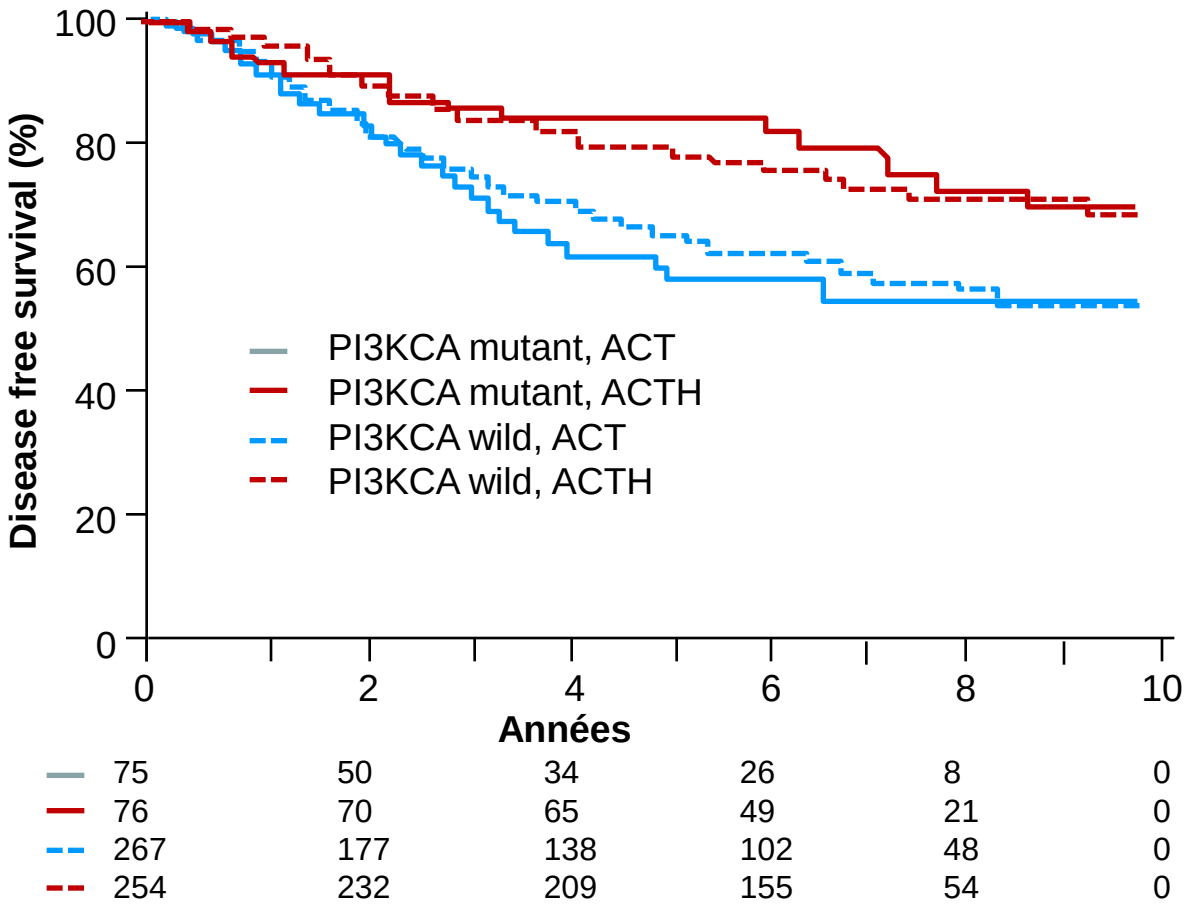
Clinical relevance: How do we manage mutational mechanisms of resistance?

Prof. Dr. Sibylle Loibl
German Breast Group
Sana Klinikum Offenbach

PI3K3CA mutations in NSABP B-31 (n = 672) *[2]*

Trastuzumab/mutation PI3KCA



A : doxorubicin ;
C : cyclophosphamide ;
T : paclitaxel ;
H : trastuzumab.

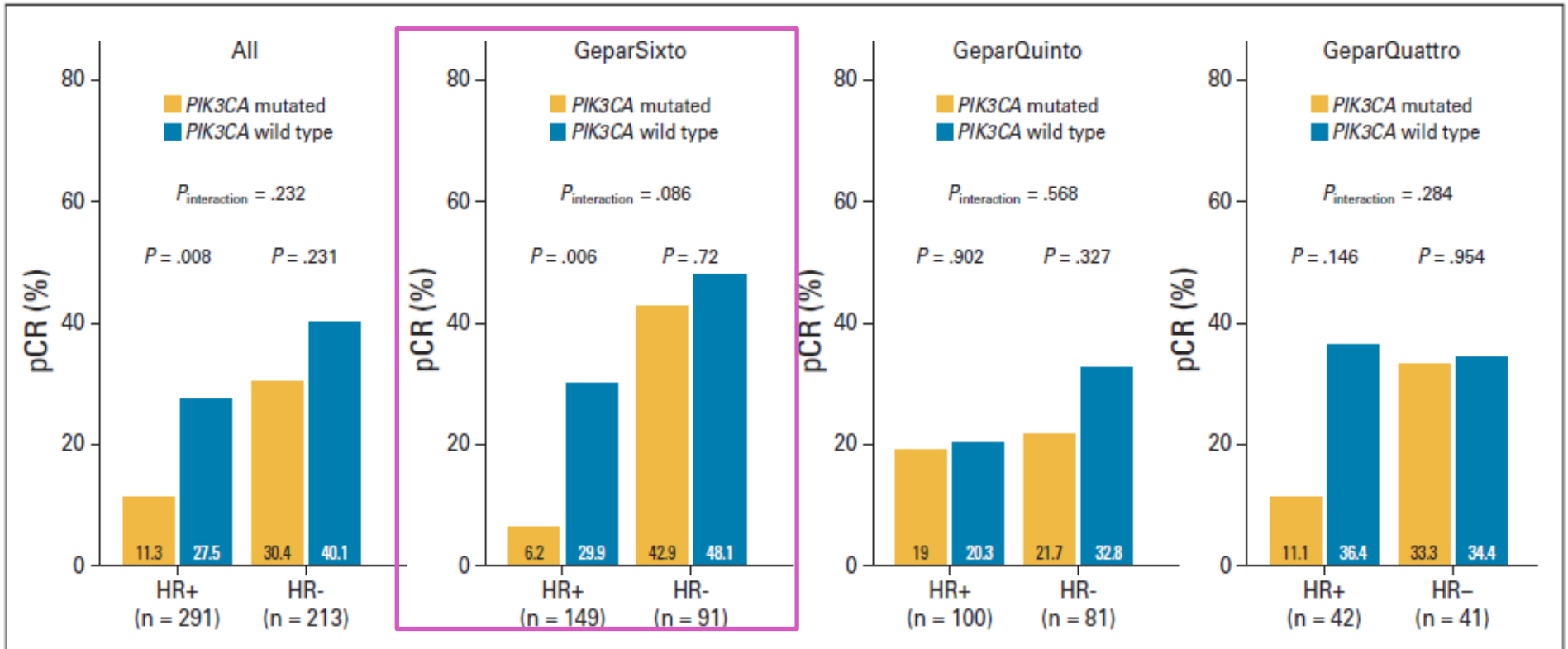
Pogue-Geile KL Paik S et al., abstr. S3-05

