# Activity of neoadjuvant Lapatinib (L) plus Trastuzumab (T) for early breast cancer (EBC) according to PIK3CA mutations: pathological complete response (pCR) rate in the CHER-LOB study and pooled analysis of randomized trials

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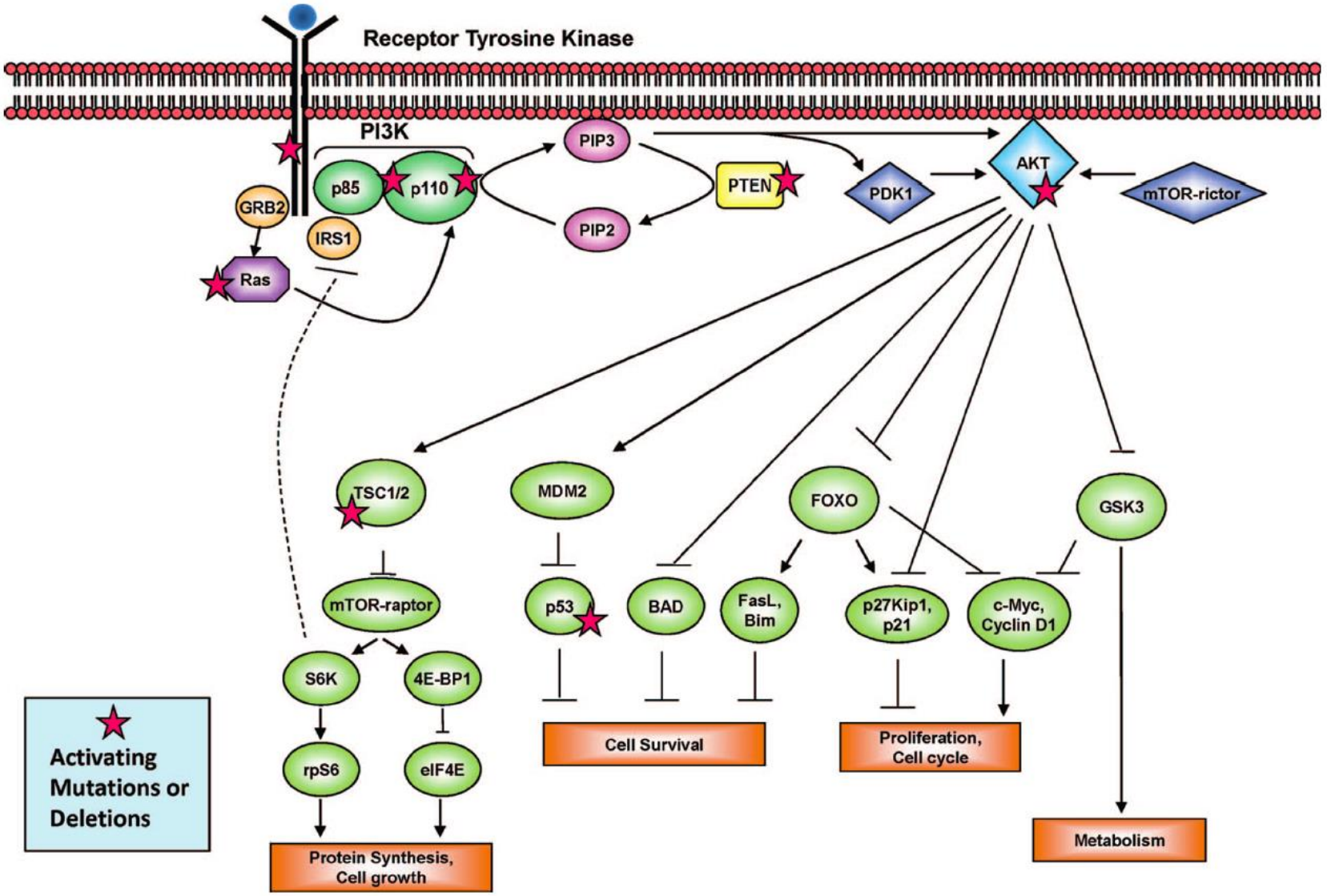
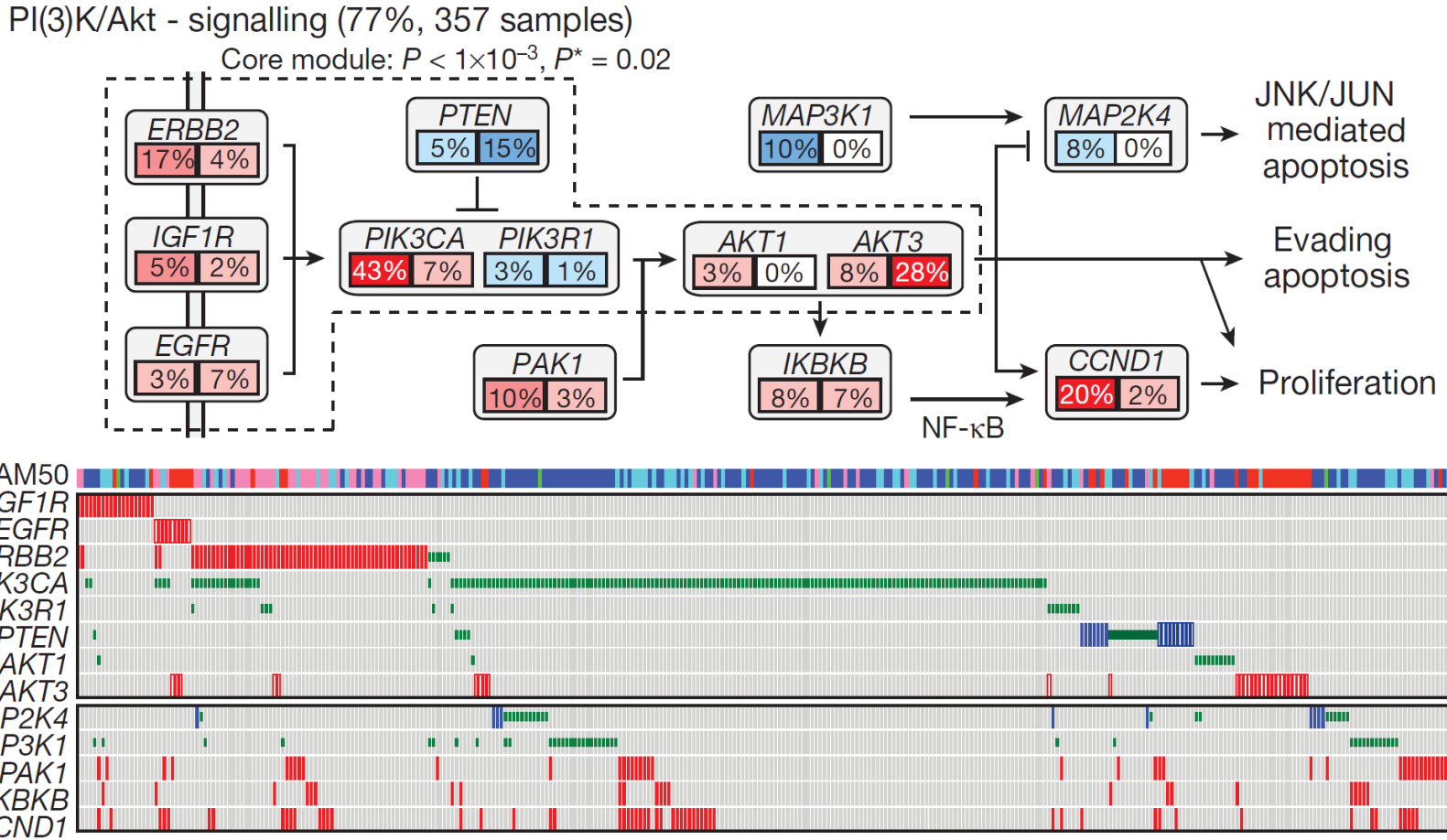
- The authors declare that they have no conflicts of interest




