Best of the Year 2015 Breast Cancer

Fabrice ANDRE
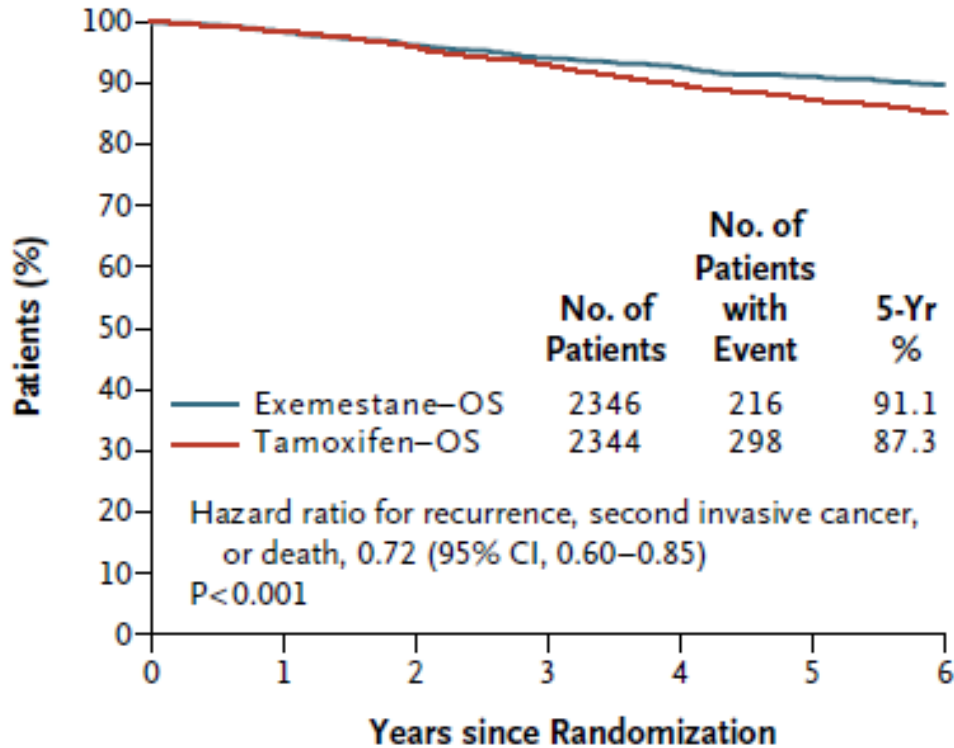
Gustave Roussy

Outline

- **Fine tuning « old » therapies to improve outcome**
  - Endocrine therapy
  - Chemotherapy

- New biomarkers for breast cancer stratification
  - TILs
