THE TWENTY LESSONS LEARNT FROM THE DEVELOPMENT OF MOLECULAR-TARGETED THERAPIES

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Guillem Argilés has reported no conflicts of interest
Ahmad Awada has reported no conflicts of interest
LESSONS LEARNT
From the development of molecular targeted therapies

Key points
Importance of the target driving carcinogenesis and the selectivity of the new agent
Take into account tumour heterogeneity and mechanisms of resistance
Each patient in a clinical trial should be analysed carefully in particular if efficacy was documented
Perform mainly prospective trials
Perform innovative and « smarter » clinical trials design taking into account:
  • The patient
  • The tumour
  • What it is known about the evolution of the disease
  • The characteristics of the experimental drug
Learn from the past experience in order to avoid mistakes
MOLECULAR BIOLOGY UNDERSTANDING
Changes the approaches of patient care in 2017

- Right patient / target
- Right drug
- Right time

Increased efficacy
New safety profile
Importance of the health-economic index
Better understanding of the tumour biology

## IMPORTANT TARGETS
Involved in carcinogenesis and their inhibitors (1)

<table>
<thead>
<tr>
<th>Target</th>
<th>Tumour</th>
<th>Inhibitor</th>
<th>Predictive markers of sensitivity/resistance</th>
<th>Disease setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>Breast</td>
<td>Tamoxifen, AI, fulvestrant</td>
<td>ER expression, ER mutation (Resistance)</td>
<td>Adjuvant &amp; advanced disease</td>
</tr>
<tr>
<td>EGFR</td>
<td>Head &amp; Neck</td>
<td>Cetuximab</td>
<td>-</td>
<td>Locally/advanced H&amp;N cancer</td>
</tr>
<tr>
<td>EGFR</td>
<td>NSCLC</td>
<td>Gefitinib/Erlotinib/Dacomitinib/Afatinib (Osimertinib)</td>
<td>Mutation of EGFR (T790M)</td>
<td>Metastatic NSCLC</td>
</tr>
<tr>
<td>EGFR</td>
<td>Colorectal</td>
<td>Cetuximab/Panitumumab</td>
<td>Ras status</td>
<td>Metastatic colorectal cancer</td>
</tr>
<tr>
<td>HER-2/neu</td>
<td>Breast, gastric</td>
<td>Trastuzumab, Pertuzumab, Lapatinib, Neratinib</td>
<td>HER-2/neu amplification</td>
<td>Adjuvant (breast) &amp; advanced disease (breast, gastric)</td>
</tr>
</tbody>
</table>
## IMPORTANT TARGETS
Involved in carcinogenesis and their inhibitors (2)

<table>
<thead>
<tr>
<th>Target</th>
<th>Tumour</th>
<th>Inhibitor</th>
<th>Predictive markers of sensitivity</th>
<th>Disease setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>NSCLC, colorectal, renal, breast, ovary, cervix</td>
<td>Bevacizumab, afibercet (colon)</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>VEGFR (MAPK and PI3K pathways*)</td>
<td>Hepatocarcinoma Colorectal Gastric</td>
<td>Sorafenib*, lenvatinib* Regorafenib* Ramucirumab</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>VEGF(R); M-TOR</td>
<td>Renal</td>
<td>MTKs, bevacizumab, everolimus, temsirolimus</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>VEGF(R); M-TOR</td>
<td>Neuroendocrine Soft tissue sarcomas</td>
<td>Sunitinib, everolimus Pazopanib</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>VEGFR, RET</td>
<td>Thyroid</td>
<td>Vandatinib, sorafenib lenvatinib</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>M-TOR</td>
<td>Breast</td>
<td>Everolimus</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>CDK 4/6</td>
<td>Breast</td>
<td>Palbociclib, ribociclib, abemaciclib</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
</tbody>
</table>
## IMPORTANT TARGETS
Involved in carcinogenesis and their inhibitors (3)