Baselga J, The Oncologist 2011

# PIK3 pathway deregulation in breast cancer




Cancer Genome Atlas Network. Nature 2012, 490:61-70

# *PIK3CA* mutations in HER2+ breast cancer

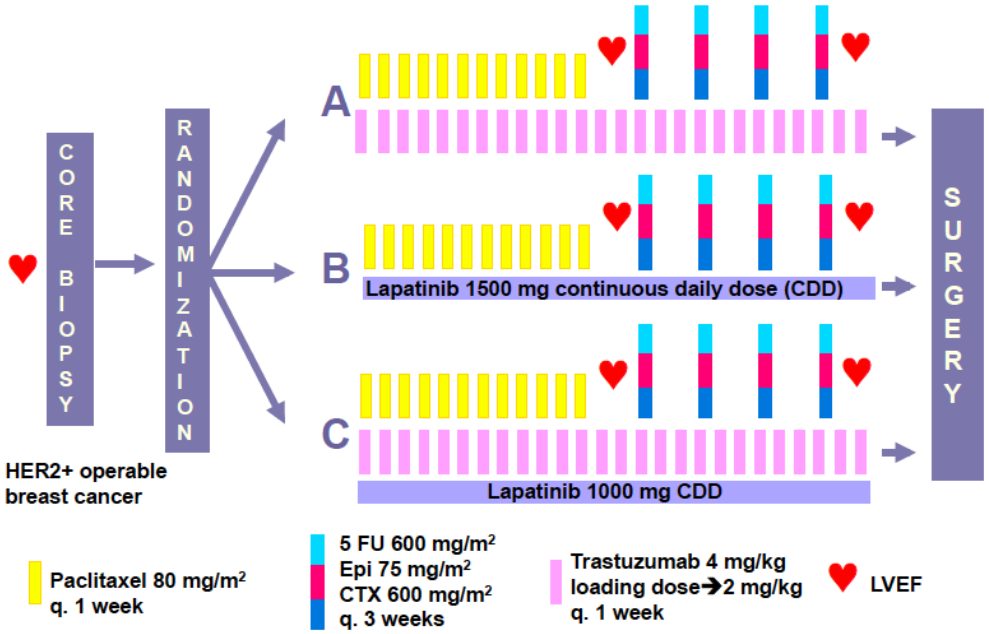
- *PIK3CA* is mutated in 20% to 25% HER2 positive breast cancer
- Preclinical data have shown mutated *PIK3CA* to be associated with resistance to lapatinib and trastuzumab
- *PIK3CA* mutations are associated with poor prognosis in advanced HER2-positive breast cancer patients treated with:
  - chemotherapy plus trastuzumab +/- pertuzumab
  - chemotherapy +/- lapatinib