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

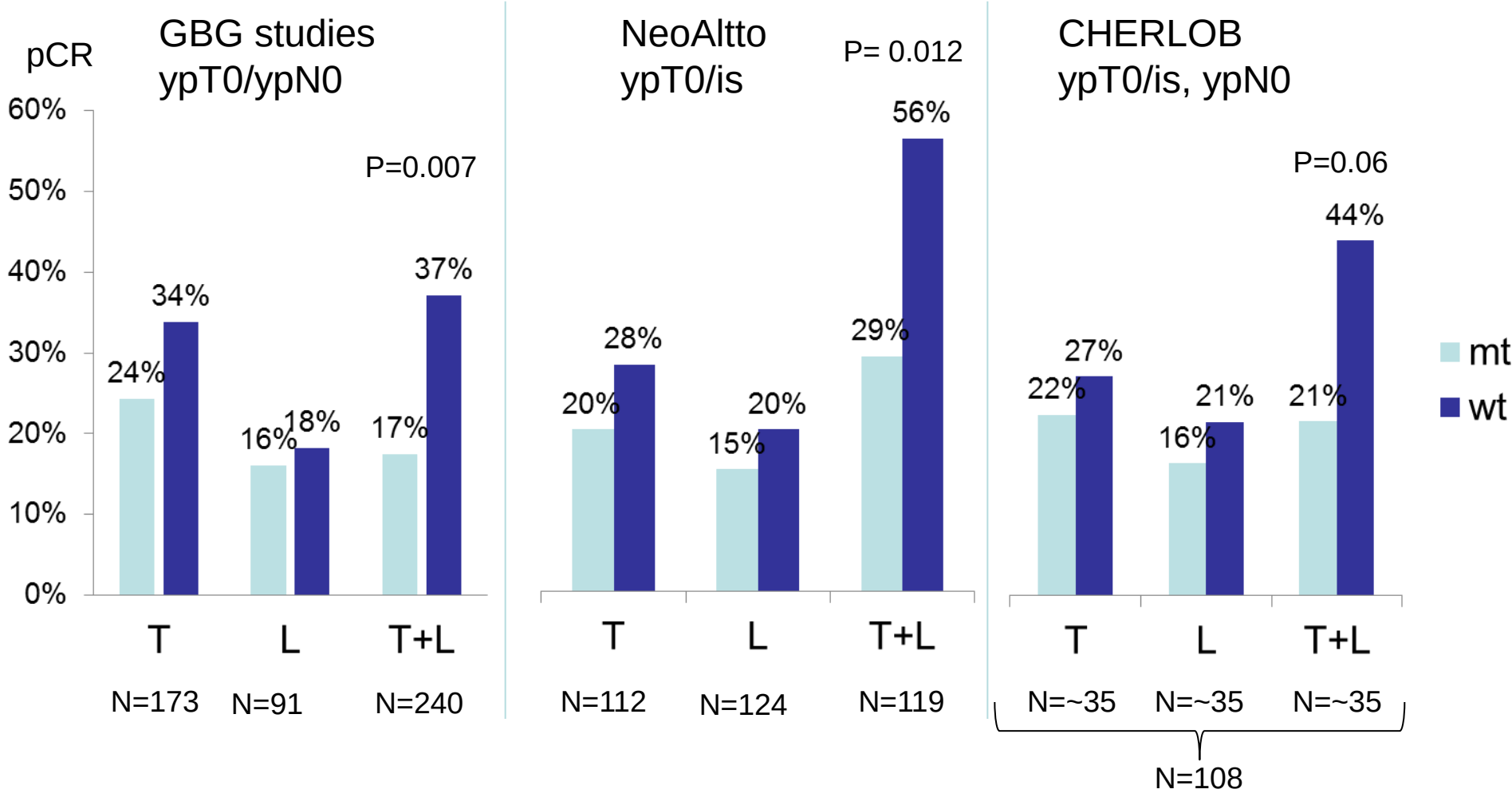
PIK3CA Mutations Are Associated With Lower Rates of Pathologic Complete Response to Anti–Human Epidermal Growth Factor Receptor 2 (HER2) Therapy in Primary HER2-Overexpressing Breast Cancer

Sibylle Loibl, Gunter von Minckwitz, Andreas Schneeweiss, Stefan Paepke, Annika Lehmann, Mahdi Rezai, Dirk M. Zahm, Peter Sinn, Fariba Khandan, Holger Eidtmann, Karel Dohnal, Clemens Heinrichs, Jens Huober, Berit Pfitzner, Peter A. Fasching, Fabrice Andre, Judith L. Lindner, Christos Sotiriou, August Dykgers, Sanxing Guo, Stephan Gade, Valentina Nekljudova, Sherene Loi, Michael Untch, and Carsten Denkert

See accompanying editorial doi: 10.1200/JCO/2014.57.6132



PIK3CA mut status and pCR



Loibl S et al. J Clin Oncol 2014; Majewski J Clin Oncol 2015; Guarneri V et al. ESMO 2014