<table>
<thead>
<tr>
<th>Target</th>
<th>Tumour</th>
<th>Inhibitor</th>
<th>Predictive markers of sensitivity/resistance</th>
<th>Disease setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Kit</td>
<td>GIST</td>
<td>Imatinib, Sunitinib, regorafenib</td>
<td>C-Kit mutation, PDGFR mutation</td>
<td>High risk or metastatic GIST</td>
</tr>
<tr>
<td>EML4-ALK R0S1</td>
<td>NSCLC</td>
<td>Crizotinib, ceritinib, Alectinib</td>
<td>EML4-ALK translocation R0S1</td>
<td>Advanced NSCLC</td>
</tr>
<tr>
<td>RANKL</td>
<td>Bone metastases; Giant cell tumours</td>
<td>Denosumab</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>Hedgehog</td>
<td>Basal cell carcinoma</td>
<td>Vismodegib</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>BRAF, MEK</td>
<td>Melanoma</td>
<td>Vemurafenib, dabrafenib, trametinib, cobimetinib</td>
<td>BRAF mutation</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>PARP</td>
<td>Breast, ovary (BRCA tumours)</td>
<td>Olaparib, niraparib…</td>
<td>BRCA mutation</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>CTLA4</td>
<td>Melanoma</td>
<td>Ipilimumab</td>
<td>-</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>PD-1/PD-L1</td>
<td>Melanoma, NSCLC, RCC, H&amp;N, urothelial, MCC</td>
<td>Nivolumab, pembrolizumab, atezolizumab…</td>
<td>(PD-L1 protein)?</td>
<td>Advanced disease</td>
</tr>
<tr>
<td>Androgen receptor; immune system; Met</td>
<td>Prostate</td>
<td>Abiraterone, enzalutamide, sipuleucel-T, cabozantinib</td>
<td>Androgen receptor variant 7 (Resistance)?</td>
<td>Advanced disease</td>
</tr>
</tbody>
</table>
LESSON 1:
Identification of a key genetic abnormality in cell carcinogenesis and the discovery of a selective targeted agent leading to a major therapeutic breakthrough
TARGETING BRAF IN ADVANCED MELANOMA

**BRAF mutation**
- 50% (V600E ++)

Vemurafenib – a selective inhibitor of **BRAF V600m**

FINDINGS OF THE EFFECT OF VEMURAFENIB

At the recommended Phase 2 dose in patients with melanoma that carried the V600E Mutation

Phase I/II study:

- 16 melanoma pts BRAF V600Em:
  - 10 PR
  - 1 CR

TARGETING EML4-ALK IN A SUBGROUP OF ADVANCED NSCLC

EML4-ALK fusion: 6% of NSCLC patients

Preliminary data with crizotinib (EML4-ALK inhibitor):

n = 82 patients; RR: 57% of patients; DCR at 8 weeks: 87% of patients

LESSON 2:
Treatment of unselected population with a targeted agent should be prohibited
**IMPORTANCE OF TARGET FOR THERAPY**

HERA trial (adjuvant trastuzumab) in breast cancer

Disease-free survival\(^1\)

The right subpopulation
The right drug
A huge treatment effect!

Simulation of HERA if conducted in unselected patients (HER2 +/−):

HER2+ : HR 0.54
HER2− : HR 0.95

# TARGETING EGFR IN ADVANCED NSCLC

1st line erlotinib or gefitinib in combination with chemotherapy (unselected population)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of pts</th>
<th>Treatment regimens</th>
<th>TTP (months) (p value)</th>
<th>OS (months) (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIBUTE</td>
<td>1059</td>
<td>Carbo/paclitaxel placebo or erlotinib</td>
<td>4.9 vs. 5.1 (p = .36)</td>
<td>10.5 vs.10.6 (p=.95)</td>
</tr>
<tr>
<td>Tarceva lung cancer inv. trial</td>
<td>1172</td>
<td>Cispatlin/gemcitabine placebo or erlotinib</td>
<td>NR</td>
<td>11 vs. 10.7 (p =.49)</td>
</tr>
<tr>
<td>INTACT-1</td>
<td>1093</td>
<td>Cispatlin/gemcitabine placebo or gefitinib</td>
<td>10.9 vs. 9.9 (p = .45)</td>
<td>6.0 vs. 5.5 (p =.76)</td>
</tr>
<tr>
<td>INTACT-2</td>
<td>1037</td>
<td>Carbo/paclitaxel placebo or gefitinib</td>
<td>5.0 vs. 4.6 (p =.56)</td>
<td>9.9 vs. 8.7 (p = .64)</td>
</tr>
</tbody>
</table>