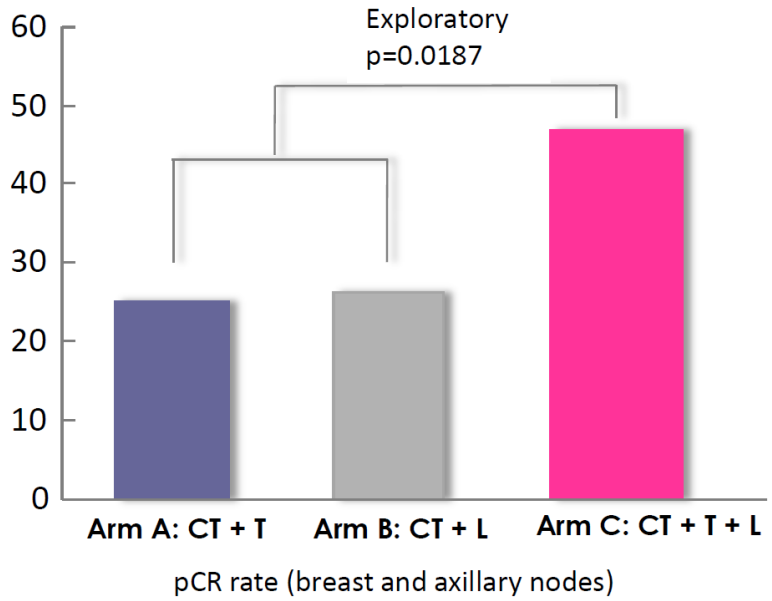
Cancer Genome Atlas Network. Nature 2012; Eichhorn, Cancer Res 2008; Berns K, Cancer Cell 2007; Baselga J, SABCS 2012; Xu B, Breast Cancer Res 2014

# Aim

To evaluate the correlation of *PIK3CA* mutational status with pathologic complete remission (pCR) in HER2 positive breast cancer patients treated with neoadjuvant chemotherapy plus trastuzumab, lapatinib or combined trastuzumab + lapatinib

# Clinical platform: CHER-LOB study






Guarneri V. et al. J Clin Oncol 2012; 30:1989-95

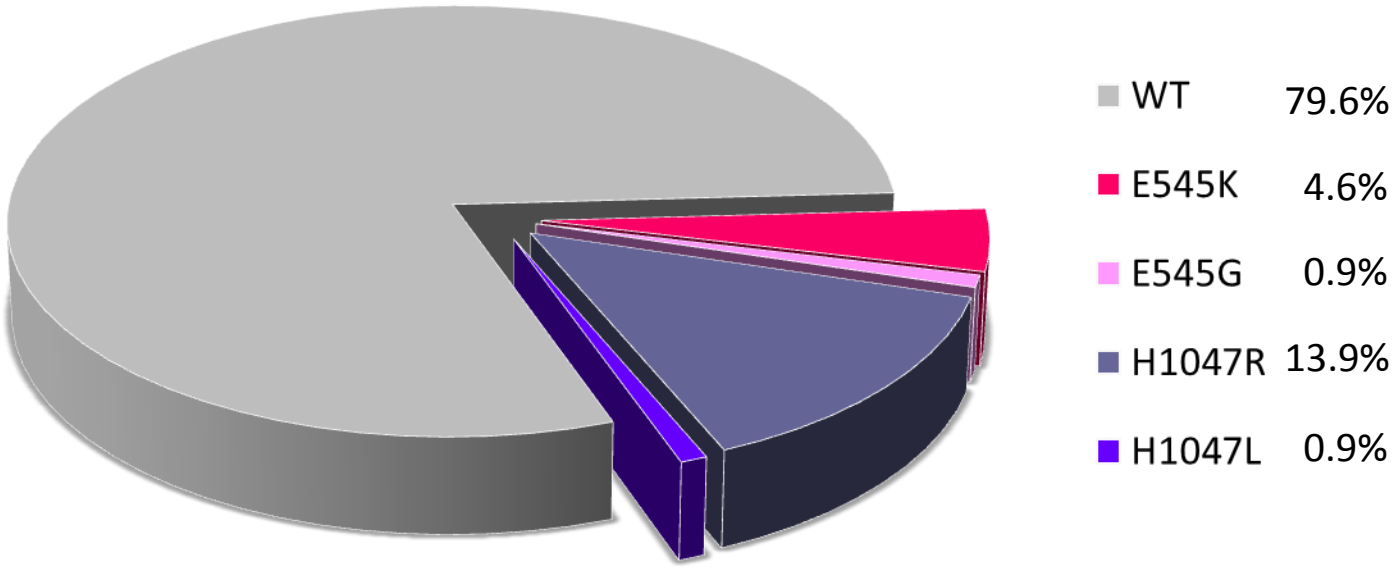
# CHER-LOB translational study

- Randomized patients: n= 121
- Centrally collected samples n= 113 (93.4%)
- Samples analyzed for *PIK3CA* mutations n=108 (89.2%)

# CHER-LOB: *PIK3CA* mutation analysis

- *PIK3CA* mutational status was evaluated in FFPE samples from primary tumor biopsy with at least 50% of tumor content
- A CE-IVD commercially available test was used to detect mutations in exon 9 (codons 542, 545, 546) and exon 20 (codons 1043, 1047, 1049)
- Specific mutations were identified by pyrosequencing

