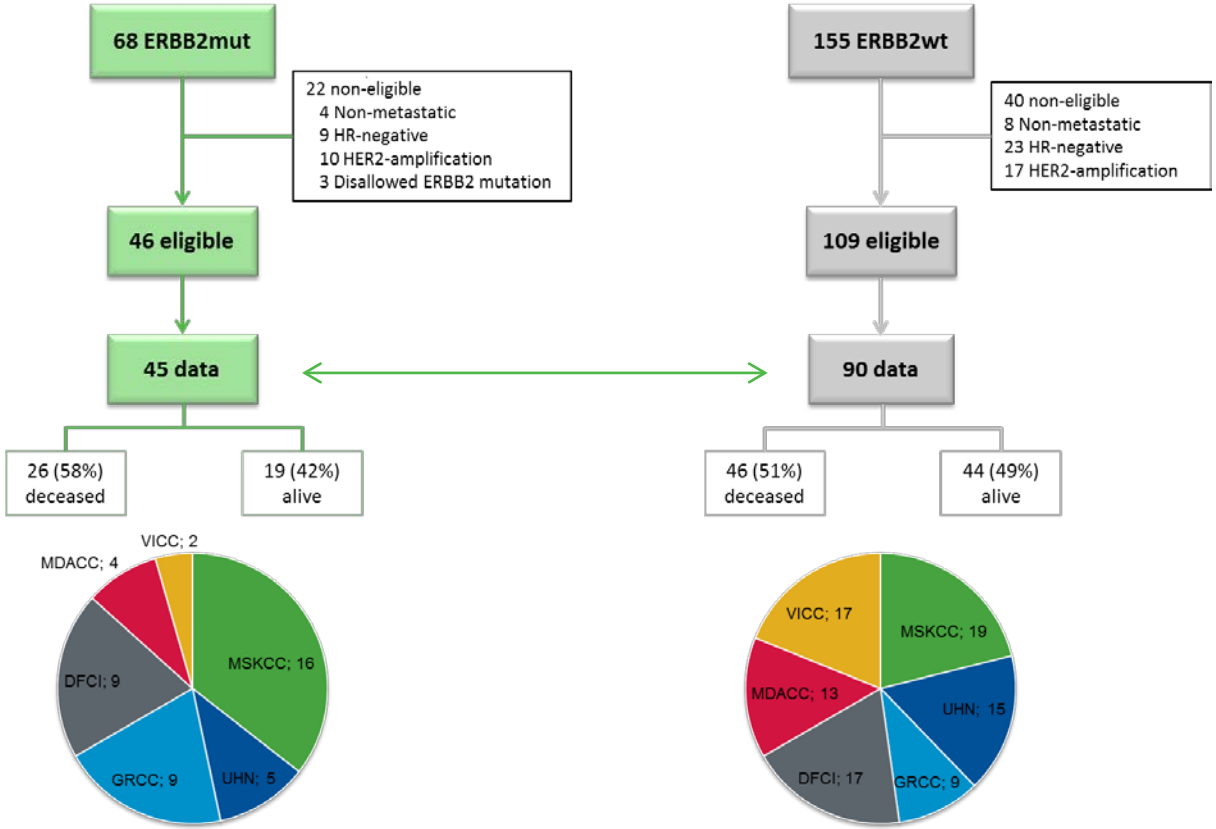
- Primary Endpoint: Overall Survival from date of metastatic relapse

