New Cytotoxics in Lung Cancer: An Update

Primo N. Lara, Jr., MD
Professor of Medicine
University of California Davis Cancer Center

Cytotoxics:
Everything old is new again

- Antimetabolites
  - Fluoropyrimidines (S1)
  - Anti-folates (Pralatrexate)
- Antimicrotubule agents
  - Tubulin binders (Nab-paclitaxel, Ixabepilone, Eribulin)
- Topoisomerase inhibitors
  - Anthracyclines (Amrubicin)
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Fluoropyrimidines
S-1 (or TS-1): oral fluoropyrimidine: Tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate (molar ratio 1:0.4:1)

MOA:
5-FU converts to 5-FdUMP, which inhibits thymidylate synthase.
5-FU converts to 5-FUTP, incorporated into RNA thus inhibiting RNA processing.

Squamous cell carcinoma has higher mRNA and protein levels for thymidylate synthase (TS)
Ceppi et al. Cancer 2006
TS in Lung Cancer: a Japanese Large-Scale Study (N=2,651)

Conclusion: “Lower TS expression in adenocarcinoma of the lung was confirmed” in this large-scale study.


S1 in NSCLC

ASCO 2011: OS Update

Overall
Carbo/S1  15.2 mos
Carbo/Pac  13.1 mos
HR 0.96 (0.79, 1.15)

Squamous subset
Carbo/S1  14 mos
Carbo/Pac  10.5 mos
HR 0.71 (0.48, 1.07)

Owamoto, JCO 2010, Hirashima ASCO 2011 #7552

Pralatrexate: Folate Antagonist

• Antifolate with preferential uptake and retention by tumor cells
• TARGET: DHFR
• Phase 1 study with vitamin supplementation allowed for lower dosing and confirmed activity in NSCLC
  - ORR 10% (4/39; 95% CI: 0.7%-20%); 2 CRs (TTP 26+, 21+ mo)
• Safety profile consistent with prior studies, RD for Phase 2 with vitamin supplementation was 190 mg/m² q2wks

Stratification based on smoking history

Light smoker: >100 lifetime cigarettes; ≤ 15 pack-year history

Heavy smoker: > 15 pack-year history

PDX-012: Phase 2b Study in Advanced NSCLC (N=201)

1:1 Randomization

PRALATREXATE
190 (initially 230) mg/m² IV push Days 1 & 15 (28-day cycle)

ERLOTINIB
150 mg/day

PDX-012 ITT Population

Efficacy Outcomes

RESPONSE & DISEASE CONTROL RATE* Pralatrexate 230 & 190 mg/m² Erlotinib 150 mg

Response rate
2%
7%

DCR: ITT
36%
43%

DCR: Patients with Response Assessment
53%
54%

Overall Survival, ITT*

Pralatrexate (N= 100)

Erlotinib (N=101)

Median (month)
6.7
7.0

HR (95% CI)*: 0.84 (0.61, 1.14)

Progression-free Survival, ITT*

Pralatrexate (N= 100)

Erlotinib (N=101)

Median (month)
3.4
2.8

HR (95% CI)*: 0.91 (0.63, 1.32)

Pralatrexate Censored

Erlotinib Censored

Pralatrexate
Censored

Erlotinib
Censored

PDX-012 Safety Summary

COMMON AEs & GRADE 3/4 AEs IN ≥5% OF PATIENTS

Non-Heme AEs
Stomatitis
66 (68)
19 (20)
3 (3)
5 (5)

Fatigue
39 (40)
7 (7)
2 (2)
24 (24)

Dyspnea
12 (12)
4 (4)
2 (2)
23 (23)

Rash
16 (16)
1 (1)
0 (0)
64 (63)

Diarrhea
15 (15)
1 (1)
0 (0)
33 (33)

Heme AEs based on lab values
Anemia
34 (35)
5 (5)
0 (0)
33 (33)

Thrombocytopenia
22 (23)
3 (3)
2 (2)
11 (11)

Neutropenia
18 (19)
4 (4)
2 (2)
5 (5)

PDX-012: Phase 2b Study in Advanced NSCLC (N=201)

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150 mg/day

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PRALATREXATE
190 (initially 230) mg/m² IV push Days 1 & 15 (28-day cycle)

ERLOTINIB
150 mg/day
PDX-012 Landmark Analysis:
Patients remaining on treatment at 30 Days

<table>
<thead>
<tr>
<th></th>
<th>Pralatrexate (n=60)</th>
<th>Erlotinib (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>9.7</td>
<td>6.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.61 (0.42, 0.90)</td>
<td></td>
</tr>
</tbody>
</table>