# CHER-LOB: *PIK3CA* mutation analysis



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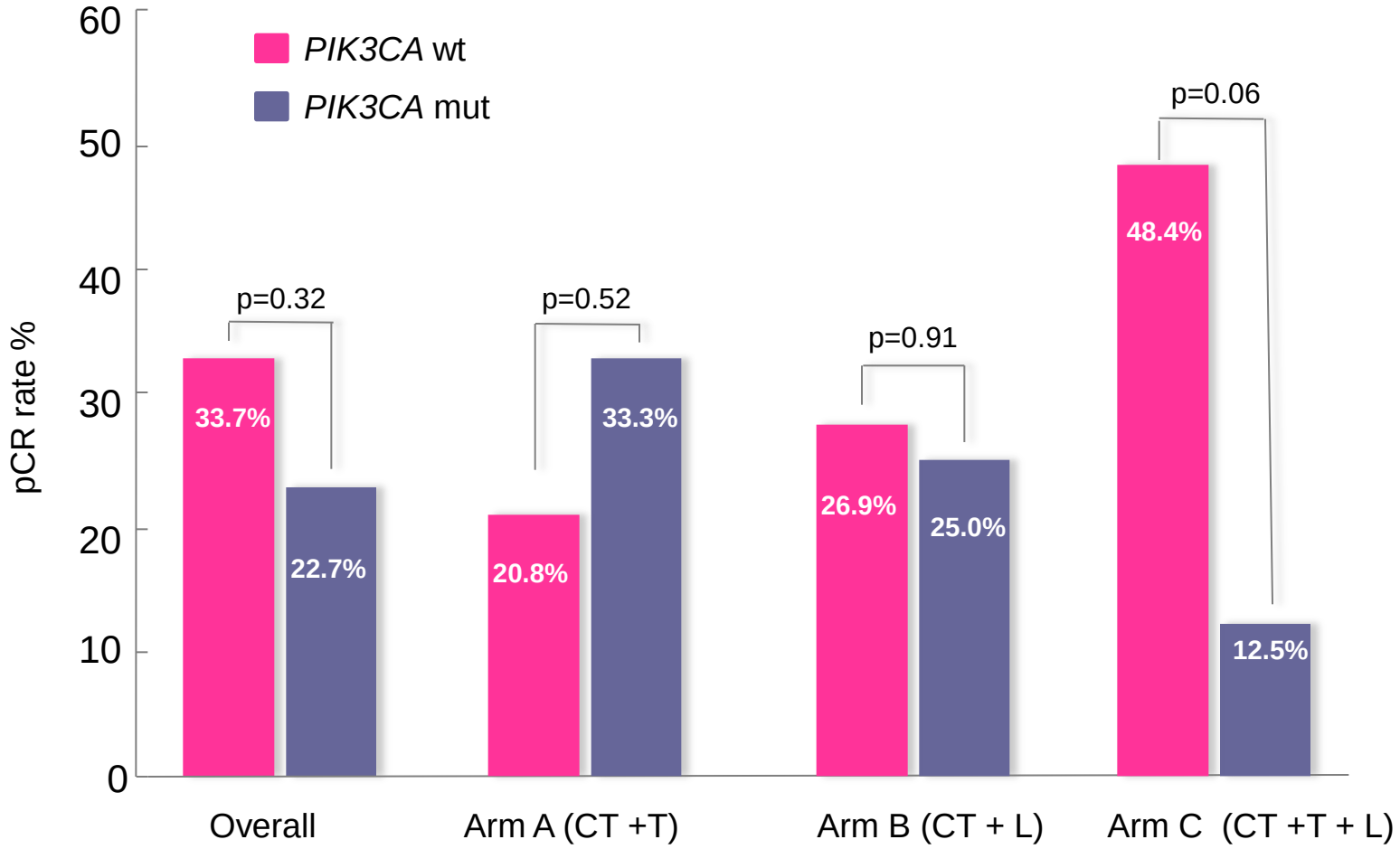
# CHER-LOB: pCR rate according to *PIK3CA* status



# Pooled analysis: methods

- An event-based pooled analysis by extracting activity events (pCR as reported by trialists) and deriving 95% confidence intervals (CI) was accomplished
  - Inclusion criteria: trials in which HER2 positive breast cancer patients cadidates to neoadjuvant chemotherapy were assigned to receive CT+ trastuzumab, lapatinib or their combination
  - pCR reported according to *PIK3CA* status (mutated and WT)
- In addition, a cumulative Odds Ratio (OR) of single versus dual HER2 inhibition was conducted (for randomized trials only), with a random effect model considering the known heterogeneity
  - Interaction according to *PIK3CA* status (mutated vs WT) was calculated as well

