Adjuvant Therapy in NSCLC
• What do we expect today from new adjuvant chemotherapy
• Which data do we have with targeted agents in the adjuvant setting
  ….according to molecular predictors
• What we expect with Immunotherapy agents
Agenda

• **What do we expect today from new adjuvant chemotherapy**

• Which data do we have with targeted agents in the adjuvant setting
  ....according to molecular predictors

• **What we expect with Immunotherapy agents**
Absolute improvements in 5-year survival of 3% for stage IA (from 70% to 73%), 5% for stage IB (from 55% to 60%), 5% for stage II (from 40% to 45%), and 5% for stage III disease (from 30% to 35%).
‘Big/High-Risk’ Stage I [NCCN]?

JBR.10

CALGB 9633

T-size $\geq 4$ cm

Butts, JCO 2010

Strauss G, JCO 2008
The current exclusion of stage IB tumors < 4 cm in the adjuvant NSCLC trials should be revisited.

Morgensztern, et al, JCO May 2016
‘Late events’ at longer F.U.

LACE

JBR.10

Pignon, JCO 2008

Butts, JCO 2010
Randomized phase III trial of adjuvant chemotherapy with or without bevacizumab in resected NSCLC: Results of E1505

**ELIGIBLE:**
- Resected
- Stage IB (≥4cm)-IIIA
- 6-12 weeks post-op
- (AJCC 6th edition)

**STRATIFIED:**
1. Cisplatin Doublet
2. Stage
3. Histology
4. Gender

**RANDOMIZE**

**Arm A:**
- Chemo, x 4 cycles*

**Arm B:**
- Chemo, x 4 cycles* + Bevacizumab, x 1 year

*Investigator Choice of 4 chemotherapy regimens
- 21 day cycles all with Cisplatin given at 75 mg/m² on day 1
- Cisplatin/Vinorelbine: 30 mg/m² day 1, 8
- Cisplatin/Docetaxel: 75 mg/m² day 1
- Cisplatin/Gemcitabine: 1200 mg/m² day 1, 8
- Cisplatin/Pemetrexed: 500 mg/m² day 1 (2009 amendment)

**Bevacizumab** 15 mg/kg IV q 3 weeks for up to 1 year

From July 2007 to September 2013, 1501 patients were enrolled
- Spring 2015: 6th planned interim analysis at 60.9% information
- Independent DSMC recommended releasing the trial results due to futility
- 230 of 1501 (15.3%) of patients were ineligible

*Wakelee HA, WCLC 2015*
The addition of bevacizumab to adjuvant chemotherapy DOES NOT improve survival for patients with surgically resected early stage NSCLC.

Overall Survival

Disease Free Survival

OS hazard ratio (B:A): 0.99
95% CI: (0.81-1.21)  
p=0.93

DFS hazard ratio (B:A): 0.98
95% CI: (0.84-1.14)  
p=0.75

Overall Survival Probability

Disease-Free Survival Probability

Months from Registration

Chemo (208 events/749 cases)
Chemo + Bevacizumab (204 events/752 cases)

Chemo (338 events/749 cases)
Chemo + Bevacizumab (334 events/752 cases)
Pooled Chemo Analysis (all patients regardless of treatment arm)

OS by chemo group
Non-squamous: Logrank p=0.18
Non-randomized
No significant differences

Squamous: Logrank p=0.99
Non-randomized
No significant differences

DFS by chemo group
Non-squamous: Logrank p=0.58
Non-randomized
No significant differences

Squamous: Logrank p=0.83
Non-randomized
No significant differences
NVALT-8 Study Design
(after adaptation of the design from low/high SUVmax)

Stratification factors:
- Institute, PS, TUM, histology, previous malignancy, R0 or R1-2

Resectable NSCLC
- PS 0-2
- Adequate organ function
- INR ≤ 1.5
- Exclusion criteria:
  - wedge/segmental resection
  - Prior chemotherapy or radiotherapy
  - Contra-indication for nadroparin

4 cycles peretriest (500 mg/m²) for non-squamous or gemcitabine 1000 mg/m²/day, 8 cycles peretriest for squamous histologies and cisplatin (75 mg/m²) on day 1 every 3 wks

+ nadroparin daily for 16 wks

- 2 wks therapeutic dose + 14 wks half therapeutic dose nadroparin

Stratification factors:
- Institute, PS, TUM, histology, previous malignancy, R0 or R1-2

RFS by treatment arm

HR 0.77 (0.52 - 1.14), p=0.19
Adjusted HR 0.74 (0.49 - 1.14), p=0.19

Median RFS 36.1 mo (95% CI, 22.7 - NA) in control vs 75.5 mo (95% CI, 36 - NA) in nadroparin arm.
Primary endpoint: 3-yrs RFS 51% (95%CI 42 - 62%) in control vs 59% (95% CI, 50 - 70%) in nadroparin arm.