Chemofree Therapy in HER2+ patients

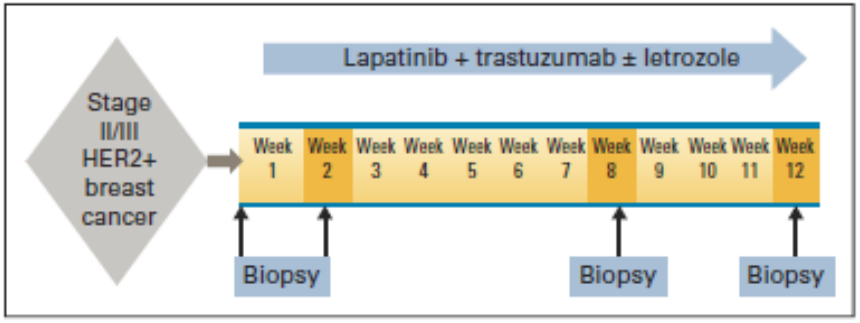
Neosphere

THP (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

HP (n=107)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

→ SURGERY

TBCR006

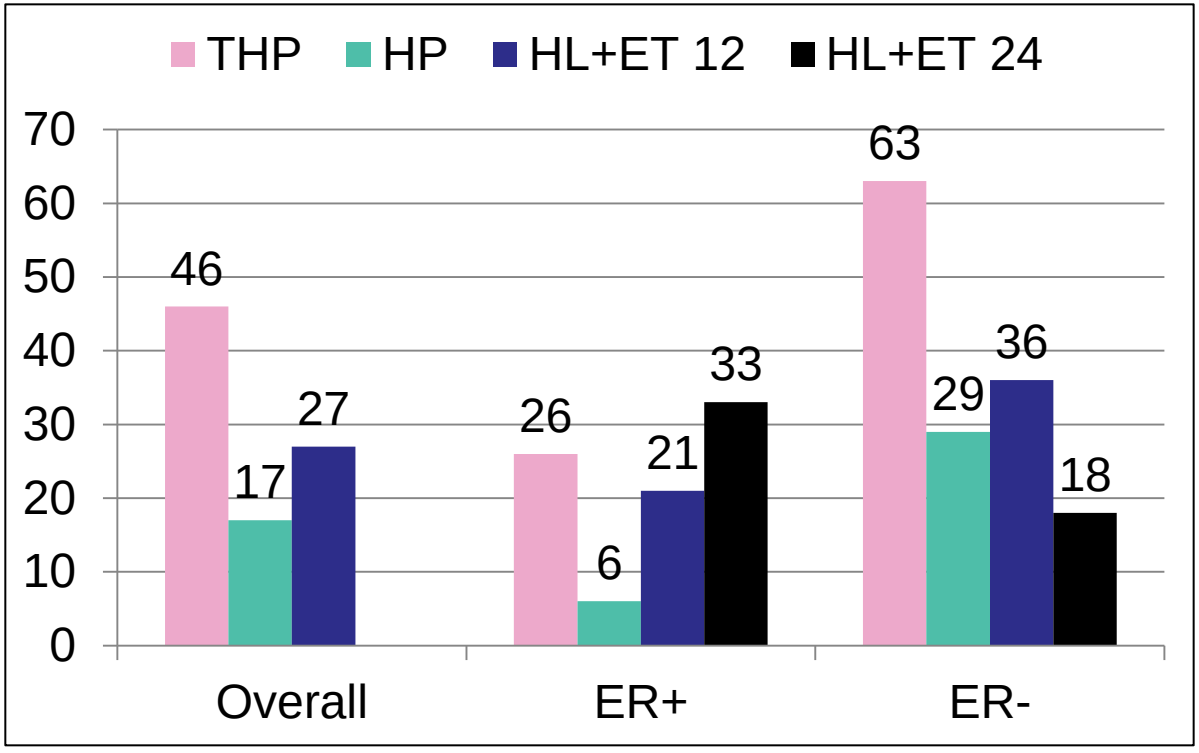


TBCRC 0023

Stage II/III HER2+ bc

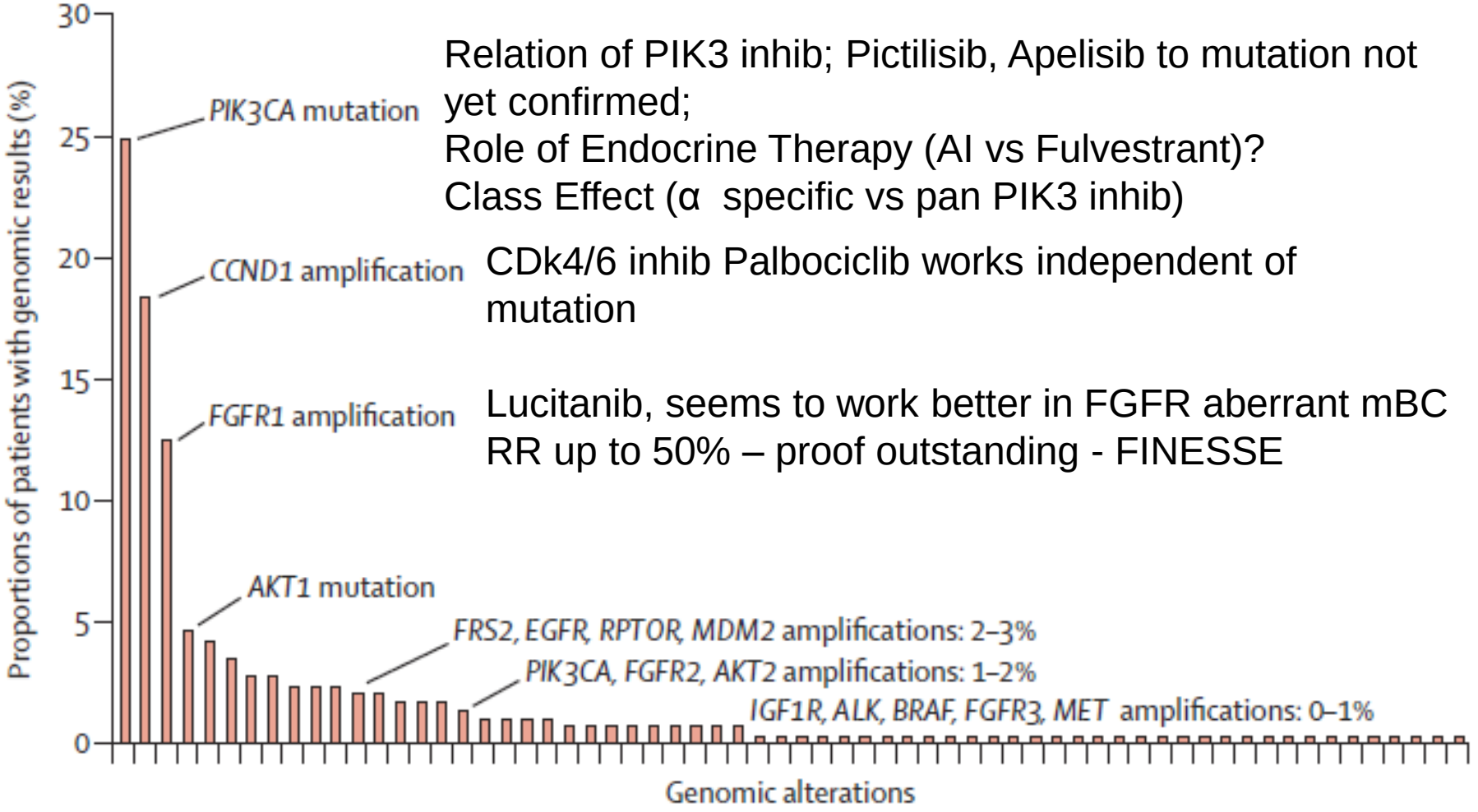
→ **12** weeks of HL +/-ET

→ **24** weeks of HL +/-ET



Gianni L, et al. Lancet Oncol 2012;
Rimawi M et al. J Clin Oncol 2013; Rimawi M, et al. SABCS 2014

Targetable Mutations in mBC



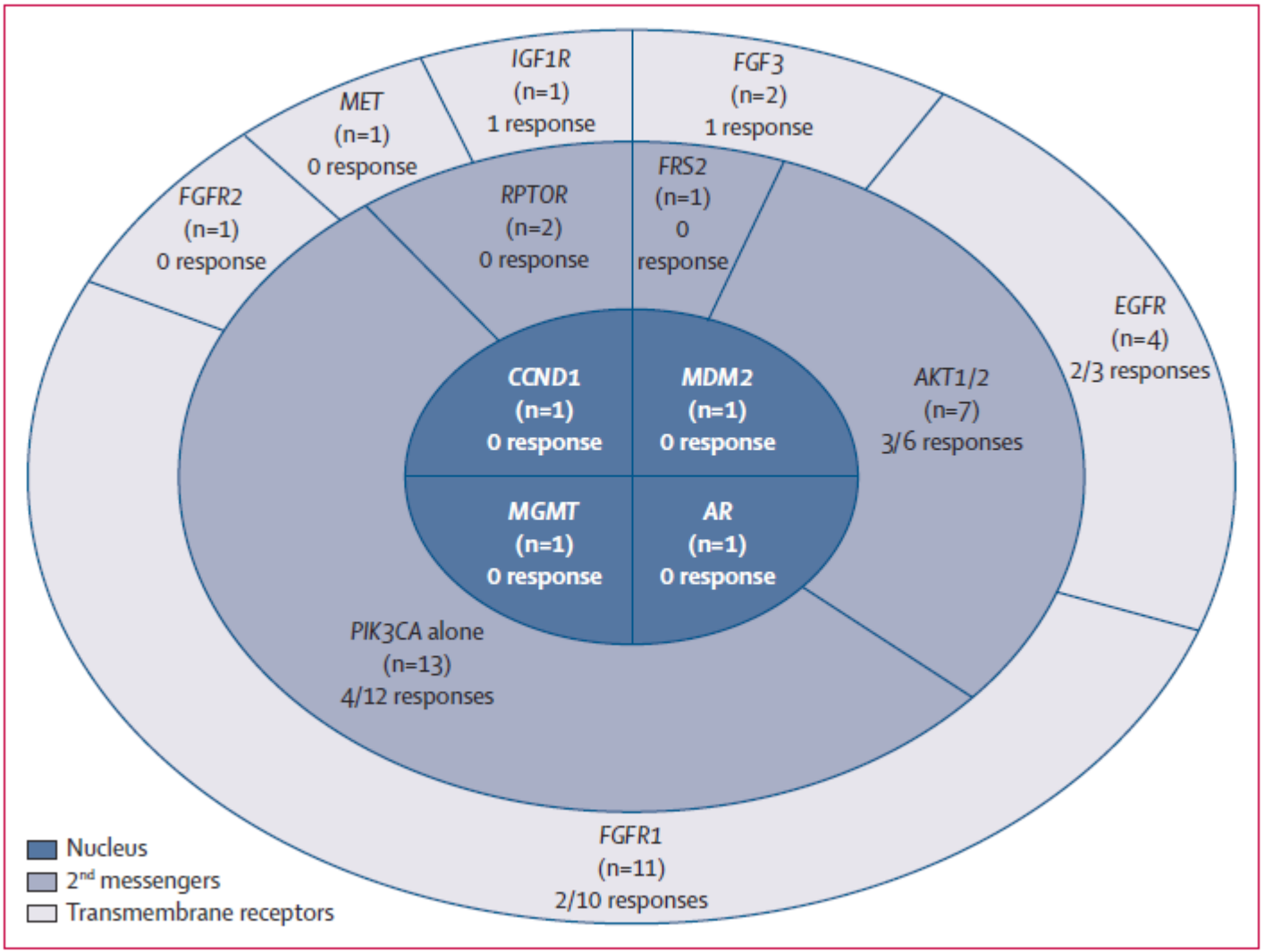
Relation of PIK3 inhib; Pictilisib, Apelisib to mutation not yet confirmed;
Role of Endocrine Therapy (AI vs Fulvestrant)?
Class Effect (α specific vs pan PIK3 inhib)

CDk4/6 inhib Palbociclib works independent of mutation

Lucitanib, seems to work better in FGFR aberrant mBC
RR up to 50% – proof outstanding - FINESSE