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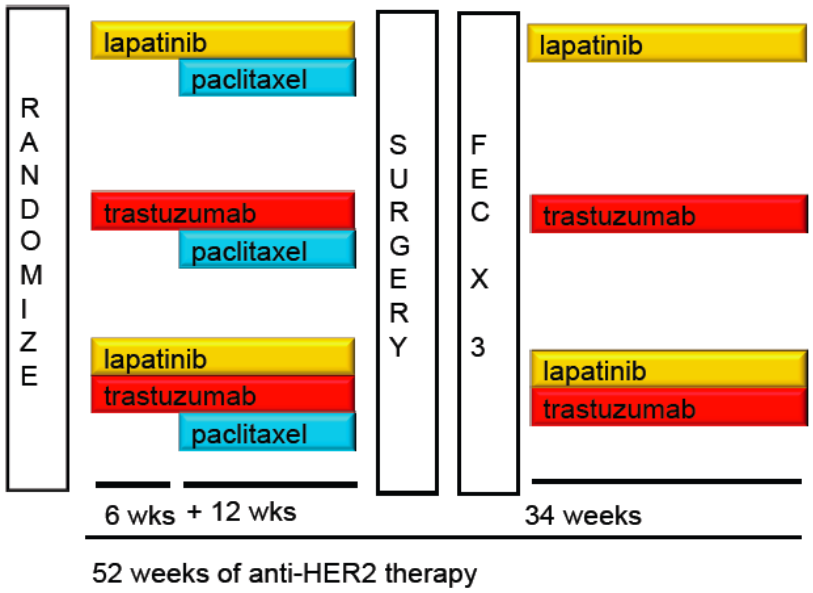
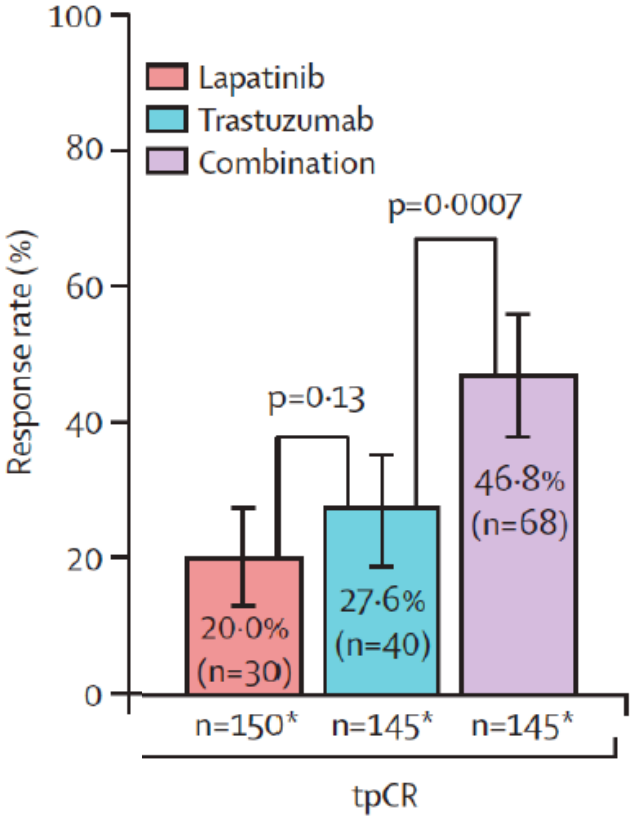
# Additional data on relation between *PIK3CA* status and pCR rates with dual anti-HER2 blockade: NeoALTTO

Invasive operable
HER2+ BC
T > 2 cm
(inflammatory BC excluded)
LVEF ≥ 50%
N=450

Stratification:
- T ≤ 5 cm vs. T > 5 cm
- ER or PgR + vs. ER & PgR –
- N 0-1 vs. N ≥ 2
- Conservative surgery or not