  - ctDNA

- New Her2-3 inhibitors

- New targets in breast cancer
  - CDK4
  - PI3K
  - Mutational load

Fine-tuning endocrine therapy: LH-RH analogs combined with exemestane in pre-menopausal women
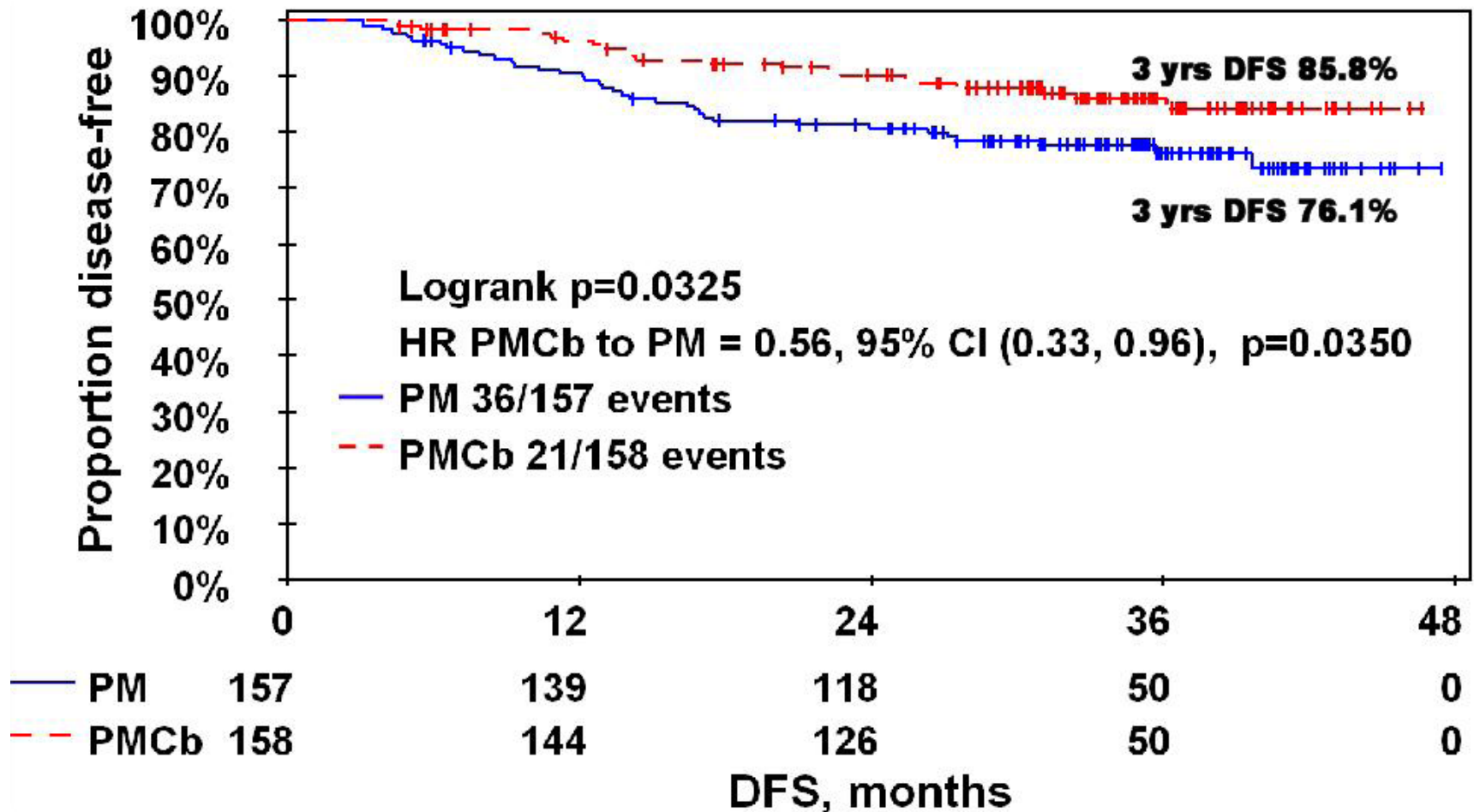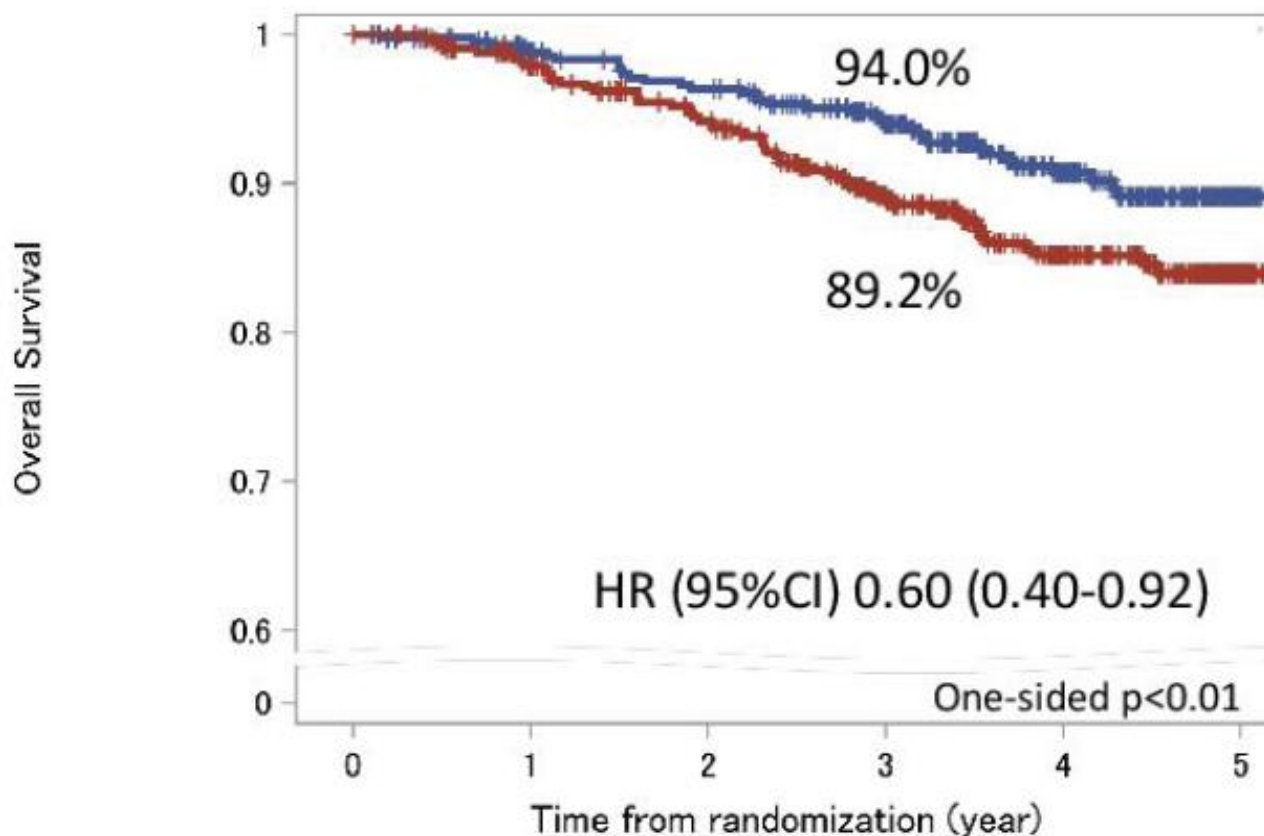