André F et al. Lancet Oncol 2014

Genomic alterations and matched targeted therapy

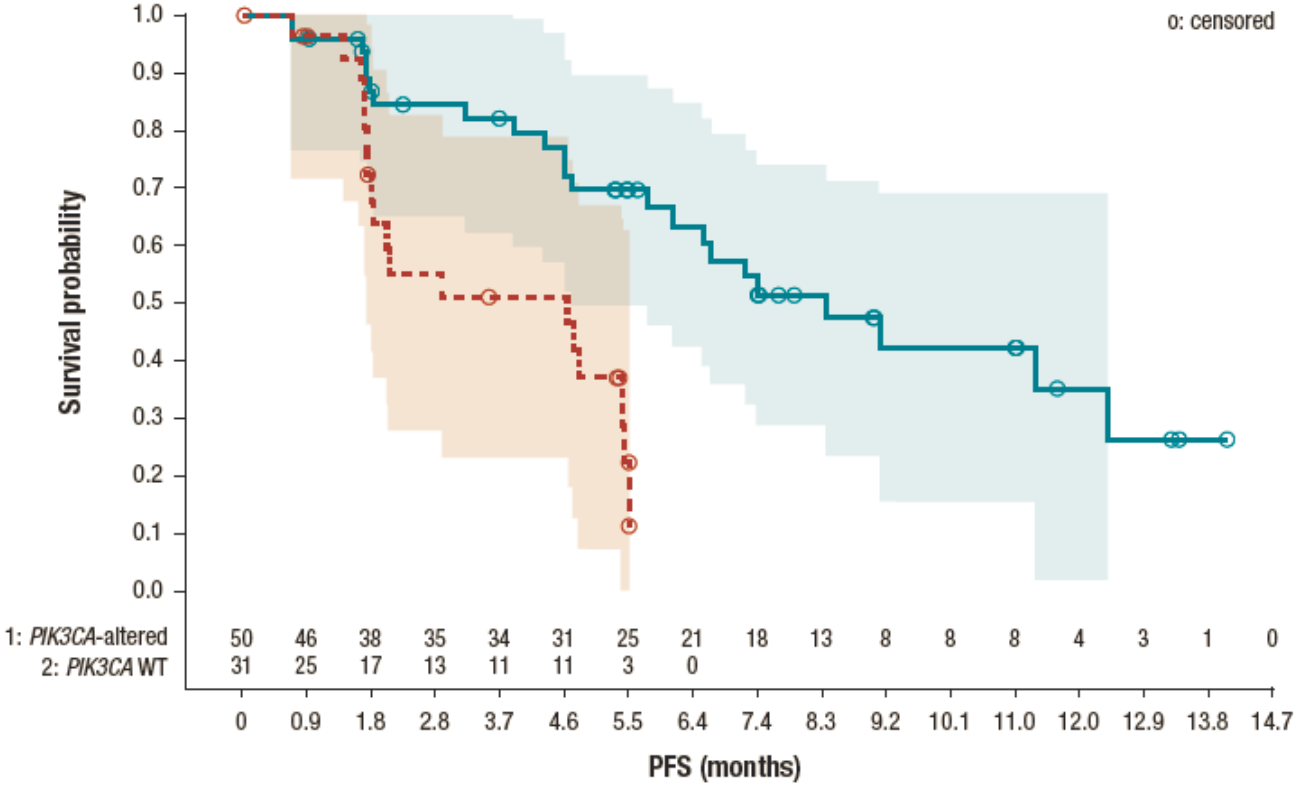


André F et al. Lancet Oncol 2014

PIK3 Inhibition in ER+ mBC with and w/o a *PIK3CA* mutation

Treatment group (QD) — *PIK3CA*-altered — *PIK3CA* WT

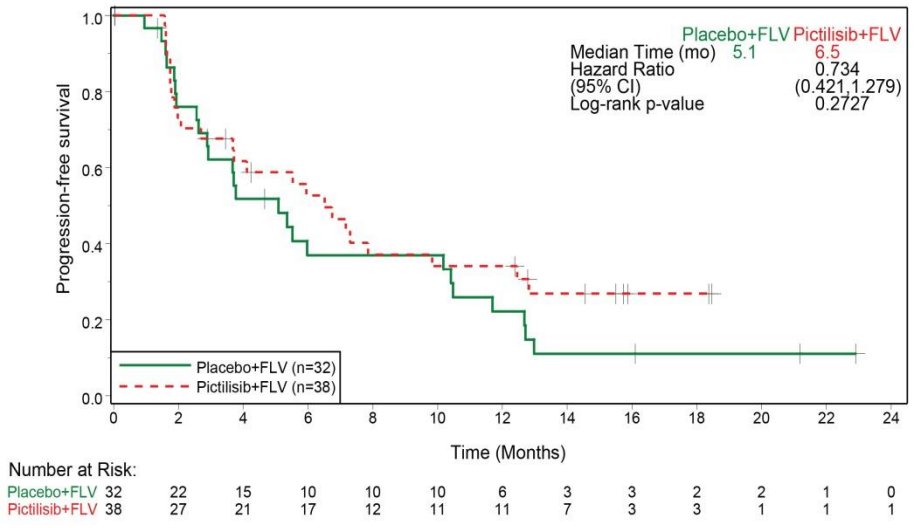
	Median PFS (months)	95% CI (months)	Total number, n	Number censored, n (%)
***PIK3CA*-altered**	8.3	6.1–12.4	50	27 (54.0)
***PIK3CA* WT**	4.7	1.8–5.5	31	13 (41.9)



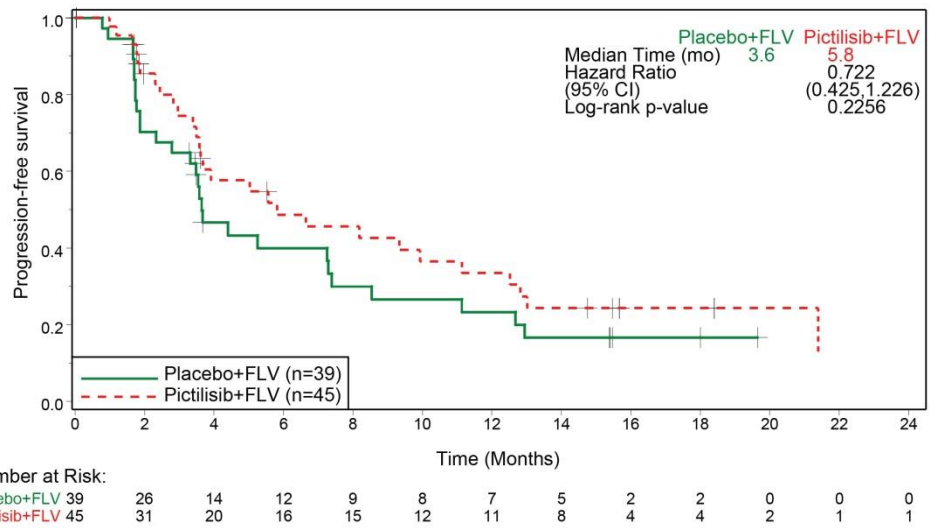
Janku et al. SABCS PD5-5

Progression-Free Survival Based on Tumor *PIK3CA* Mutation Status

PIK3CA-Mutant Population



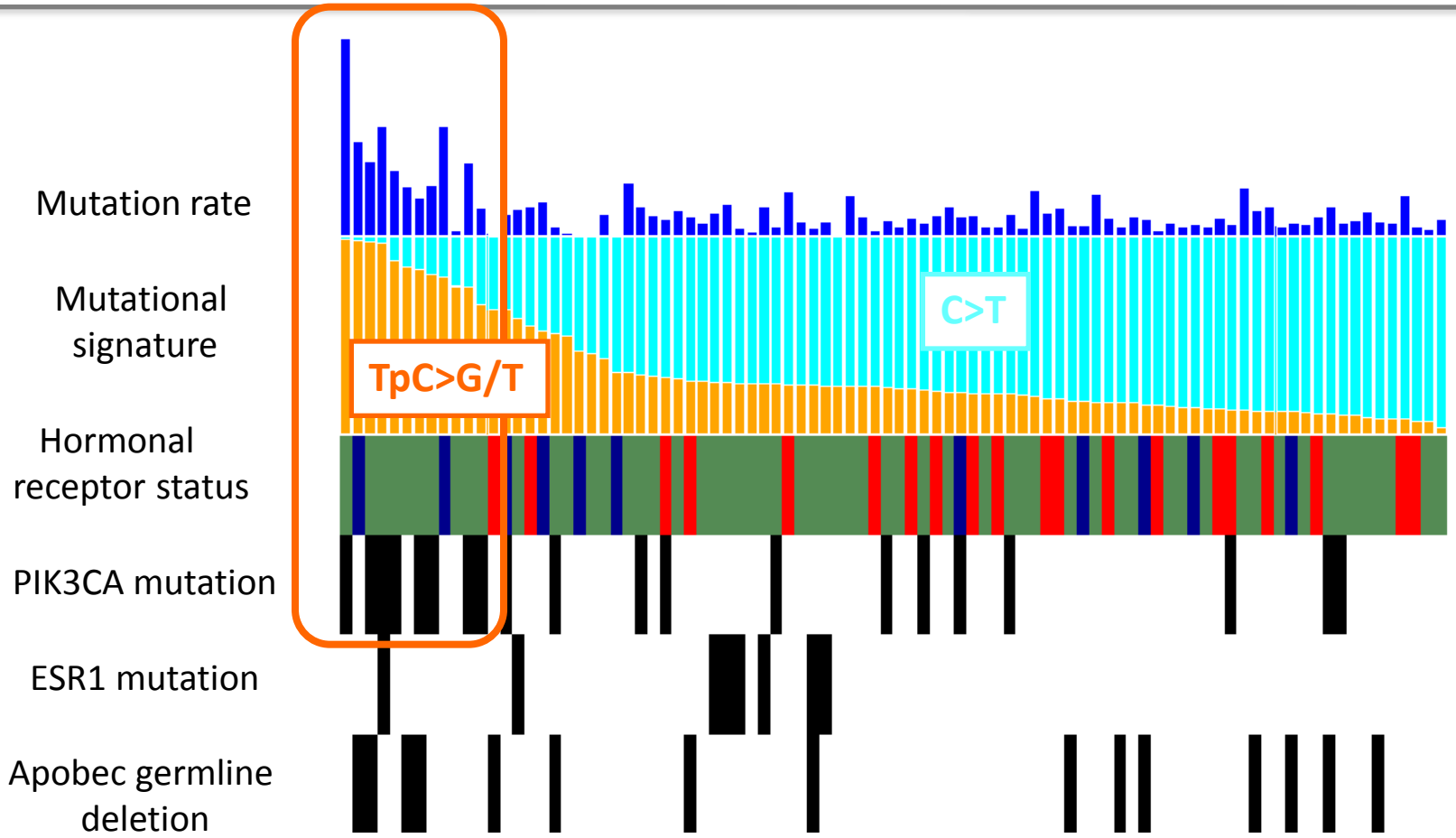
PIK3CA "Wild-Type" Population



- PIK3CA mutation status does not predict benefit of the addition of pictilisib to fulvestrant