- 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

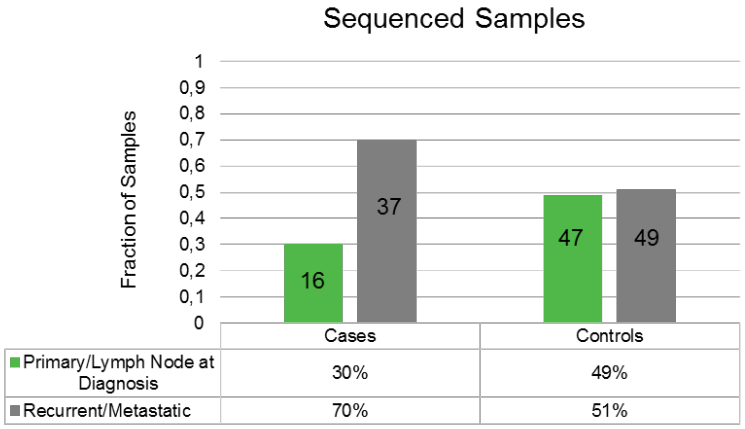
Statistical methods

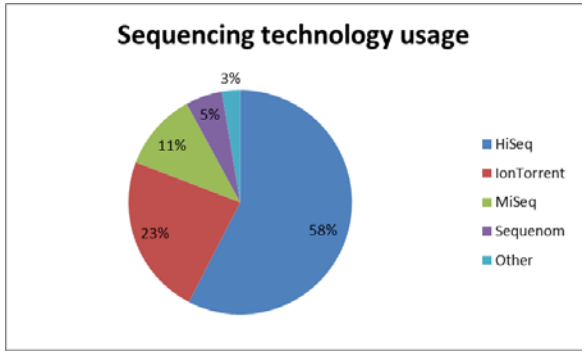
- For single time-point data, the paired t-test or Wilcoxon signed-rank test or McNemar’s Chi-square
- Between-group comparisons assessed using either analysis of variance (ANOVA) with adjusted least squares means or Fisher’s exact test
- Survival outcome and time-to-event data evaluated by constructing 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
22 non-eligible
4 Non-metastatic
9 HR-negative
10 HER2-amplification
3 Disallowed ERBB2 mutation
46 eligible
45 data
26 (58%) deceased
19 (42%) alive
VICC; 2
MDACC; 4
MSKCC; 16
DFCI; 9
GRCC; 9
UHN; 5
155 ERBB2wt
40 non-eligible
8 Non-metastatic
23 HR-negative
17 HER2-amplification
109 eligible
90 data
46 (51%) deceased
44 (49%) alive
VICC; 17
MSKCC; 19
MDACC; 13
UHN; 15
DFCI; 17
GRCC; 9

Sample Characteristics





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

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

Clinical characteristics at diagnoses between ERBB2mut vs ERBB2wt

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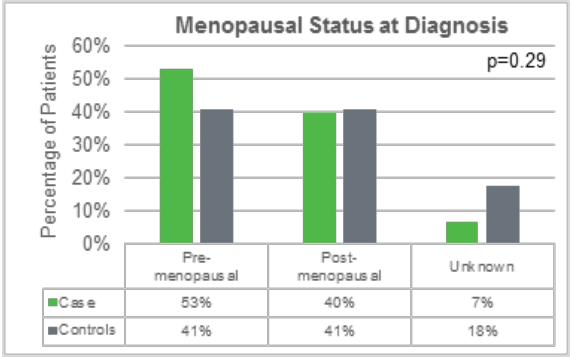

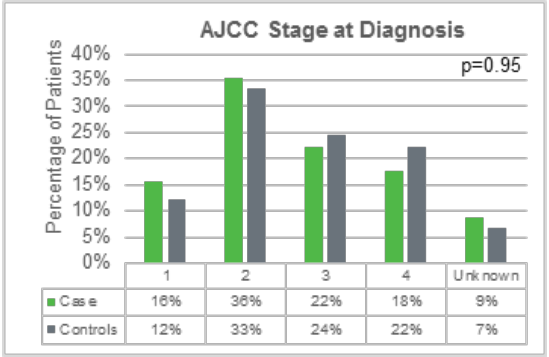

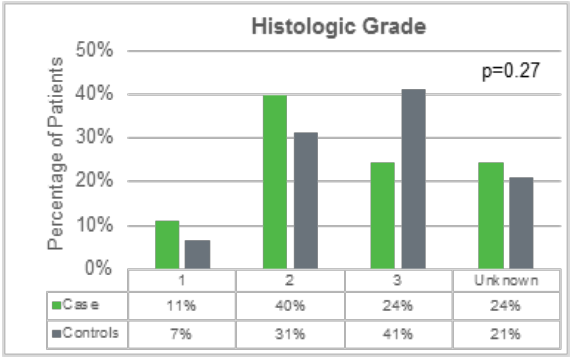

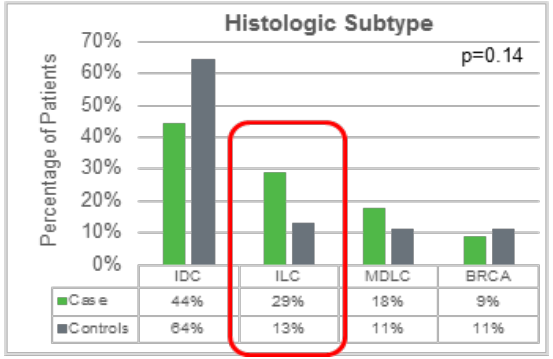

No significant differences in major clinicopathological features between ERBB2mut vs ERBB2wt