A **Disease-free Survival**

	No. of Patients	No. of Patients with Event	5-Yr %
Exemestane–OS	2346	216	91.1
Tamoxifen–OS	2344	298	87.3

Hazard ratio for recurrence, second invasive cancer, or death, 0.72 (95% CI, 0.60–0.85) $P<0.001$

No. at Risk

Exemestane–OS	2346	2217	2128	1848	1517	1289	866
Tamoxifen–OS	2344	2247	2148	1845	1486	1261	834

Pagani, NEJM, 2014

Fine-tuning chemotherapy: carboplatin in TNBC

Von Minckwitz, SABCS, 2015

Fine-tuning chemotherapy:
capecitabine in patients with high risk breast cancer

94.0%

89.2%

HR (95%CI) 0.60 (0.40-0.92)

One-sided p<0.01

Overall Survival

Time from randomization (year)

|	0	1	2	3	4	5
Capecitabine	440	408	391	321	197	43
Non-capecitabine	445	407	376	298	180	27

Take home message

- Fine-tuning « old » therapies could be a research strategy to improve outcome

- Need massive investment in academic research

- This academic research on drug repositioning and fine-tuning could decrease expenses on new drugs by improving outcome
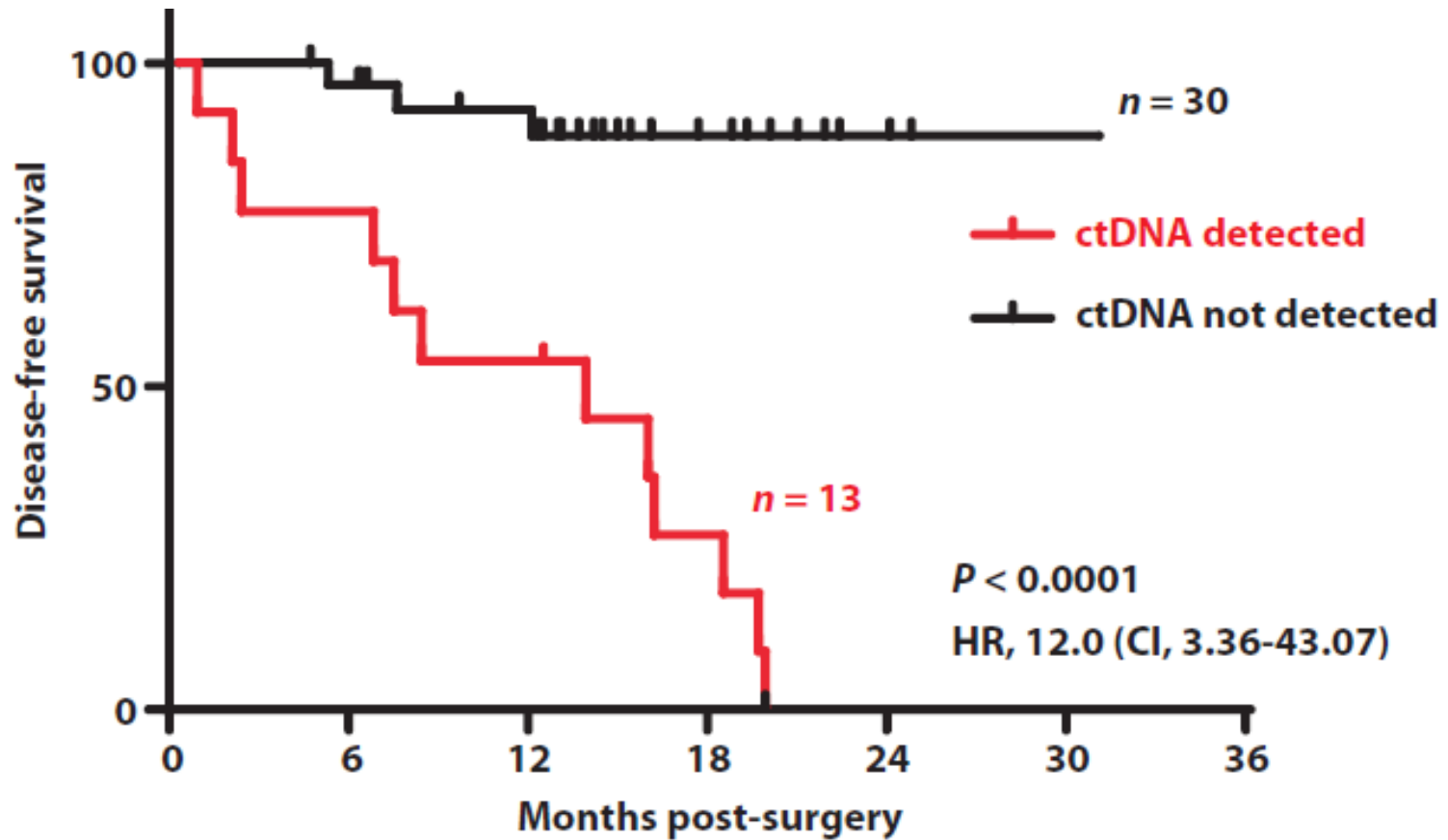
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TILs to predict risk of distant recurrence in TNBC: A meta-analysis
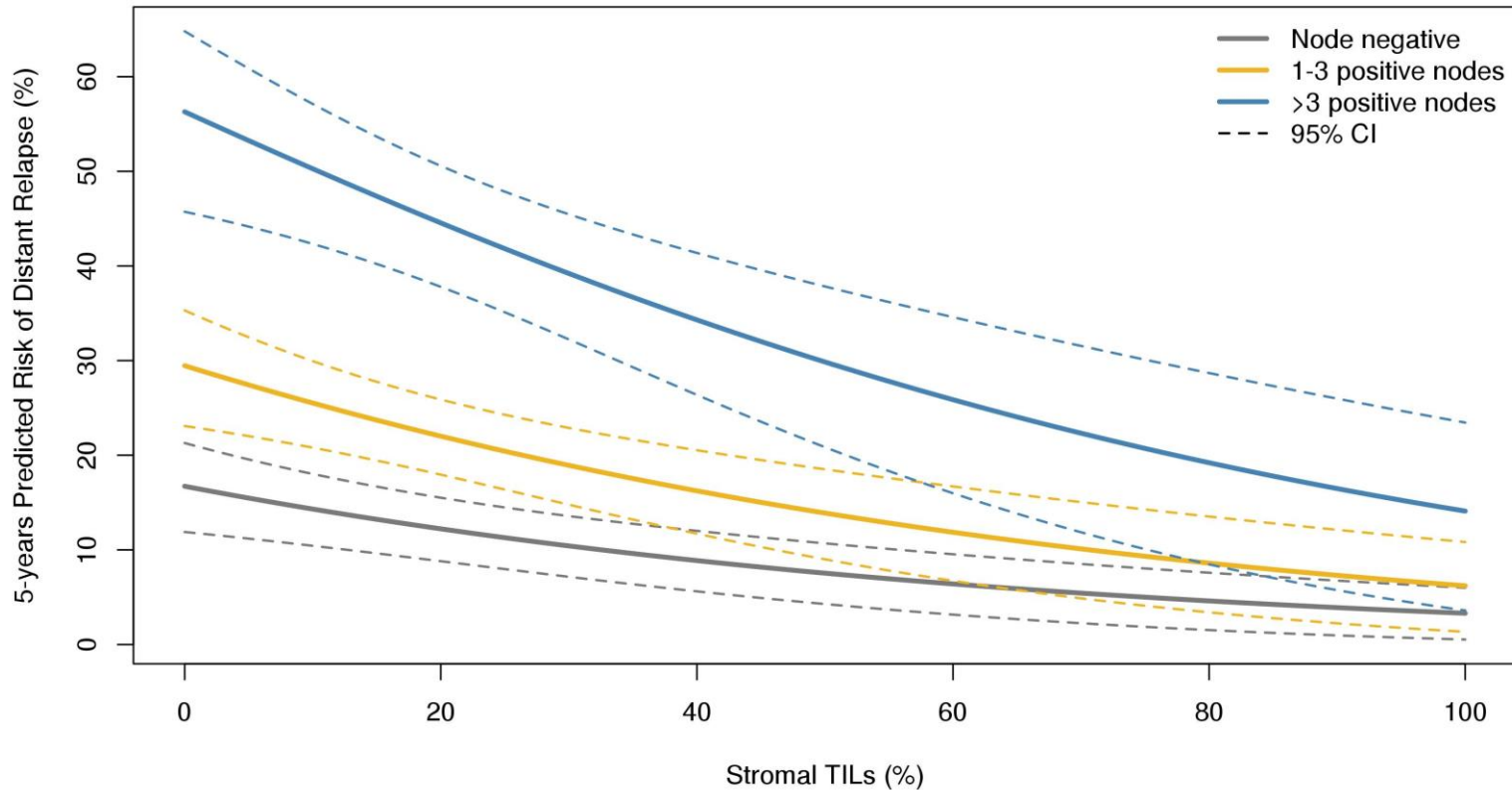
Patients with TIL+ / N0 TNBC do not need any additional therapy than chemo