Krop I et al, proc. SABCS 2014

Correlation betwen mutation rate, mutational signature and genomic alterations

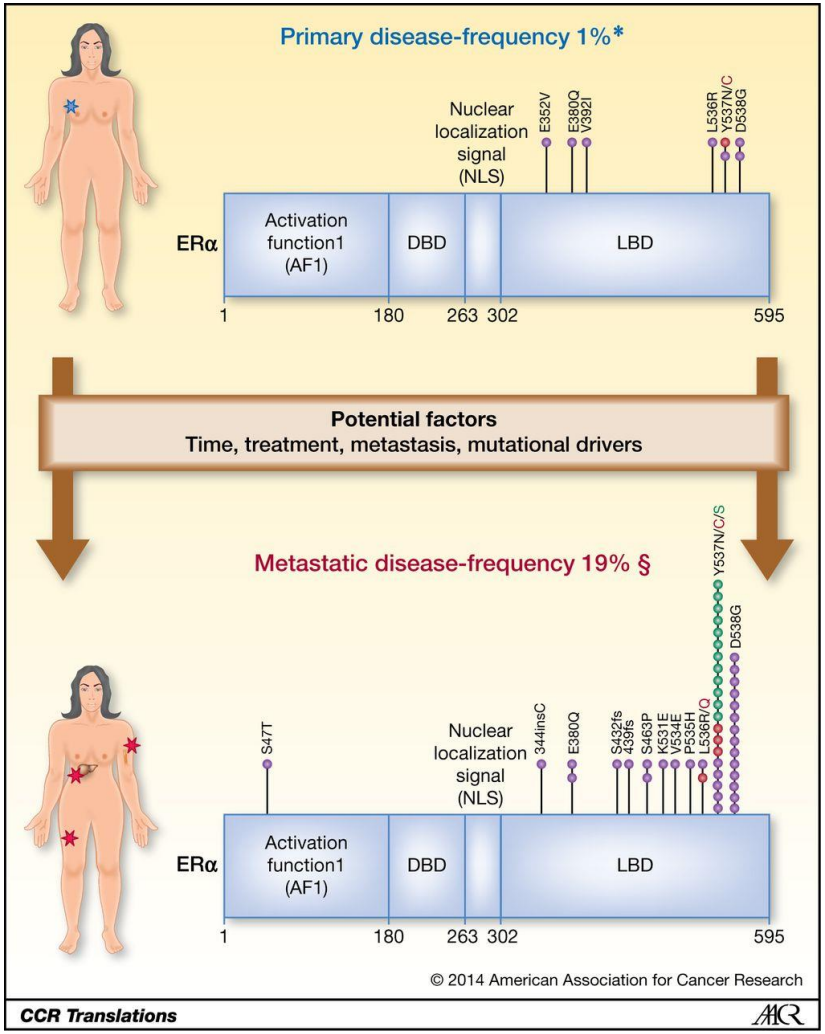


Cluster of patients present with ER+, PIK3CA mutations, high mutation rate, TpC>G/T mutations,

Ande F et al. ESMO 2014

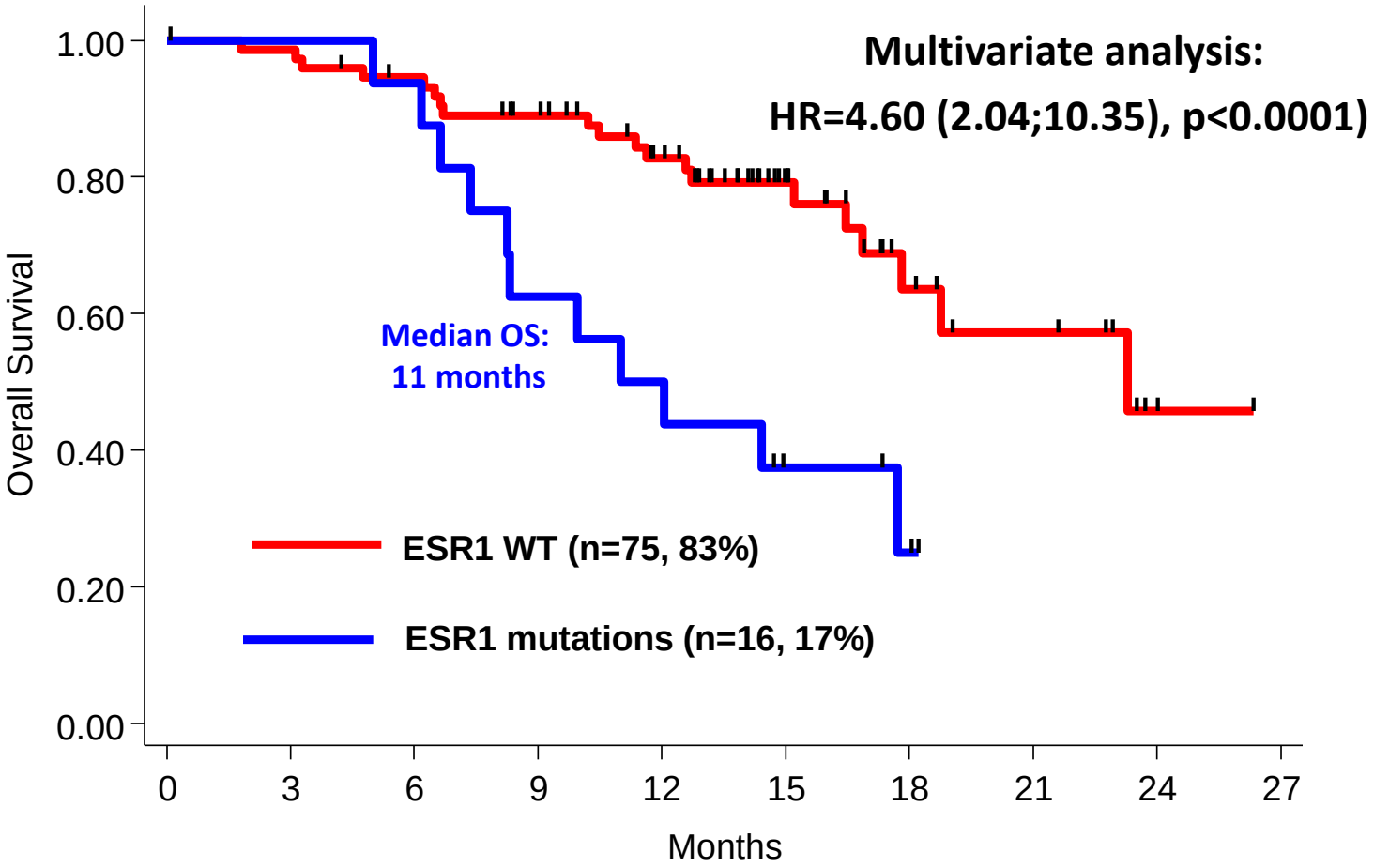
Schematic of ESR1 mutations identified in primary and metastatic advanced ER+ breast cancer and factors that may influence their development.

ESR1 Mutations



Segal C V , and Dowsett M Clin Cancer Res 2014;20:1724-1726

ESR1 mutations & patient outcome



ESR1 mutations are associated with poor outcome

Ande F et al. ESMO 2014

Publication Number: PD6-5

Title: Profiling of ESR1-mutated metastatic breast cancers by FoundationOne® allows a broad genomic understanding for potential clinical implications

Norma A Palma[1], Siraj Ali[1], Garrett Frampton[1], Kai Wang[1], Hannah Gilmore[2], Julio Peguero[6], Lyndsay N Harris[2], Massimo Cristofanilli[5], Juliann Chmielecki[1], Jeffrey S Ross[1,4], Deborah Morosini[1], Vincent A Miller[1], Phil J Stephens[1], Gary Palmer[1] and Joyce O'Shaughnessy[3]. [1]Foundation Medicine, Cambridge, MA; [2]Case Western Reserve University, Cleveland, OH; [3]Baylor Charles A. Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, TX; [4]Albany Medical College, Albany, NY; [5]Thomas Jefferson University, Kimmel Cancer Center, Philadelphia, PA and [6]Oncology Consultants Research, Houston, TX.