Clinical characteristics at relapse between ERBB2mut vs ERBB2wt

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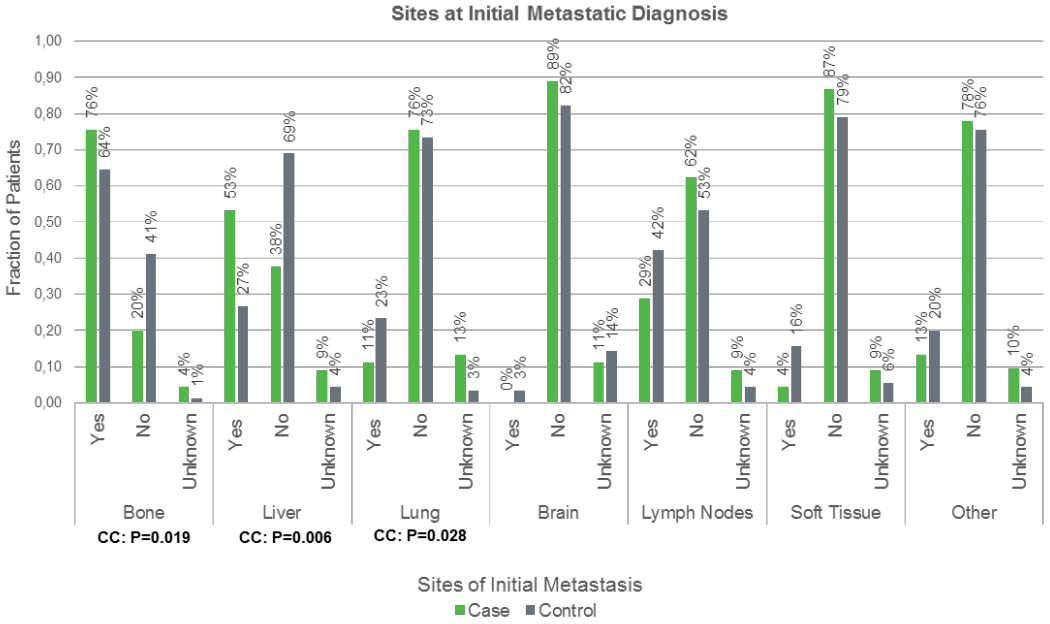
Overall no differences frequency visceral metastases
(64% vs 53%,p=0.37 ERBB2mut vs ERBB2wt, respectively)

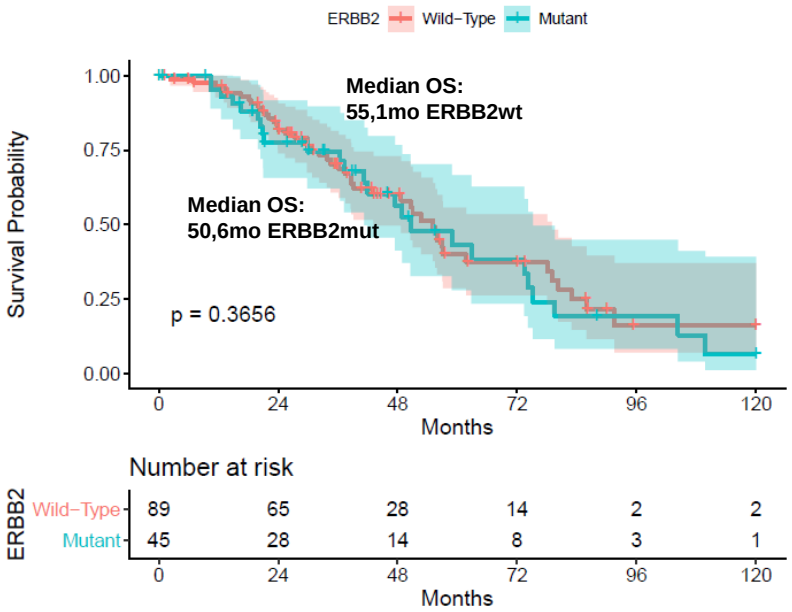


ERBB2mut vs ERBB2wt:

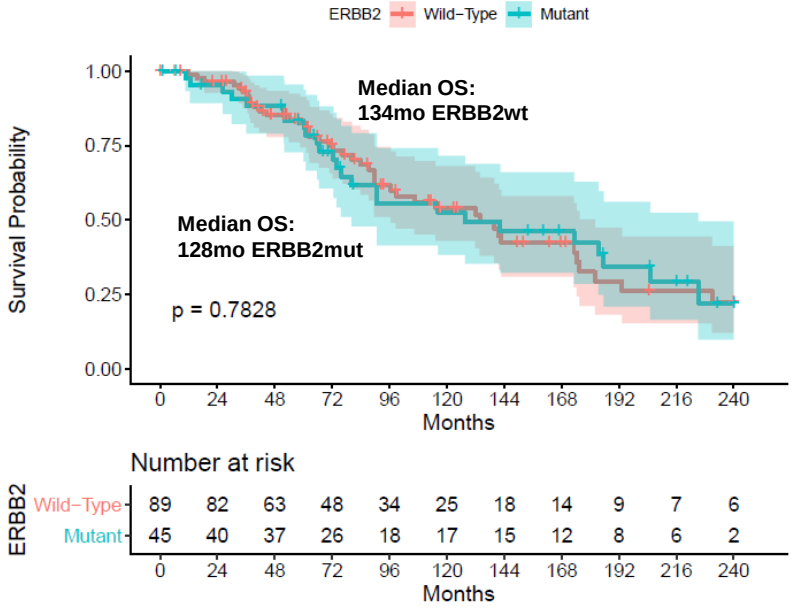
- Higher frequency liver metastases (53% vs 38%, p=0.006)
  bone metastases (76% vs 64%, p=0.019)
- Lower frequency lung metastases (11% vs 23%, p=0.028)