Loi S, SABCS, 2015

Patients with ctDNA during follow-up have a high risk of relapse

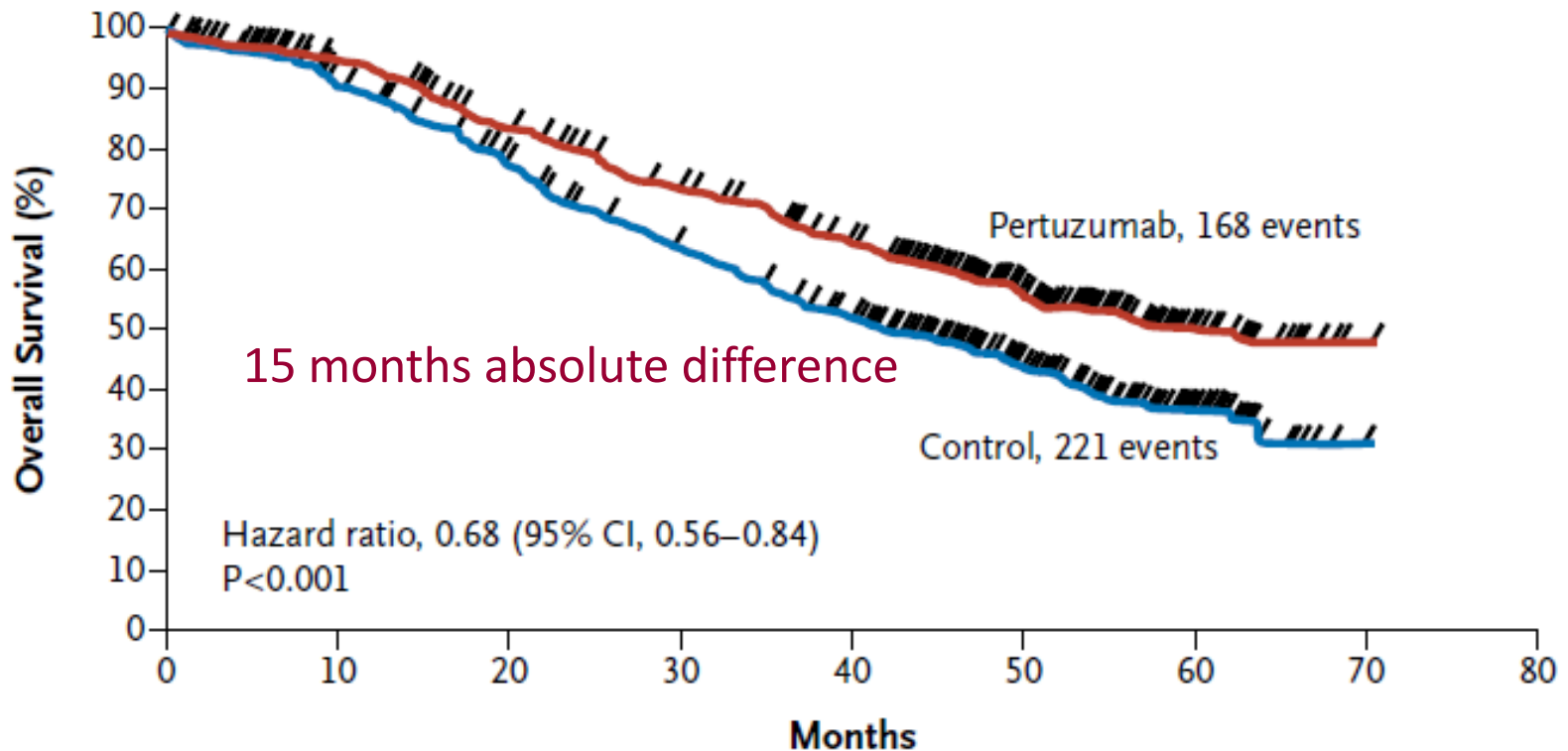**Garcia-Murillas, Science Transl Med, 2015**

Take home message

- New biomarkers could help better defining which population should be the target of adjuvant trials & further approvals in early breast cancers:
  - TIL- TNBC
  - ctDNA+ ER+ BC

- First reports of prospective genomic trials (Sparano, NEJM, 2015)

- Investment on academic research could allow narrowing the labels of new drugs
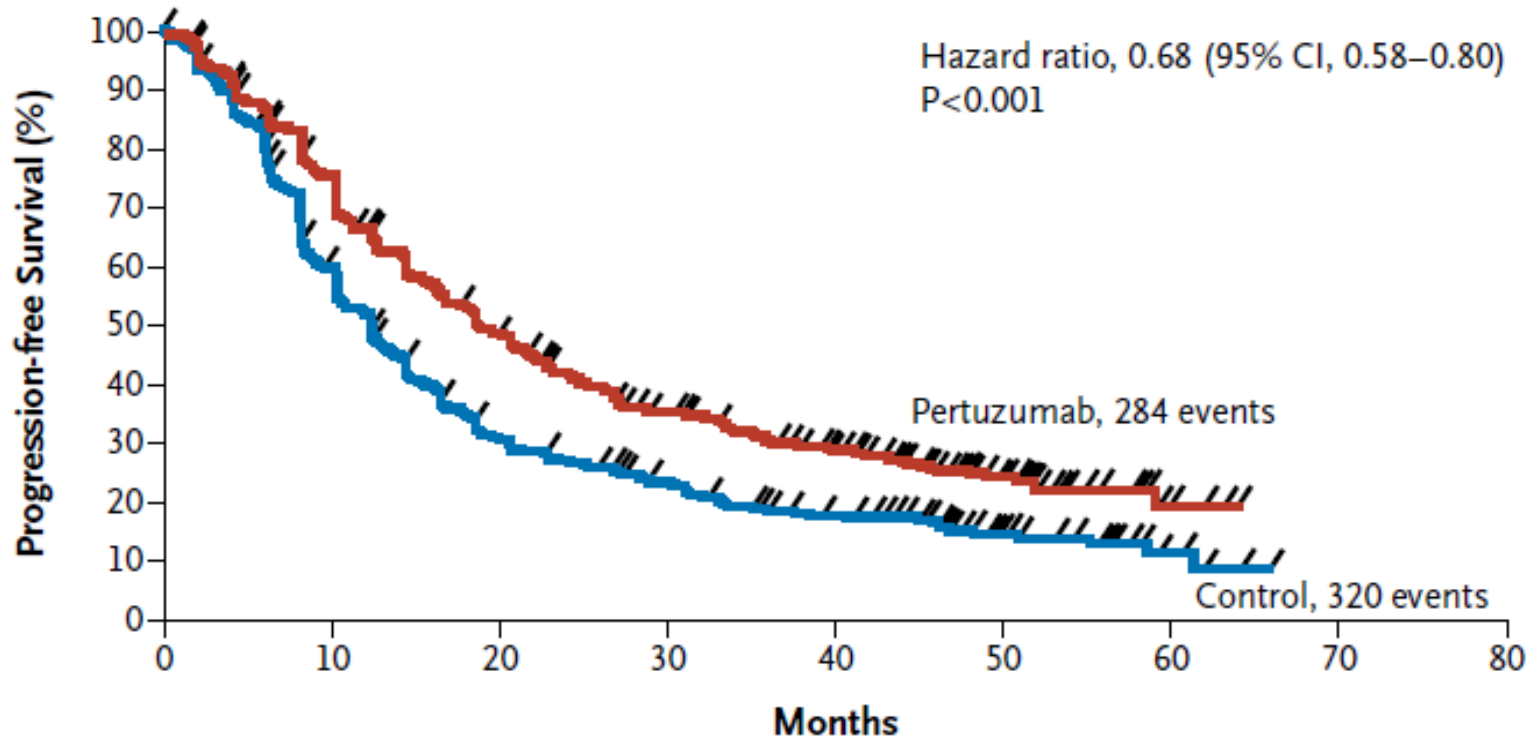
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  - Prospective validation of gene signatures

