Is there a role for another taxane in NSCLC?

**NO!**

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**Taxanes in NSCLC**

- Taxanes play essential roles in systemic therapy of NSCLC
  - Curative: Early stage disease as adjuvant or concurrently with radiation
  - Palliative: Metastatic disease
- FDA-approved agents: Paclitaxel, Docetaxel
- Nearly 20 years of clinical experience: taxanes essentially interchangeable
- Disadvantages: relative insolubility, toxicity
**Docetaxel/cisplatin (DC) vs vinorelbine/cisplatin (VC) in advanced NSCLC:**

*A taxane may be better than a vinca alkaloid*

- Hazard ratio: 1.183 (97.2% CI, 0.989 to 1.416)
- Median survival:
  - 11.3 (DC) vs 10.1 (VC) months


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**... but in the vast universe of trials, taxane-based platinum doublets yield similar survival outcomes**

- **Cis/Gem**
- **Cis/Docetaxel**
- **Carbo/Paclitaxel**

Novel Taxanes?

- **Tesetaxel** – not being developed in NSCLC
- **BMS-184476** – studied in phase II second line setting; not developed further
- **Cabazitaxel** – approved for prostate cancer, no formal trials in NSCLC
- **Larotaxel**
  - studied in combination with gemcitabine*, cisplatin*, and carboplatin** in NSCLC
  - no clear advantages; not pursued further

*Camps, Ann Oncol 2005; *Zatloukal, JTO 2008; Robert, **Cancer Chemo Pharm 2009

What about taxane reformulations?
Paclitaxel poliglumex (PPX)

- Macromolecular polymer–drug conjugate that links paclitaxel to a biodegradable polymeric backbone (L-glutamic acid residues)
- PPX passively accumulates in tumors thru the enhanced permeation and retention (EPR) effect
- Results in a 10- to 100-fold increase in intratumoral drug concentrations
**STELLAR 2: Trial Design**

Platinum chemotherapy-pre-treated patients with advanced NSCLC

**Stratified by:**
- PS
- Stage
- Sex
- Prior taxane
- Start of front-line (platinum-based) chemotherapy

<table>
<thead>
<tr>
<th>Randomize</th>
<th>PPX 210 mg/m² (or 175 mg/m² for PS2) q3w</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 427</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomize</th>
<th>Docetaxel 75 mg/m² q3w</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 422</td>
</tr>
</tbody>
</table>

**PPX vs Docetaxel: STELLAR-2**

- **Median Survival**:
  - PPX: 6.9 months
  - Docetaxel: 6.9 months

- **1-Year Survival**: 25% for PPX, 29% for Docetaxel
- **2-Year Survival**: 9% for PPX, 12% for Docetaxel

**HR** = 1.09

**Log-rank P = 0.26**

Paz Ares, BJC 2008
STELLAR 3: Trial Design

Chemotherapy-naïve PS2 patients with advanced NSCLC

Randomize:
- Stage
- Sex
- History of brain mets
- Geographic region

STELLAR 3: Overall Survival

(Intent-to-Treat)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median 1 yr</th>
<th>18 mo</th>
<th>2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPX/Carboplatin</td>
<td>7.8 mo</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>Paclitaxel/Carboplatin</td>
<td>7.9 mo</td>
<td>31%</td>
<td>11%</td>
</tr>
</tbody>
</table>

HR=0.97
Log-rank P value=0.769
STELLA 4: Trial Design

Eligibility Requirements:
- Chemotherapy-naive
- Advanced NSCLC
- PS2

Stratified by:
- Stage
- Sex
- History of brain metastasis
- Geographic region

PPX 175 mg/m² every 3 weeks
(N=191)

Gemcitabine 1000 mg/m² days 1, 8, and 15
every 28 days
or
Vinorelbine 30 mg/m² days 1, 8, and 15
every 21 days
(N=190)

80% power to detect 1.5-month difference (4-5.5); hazard ratio (HR)=1.37

STELLA 4: Overall Survival

PPX vs. Gemcitabine/Vinorelbine (Intent-to-Treat)

<table>
<thead>
<tr>
<th></th>
<th>PPX</th>
<th>Gemcitabine/Vinorelbine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>191</td>
<td>190</td>
</tr>
<tr>
<td>Median</td>
<td>7.3 mo</td>
<td>6.6 mo</td>
</tr>
<tr>
<td>1 yr</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>18 mo</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>24 mo</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

HR=0.95
Log-rank P value=0.686
Phase III nab-P/C vs P/C Study Design

- **Chemo-naive**
  - PS 0-1
  - Stage IIIb/IV NSCLC
  - N = 1,050

- **nab-Paclitaxel** 100 mg/m² d1, 8 15 Carboplatin AUC 6 d1
  - No Premedication
  - n = 525

- **Paclitaxel** 200 mg/m² d1
  - Carboplatin AUC 6 d1
  - With Premedication of Dexamethasone + Antihistamines
  - n = 525

Stratification factors:
- Stage (IIIb vs IV)
- Age (<70 vs >70)
- Sex
- Histology (squamous vs nonsquamous)
- Geographic region

Socinski, ASCO 2009

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Response rate was higher in nab-P/C arm....

- **Response Ratio** = 1.31
  - (1.082 – 1.593)
  - *P* = 0.005

- **Response Ratio** = 1.26
  - (1.060 – 1.496)
  - *P* = 0.008

- **Percent Responses**
  - *nab-P/C* (n = 521)
  - *P/C* (n = 531)
  - Independent Radiologic Review
  - 33% vs 25%
  - Investigator Assessment
  - 37% vs 30%
...but PFS was no better than paclitaxel!

UPDATE 2-Celgene shares fall on disappointing data, results
Mon, Jan 10 2011

* Abraxane fails to significantly extend lung cancer PFS
* Non-GAAP EPS 73 cents vs Street view 75 cents
* Q4 Revivmed sales up 42 pct to $708 million
* Sees 2011 non-GAAP EPS of $3.30 to $3.35
* Celgene shares fall 4.3 percent in midday trading (Adds analyst comment, recasts)

By Toni Cante

BOSTON, Jan 10 (Reuters) - Celgene Corp (CELG.O: Quote, Profile, Research, Stock Buzz) said on Monday that data from a late-stage trial showed its drug Abraxane did not significantly extend progression-free survival in patients with the most common form of lung cancer. That, along with 2010 earnings that fell short of Wall Street's expectations, drove the Summit, New Jersey-based

Taxane Toxicity

- Neuropathy and myelosuppression: principal side effects
  - Improvements in patient selection and supportive care in past 10 years have mitigated toxicities
- Taxane reformulations not necessarily less toxic!
  - Nab-paclitaxel associated with increased neuropathy compared to paclitaxel in breast cancer
... and oh yes, the cost!

Paclitaxel (generic): 300 mg vial = $50.00
Nab-Paclitaxel 100 mg vial = $644.00
Ixabepilone 45 mg vial = $2125.00

Assuming a BSA of 2.0 m²
- Paclitaxel 200 mg/m² = 400 mg = $67
- Nab-Paclitaxel 260 mg/m² = 520 mg = $3350
- Ixabepilone 32 mg/m² = 64 mg = $3022

➢ High cost of alternative taxanes in the absence of enhanced benefit does not justify their use

Conclusions

• Taxanes are important components of NSCLC therapy
  – However, outcomes with taxanes appeared to have reached a plateau
  – No new taxane-based regimens beyond paclitaxel or docetaxel have prospered
• There are limited resources available for drug development and clinical trials
  – Let’s spend those resources wisely!
• Higher priority must be given to agents that improve outcomes, ideally in molecularly enriched patients