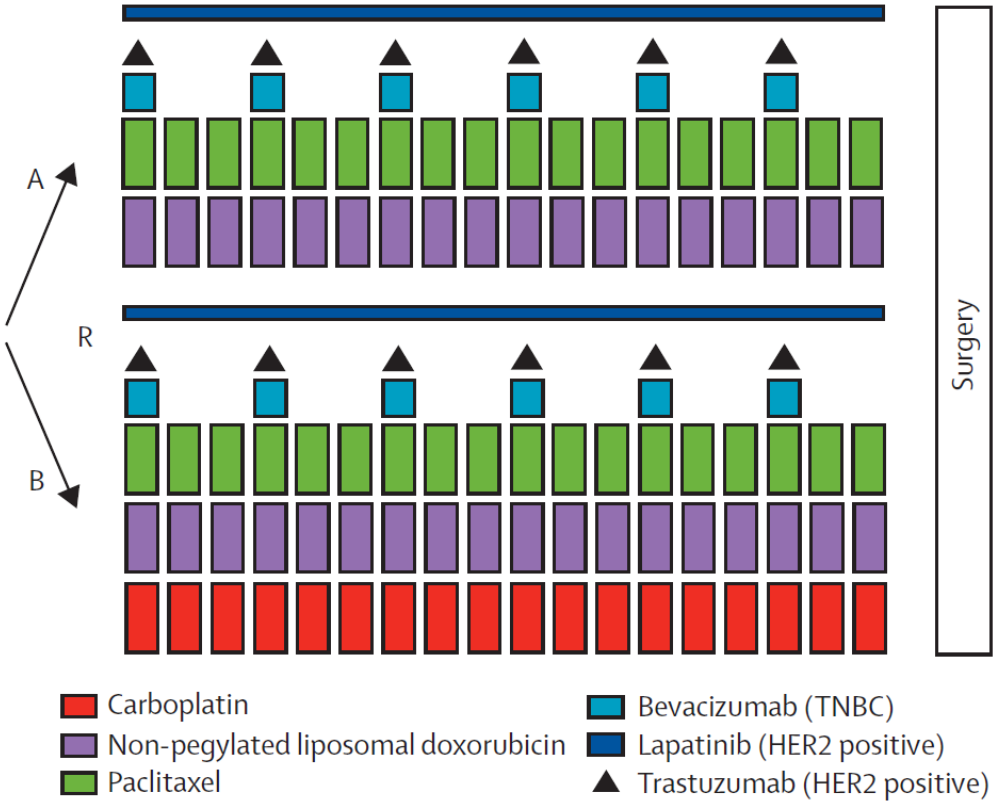



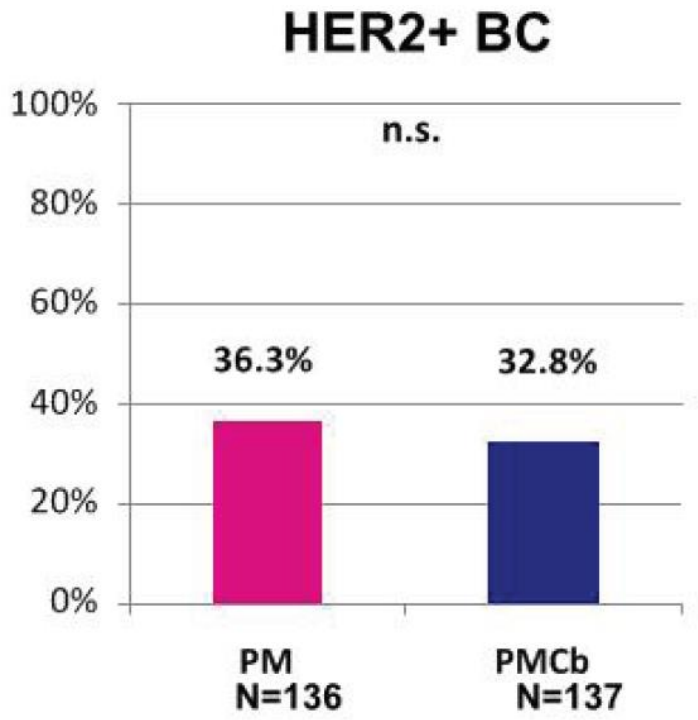

Evaluable for *PIK3CA* mutations: n=355/455 (78%)
Prevalence of *PIK3CA* mutations: 23%

esmo.org

Baselga J et al. Lancet 2012; 379(9816):633-40

# Additional data on relation between *PIK3CA* status and pCR rates with dual anti-HER2 blockade: GeparSixto



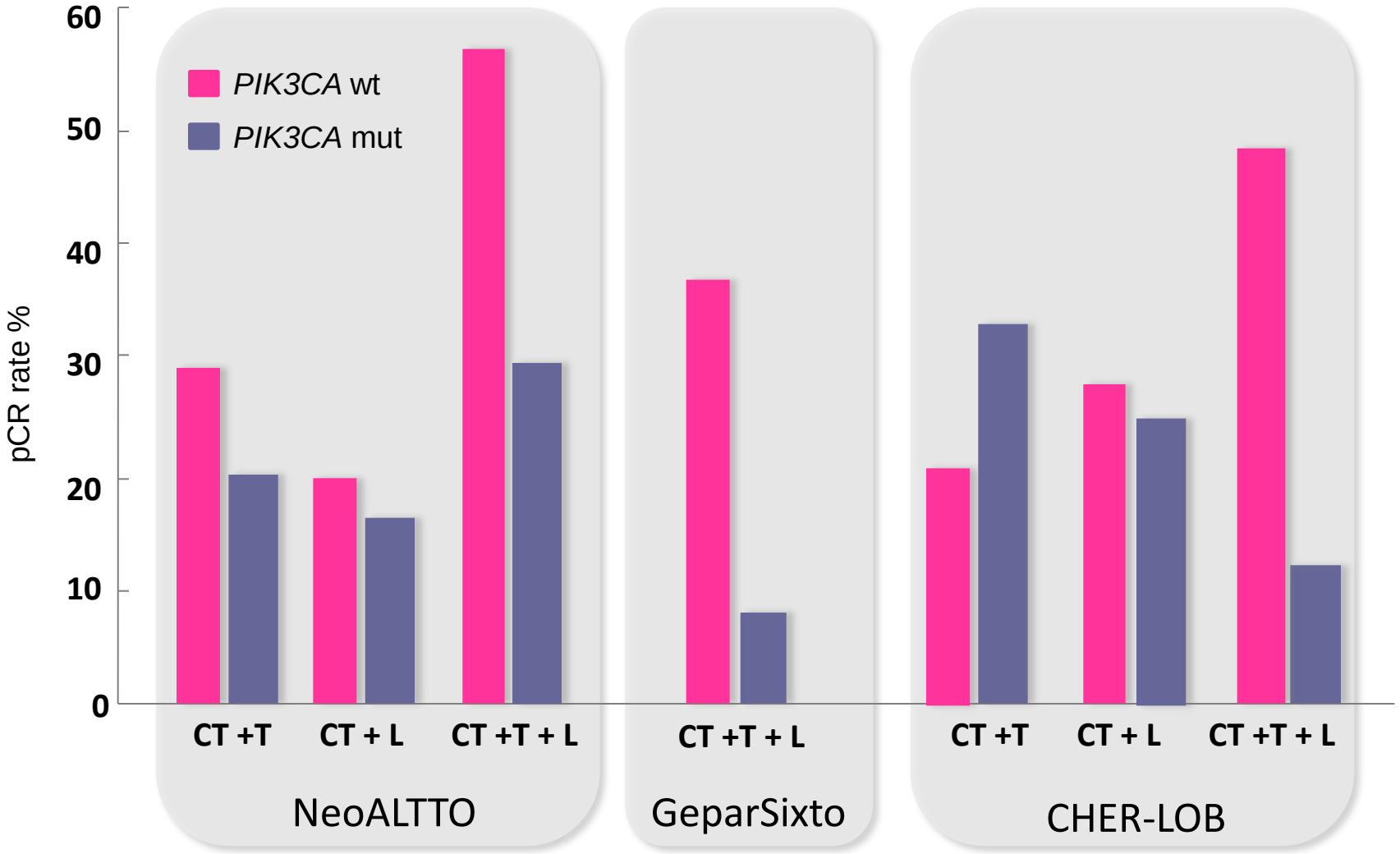

Evaluable for *PIK3CA* mutations: n=240/273 (87.9%)