- **New Her2-3 inhibitors**

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# Pertuzumab improves dramatically OS in Her2-overexpressing mBC...

Overall Survival (%) vs Months

Pertuzumab, 168 events

Control, 221 events

15 months absolute difference

Hazard ratio, 0.68 (95% CI, 0.56–0.84)
P<0.001

Swain, ESMO 2014, NEJM 2015

… but only modestly improves PFS

Need to substitute PFS by other surrogates of OS in drugs that activate immune system: Spider plots ? Tumor growth rate ? Lymphocytic infiltration at PD ? Etc…

Neratinib (TKI) after trastuzumab
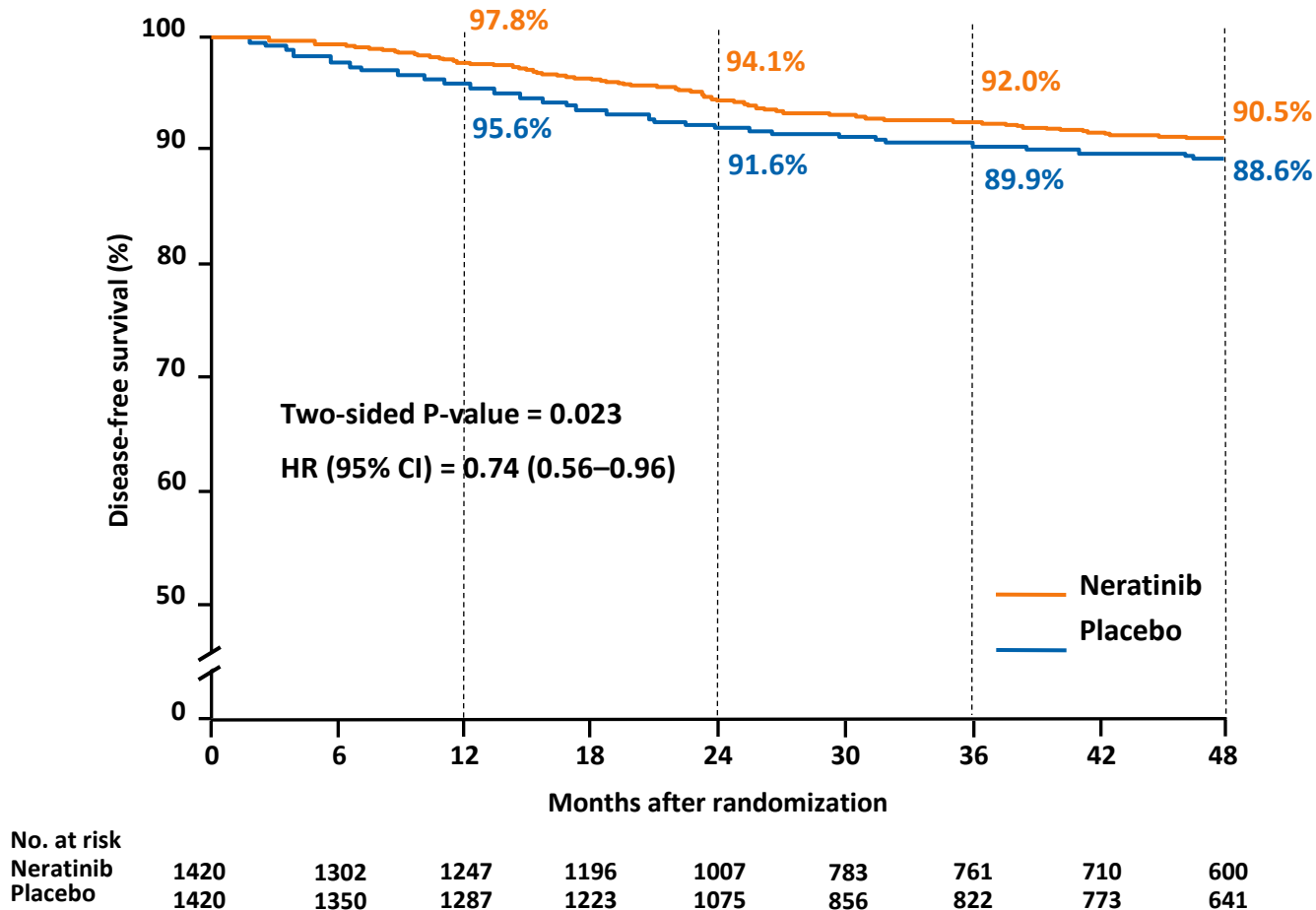
First trial showing that a TKI targeting oncogenic event
can improve outcome in the adjuvant setting
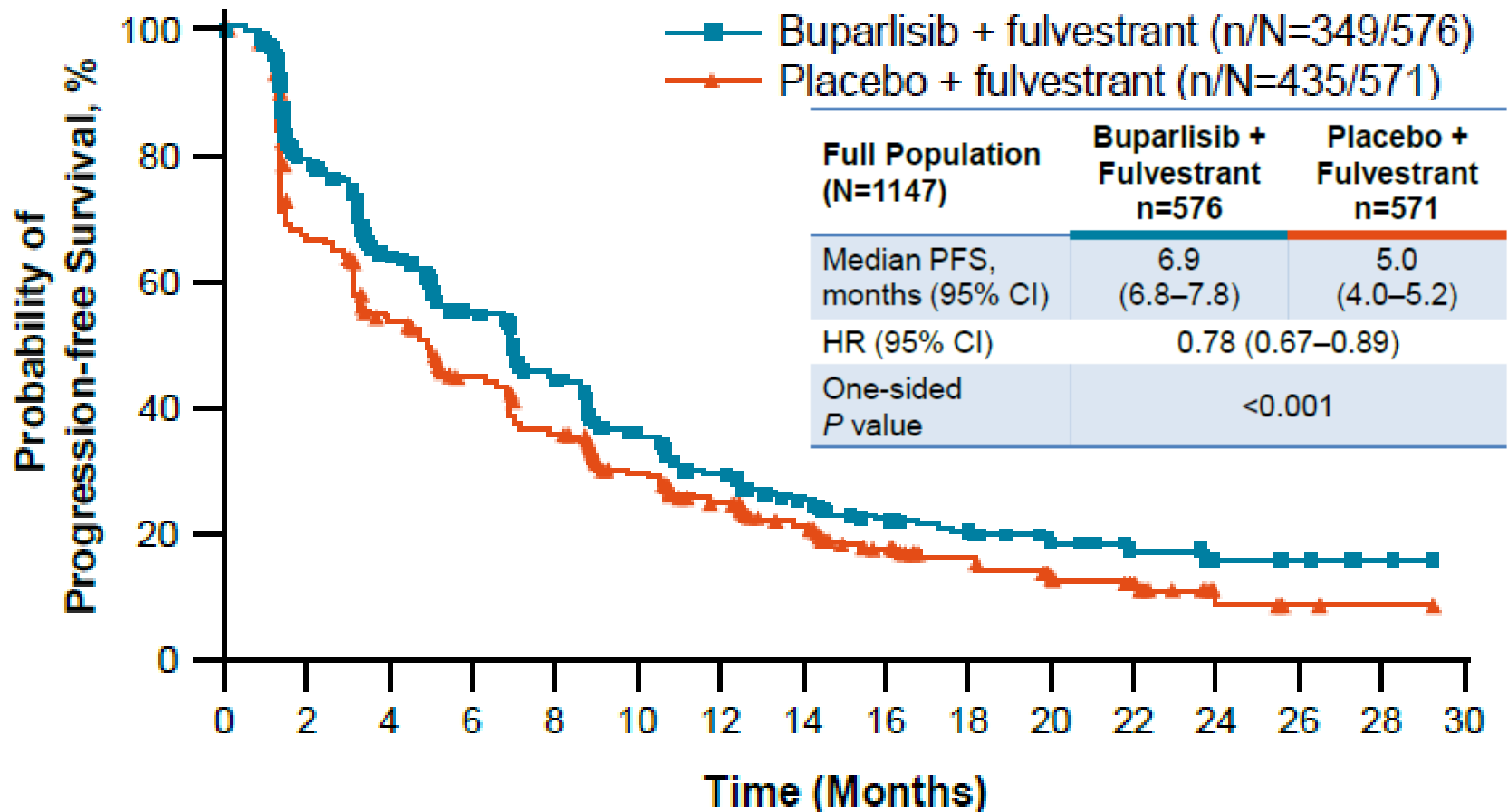
Chan, SABCS, 2015