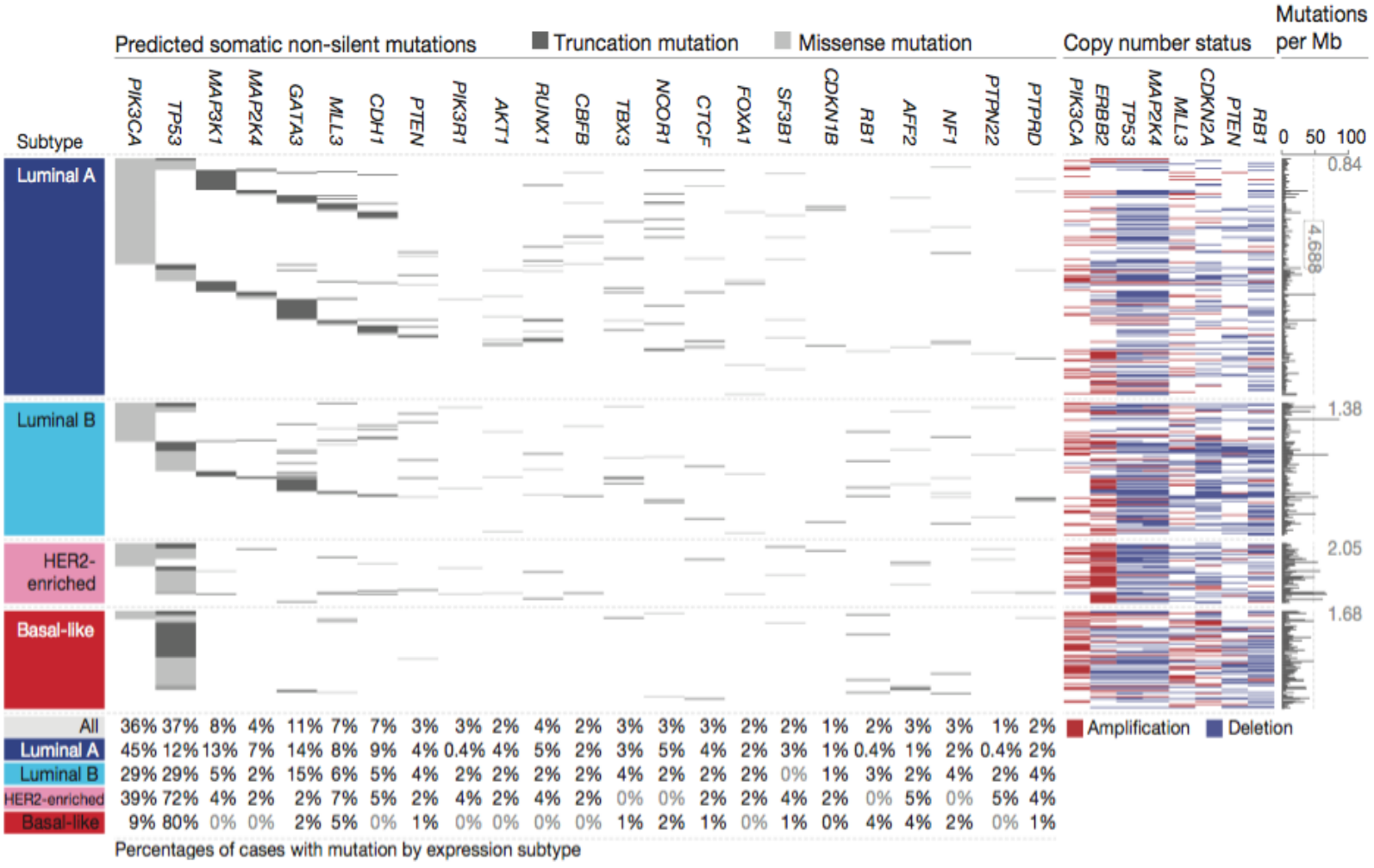
2.200 BCs; 8% harbouring ESR1 alterations.

Publication Number: PD6-6

Title: Estrogen receptor (ESR1) mutations confer resistance to hormone therapy using a common mechanism

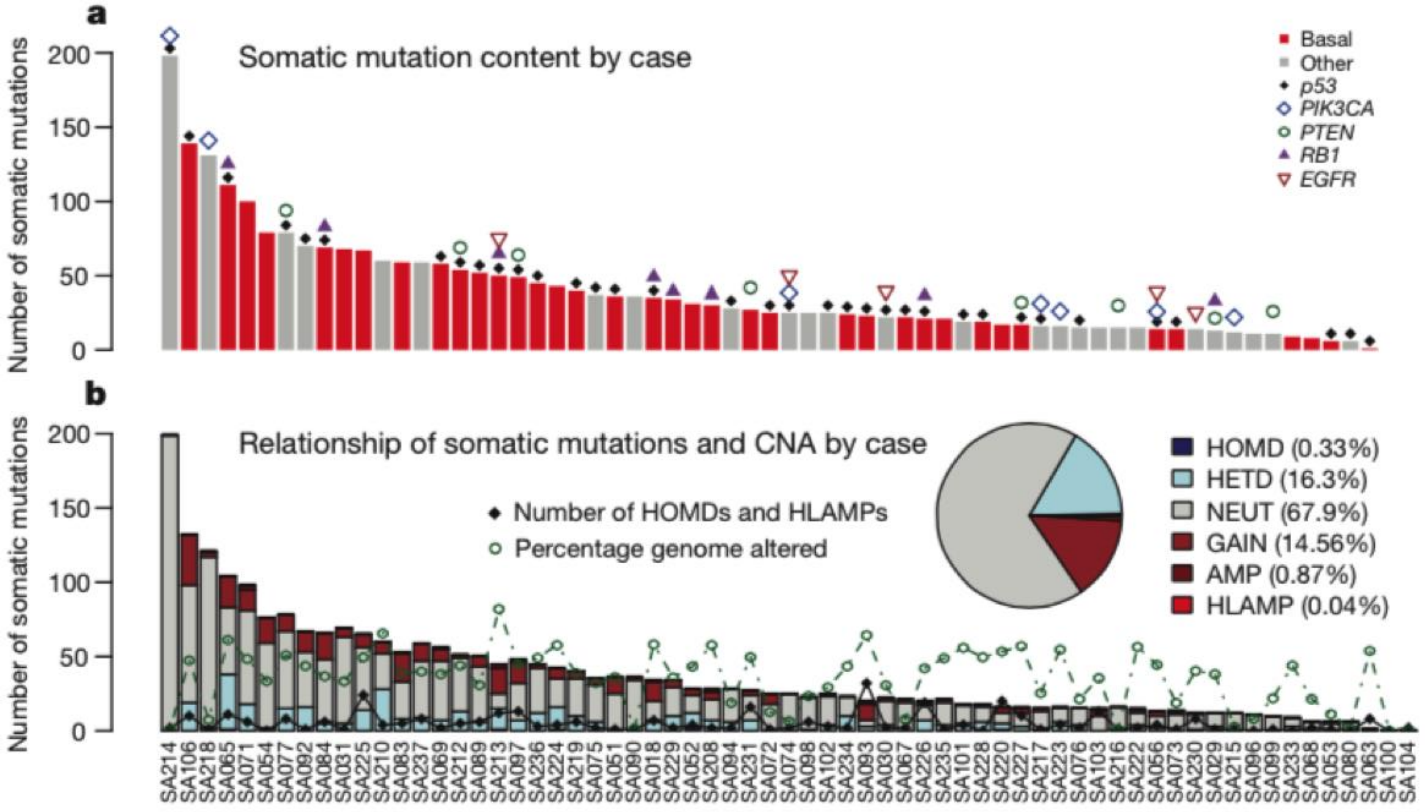
Luca Gelsomino[1], Guowei Gu[1], Yassine Rechoum[1], Sebastiano Ando[2] and Suzanne AW Fuqua[1]. [1]Baylor College of Medicine, Houston, TX and [2]Universita' della Calabria, Arcavacata di Rende, Cosenza, Italy.

ESR1 mutants conferring resistance to hormonal therapy in experimental systems.



