# Xenograft models: Problems, pitfalls and future developments Contra


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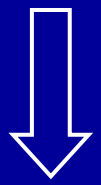
# The clinical research context in 2014

a) Neo-adjuvant and “window of opportunity” studies facilitate “in vivo” understanding of new agents pharmacodynamics

b) Access to biological samples is becoming common in the context of clinical studies (tumor tissue, CTC, circulating biomarkers)

c) Increasing knowledge is available on drugs mechanism of action and tumor biology



High level of selectivity in considering results from pre-clinical models

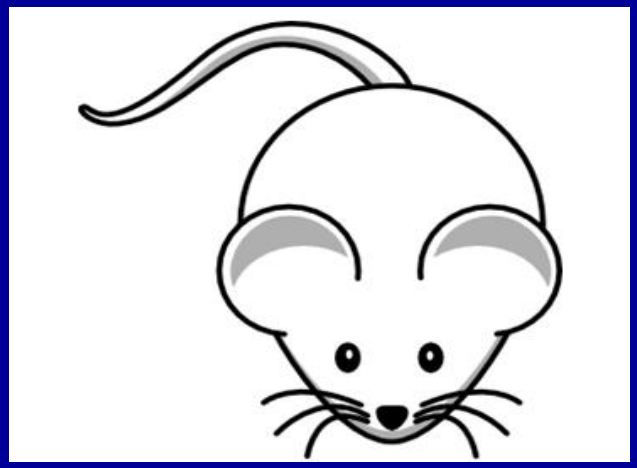
# Methods: Review of studies in which Patient-Derived breast cancer Xenografts (PDX) were generated

## Twelve studies were identified:

- Visonneau S et al, Am J Pathol 1998
- Al-Hajj M et al, Proc Natl Acad Sci USA 2003
- Beckhove P et al, Int J Cancer 2003
- Marangoni E et al, Clin Cancer Res 2007
- Bergamaschi A et al, Mol Oncol 2009
- Liu H et al, Proc Natl Acad Sci USA 2010
- De Rose YS et al, Nat Med 2011
- Cottu P et al, Breast Cancer Res Treat 2012
- Kabos P et al, Breast Cancer Res Treat 2012
- Petrillo LA et al, Breast Cancer Res Treat 2012
- Reyal F et al, Breast Cancer Res 2012
- Zhang X et al, Cancer Res 2013

# The different phases of my preparation for this talk

## After reviewing the 1st study



## After reviewing a few more studies

## After reviewing the 12th study

# Bottom-line message from the review of the twelve published studies

- Good evidence that PDX have consistency with the tumor of origin in terms of morphology, genomics, transcriptomics and proteomics

- Very limited evidence that response to anti-cancer agents in the PDX reflects response to the same agent in the patient of origin

# Breast cancer studies comparing response to a given agent in the PDX and in the matched tumor of origin (2 out of 12 studies)

| | Study | |
|---|---|---|
| | Zhang et al. | Marangoni et al. |
| - Site of response evaluation | Fat pad | Fat pad |
| - Anti-cancer agent | Doxorubicin or Docetaxel | Docetaxel or Trastuzumab |
| - Treatment duration | Single injection | 8-9 weeks |
| - Outcome measure | Tumor shrinkage | Tumor shrinkage |
| - Concordance PDX/patient | 12/13 cases | 5/7 cases |

Marangoni E et al, Clin Cancer Res 13: 3989-98, 2007; Zhang X et al, Cancer Res 73: 4885-97, 2013

# Issues

- Limited experience (only 20 cases PDX/patient reported overall)

- Limited number of agents (essentially Doxorubicin or Docetaxel)

- Response assessment in patients implies evaluation of multiple M+ sites (only the fat pad site in the PDX)

- Treatment duration ≤ 9 wks. Implications:

-no data on late responses (i.e. HT agents)