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  - **CDK4**
  - **PI3K**
  - **AKT**
  - **Mutational load**

Randomized trials testing CDK4 inhibitors

| Treatment	setting	Pre treatment	phase	n	Effect on primary endpoint
Letrozole +/- palbociclib *(Finn, Lancet Oncol, 2015)*	meta	Endocrine sensitive	Phase II randomized	165	PFS: 20 versus 10 months HR: 0.49 (0.32–0.75) P: 0.0004
Fulvestrant +/- palbociclib *(Turner, NEJM, 2015)*	meta	Resistant to AI	Registration trial	521	PFS: 9.2 versus 3.8 months PFS: HR: 0.42 (0.32–0.56) <0.001

Palbociclib prolongs PFS in two randomized trials
Results pending for abemaciclib and ribociclib
Adjuvant trials started

Efficacy of non-selective PI3K inhibitors in overall **trial** population

Legend:
- Buparlisib + fulvestrant (n/N=349/576)
- Placebo + fulvestrant (n/N=435/571)

Full Population (N=1147)	Buparlisib + Fulvestrant n=576	Placebo + Fulvestrant n=571
Median PFS, months (95% CI)	6.9 (6.8–7.8)	5.0 (4.0–5.2)
HR (95% CI)	0.78 (0.67–0.89)	
One-sided P value	<0.001	

Y-axis: Probability of Progression-free Survival, %

X-axis: Time (Months)

Baselga, SABCS, 2015

Efficacy of non-selective PI3K inhibitors in patients with PIK3CA mutation on ctDNA

ctDNA *PIK3CA* Mutant n=200	Buparlisib + Fulvestrant n=87	Placebo + Fulvestrant n=113
Median PFS, months (95% CI)	7.0 (5.0–10.0)	3.2 (2.0–5.1)
HR (95% CI)	0.56 (0.39–0.80)	
One-sided nominal *P* value	<0.001	

Baselga, SABCS, 2015
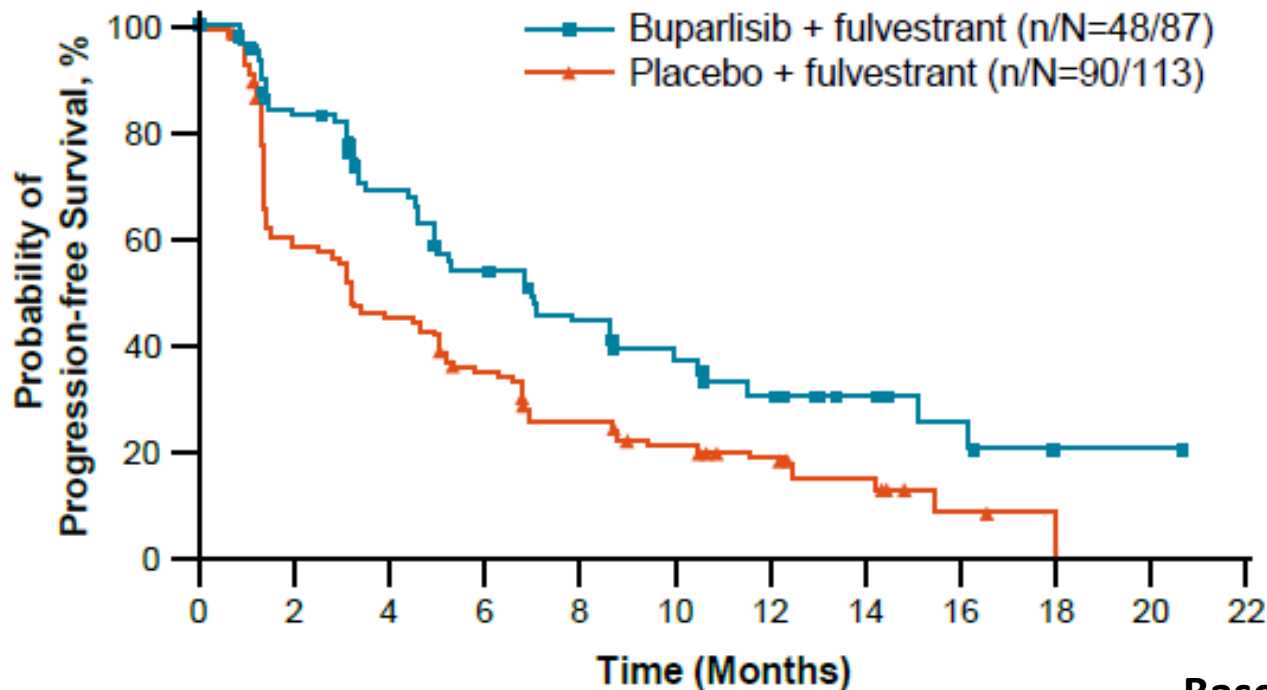
The best is still to come: Alpha-selective PI3K inh