OS analyses

OS from metastatic relapse

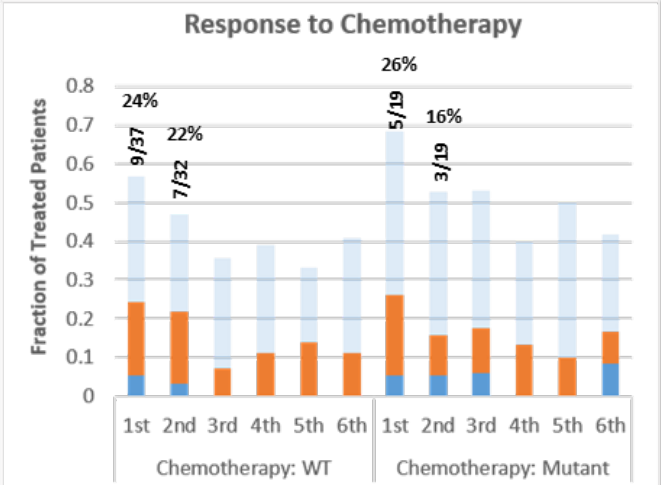


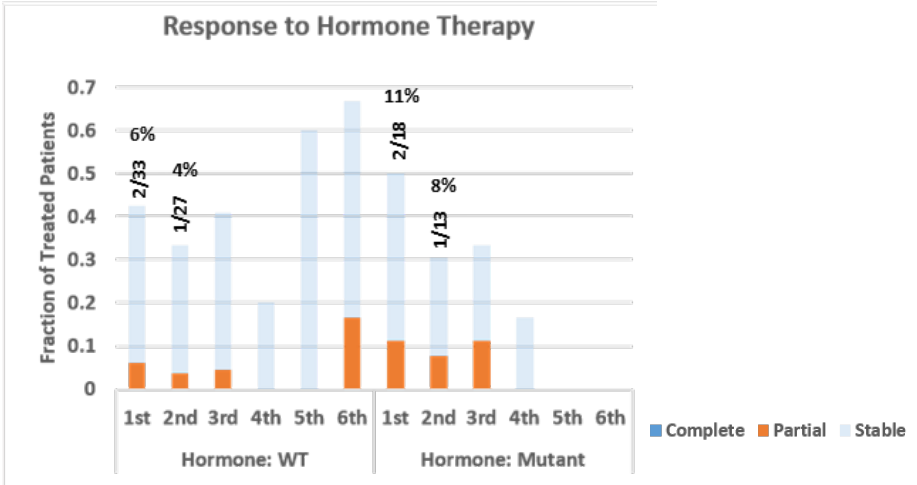
OS from date of primary diagnoses



ERBB2 mutation and benefit from treatment

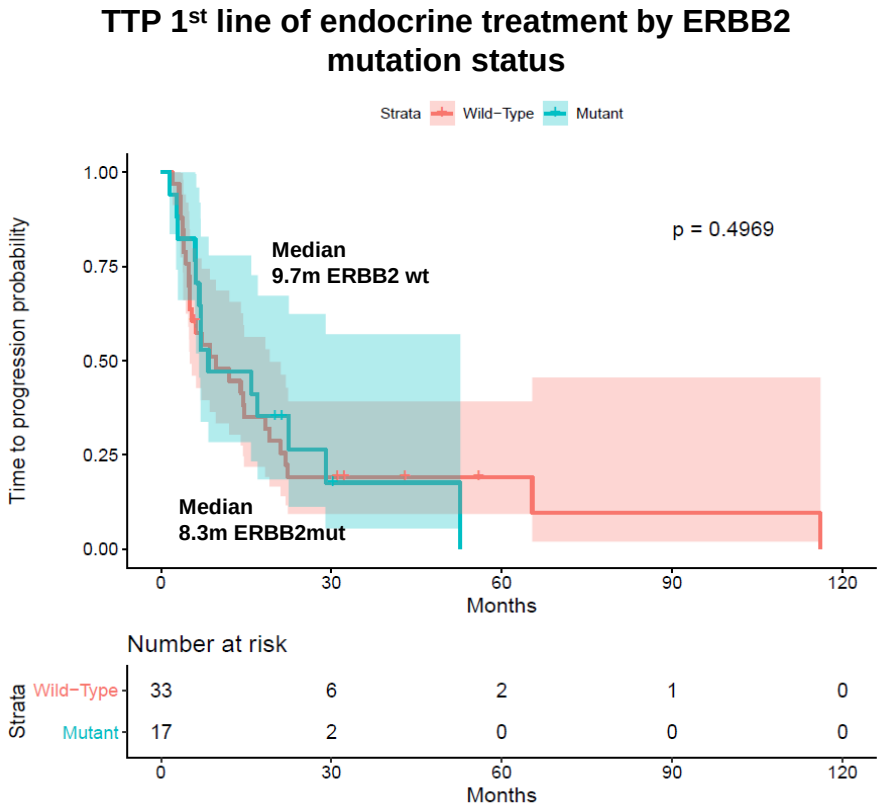
Median of lines treatment in the metastatic setting was 5.0 for both ERBB2mut and ERBB2wt (P=0.67)





No differences in terms of ORR ascertained by clinical notes between ERBB2mut vs ERBB2wt