Presented by Harry J.M. Groen

Adjuvant nadroparin in patients with resected NSCLC added to adjuvant chemotherapy does not improve RFS.
Agenda

- What do we expect today from adjuvant chemotherapy
- **Which data do we have with targeted agents in the adjuvant setting**
  ....according to molecular predictors
- What we would expect with immunotherapy agents
Prognostic and predictive biomarkers for ACT (adjuvant chemotherapy) in resected non-small cell lung cancer (R-NSCLC): LACE-Bio

While a number of biomarkers were identified in single studies that could have predictive or prognostic value, cross-validation with the other studies did not confirm the utility of the majority of markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Trial 1st tested in</th>
<th>Predictive?</th>
<th>Prognostic?</th>
<th>Validated?</th>
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<tbody>
<tr>
<td>ERCC1</td>
<td>IALT</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Lymphocyte infiltrate</td>
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<td>Yes</td>
<td>Prognostic (OS/DFS)</td>
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<tr>
<td>Mucin</td>
<td>CALGB</td>
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<td>Yes</td>
<td>No</td>
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<tr>
<td>β-tubulin</td>
<td>JBR10</td>
<td>Trend</td>
<td>Yes</td>
<td>Prognostic (OS/DFS)</td>
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<tr>
<td>P27</td>
<td>IALT</td>
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<td>No</td>
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<td>FASL</td>
<td>IALT</td>
<td>Trend</td>
<td>No</td>
<td>Predictive (OS)</td>
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<tr>
<td>FAS/FASL</td>
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<td>Yes</td>
<td>No</td>
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<tr>
<td>BAX</td>
<td>IALT</td>
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<td>Cyclin E/P16*</td>
<td>IALT, JBR10</td>
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<td>P53*</td>
<td>IALT, JBR10, CALGB</td>
<td>Yes**</td>
<td>Yes**</td>
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</tr>
</tbody>
</table>

** Conclusion

- IHC assays from single trials may be misleading and should be validated before being implemented

Seymour et al, ESMO 2014
A Single Biomarker Can Have Both Prognostic and Predictive Values

The Case of EGFR-M+

Prognostic marker
Influences clinical outcomes regardless of the therapy received

Does not help to personalise treatment

Predictive marker
Influences clinical outcomes with a specific therapy

Select patients who are likely to benefit
Exclude patients who are not likely to benefit

IPASS (OS) 2010

Mutation +
Mutation -

OPTIMAL (PFS) 2010

HR=0.16 (0.10–0.26)
Log-rank p<0.0001

Erlotinib (n=82)
Gem/carbo (n=72)

4.6
13.1

Courtesy of Zhou & Soria, ESMO 2010; Wolf J, PeerView Press 2010
RADIANT: Adjuvant Erlotinib vs Placebo in stage Ib-IIIa

Primary endpoint: DFS
Secondary endpoints: OS; DFS and OS in pts with del(19)/L858R (EGFR M+)

DFS (overall population)

DFS (del19 and L858R)

Kelly K, JCO 2015
Phase III ALCHEMIST Study: genetic testing in resectable stage IB-III A NSCLC

Nonsquamous NSCLC (N = 6000-8000) Clinical/pathologic stage IB (≥ 4 cm), II, IIIA
Post-op cohort with negative surgical margins

Trials conducted at sites in the NCI Clinical Trials Networks: NCTN & NCORP

EGFR mutation:
Phase III trial of erlotinib vs placebo x 2 yrs (n = 410) after any adj tx

ALK rearranged:
Phase III trial of crizotinib vs placebo x 2 yrs (n = 360) after any adj tx

Without molecular alterations: Followed every 6 mos x 5 yrs after any adj tx

FFPE tissue & blood specimen

FFPE tissue from biopsy done at recurrence
ITACA: trial design

Stratification Factors:
- stage (II vs III)
- smoking habit

ERCC1

TS

High

Low

Profile 4

High

Low

Profile 3

Profile 2

Profile 1

Taxanes

Control

Pem

Cis/Gem

Cis/Pem

Control

Control

Control

Control

PERSONALIZED

STANDARD

STANDARD

STANDARD

Control = investigators’ choice of cisplatin-based doublet
Trial was amended with the new Staging System (7th) on December 2010
Results Ph III trial customized adjuvant CT after resection of NSCLC with lymph node metastases SCAT: A Spanish Lung Cancer Group trial

n=456

Statification factors:
- Stage: N1 vs. N2
- Age <65 vs > 65 y
- Histology: Non-SCC vs. SCC
- Type of resection: Lobectomy vs Pneumonectomy

Planned number of patients: 432 (amended)

CT should be started before 8 weeks after surgery

PORT in N2 patients

Primary end-point: OS

Abstract ID 2983, Massuti et al
Low BRCA1: Cis-Gem regimen is superior to Cis-Doc (HR = 0.50; p= 0.016)
High BRCA1: treatment without platinum is inferior to Cis-Doc (HR = 1.24)
Agenda