Cytotoxics: Everything old is new again

- Antimetabolites
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  - Anti-folates (Pralatrexate)
- Anti-microtubule agents
  - Tubulin binders (Nab-paclitaxel, Ixabepilone, Eribulin)
- Topoisomerase inhibitors
  - Anthracyclines (Amrubicin)

Anti-microtubule agents

- Taxanes, Epothilones
  - Decreases dissociation of αβ-tubulin heterodimer subunits, stabilizes microtubules
  - Examples: Nab-paclitaxel, cabazitaxel, ixabepilone
- Halichondrin B Analogs
  - Inhibits microtubule polymerization
  - Example: Eribulin
Novel Taxanes

- Tesetaxel (Genta) – not being developed in NSCLC
- BMS-184476 (Bristol Myers) – studied in phase II second line setting; not developed further
- Cabazitaxel (Sanofi Aventis) – approved for prostate cancer, no formal trials in NSCLC
- Larotaxel (Sanofi Aventis) – 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

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Phase III nab-P/C vs P/C

Study Design

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

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

- With Premedication of Dexamethasone + Antihistamines

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

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...but PFS was no better than paclitaxel!

Socinsky, ASCO 2011 #7551

"Interim PFS analysis with 47% events revealed no significant differences between the 2 arms."

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Ixabepilone

- Microtubule stabilizing epothilone B analog
- FDA-approved for metastatic breast cancer (MBC)
- Activity in βIII-tubulin expressing, taxane-resistant tumors (MBC)¹
- Modest activity in previously platinum treated advanced NSCLC

Perez, J Clin Oncol, 2007
Vansteenkiste, J Clin Oncol, 2007

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βIII-Tubulin (β3T) Expression is Associated with Poor Response to Taxanes in Advanced NSCLC

- High β3T levels associated with shorter PFS and OS in retrospective study of patients with advanced NSCLC treated with taxane

β3T(+) vs. β3T(-) in terms of PFS and OS
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**Ixabepilone Exhibits Sensitivity to Lung Tumors Overexpressing βIII Tubulin**

- Two lung tumor xenografts overexpressing βIII tubulin were resistant to docetaxel and vinorelbine at their MTD.
- In contrast, ixabepilone was active in all of them.

<table>
<thead>
<tr>
<th>Lung Tumor Model</th>
<th>Antitumor Efficacy (LCK)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ixabepilone</td>
</tr>
<tr>
<td>H1155</td>
<td>4.2</td>
</tr>
<tr>
<td>LX-1</td>
<td>2.6</td>
</tr>
</tbody>
</table>

LCK, log cell kill; MTD, maximum tolerated dose.

Milross CG, J Natl Cancer Inst, 1996

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**Ixabepilone Preclinical Activity in β3T Over-expressing Tumors**

- Antitumor efficacy of ixabepilone and paclitaxel in β3T overexpressing tumors.

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**Ixabepilone/Carboplatin First-line Phase II Study Stratified by βIII Tubulin Expression**

- Primary Endpoint: PFS in βIII tubulin positive subgroup.
- Secondary Endpoints: PFS in all comers; ORR; OS.

Edelman, Multidisciplinary Symposium in Thoracic Oncology, Chicago, IL. 2010
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**β3T IHC Assay and Scoring**

**Immunohistochemistry (IHC) assay for β3-tubulin**
- Used monoclonal antibody (TUJ-1)
- Optimized assay conditions (Dako)

**Staining intensity scores**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description of staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1+</td>
<td>Weak</td>
</tr>
<tr>
<td>2+</td>
<td>Moderate = internal control (endothelial cells)</td>
</tr>
<tr>
<td>3+</td>
<td>Strong</td>
</tr>
</tbody>
</table>

**β3T status**

<table>
<thead>
<tr>
<th>Score</th>
<th>Staining intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 1+</td>
<td>Negative</td>
</tr>
<tr>
<td>2+, 3+</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Multiple cut-offs for β3T positivity were explored.

