Can neo-adjuvant breast cancer treatment data be used to accelerate drug approval?

Ian F Tannock MD, PhD, DSc
Princess Margaret Hospital and University of Toronto, Canada
Potential conflicts of interest

I have advised multiple companies about design of trials for which I have received contributions to my research fund.

I do not accept personal remuneration from companies.
Tilting at windmills

Clinical trial
Don Baselga
Sancho
FDA
What do we want from drug development?
There are only two goals of any new treatment:

To allow the patient to live longer
and/or
To allow the patient to live better

Hence, there are only two important endpoints of a drug registration trial:

1. Overall Survival
2. Quality of Survival

Anything else is a surrogate endpoint
We do want:

- New drugs that produce a meaningful impact on survival
- New drugs that decrease symptoms and improve quality of life

We do not need:

- Drugs that have a trivial impact on survival with high cost and toxicity
The classical route to drug approval

- Phase I trial to demonstrate safety and establish the MTD
- Phase II trial to show activity in patients with metastatic cancer
  - N.B. Drug activity ≠ patient benefit
- Phase III trial comparing addition of new agent to standard therapy in patients with advanced cancer
  - Endpoints must reflect patient benefit
- Phase III trials evaluating new agent in the adjuvant setting
Drugs approved for breast cancer in last 5 years

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date</th>
<th>Condition</th>
<th>Trial</th>
<th>Endpoint</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>Mar 2007</td>
<td>HER2+ with capcitabine after trastuzumab, anthra, taxane</td>
<td>RCT</td>
<td>TTP</td>
<td>N = 399, (6.0 vs. 4.5)</td>
</tr>
<tr>
<td></td>
<td>Jan 2010</td>
<td>HR+ HER2+ with letrozole</td>
<td>RCT: HER2+</td>
<td>PFS</td>
<td>N = 219, (8.9 vs. 3.3)</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>Oct 2007</td>
<td>With capcitabine in pts resistant to anthra, taxanes</td>
<td>RCT</td>
<td>PFS</td>
<td>N=752, (5.7 vs. 4.1)</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>June 2012</td>
<td>HER2+ with trastuzumab and docetaxel</td>
<td>RCT</td>
<td>PFS</td>
<td>N=808, (18.5 vs. 12.4)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>July 2012</td>
<td>HR+, HER2- with exemestane after progression on other AI</td>
<td>RCT</td>
<td>PFS</td>
<td>N =724, (7.8 vs. 3.2)</td>
</tr>
</tbody>
</table>

All of these drugs were approved for advanced breast cancer

9/30/2012  ESMO, Vienna
“FDA may grant marketing approval for a new drug... on the basis of well-controlled trials establishing that it has an effect on a surrogate endpoint that is reasonably likely.....to predict clinical benefit”

“Approval....will be subject to the requirement that the drug be studied further....to verify its clinical benefit”

The FDA is proposing that neoadjuvant trials in women with high-risk breast cancer might be used for accelerated approval of new drugs.
Neoadjuvant trials for accelerated approval?

I accept that in neoadjuvant trials:

1. Patients who achieve pCR have better survival

2. Tissue at surgery allows study of target inhibition

The main problems are:

1. Giving a new drug with unknown safety to women with potentially curable disease

2. Is the surrogate endpoint (response) “reasonably likely to predict clinical benefit”
Even large RCTs are insufficient to disclose serious toxicity when new agents are prescribed.

58% of potentially fatal adverse events are not in the initial FDA drug label, and 39% are not reported in any published randomized trial.

There are ethical concerns about prescribing a new drug to patients after accelerated approval based on a small neoadjuvant trial.
And if the confirmatory trial is an adjuvant trial, there are ethical concerns...

...about selling a drug to women who can afford it while recruiting others to a controlled trial.

Also, women will perceive benefit because of the conditional approval and will be reluctant to take part in a controlled trial.

So the whole process may be RETARDED rather than accelerated!
The key question: Is the surrogate endpoint (response) “reasonably likely to predict clinical benefit”
Achieving CR in a neoadjuvant trial is an imperfect predictor of subsequent longer survival

Analysis of survival by tumor response
............is statistically invalid
Consider results of a neoadjuvant trial evaluating the new drug **miraculin**

Locally-advanced breast cancer, N=200

- Chemo + miraculin
  - %pCR: 30%

- Chemo
  - %pCR: 15%

<table>
<thead>
<tr>
<th></th>
<th>with pCR</th>
<th>without pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year survival</td>
<td>80%</td>
<td>60%</td>
</tr>
</tbody>
</table>

This does **NOT** imply better overall survival in the group receiving miraculin
The key question: Is the surrogate endpoint (response) “reasonably likely to predict clinical benefit”

Let’s look at some examples....
Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer


José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*
There were no significant differences in toxicity
So we might be tempted to conclude....

