CHEMIOTERAPIA
ADIUVANTE NEL NSCLC
Dr. RITA CHIARI
Oncologia Medica - Perugia
DICHIARAZIONE
Relatore: RITA CHIARI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

• Posizione di dipendente in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
• Consulenza ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
• Fondi per la ricerca da aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
• Partecipazione ad Advisory Board (BOHERIGER INGHELEIM, ASTRAZENECA, PFIZER)
• Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
• Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
Presentation’ Outline

- What do we expect today from adjuvant chemotherapy
- Which data do we have with targeted agents in the adjuvant setting
- What we (foresee) or we would love to expect with targeted agents
  - …according to molecular predictors
• What do we expect today from adjuvant chemotherapy
• Which data do we have with targeted agents in the adjuvant setting
• What we (foresee) or we would love to expect with targeted agents
  – …..according to molecular predictors
1995:
- Controversial (underpowered) RCTs
- LCCG meta-analysis
  - Not-significant trend for platinum-based Chemotherapy

2008-10:
- Long-term concerns for chemo......?
- LCCG final release

2005-8
- Powered RCTs
- Several meta-analyses
- LCCG update plus LACE
  - Significant benefit for Chemo

Modified by Kelly K, WCLC 2013
Overall Relative Benefit of Adjuvant Chemo is Consistent across all Meta-Analyses Results REGARDLESS of the Method (IPD/AD)

<table>
<thead>
<tr>
<th>Author</th>
<th>Meta-analysis (method)</th>
<th>Number of patients</th>
<th>HR/RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC-CG-MA [6]</td>
<td>IPD</td>
<td>1,394</td>
<td>0.87 (0.74, 1.02)</td>
</tr>
<tr>
<td>Pignon et al. [36]</td>
<td>IPD</td>
<td>4,584</td>
<td>0.89 (0.82, 0.96)</td>
</tr>
<tr>
<td>Hotta et al. [42]</td>
<td>AD</td>
<td>3,786</td>
<td>0.89 (0.81, 0.97)</td>
</tr>
<tr>
<td>Sedrakyan et al. [43]</td>
<td>AD</td>
<td>3,518</td>
<td>0.89 (0.82, 0.96)</td>
</tr>
<tr>
<td>Berghmans et al. [41]</td>
<td>AD</td>
<td>4,602</td>
<td>0.83 (0.80, 0.92)</td>
</tr>
<tr>
<td>Present meta-analysis</td>
<td>AD</td>
<td>7,334</td>
<td>0.93 (0.88, 0.97)</td>
</tr>
</tbody>
</table>

Platinum-based Adjuvant Chemo for NSCLC
‘The Stage Effect’ according to RCTs & LACE

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Events / No. Patients</th>
<th>Hazard Ratio</th>
<th>Probability of interaction/ trend* test</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IA</td>
<td>104 / 347</td>
<td></td>
<td>.06</td>
</tr>
<tr>
<td>Stage IB</td>
<td>515 / 1,371</td>
<td>.04*</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>893 / 1,616</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>878 / 1,247</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RCTs</th>
<th>Stage IA</th>
<th>Stage IB</th>
<th>Stage II</th>
<th>Stage IIIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>IALT</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>JBR.10</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB</td>
<td>Negative</td>
<td></td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>ANITA</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
</tr>
</tbody>
</table>

LACE Group, JCO 2008
Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data

34 RCTs – 8447 pts [F.U. 5.5 yrs]

NSCLC Meta-analyses Collaborative Group*

- S alone: 1729 events, 4142 totals
- S+CT: 1594 events, 4305 totals
- S+RT: 993 events, 1345 totals
- S+CT+RT: 916 events, 1315 totals

HR 0.86 (95% CI, 0.81-0.92; P<.0001)

AB at 5 yrs of 4%

13 RCTs – 2660 pts [F.U. 6.4 yrs]

HR 0.88 (95% CI, 0.81-0.97; P=.009)

AB at 5 yrs of 4%

NSCLC MACG, Lancet 2010
Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data

NSCLC MACG, Lancet 2010
Adjuvant chemotherapy for resected early-stage non-small cell lung cancer (Review)

<table>
<thead>
<tr>
<th>Age</th>
<th>[no. entered/no. entered]</th>
<th>O-E Variance</th>
<th>Hazard Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80</td>
<td>S + CT: 636/1027</td>
<td>-58.94</td>
<td>316.36</td>
</tr>
<tr>
<td>60-64</td>
<td>S + CT: 343/691</td>
<td>-17.35</td>
<td>173.70</td>
</tr>
<tr>
<td>65-69</td>
<td>S + CT: 351/872</td>
<td>4.47</td>
<td>174.43</td>
</tr>
<tr>
<td>&gt;70</td>
<td>S + CT: 237/591</td>
<td>-36.11</td>
<td>121.92</td>
</tr>
</tbody>
</table>

| Sex   | Male: 1207/2640           | -70.67       | 610.03               |
|-------| Female: 362/1230          | -46.62       | 161.25               |