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**Tumor Response Rates**

<table>
<thead>
<tr>
<th></th>
<th>β3T(+) Patients</th>
<th>β3T(-) Patients</th>
<th>Overall Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pac/Carb (N=51)</td>
<td>Ixa/Carb (N=48)</td>
<td>Pac/Carb (N=99)</td>
</tr>
<tr>
<td>Response rate, %</td>
<td>17.0</td>
<td>26.7</td>
<td>27.1</td>
</tr>
<tr>
<td>Disease control rate, %</td>
<td>77.4</td>
<td>76.5</td>
<td>77.8</td>
</tr>
<tr>
<td>Tumor Response, %</td>
<td>Complete response (CR)</td>
<td>Partial response (PR)</td>
<td>Stable disease (SD)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>82.2</td>
<td>31.1</td>
<td>38.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>86.9</td>
<td>13.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75.1</td>
<td>15.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>82.2</td>
<td>31.1</td>
<td>3.3</td>
</tr>
</tbody>
</table>

**ND**=not determined due to unavailability of data, early discontinuation, death, or because the patient was never treated in the study; **1CR+PR/number of patients; 2CR+PR+SD/number of patients**

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**Hematologic Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Ixa/Carb (N=90)</th>
<th>Pac/Carb (N=93)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormality, %</td>
<td>All Grades Grade 3 Grade 4</td>
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<tr>
<td>Neutropenia</td>
<td>82.2</td>
<td>21.1</td>
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* N=92 for neutropenia

**Legend for response**

Partial Response: PR
Complete Response: CR
Stable Disease: SD
Progressive Disease: PD

**Legend for abnormality**

Grade 1: 1-<25%
Grade 2: 25-<50%
Grade 3; 50-<75%
Grade 4: ≥75%

**Legend for cut-offs**

β3T status: 0, 1+ Negative; 2+, 3+ Positive

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PFS in All Patients

No. of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>Ixa + Carb</th>
<th>Pac + Carb</th>
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<tbody>
<tr>
<td>98</td>
<td>76</td>
<td>52</td>
</tr>
<tr>
<td>22</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
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PFS in β3T(+) Patients

HR = 0.92 (80% CI, 0.73-1.15); P = 0.63

No. of patients at risk:

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<td>28</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
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HR = 1.04 (80% CI, 0.78-1.41); P = 0.85

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PFS in β3T(+) Patients

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HR = 1.04 (80% CI, 0.78-1.41); P = 0.85

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Eribulin (E7389): A Synthetic Analog of Halichondrin B

Marine sponge Halichondria okadai

- Pharmacokinetic
  - 49–65% protein binding
  - T1/2 distribution = 0.43 hours
  - T1/2 elimination = 39 hours
  - Large Vss = 1.81 L/hr/m²
  - ~7% renal excretion
  - Dose proportional over 0.25–1.4 mg/m²
  - No accumulation on weekly schedule
  - Primarily metabolized by CYP3A4
  - First in humans trial showed activity in NSCLC
Eribulin: Microtubule Dynamics Inhibitor

- Eribulin inhibits microtubule polymerization
- Eribulin prevents microtubule depolymerization
- Eribulin leads to nonproductive tubulin aggregates

Eribulin has no measurable effect on microtubule shortening

Eribulin inhibits microtubule growth (promote depolymerization)

Growing microtubule
Shortening microtubule

Tubulin depolymerization
Tubulin polymerization

Eribulin: Microtubule Dynamics Inhibitor

- Pharmacological profile
- Mechanism of action
- Clinical effects

Eribulin in NSCLC: Phase II

- Platinum- and taxane-pretreated NSCLC (n=41)
  - TS: Taxane sensitive (PD > 90 days after taxane, n=20)
  - TR: Taxane resistant (PD during or < 90 d after taxane, n=21)
- Eribulin 1.4 mg/m² D1 & 8, q 21 days
- Response rate = 15% (3 pts, all TS)
- Stable disease = 60% in TS, 24% in TR
- mPFS = 6.3 months in TS, 1.2 months in TR
- Conclusion: Active in taxane sensitive cohort

Eribulin in NSCLC: Another Phase II

- Prior platin-treated NSCLC (N=103)
  - Taxane naïve (n=83)
  - Taxane pre-treated (n=20)
- Eribulin 1.4 mg/m² d1, 8, 15 q28 days
  - Later changed to d1, 8 q 21 days
- Response rate = 10%
- Disease control rate = 53%
- Median OS = 9.6 months

Spira, ASCO 2007

Gitlitz, ASCO 2009
**Combination Eribulin Trials in NSCLC**
- Eribulin + Carboplatin (1st line Phase Ib) complete
- Eribulin + erlotinib (phase II) complete
- Eribulin + pemetrexed (relapse; Phase Ib/II), enrolling
- Eribulin + gemcitabine v. cisplatin + gemcitabine (phase III), planned for Asia

**Conclusions: New Cytotoxics in NSCLC**
- Cytotoxic chemotherapy is a cornerstone of therapy
- However, efficacy has plateaued
- New cytotoxics are in development
- Early results show only modest activity
- Need to optimize patient selection based on biology