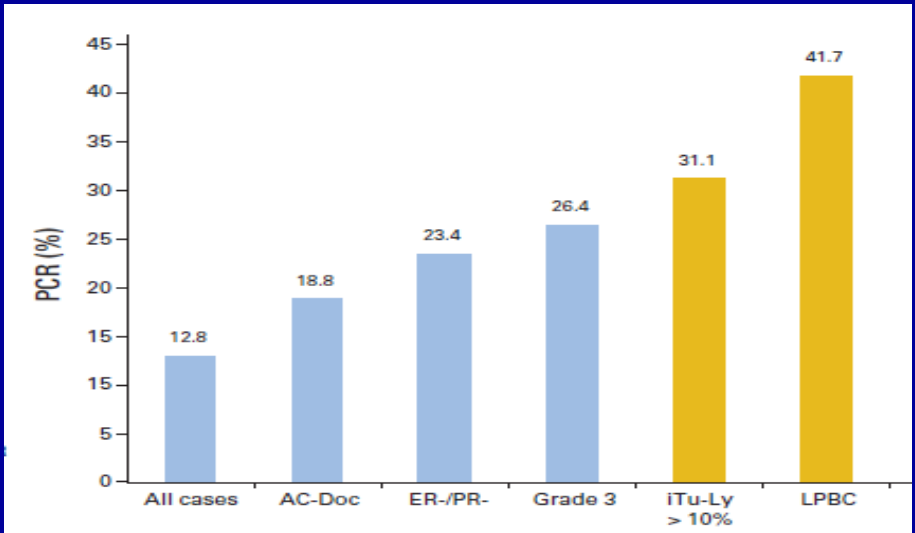
-no data on acquired resistance

- No information on the quality of the observed response (i.e. duration, disease stabilization)

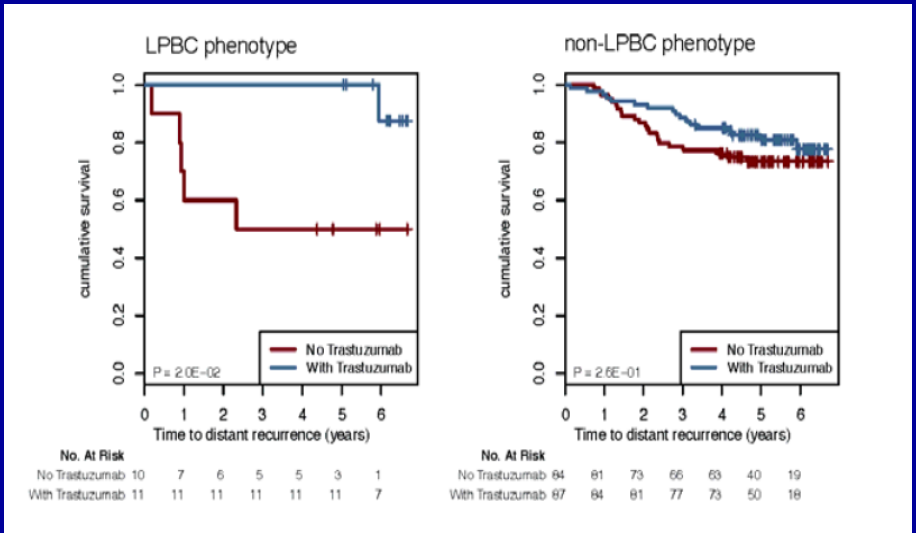
# Additional issues with the PDX model
# No. 1: The host is severely immuno-compromised

## Tumor-associated lymphocytes and sensitivity to:

### Neo-adjuvant chemo*




### Adjuvant Trastuzumab + chemo**




**Implications: potential risk of under-estimating treatment activity with the PDX model, particularly in cases where immuno-competence is relevant**

* Denkert C et al, J Clin Oncol 28:105-113, 2009 ; ** Loi S et al, Ann Oncol 2014 Mar 7 (ahead of print)

# Additional issues with the PDX model
# No. 2: In Luminal tumors the engraftment rate is low

- Engraftement rate = 2.5% in Luminal vs 24.7% in non-Luminal cancers (Cottu P et al, Breast Cancer Res Treat 2012)
- The engraftement rate can potentially be improved by stimulating tumor growth at the fat pad site (by estrogens, matrigel, human mesenchymal stem cells, …)

⇩

**Potential selection bias:**

**Only highly proliferating tumors will be engrafted successully**

# Last (but not least) questions

- Are PDX reproducing the complex intra-tumor heterogeneity of their tumors of origin?

- Is the lack of the human stromal component in the PDX model alterating the biology and the behaviour of the engrafted tumors?

- Are results observed with the PDX model reproducible across different labs?

# Conclusions: PDX as a reliable pre-clinical model to investigate drugs activity in breast cancer

- Only preliminar experience is available, particularly with regard to the comparison in terms of response to anti-cancer agents between PDX and the matched tumor of origin
- Potentially inadequate model to assess the activity of anti-cancer agents requiring a functional immune-system and/or interacting with the stroma component
- Still disappointing for Luminal tumors (low take rate, only aggressive ER+ tumors)
- Important developments have been presented today ⟶ increase the model's reliability