... that we could have used the results of a 214 patient neoadjuvant trial to support registration of pertuzumab (with docetaxel + trastuzumab)

... and that the results would be confirmed in a larger RCT which recruited 808 women with metastatic breast cancer
Finding that the results of one neoadjuvant trial is concordant with results of a large trial for metastatic disease…

…does not imply that there will be similar concordance of results of other neoadjuvant trials and large RCTs

…even if you are comfortable with giving a new and untried agent to women with potentially curable localised breast cancer…
Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D.,

adverse events occurred in 22.6% of patients who received everolimus alone, and 40.0% of patients who received placebo.

Conclusion

Central Assessment

Hazard ratio, 0.36 (95% CI, 0.27–0.47)
P<0.001 by log-rank test

Everolimus plus exemestane (median PFS, 10.6 mo)

Placebo plus exemestane (median PFS, 4.1 mo)

Weeks

Probability of Event (%)

Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

Jose Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D.,

adverse events occurred in 22.6% of patients who received everolimus alone, and 40.0% of patients who received placebo.

Conclusion

Central Assessment

Hazard ratio, 0.36 (95% CI, 0.27–0.47)
P<0.001 by log-rank test

Everolimus plus exemestane (median PFS, 10.6 mo)

Placebo plus exemestane (median PFS, 4.1 mo)

Weeks

Probability of Event (%)

18/12/2012

ESMO, Vienna
Results
Response rate by clinical palpation in the everolimus arm was higher than that with letrozole alone (ie, placebo; 68.1% vs 59.1%), which was statistically significant at the preplanned, one-sided, $\alpha = 0.1$ level ($P = .062$).

Adverse events occurred in 22.6% of patients who received everolimus and in 3.8% of patients who received placebo.

Conclusion
Everolimus significantly increased letrozole efficacy in neoadjuvant therapy of patients with ER-positive breast cancer.

Would any person in this room favour approval of a drug on the basis of:

1. A difference in response rate of 68% vs. 59%, with a 2-sided p-value of 0.124

2. A difference in grade 3-4 toxicity of 23% vs. 4%, with 2-sided p-value of <0.0001? (my calculation)
Addition of Bevacizumab to Chemotherapy for Treatment of Solid Tumors: Similar Results but Different Conclusions

Alberto Ocaña and Eitan Amir, Princess Margaret Hospital and University of Toronto, Toronto, Canada
Francisco Vera, Centro Universitario Contra el Cáncer, Hospital Universitario Universidad Autónoma de Nuevo León, Monterrey, México
Elizabeth A. Eisenhauer, National Cancer Institute of Canada Clinical Trials Group, Queen’s University, Kingston, Canada
Ian F. Tannock, Princess Margaret Hospital and University of Toronto, Toronto, Canada

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Diff (mo)</th>
<th>PFS HR</th>
<th>P</th>
<th>Diff (mo)</th>
<th>OS HR</th>
<th>P</th>
<th>Reported as</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG</td>
<td>722</td>
<td>+5.9</td>
<td>0.60</td>
<td>.0001</td>
<td>+1.5</td>
<td>0.88</td>
<td>.16</td>
<td>positive</td>
</tr>
<tr>
<td>AVADO</td>
<td>736</td>
<td>+0.8</td>
<td>0.86</td>
<td>.12</td>
<td>-1.1</td>
<td>1.05</td>
<td>.72</td>
<td></td>
</tr>
<tr>
<td>RIBBON-1</td>
<td>1237</td>
<td>+2.9</td>
<td>0.69</td>
<td>.0002</td>
<td>+1.4</td>
<td>0.85</td>
<td>.27</td>
<td>positive</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>2447</td>
<td>+2.5</td>
<td>0.64</td>
<td>.0001</td>
<td>+0.3</td>
<td>0.97</td>
<td>.56</td>
<td></td>
</tr>
</tbody>
</table>
Inhibiting VEGF with a monoclonal antibody was a great idea....

.... that unfortunately didn’t work!
I’m not convinced that it has added much benefit in any area of oncology
Yet we oncologists made it the most profitable drug in 2010 (world sales of ~$6 billion)
What a waste of resources - and poor choice of treatment
We must learn earlier from our mistakes

9/30/2012
ESMO, Vienna
The FDA (Feb 2008) and subsequently EMA approved paclitaxel + bevacizumab for treatment of metastatic breast cancer based on a trial showing ↑PFS but no difference in OS.