Prevalence of *PIK3CA* mutations: 19.1%



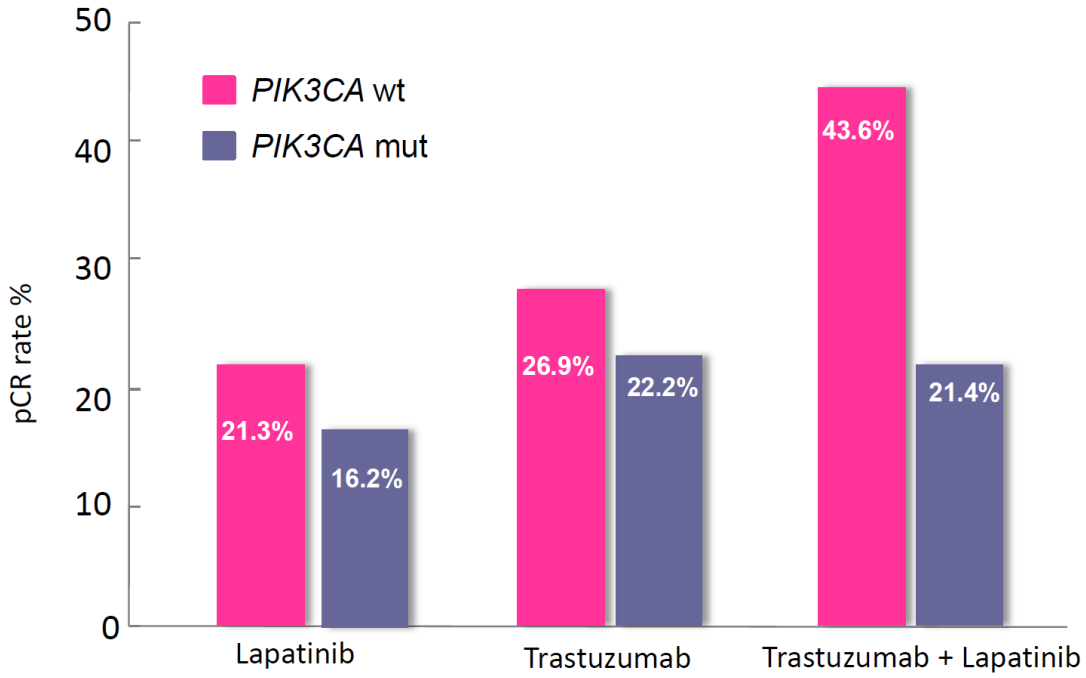
Von Minckwitz G, et al. Lancet Oncol 2014; Loibl S, J Clin Oncol 2014

# *PIK3CA* status and pCR rates with dual anti-HER2 blockade:NeoALTTO, GeparSixto and CHER-LOB



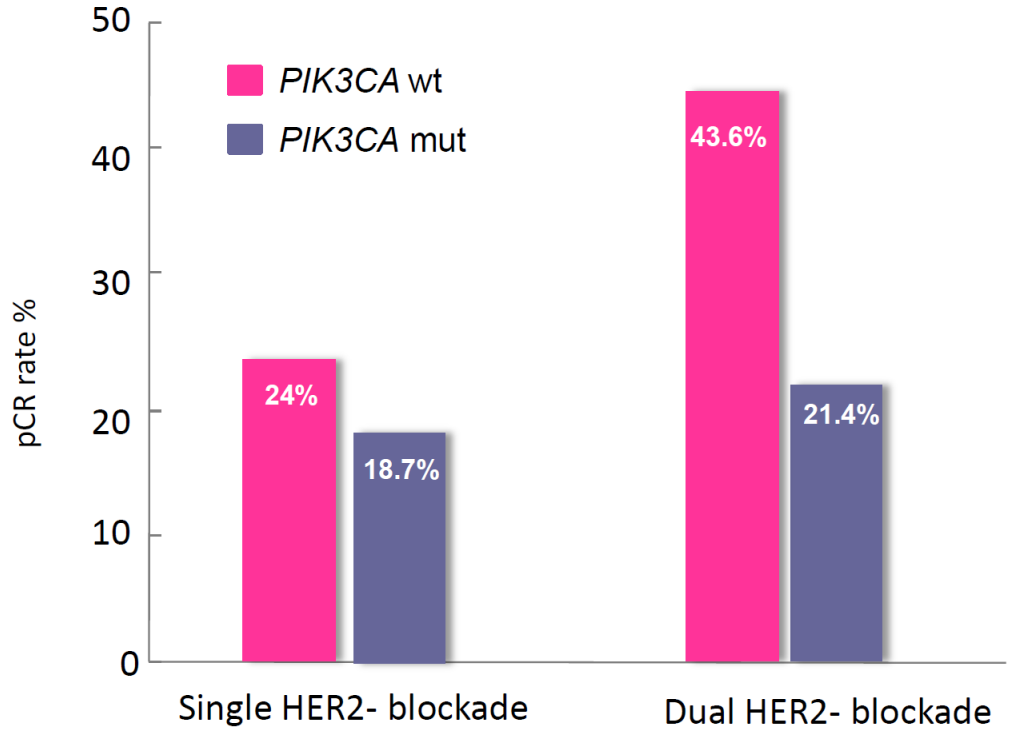

Baselga J, et al,. ECCO-ESMO 2013; Loibl S, et al. J Clin Oncol 2014

# Results: pCR rates by *PIK3CA* status




| *PIK3CA* | Arms | Events | Pts | pCR (95% CI) |
|---|---|---|---|---|
| Mut | L | 6 | 37 | 16.2% (4.3-28.1) |
| | T | 6 | 27 | 22.2% (6.5-37.9) |
| | L + T | 18 | 84 | 21.4% (12.6-30.2) |
| WT | L | 26 | 122 | 21.3% (14.0-28.5) |
| | T | 31 | 115 | 26.9% (18.8-35.1) |
| | L + T | 138 | 316 | 43.6% (38.2-49.1) |