ERBB2 mutation and benefit from treatment

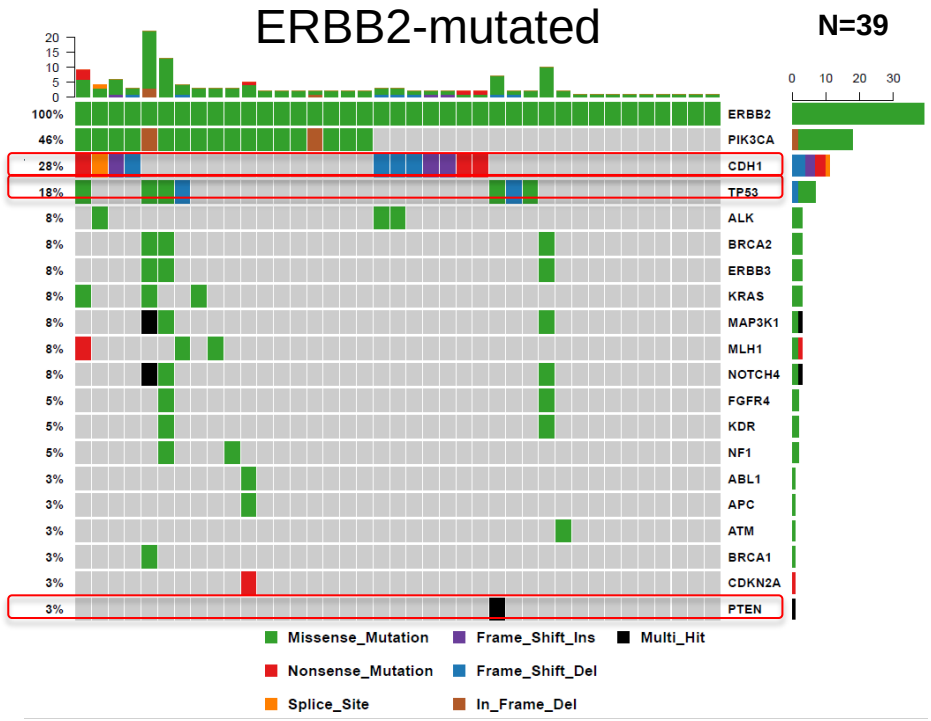


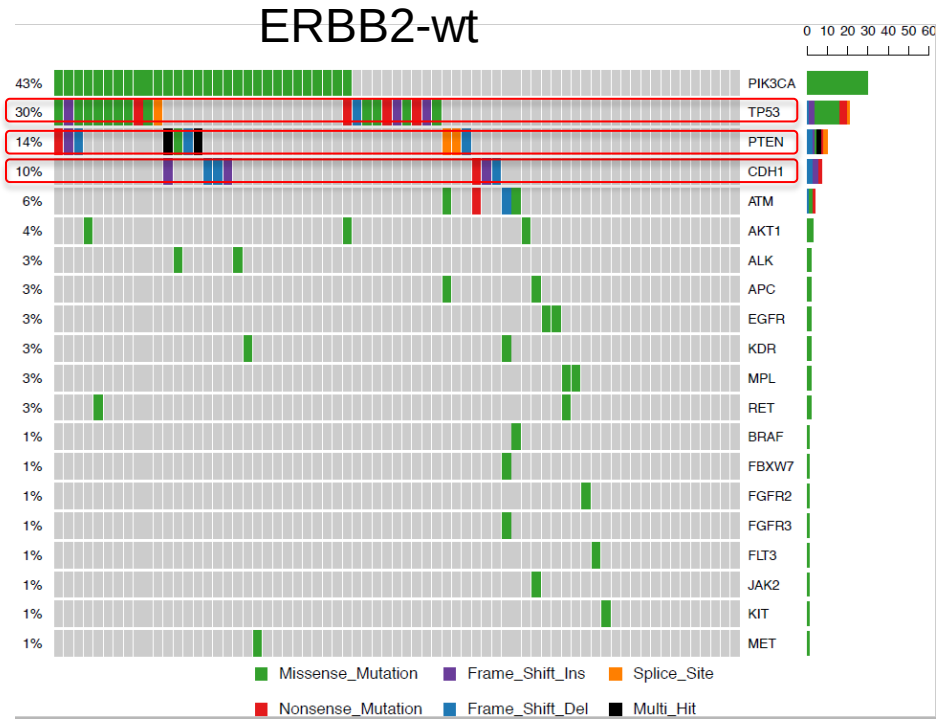
- No differences in TTP between ERBB2-mut vs ERBB2wt in first-line endocrine therapy (p= 0.4969)

- 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%)