The FDA reversed that approval in Nov 2011 “the drug was not helping breast cancer patients to live longer or to meaningfully control their tumors, but did expose them to potentially serious side effects like severe high blood pressure and hemorrhaging.

But how does bevacizumab perform in neoadjuvant trials?
Bevacizumab Added to Neoadjuvant Chemotherapy for Breast Cancer

Harry D. Bear, M.D., Ph.D., Gong Tang, Ph.D., Priya Rastogi, M.D.,

Neoadjuvant Chemotherapy and Bevacizumab for HER2-Negative Breast Cancer

Gunter von Minckwitz, M.D., Holger Eidtmann, M.D., Mahdi Rezai, M.D., Peter A. Fasching, M.D.,

C Breast

P=0.02 by chi-square test

Percent pCR

Without Bevacizumab (N=595)

Bevacizumab (N=591)

0 10 20 30 40

34.5

28.2

Figure 2. Pathological Complete Response (pCR), According to Subgroup.
Bevacizumab “works” in neoadjuvant trials. Perhaps they have...
FDA/EMA approved 4 new drugs to treat breast cancer in the last 5 years.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date</th>
<th>Condition</th>
<th>Trial</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>Mar 2007</td>
<td>HER2+ with capecitabine after trastuzumab, anthra, taxane</td>
<td>RCT: N = 399</td>
<td>TTP</td>
</tr>
<tr>
<td></td>
<td>Jan 2010</td>
<td>HR+ HER2+ with letrozole</td>
<td>RCT: HER2+ N = 219</td>
<td>PFS</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>Oct 2007</td>
<td>With capecitabine in pts resistant to anthra, taxanes</td>
<td>RCT: N=752</td>
<td>PFS</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>June 2012</td>
<td>HER2+ with trastuzumab and docetaxel</td>
<td>RCT: N=808</td>
<td>PFS</td>
</tr>
<tr>
<td>Everolimus</td>
<td>July 2012</td>
<td>HR+, HER2- with exemestane after progression on other AI</td>
<td>RCT: N =724</td>
<td>PFS</td>
</tr>
</tbody>
</table>

If the system is broken, how should we improve it?
In my view, there are two problems

1. The lack of good drugs in development
   - We do not need a process that increases the approval of marginal drugs

2. The slow speed at which the few good drugs are brought to market
   - We do need to develop the effective drugs more quickly
These problems are due in part to FDA/EMA policy of approving any new drug that gives a significant improvement in OS or PFS.

This policy encourages Big Pharma to pursue large trials to detect trivial differences in outcome that allow drug registration.

...and then to market these drugs at an obscene price.
Three groups of agents FDA approved since 2000:

(A) Targeted agents where population is selected by a biomarker
(B) Less specific biological targeted agents
(C) Chemotherapy

<table>
<thead>
<tr>
<th>Group</th>
<th>No of drugs/trials</th>
<th>HR for OS</th>
<th>Median monthly cost (in USA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6/7</td>
<td>0.69</td>
<td>$5,375</td>
</tr>
<tr>
<td>B</td>
<td>7/14</td>
<td>0.78</td>
<td>$5,644</td>
</tr>
<tr>
<td>C</td>
<td>8/12</td>
<td>0.84</td>
<td>$6,584</td>
</tr>
</tbody>
</table>

Only 37% of new cancer drugs were cost effective by standard criteria
When we are prescribing new drugs we are buying a....

Ford

But we are paying for a...

Ferrari
A potential answer to the problems of unwanted marginal drugs and waste of resources on large trials to develop them...

... is **NOT** approval based on results of neoadjuvant trials

... it is the requirement for value-based pricing as a condition of approval – so that the price of new drugs is related to their effectiveness
If FDA and EMA changed policy to require cost-effectiveness for drug approval……

...with the caveat that it would have to allow companies to recover the real costs of research:

1. Trials for effective drugs would be smaller
   - since sample size depends on the effect size that the trial is designed to detect or exclude

2. Companies would be discouraged from developing drugs where early trials suggest marginal effectiveness
In summary, neoadjuvant trials involving new agents...

1. Require the new drug to be given to women with potentially curable disease - not always a good strategy for potentially toxic new drugs

2. Are NOT reliable predictors of clinical benefit in larger trials
Can this house *really* believe that...

Neo-adjuvant breast cancer treatment data can be used to accelerate drug approval?
No!
Are you crazy?

You must be joking

Get out of here

Only if you believe in fairies

Nein
Nee
Niet
Nej
Não
Nei
Óχι
No way, José

...and returning to my opponent's Spanish heritage