4361 patients randomised across four phase III trials

Unselected patients according to EGFR mutation status was probably the main reason of the observed negative results.
TARGETING EGFR IN ADVANCED NSCLC

1st line gefitinib *versus* chemotherapy – IPASS study

Untreated Asian patients* with stage IIIb/IV NCSLC and PS 0-2 (N = 1217)

- Gefitinib 250 mg/day (n = 609)
- Carboplatin AUC 5-6 + Paclitaxel 200 mg/m² q3w (n = 608)

*Never smokers or ex-light smokers.*

Primary endpoint: PFS

Biomarker analysis: EGFR mutation, expression, and gene copy number
TARGETING EGFR IN ADVANCED NSCLC

1st line gefitinib versus chemotherapy – IPASS study

**PFS: Mutated EGFR**
- Median PFS
  - Gefitinib (n = 132): 9.5 mos
  - CP (n = 129): 6.3 mos

**PFS: Wild-Type EGFR**
- Median PFS
  - Gefitinib (n = 91): 1.6 mos
  - CP (n = 85): 5.5 mos

HR: 0.48
$P < 0.0001$

HR: 2.85
$P < 0.0001$

TARGETING EGFR IN ADVANCED NSCLC

1st line gefitinib versus chemotherapy – IPASS study

- OR: 2.75  \( P = 0.0001 \)
- OR: 0.94  \( P = 0.0013 \)
- OR: 1.79  \( P = 0.0243 \)
- OR: 0.80  \( P = 0.5580 \)
- OR: 1.49  \( P = 0.1093 \)
- OR: 1.44  \( P = 0.4146 \)

LESSON 3:
Unitargeted or multitargeted kinase inhibitors for solid tumours?:
Tumour dependency
The appropriate approach depends on tumour type and the critical carcinogenesis process.
MULTITARGETED KINASES INHIBITORS IN RENAL CANCER:

Tumour responses

A,B,C: responses in patient 1 with multiple metastatic sites from a large primary RCC.

D,E: responses in patient 2 with multiple hepatic, lung, and pleural metastases.

F,G: responses in patient 3 with large retroperitoneal lymphadenopathy and hepatic metastases.
**LESSON 4:**

Different tumour types might share common molecular aberrations that could be targeted (such as BRAF mutations) but responding differently to the same targeted therapy depending on the context.

Although BRAF inhibitors have been approved for treating BRAF mutated metastatic melanoma, disappointingly, these drugs had only scant activity when used as a monotherapy in mCRC when constitutively expressed EGFR led to resistances. Therefore the addition of anti-EGFR monoclonal antibodies and MEK inhibitors is needed in mCRC.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tumour type</th>
<th>ORR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td>BRAFV600m metastatic melanoma</td>
<td>48%</td>
<td>Chapman PB, <em>et al.</em> NEJM. 2011</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAFV600m metastatic CRC</td>
<td>5%</td>
<td>Kopetz S, <em>et al.</em> JCO 2015</td>
</tr>
<tr>
<td>Vemurafenib + cetuximab</td>
<td>BRAFV600m metastatic CRC</td>
<td>20%</td>
<td>Tabernero J, <em>et al.</em> JCO 2014 no. 15_suppl</td>
</tr>
<tr>
<td>Dabrafenib + trametinib + panitumumab</td>
<td>BRAFV600m metastatic CRC</td>
<td>18%</td>
<td>Corcoran RB, <em>et al.</em> ESMO 2014</td>
</tr>
</tbody>
</table>

LESSON 5:
Rare (orphan) tumours are “good” niches of selected targeted agents

- Hedgehog signaling inhibitors and basal cell carcinoma
- PARP inhibitors in BRCA mutated tumours
- Rank ligand inhibition in giant cell tumours
**BASAL CELL CARCINOMA**

Abnormalities in hedgehog signaling pathway and mechanism of vismodegib activity in basal cell carcinoma

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Reprinted from Clin Cancer Res, 2011, 17(8), 2502–11, Lo Russo PM, et al., Phase I Trial of Hedgehog Pathway Inhibitor Vismodegib (GDC-0449) in Patients with Refractory, Locally Advanced or Metastatic Solid Tumors, with permission from AACR.
## Phase II Studies with Olaparib