Co-Molecular aberrations Large Panels139 genes

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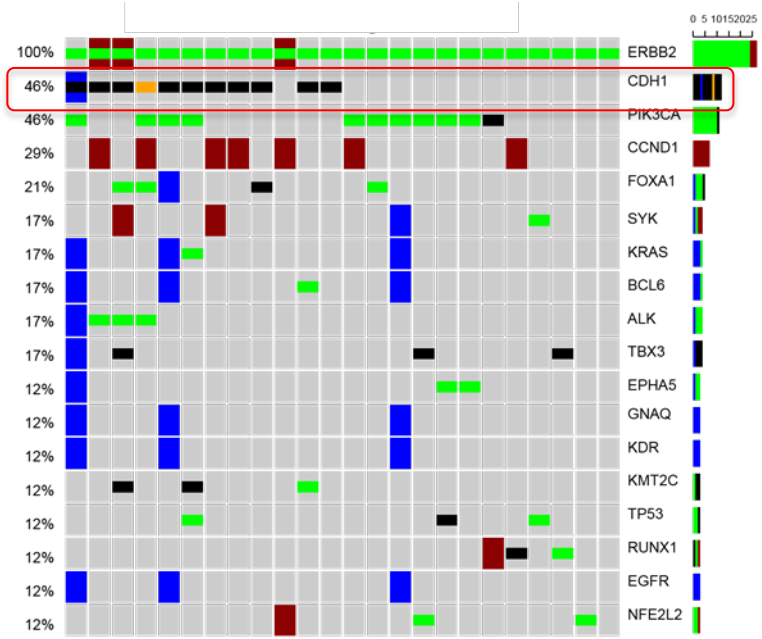
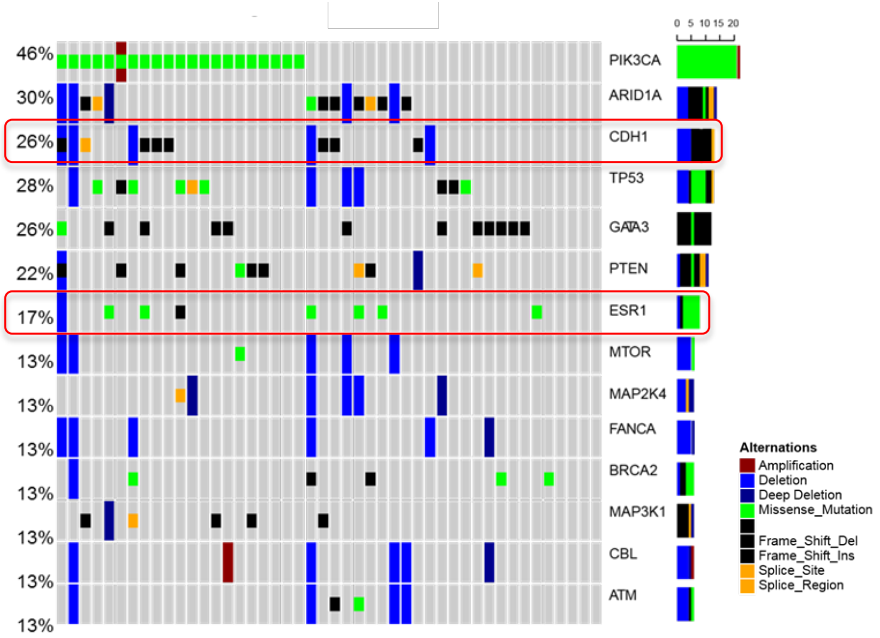
ERBB2-mutated



ERBB2-wt

N=24



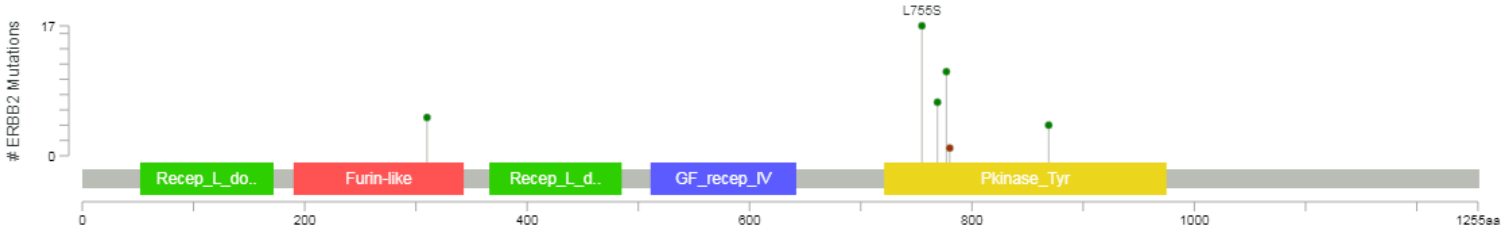
CDH1 mutation enriched in ERBB2mut (28%) vs ERBB2wt (10%) (p=0.07)

ERBB2 mutant population

	N=45
ERBB2_variant	
L755S	38% (17)
V777L	25% (11)
D769Y/H	15% (7)
S310F/Y	10% (5)
L869R	9% (4)
P780_Y781insGSP	2% (1)

6 ERBB2mut cases were sequenced more than once
3 showed differences:

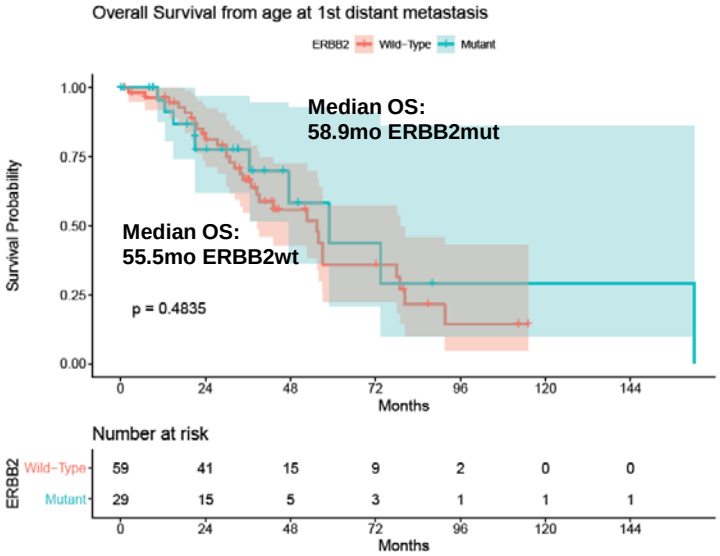
- Two gain ERBB2 mutation at distant metastases
- One lost ERBB2 mutation in later metastatic setting (untreated with anti-HER2 therapy)



Gao et al. *Sci. Signal.* 2013 & Cerami et al. *Cancer Discov.* 2012.