<table>
<thead>
<tr>
<th>Histology</th>
<th>[no. entered/no. entered]</th>
<th>O-E Variance</th>
<th>Hazard Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeno</td>
<td>S + CT: 768/2257</td>
<td>-61.57</td>
<td>389.81</td>
</tr>
<tr>
<td>Squamous</td>
<td>S + CT: 645/1648</td>
<td>-55.23</td>
<td>331.71</td>
</tr>
<tr>
<td>Other</td>
<td>S + CT: 177/384</td>
<td>-5.60</td>
<td>66.23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Performance Status</th>
<th>[no. entered/no. entered]</th>
<th>O-E Variance</th>
<th>Hazard Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>S + CT: 1155/3172</td>
<td>-104.72</td>
<td>591.81</td>
</tr>
<tr>
<td>Poor</td>
<td>S + CT: 45/89</td>
<td>1.23</td>
<td>20.12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Performance status (exploratory)</th>
<th>[no. entered/no. entered]</th>
<th>O-E Variance</th>
<th>Hazard Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS=0</td>
<td>S + CT: 715/2139</td>
<td>-82.56</td>
<td>366.63</td>
</tr>
<tr>
<td>PS=1</td>
<td>S + CT: 446/1033</td>
<td>-23.28</td>
<td>222.46</td>
</tr>
<tr>
<td>PS=2</td>
<td>S + CT: 45/89</td>
<td>1.23</td>
<td>20.12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>[no. entered/no. entered]</th>
<th>O-E Variance</th>
<th>Hazard Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>S + CT: 864/2847</td>
<td>-91.22</td>
<td>427.88</td>
</tr>
<tr>
<td>Stage II</td>
<td>S + CT: 399/804</td>
<td>-32.39</td>
<td>200.76</td>
</tr>
<tr>
<td>Stage III</td>
<td>S + CT: 384/626</td>
<td>-12.02</td>
<td>175.79</td>
</tr>
</tbody>
</table>

Burdett, Cochrane Dat. 2015
‘The Age Effect’ according to LACE

No statistically significant interaction \( (P=.26) \) or test for trend \( (P=.29) \)

LACE Group, JCO 2008

No differences in severe toxicity rates were observed.
‘Big/High-Risk’ Stage I

[NCCN]?

JBR.10

CALGB 9633

T-size ≥ 4 cm

Butts, JCO 2010

Strauss G, JCO 2008
**Italian Survey on Adjuvant Treatment of Non-Small Cell Lung Cancer (ISA)**

- 46-item questionnaire
- 78 physicians - 68 out of 98 Italian Centers (53% North – 4% South-Centre-Islands)
- Disclosed adherence to GL 97%
- 3 confirmation questions by 65 phys.

### Indication for adjuvant chemotherapy by stage

- **IIIA**
  - 51 (78%)
- **IIIB**
  - 61 (94%)
- **II**
  - 48 (74%)
- **IIB**
  - 56 (86%)
- **I**
  - 9 (14%)

### Indication for post-operative radiotherapy

- Surgical +ve margins
  - 18 (24%)
- pN2 and/or surgical +ve margins
  - 41 (54%)
- Pathological N2
  - 11 (14%)
- Other: in selected cases
  - 6 (8%)
- Never
  - 1 (1%)
- NA
  - 0 (0%)

### Preferred adjuvant chemotherapy regimen

- Cis-Vin
  - 50 (64%)
- Cis-Gem
  - 26 (33%)
- Carbo-Pac
  - 1 (1%)
- Carbo-Gem
  - 1 (1%)
- >1 regimen
  - 25 (32%)

### Prognostic factor used for indication for AT

- Performance status
  - 74 (99%)
- Disease stage
  - 75 (97%)
- Age
  - 57 (79%)
- Other
  - 10 (14%)

*Banna G, ISA Investigators, Lung Cancer 2011*
# Adjuvant Chemotherapy – Optimal Regimen

**Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study**


<table>
<thead>
<tr>
<th></th>
<th>Cis/Vb N-67</th>
<th>Cis/Pem N-65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility</td>
<td>74%</td>
<td>96%</td>
</tr>
<tr>
<td>Completion of Therapy</td>
<td>63%</td>
<td>22%</td>
</tr>
<tr>
<td>Grade 3-4 hematological toxicity</td>
<td>78%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>$p = .001$</td>
<td></td>
</tr>
<tr>
<td>Grade 3-4 non-hematological toxicity</td>
<td>33%</td>
<td>31%</td>
</tr>
<tr>
<td>Dose Delivery (% Planned)</td>
<td>Cis 66%</td>
<td>Cis 90%</td>
</tr>
<tr>
<td></td>
<td>Vb 64%</td>
<td>Pem 90%</td>
</tr>
</tbody>
</table>
‘Late events’ at longer F.U.