In BRCA-deficient advanced breast cancer

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Tutt et al. Lancet 2010 (n=54)</th>
<th>Gelmon et al. Lancet Oncol 2011 (n=26; 10 g BRCAm)</th>
<th>Kaufman et al. JCO 2015 (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally advanced/metastatic BRCAm BC</td>
<td>Advanced metastatic or recurrent BC, TN or known BRCAm</td>
<td>Advanced BRCAm BC; ≥ 3 previous lines of chemotherapy for locally advanced/metastatic BC</td>
<td></td>
</tr>
<tr>
<td>Prior lines of therapies for advanced disease</td>
<td>3 (median, including adjuvant)</td>
<td>3 (median, including adjuvant)</td>
<td>4.6 (mean, metastatic only)</td>
</tr>
<tr>
<td>ORR</td>
<td>41%</td>
<td>0% (50% unconfirmed ORR in BRCAm)</td>
<td>13%</td>
</tr>
<tr>
<td>Median DoR</td>
<td>144 days</td>
<td>-</td>
<td>204 days</td>
</tr>
</tbody>
</table>
OLYMPIAD TRIAL

Olaparib slows significantly the growth of BRCA-mutated metastatic breast cancer

Primary endpoint: progression-free survival by BICR

LESSON 6:
One gene could predict resistance to a family of targeted therapy but no single gene, protein, pathway predict full activity of a targeted agent

KRAS wild type/mutation and efficacy to EGFR monoclonal antibodies and colorectal cancer
BENEFIT FROM PANITUMUMAB (EGFR INHIBITOR)

According to K-RAS in mCRC

THE 4 GOOD REASONS FOR TESTING RAS STATUS

In order to guide anti-EGFR mabs in mCRC

1. Possible benefit if Ras « wild »
2. Avoid potential harm if « mutated »
3. Avoid undue toxicity
4. Avoid extra cost
LESSON 7:
The discovery of resistance mechanisms to targeted agents remains a key field as well as the development of active agents to the resistant mutations.

C-Kit resistant mutations to imatinib in GIST

EGFR resistant mutations to gefitinib and erlotinib in NSCLC

New generation of targeted agents are available in clinical practice.
LESSON 8:
Patient and tumour characteristics remain important in selecting systemic targeted therapies: The example of NSCLC

Ethnicity, gender, smoking habit and the efficacy of small molecules EGFR inhibitors in NSCLC

Location of metastatic sites (central versus peripheral): Antiangiogenic agents

Histology (squamous versus non-squamous)

Tumour EGFR mutational status
LESSON 9:

Mechanism-based and unexpected side effects arose from targeted therapy and could be cumbersome

Side effects of targeted agents were considered as predictive markers of clinical response but not fully validated for clinical practice use
### TARGETED AGENTS:

Main side effects

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI, skin</td>
<td>Anti-EGFR; Multi-targeted kinases</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Gefitinib, mTor inhibitors</td>
</tr>
<tr>
<td>Hypomagnesemia, hypocalcemia</td>
<td>Monoclonal Antibody Anti-EGFR</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>Trastuzumab, multi TKI, others</td>
</tr>
<tr>
<td>Bleeding, thrombosis, perforation, HTA</td>
<td>Anti-VEGF(R)</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Motesanib</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Bevacizumab, multi TKI</td>
</tr>
<tr>
<td>Reversible posterior Leukoencephalopathy syndrom</td>
<td>Bevacizumab, multi TKI</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Sunitinib (Sorafenib)</td>
</tr>
<tr>
<td>Auto-immune disorders</td>
<td>Anti-CTLA-4 monoclonal antibodies</td>
</tr>
<tr>
<td>Hematological</td>
<td>Sunitinib, mTor inhibitors</td>
</tr>
</tbody>
</table>
« I stopped taking the medicine because I prefer the original disease to the side effects »
**CORRELATION OF SKIN REACTION AND EFFICACY OF CETUXIMAB:**