• What do we expect today from adjuvant chemotherapy
• Which data do we have with targeted agents in the adjuvant setting
• ….according to molecular predictors
• **What we expect with Immunotherapy agents**
MAGRIT: Phase III Study - MAGE-A3 as Adjuvant Non-Small Cell Lung Cancer ImmunoTherapy

Key patient inclusion criteria:
- Stages IB, II, IIIA NSCLC
- Completely resected tumour
- MAGE-A3-positive
- PS 0–2
(n=2,272)

13 IM injections of MAGE-A3 CI (n=1,515) → PD

Stratification:
- Chemotherapy
- Primary endpoint
  - DFS

13 IM injections of placebo (n=757) → PD

Dec 2007
Start of recruitment

Dec 2011
Stage IB CT cohort closure

Oct 2012
Interim analysis

Mar 2011
Stage IIIA no-CT cohort closure

Jul 2012
End of recruitment

Jan 2014
Final analysis

<table>
<thead>
<tr>
<th>Screened</th>
<th>MAGE-A3 Valid test</th>
<th>MAGE-A3 (+) n (%)</th>
<th>Randomized</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>13,849</td>
<td>12,820</td>
<td>4,210 (33%)</td>
<td>2,312</td>
<td>2,272</td>
</tr>
</tbody>
</table>

Main protocol amendment: addition of DFS in Gene Signature positive (GS+) patients as co-primary endpoint.
MAGRIT: Phase III Study - MAGE-A3 as Adjuvant Non-Small Cell Lung Cancer ImmunoTherapy

![Graph showing disease-free survival (DFS) with MAGE-A3 CI and Placebo, including median and 95% CI for median time to event.]

- **MAGE-A3 CI**: 597 events, Median: 60.5 (95% CI 57.2, -)
- **Placebo**: 298 events, Median: 57.9 (95% CI 55.7, -)

- \( p^* = 0.7379 \)
- HR 1.02 (95% CI 0.89, 1.18)

Number at risk:
- **MAGE-A3 CI**: 1,515 1,257 1,115 1,013 887 656 476 339 220 127 19 2
- **Placebo**: 757 639 562 514 448 328 253 180 114 62 6 0

*Vansteenkiste et al. ESMO 2014*
Early stage NSCLC > adjuvant immunotherapy?

PEARLS (ETOP/EORTC/MSD)
- Post R0 surgery
- Stage IB (>4 cm)
- Stage II and IIIA
- PS 0-1
- ACT as indicated

BR31* (NCI-C & other groups)
- N=550
- Pembrolizumab 200 mg q3w (max 18 doses)
- Placebo i.v. q3w (max 18 doses)

ANVIL* (ECOG-ACRIN)
- N=307
- Durvalumab 10 mg/kg q2w (max 12 months)
- Placebo 10 mg/kg q2w (max 12 months)
- Nivolumab 3 mg/kg q2w (max 12 months)
- Observation

Primary endpoint:
- PEARLS: DFS
- BR31: DFS in PD-L1+ patients
- ANVIL: DFS and OS
Take Home Messages
Early Stage Adjuvant Therapy

- Standard adjuvant therapy remains cisplatin-based doublet
  [for resected stage II/IIIA, controversy upon stage IB]

- Progress in stage IV is NOT translated to curative setting
  [In the current state of knowledge, the choice of adjuvant
  therapy should not be guided by molecular analyses]

- In the current state of knowledge, targeted agents should not
  be used as adjuvant therapy in any patient (unless into a
  clinical trial)

- Therapeutic vaccination with current technology does not
  work as adjuvant tx for lung cancer
Locally Advanced NSCLC: Concurrent chemoradiation, if tolerable, is recommended vs sequential approach or Rt alone [Chemo: cispl/etop and Carb/pacl; RT: 60 Gy in 2 Gy fractions, over 6 weeks]

No role for the induction chemotherapy before chemoradiation, neither consolidation chemotherapy

Bezjak, JCO 2015

<table>
<thead>
<tr>
<th></th>
<th>CISPLATIN/ETOPOSIDE</th>
<th>CARBOPLATIN/PACLITAXEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>58% (CI 55%-61%); N=1457</td>
<td>56% (CI 54%-58%); N=2385</td>
</tr>
<tr>
<td>3 years survival rates</td>
<td>30% (CI 27%-34%); N=763</td>
<td>25% (CI 22%-28%); N=951</td>
</tr>
<tr>
<td>Overall survival</td>
<td>Weighted median survival = 19.4 months (N=2770)</td>
<td>Weighted median survival = 18.4 months (N=3602)</td>
</tr>
</tbody>
</table>

Santana-Davila R, JCO 2015

Steuer CE, WCLC 2015
Locally Advanced NSCLC: Concurrent chemoradiation, if tolerable, is recommended vs sequential approach or Rt alone [Chemo: cispl/etop and Carb/pacl; RT: 60 Gy in 2 Gy fractions, over 6 weeks]

PROCLAIM, Senan S et al, JCO 2016
Thank you!