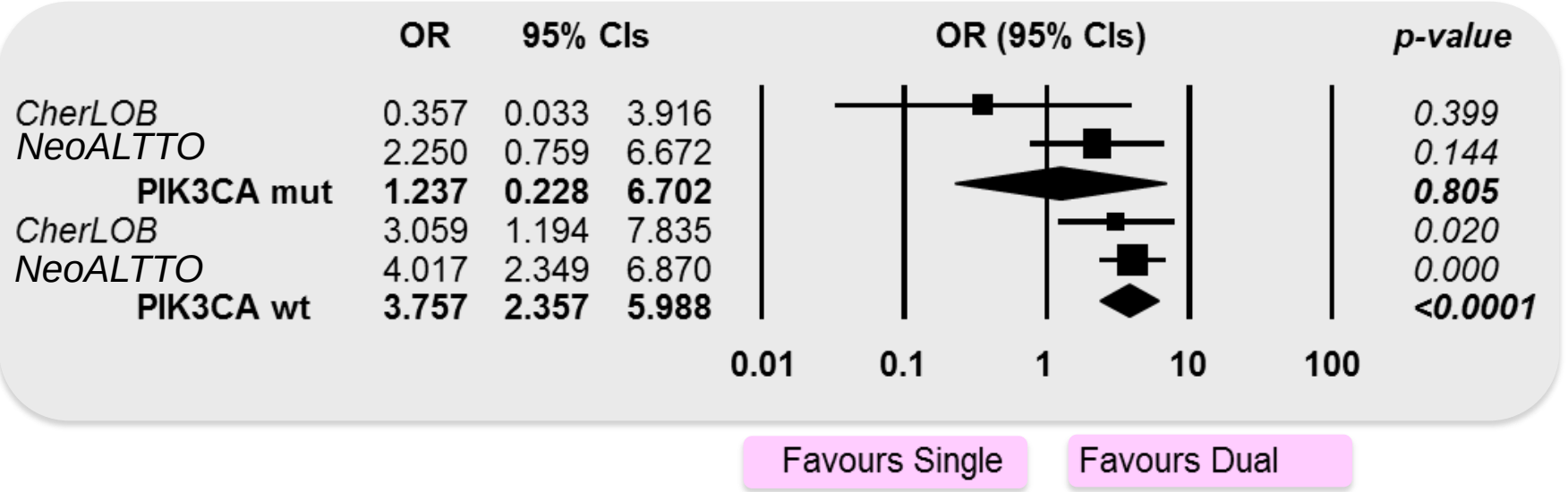
# Results: pCR rates by *PIK3CA* status (single vs dual blockade)




| *PIK3CA* | Arms | Events | Pts | pCR (95% CI) |
|---|---|---|---|---|
| Mut | Single | 12 | 64 | 18.7% (9.1-28.3) |
| | Dual | 18 | 84 | 21.4% (12.6-30.2) |
| WT | Single | 57 | 237 | 24.0% (18.6-29.4) |
| | Dual | 138 | 316 | 43.6% (38.2-49.1) |

# Results: pCR for Dual vs Single HER2 inhibition according to *PIK3CA* status

- Cumulative data of CHER-LOB and NeoALTTO




- Overall Heterogeneity: [Q-test 4.321] *p=0.229*
- Interaction: [Q-Test 2.196] *p=0.138*

## Strenghts

- *PIK3CA* analysis prospectively planned in all trials
- Effective sample collection and analysis (78%-89% of patients )
- Consistent results regardless of the adopted technique
- Similar effects across studies

## Limitations

- Relatively limited sample size
- Too few studies for definitive conclusions
- Unknown surrogacy of pCR in *PIK3CA* wild type vs mutated
- Potential imbalance of HR status in wt vs mutated tumors
- Not uniform pCR definition across studies
- Chemotherapy as a confounder

# Summary and conclusions

- *PIK3CA* mutations are detected in 21.1% of HER2+ BC
- *PIK3CA* wild type status is related to a higher pCR rate following CT + dual blockade with trastuzumab and lapatinib
- *PIK3CA* mutational status does not predict any differential sensitivity to chemotherapy + either trastuzumab or lapatinib
- These data warrant further investigation in the adjuvant setting
- If confirmed, the wild-type *PIK3CA* status might be a marker to select patients to be treated with trastuzumab and lapatinib

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# Acknowledgments


Patients participating to the trials
CHER-LOB Clinical Investigators

Medical Oncology,
Department of Medicine
University of Verona

Dept. of Surgery, Oncology
and Gastroenterology,
University of Padova

Department of Pathology
University of Modena and
Reggio Emilia

Istituto Oncologico Veneto
IRCCS, Padova

GlaxoSmithKline