Bond subgroup analysis in colorectal cancer

<table>
<thead>
<tr>
<th>Grade of skin reaction (up to Week 4)</th>
<th>Percentage of patients</th>
<th>Response rate</th>
<th>mTTP</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14.7</td>
<td>6.3%</td>
<td>1.4 months</td>
<td>3.0 months</td>
</tr>
<tr>
<td>1</td>
<td>26.6</td>
<td>8.6%</td>
<td>1.5 months</td>
<td>6.5 months</td>
</tr>
<tr>
<td>2</td>
<td>45.4</td>
<td>27.3%</td>
<td>4.2 months</td>
<td>10.3 months</td>
</tr>
<tr>
<td>3</td>
<td>13.3</td>
<td>55.2%</td>
<td>8.2 months</td>
<td>13.7 months</td>
</tr>
</tbody>
</table>

OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL

By hypertension during bevacizumab-containing treatment for metastatic colorectal cancer

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Log-rank: $P < 0.001$

Log-rank: $P = 0.008$
LESSON 10:
Even in the presence of targeted therapies, chemotherapeutic agents remain key backbone for successful combinations in selective solid tumours such as breast and GI tumours

Bevacizumab experience in solid cancers (breast and CRC)
HER-2 therapy in breast and gastric cancer
LESSON 11:
Continue the development of new cytotoxics or new formulations of existing anticancer agents is important for improving outcome of our patients

Nab-paclitaxel, ixabepilone, eribulin, etirinotecan
Antibody drug conjugates: TDM-1, …
LESSON 12:
Combining different therapeutic approaches in some circumstances could be detrimental for the patient

Bevacizumab + EGFR monoclonal antibodies + chemotherapy in advanced CRC: Negative results
PACCE STUDY:
Panitumumab + chemotherapy + bevacizumab for mCRC

Patients with measurable metastatic colorectal cancer per modified RECIST criteria and ECOG performance score 0 or 1

Ox-based CT (eg, FOLFOX) (n = 800)

Panitumumab 6 mg/kg Q2W + Ox-CT + Bevacizumab

Ox-CT + Bevacizumab

Iri-based CT (eg, FOLFIRI) (n = 200)

Panitumumab 6 mg/kg Q2W + Iri-CT + Bevacizumab

Iri-CT + Bevacizumab

Tumour assessments: Every 12 weeks until disease progression or intolerability

PACCE TRIAL IN ADVANCED COLON CANCER:

Summary

Adding panitumumab to chemotherapy with bevacizumab did not prolong PFS.

Trend toward inferior PFS and OS!

Toxicity frequent in both arms; incidence of serious adverse events higher in patients receiving panitumumab.

LESSON 13:
Targeted therapy in combination with radiotherapy: A major delay in clinical research

Cetuximab (EGFR inhibitor) in Head & Neck cancer is the only approved agent in combination with radiotherapy
RADIOTHERAPY PLUS CETUXIMAB

For locoregionally advanced head and neck cancer:
5-year survival data from a Phase 3 randomised trial

Overall survival:
- RT cetuximab: 49 months
- RT: 29.3 months

LESSON 14:
Immune modulation is revisited with success

Checkpoint inhibitors
- In melanoma
- In NSCLC
- In Head and Neck SCC
- In bladder cancer and RCC
- MSI-H tumours
- More to come…

Vaccine in prostate cancer
IMMUNOTHERAPIES/
CHECKPOINTS INHIBITORS

Reprinted from Immunity;39(1), Motz GT, Coukos G. Deciphering and reversing tumour immune suppression, 61-73. Copyright 2013 with permission from Elsevier.


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ESMO
MECHANISMS OF ACTION

Anti-CTLA-4
Ipilimumab, ...

Anti PD1: Pembrolizumab, Nivolumab, ...
Anti-PD-L1: Atezolizumab, ...

Reprinted from Immunity;39(1), Motz GT, Coukos G. Deciphering and reversing tumour immune suppression, 61-73. Copyright 2013 with permission from Elsevier.
CHECKMATE 067:
Phase 3 study in previously untreated patients with advanced melanoma

<table>
<thead>
<tr>
<th></th>
<th>Nivo + Ipi (n=314)</th>
<th>Nivo (n=316)</th>
<th>Ipi (n=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (IC$_{95}$)</td>
<td>11.5 (8.9-16.7)</td>
<td>6.9 (4.3-9.5)</td>
<td>2.9 (2.8-3.4)</td>
</tr>
</tbody>
</table>

*p < 0.00001 versus IPI

Wolchok JD, et al. J Clin Oncol 34, 2016 (suppl; abstr 9505). Reproduced with permission from Dr Jedd Wolchok.
LESSON 15:
Targeted therapy in selected tumours failed so far

The example of pancreatic cancer: >30 randomised trials failed to show survival advantage!!!