TCGA, Nature 2012

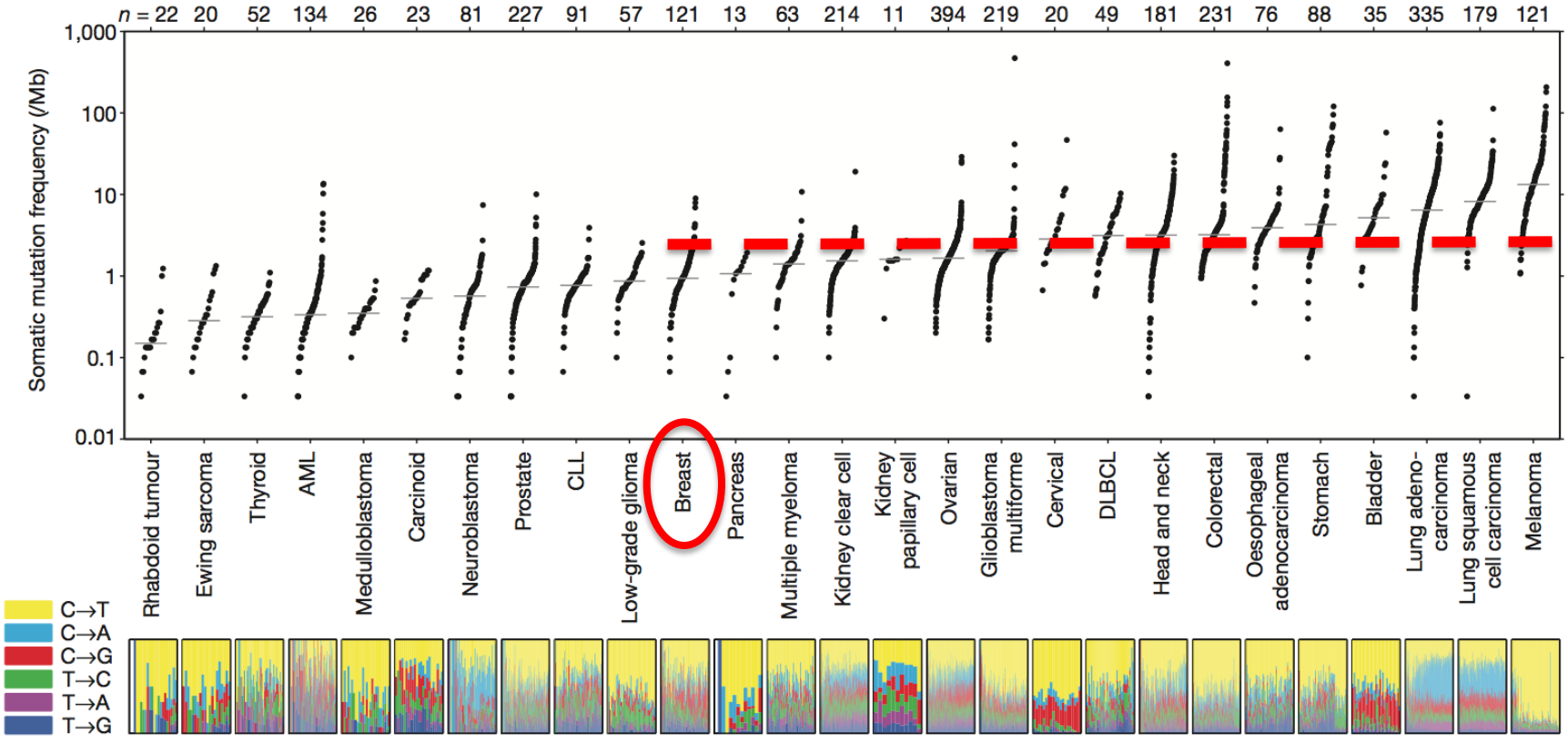
Mutation frequency in TNBC



Shah et al. Nature 2012

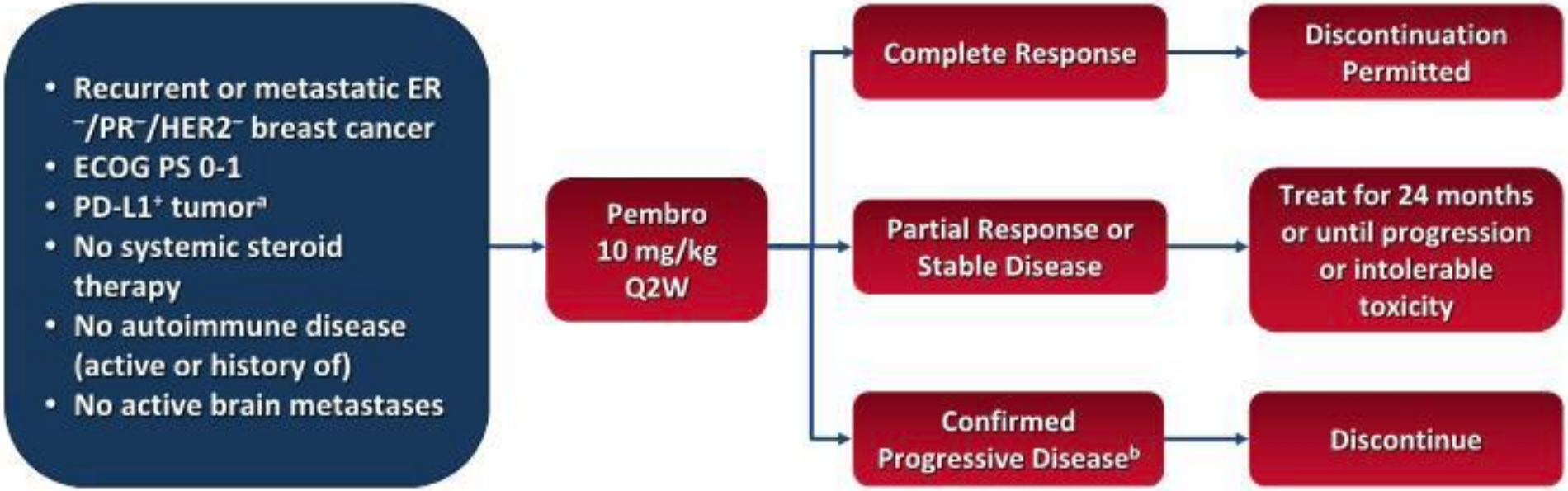
Correlation of mutations and immunogenicity

Mutational burden → Immunogenic (neo-antigens) threshold?



Lawrence M et al. Nature 2013

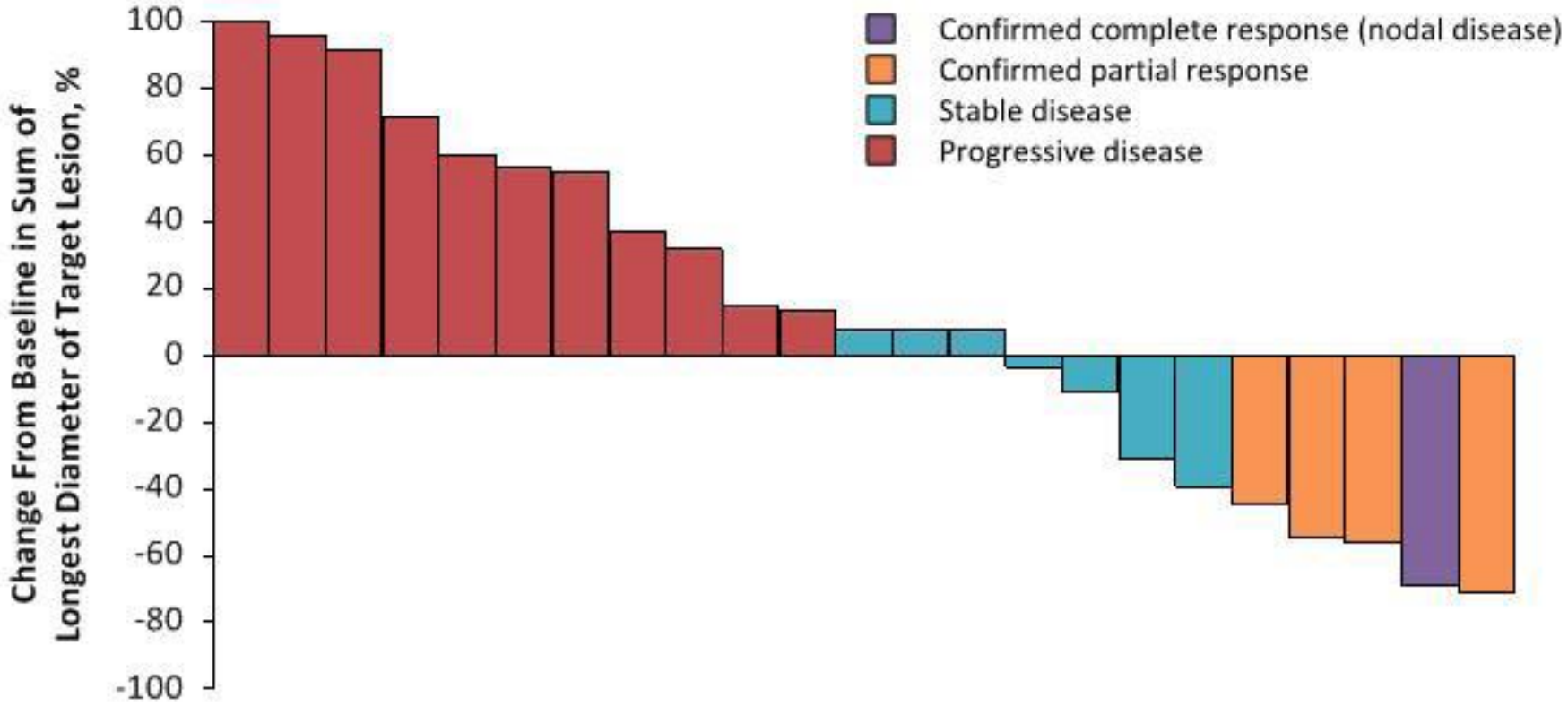
KEYNOTE-012:
Triple-Negative Breast Cancer Cohort



- **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

[a]PD-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.
[b]If 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.