Alpelisib + FUL
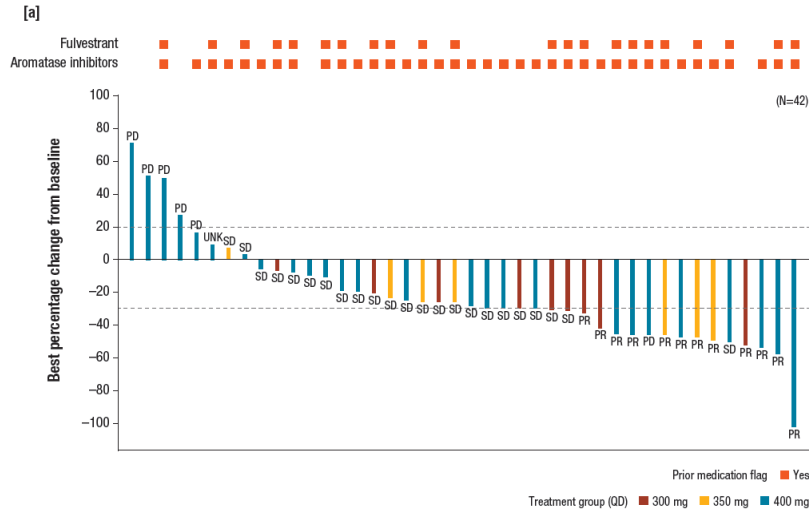
Taselisib + FUL

Juric, SABCS, 2015
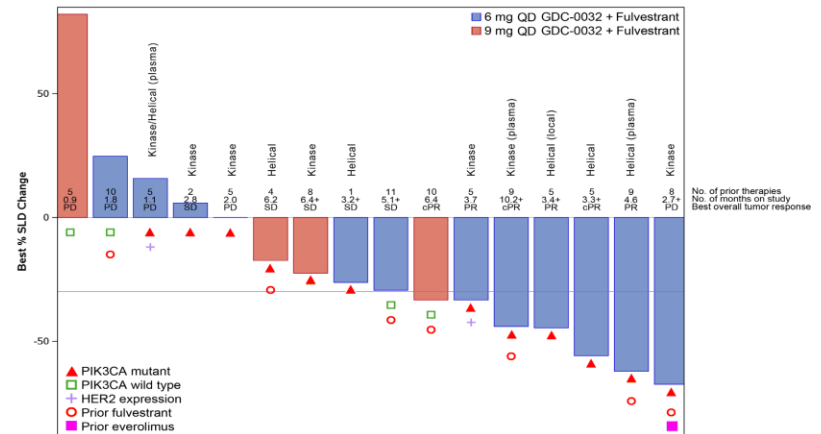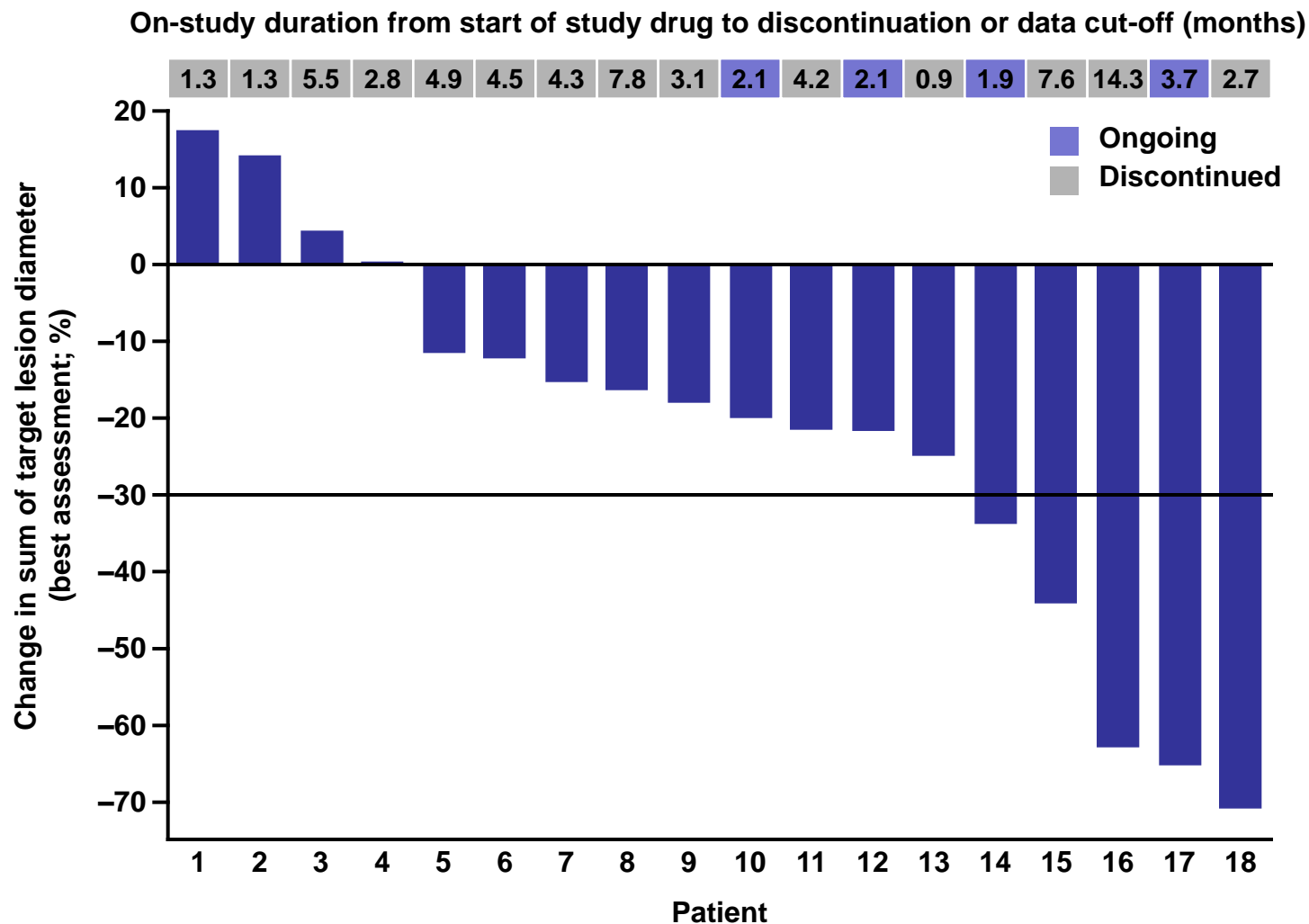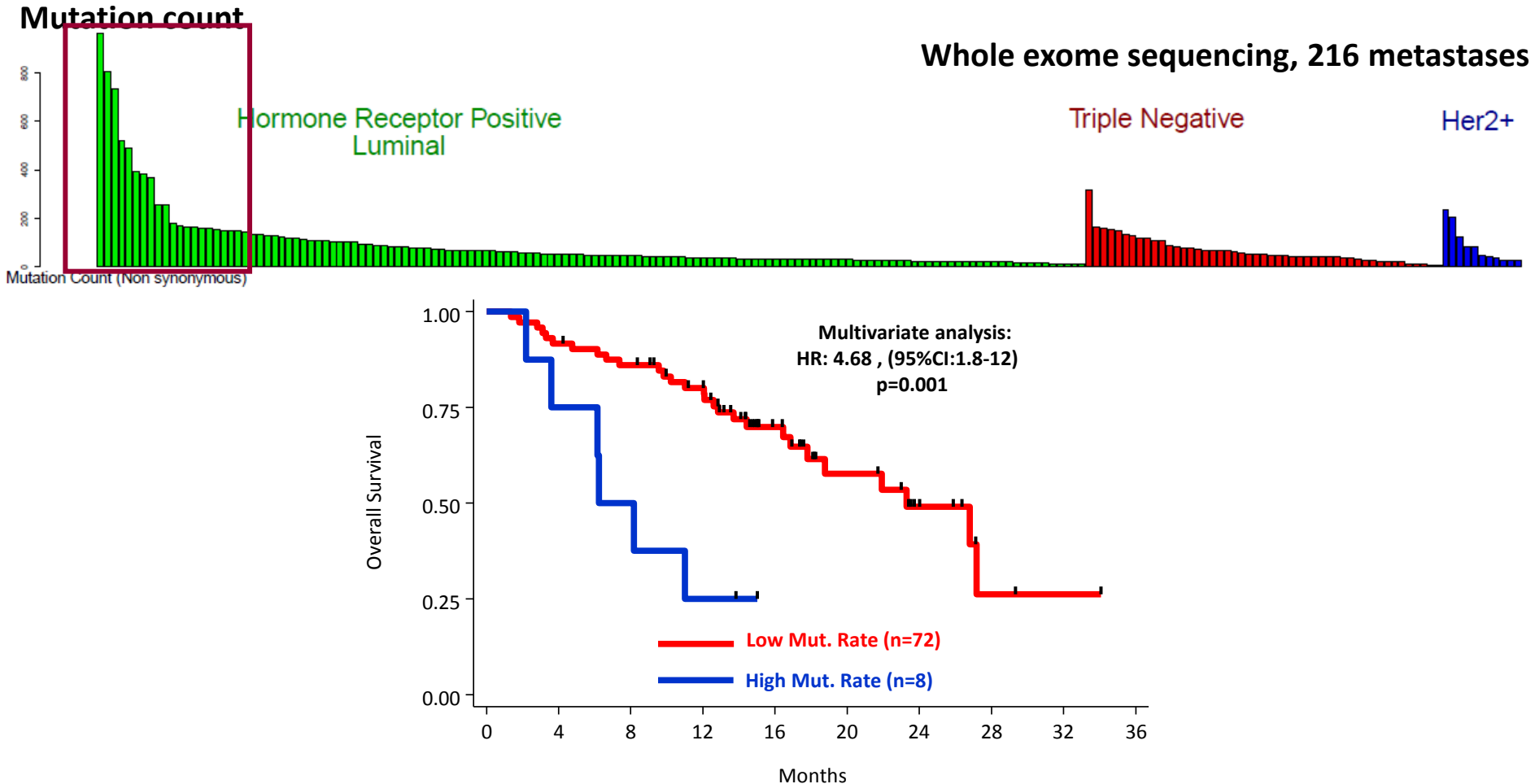
Juric, SABCS, 2013

Promising antitumor activity in PIK3CA mutant, in combination with ET
Ongoing phase III registration trials (SOLAR1, SANDPIPER)

Efficacy of AZD5363 in patients with AKT1 mutations (breast cancer)

On-study duration from start of study drug to discontinuation or data cut-off (months)

| 1.3 | 1.3 | 5.5 | 2.8 | 4.9 | 4.5 | 4.3 | 7.8 | 3.1 | 2.1 | 4.2 | 2.1 | 0.9 | 1.9 | 7.6 | 14.3 | 3.7 | 2.7 |

Ongoing
Discontinued

Tumor shrinkage but early relapse, need to combine with endocrine therapy

Hyman, AACR/NCI/EORTC, 2015

Mutational load and metastases

Whole exome sequencing, 216 metastases

Mutation count

Hormone Receptor Positive Luminal

Triple Negative

Her2+

Mutation Count (Non synonymous)

Multivariate analysis:
HR: 4.68 , (95%CI:1.8-12)
p=0.001

Overall Survival

Low Mut. Rate (n=72)

High Mut. Rate (n=8)

Months

A subset of ER+/Her2- mBC (10%) present a high mutational load
This subset does not exist in eBC and is associated with very poor outcome

Lefebvre, MAP conference, 2015

Conclusion

- Fine-tuning & repositioning old drugs could improve outcome in BC

- New biomarkers are being validated that would allow narrowing the population that would be eligible for adjuvant therapies & future approvals

- Pertuzumab is an illustration that PFS is not an appropriate surrogate for mAb

- Neratinib is an illustration that a TKI can improve outcome in the adjuvant setting

- New targets include: CDK4, PI3K, AKT1 and PD1