Absence of effective biomarkers for screening and early detection
Aggressive behaviour and resistance to the currently available chemotherapy
Inter-/intra- tumour genetic heterogeneity
Targeting key dysregulated signaling pathways in advance pancreatic cancers
LESSON 16:
Emergence of brain metastases is a major challenge in some tumours

Brain metastasis are more frequently seen as systemic control through targeted therapies improves

Major clinical problem in patients with advanced breast cancer, lung cancer, melanoma, and renal cell carcinoma

Challenge: Better understand how to optimise the activity of targeted agents in the CNS and how to best incorporate them into the clinical research and the current treatment paradigms
INCIDENCE OF CNS METASTASES
In HER2 advanced breast cancer treated with trastuzumab: 25-50%

Bendell et al. Cancer 2003 34%
Heinrich et al. ASCO 2003 43%
Brufsky et al. ASCO 2003 50%
Clayton et al. Br J Cancer 2004 25%
Altaha et al. ASCO 2004 33%
Stemmler et al. ASCO 2005 31%
Yau et al. Acta Oncol 2006 30% (at 1 y)
Gori et al. The Oncologist 2007 35%
Brufsky et al. ASCO BCS 2008 33.4%
TBRC 022: NERATINIB/CAPECITABINE
For the treatment of brain metastases in HER2 positive advanced breast cancer

Median survival: 13.5 mo (19 pts)
LESSON 17:
No single methodology to the development of new targeted agents is available. “Individualising” and “innovative” drug development methodology are a key for success.
LESSON 18:
Standard radiological evaluation of tumour responses (RECIST) to targeted therapies could be misleading in some circumstances.

RECIST-based criteria, originally developed to assess response to cytotoxic chemotherapeutic agents

Prolong disease stabilisation rather than substantial tumour regression was seen with targeted agents as well as changes in tumour density, …

- Development of new response evaluation criteria is needed for selective drugs
  - Tumour growth rate index was proposed

New imaging techniques: PET-CT, DCE, US
DRAWBACKS OF STANDARD RESPONSE CRITERIA

With targeted agents: tumour volume vs. tumour necrosis

Sorafenib treatment (400 mg b.i.d.)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 weeks</th>
<th>16 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour volume (cm^3)*</td>
<td>295</td>
<td>341</td>
<td>285</td>
</tr>
<tr>
<td>Tumour necrosis (%)*</td>
<td>2.09</td>
<td>53.07</td>
<td>51.03</td>
</tr>
</tbody>
</table>

*Assessed by modified WHO criteria

LESSON 19:
Major challenges in the era of targeted therapies

Not to repeat mistakes
To learn from the past history in clinical research
Not to be prisoner of administrative bodies
To be rational and innovative
To individualise clinical research
LESSON 20 AS A CONCLUSION:

What could be done to maximise the patient’s chance of benefiting from a new targeted therapy (1)

1. Importance of the target and the selectivity of the new agent
2. Keep in mind to find whenever possible the « context of vulnerability » in the host as well as in the cancer cell:
   - Clinical data
   - IHC/FISH, …
   - Genomic (specific gene sequencing, CGH, complete sequencing, …)
   - Other technics to come
3. Use of all available and validated tools to maximise the value of the results from a clinical trial
LESSON 20 AS A CONCLUSION:
What could be done to maximise the patient’s chance of benefiting from a new targeted therapy (2)

4. Each patient in a clinical trial should be analysed carefully in particular if efficacy was documented
5. Perform mainly prospective trials
6. Perform innovative and « smarter » clinical trials design taking into account:
   - The patient
   - The tumour
   - What it is known about the evolution of the disease
   - The characteristics of the experimental drug
Targeting the molecular mechanisms involved in cancer improves outcome

HYPOTHESIS:
THANK YOU!