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 cancer[1]

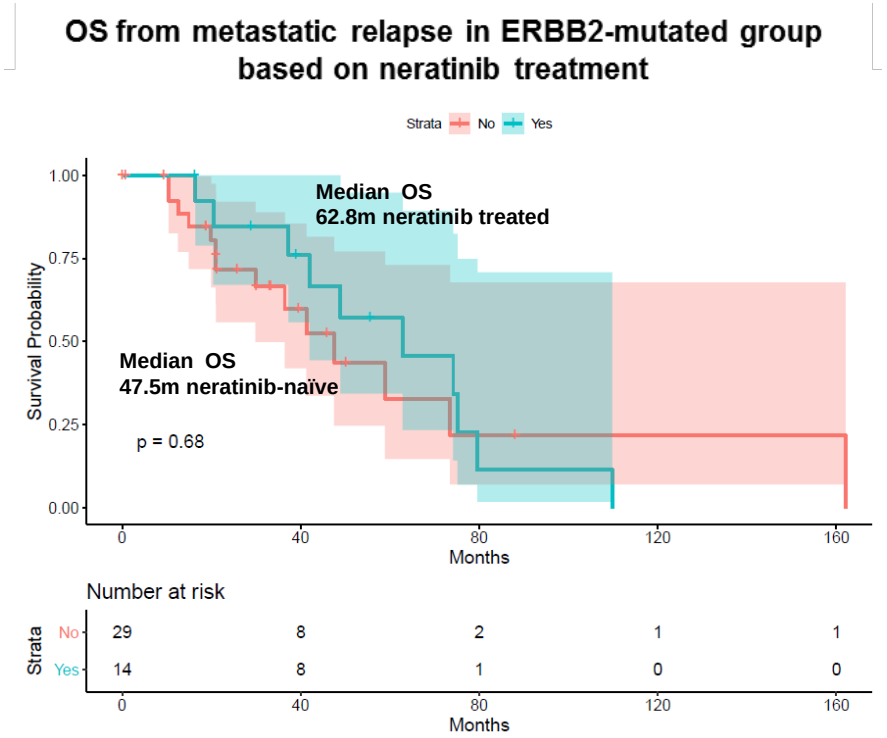


No differences in OS between ERBB2mut and ERBB2wt when excluding neratinib-treated patients

1. Hyman et al, Nature. 2018;554:189-194

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>24weeks) = 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 publications[1-3]
  - 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-muttant population in BC
  - Data had been compared to matched cases
  - CLIA-/ISO-certified genomic data

1. Griffith et al. Nature Communications 2018; 9:3476
2. Wang et al, Cancer Science 2017; 108:671
3. Jongen et al, BCRT 2019; 174:55

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)

Acknowledgements

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Gustave Roussy Cancer Campus Grand Paris
DITEP Drug Development Department
Fabrice André
Semih Dogan
Suzette Delaloge
Fadi Sabbagh
Cristophe Massard
Ludovic Lacroix

The University of Texas MD Anderson Cancer Center
Funda Meric-Bernstam
Kenna Shaw
Chetna Wathoo
Kristin Hargrave

Vanderbilt-Ingram Cancer Center
Christine Micheel
Michele LeNoue-Newton
Thomas Stricker
Mia Levy
Fei Ye
Sheau-Chiann Chen

unicancer Personalized Medicine Group
Marta Jimenez
Alexandra Jacquet
Thomas Filleron

Memorial Sloan Kettering Cancer Center
David Hyman
Lillian Smyth

UHN Princess Margaret Cancer Centre
Philippe Bedard
Celeste YU

Centre Léon Bérard
Thomas Bachelot
Olivier Tredan

Dana-Farber Cancer Institute
Rinaa Sujata Punglia
Eva Lepisto
Deborah Schrag

AACR American Association for Cancer Research
Shawn Sweeny

Puma Biotechnology