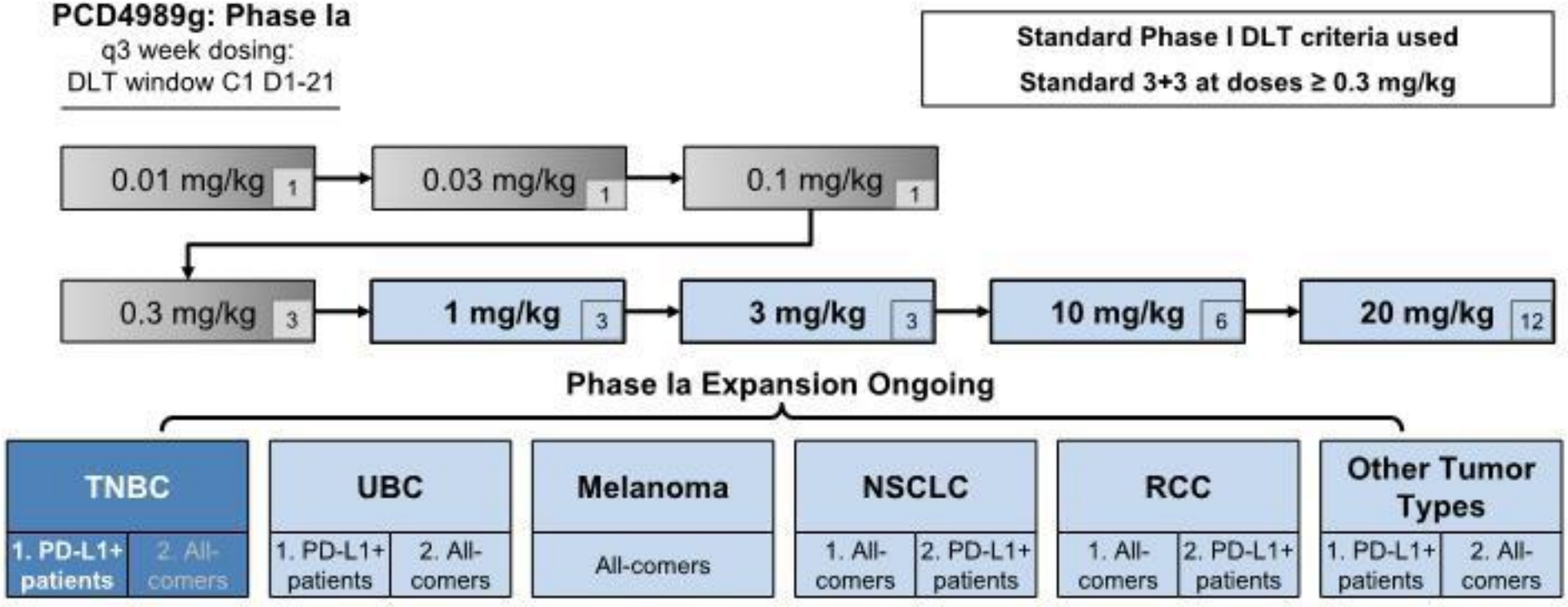
Maximum Percentage Change From Baseline in Target Lesions (RECIST v1.1, Central Review)[a,b]



[a]5 patients were excluded from the analysis because they did not have measurable disease at baseline per RECIST v1.1 by central review.
[b]Only patients with evaluable tumor measurements by central review at baseline and ≥1 post-baseline assessment are included.
Analysis cut-off date: November 10, 2014.

Methods

- Objective: Conduct a Phase Ia study to explore the safety, efficacy and biomarkers of the anti-PD-L1 antibody MPDL3280A in women with TNBC

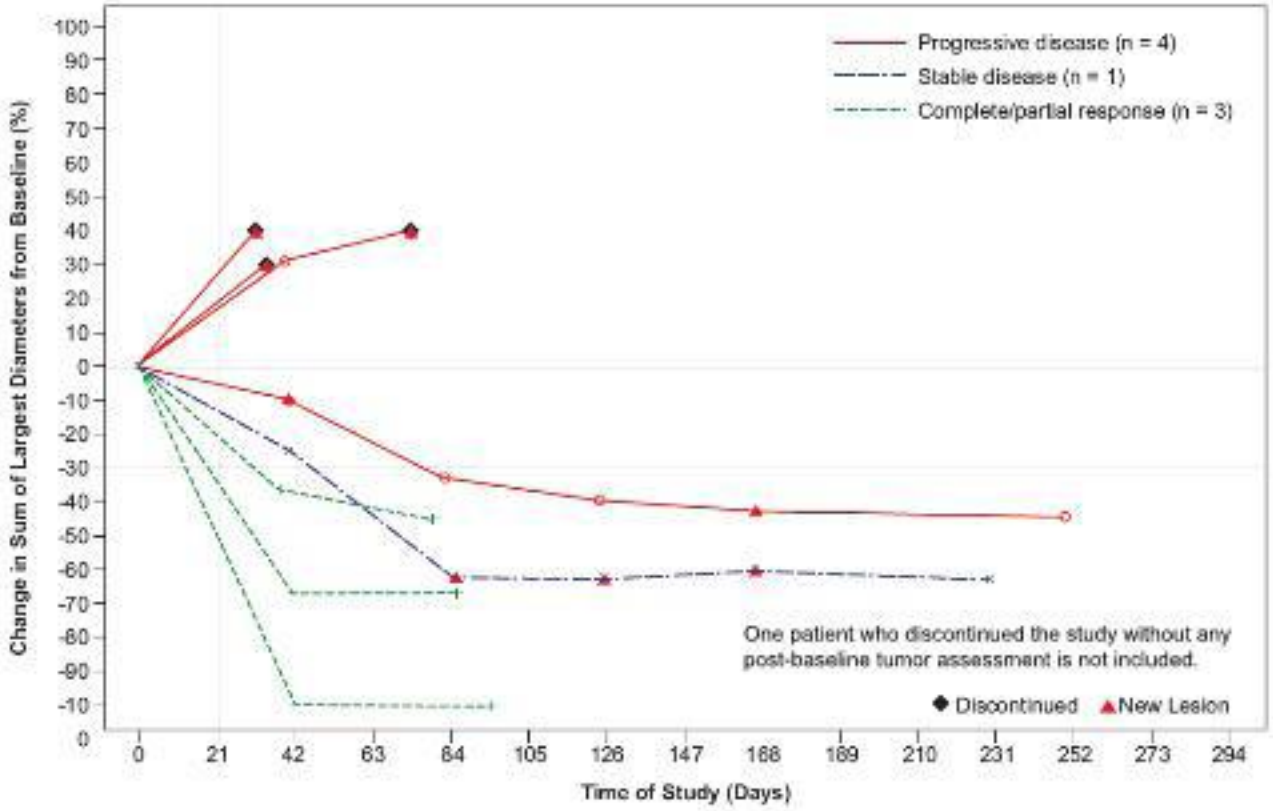


- PD-L1 expression was assessed on tumor-infiltrating immune cells (ICs) using immunohistochemistry (IHC)
- PD-L1 positivity was defined as IHC 3 (≥ 10% of ICs PD-L1 positive) or IHC 2 (≥ 5% but < 10% of ICs PD-L1 positive)

Emens LA, et al. SABCS, 2014.

Tumor Burden Over Time in Patients With TNBC

- MPDL3280A was well tolerated in patients with TNBC (N = 12), with only 1 patient experiencing a Grade 3-4 treatment-related adverse event and no treatment-related deaths observed
- ORR for patients with TNBC (n = 9; IHC [IC] 3 or 2): 33%



Emens LA, et al. SABCS, 2014.

Summary

No drug targeting mutations found yet

Several promising agents/mutations

- ***PIK3CA* mutation – PIK3 inhibitor (alpha specific?)**
- **FGFR mutation/amplification – FGFR inhibitor**
- **Immunotherapy in TNBC with mutations only?**