- **LACE**
- **JBR.10**

**Graphs**

- Observations and chemotherapy-related events over time.
- Log-rank test for non-disease-related deaths: $P = .660$.
- Fine-Gray test for non-disease-related deaths: $P = .622$.
- Log-rank test for disease-related deaths: $P = .027$.
- Fine-Gray test for disease-related deaths: $P = .023$.

*Pignon, JCO 2008*  
*Butts, JCO 2010*
What do we expect today from Adjuvant chemotherapy

• CDDP-based (not carboplatin) adjuvant CHT is indicated for stage II and IIIA PS 0-1 pts (controversy upon Stage IB)
  - Subset analyses suggest a benefit for pts with a tumor size > 4 cm
• Elderly patients should not be excluded
• Clear benefit…but someway small
  —…may be smaller at longer follow-up?
• Non-cancer related mortality may be higher in pts receiving adjuvant CHT

Can we do better with curves?
What do we expect today from adjuvant chemotherapy

**Which data do we have with targeted agents in the adjuvant setting**

What we (foresee) or we would love to expect with targeted agents
- ....according to molecular predictors
‘Maximization’ Of Benefit

• Increasing the ‘clinical therapeutic index’ of drugs, so ‘tailoring’ the treatment, on the basis of:
  – New predictive factors, through, for example genomics:
    • Increase the rate of ‘sensitive’ patients
    • Decrease the rate of ‘resistant’ patients

• Improving the clinical trial design
  – Clinical and Molecular Surrogates of survival
    • Smaller sample size
    • Earlier indication of benefit
What should we expect?

**AIM:** select patients ‘spared’ from chemo

*Modified - Heymach, ASCO 2010*
- Retrospective Analyses -

‘Seeking for a biomarker’

IALT

ERCC-1\(^1\)

RAS\(^4\)

JBR.10

p53\(_{\text{ihc}}^4\)

p53\(_{\text{M+}}^4\)

p27\(^2\)

15-gen sign.\(^5\)

MSH\(^3\)/ERCC-1

p53\(_{\text{M+}}^4\)

Validation

[4 ext. Series]\(^5\)

Prognostic/Predictive Nomograms?

\(^1\)Olaussen NEJM 2006; \(^2\)Filipits JCO 2007; \(^3\)Kamal CCR 2010; \(^4\)Tsao JCO 2007; \(^5\)Zhu JCO 2010
**LACE-Bio**

The validation of biomarkers, based on immunohistochemical (IHC) tests* which are prognostic for relapse/death or predictive of benefit from ACT.

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Chemotherapy</th>
<th>RT</th>
<th>N</th>
<th>Year</th>
<th>Biobank</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCIC CTG JBR10</td>
<td>I, II</td>
<td>Cisplat, vinorelbine</td>
<td>No</td>
<td>482</td>
<td>1994-2001</td>
<td>Y</td>
</tr>
<tr>
<td>CALGB 9633</td>
<td>IB</td>
<td>Carboplat, paclitaxel</td>
<td>No</td>
<td>344</td>
<td>1996-2003</td>
<td>Y</td>
</tr>
</tbody>
</table>

Database pooled and maintained at Gustave Roussy, Villejuif, France

**For lymphocyte infiltration**
- slides were reviewed by both pathologists
- any discrepancies were reconciled

For Immunohistochemistry:
- **JBR10**
  - Database
  - Biobank
- **CALGB9633**
  - Database
  - Biobank
- **ANITA**
  - Database
  - Biobank
- **IALT**
  - Database
  - Biobank

Virtual Pooled BioBank: Maintained by each group. Access governed by a research plan and contracts. ± 1500 samples

Seymour et al, ESMO 2014
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 (see table on next slide)

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

Predictive marker
Influences clinical outcomes with a specific therapy

Does not help to personalise treatment

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
Adjuvant Gefitinib: JBR 19

N = 503

- Path stage IB - III NSCLC
- Complete surgical resection
- PS 0-2
- Adjuvant chemo and /or XRT allowed

Gefitinib
250 mg po q day
x 2 years

Placebo
PO q day
x 2 years

All patients

EGFR Mutated

Adjuvant Therapy: Erlotinib

**RADIANT**

Stage IB-IIIA → Surgery → CTX4 (platinum based) vs No CT

* Selection
  FISH + and/or IHC+

N = 945

Erlotinib

Placebo

Primary endpoint: Disease Free Survival

**HISTORICAL CONTEST**

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
<th>Source Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Protocol</td>
<td>2006 May</td>
<td>(from BR21 data FISH+ and IHC+)</td>
</tr>
<tr>
<td>Amendment</td>
<td>2010</td>
<td>(from Saturn data FISH+ IHC+ and EGFR mut+)</td>
</tr>
<tr>
<td>First Report</td>
<td>2014 May</td>
<td></td>
</tr>
</tbody>
</table>

8 years
RADIANT: Adjuvant erlotinib did not prolong disease-free survival

DFS (overall population)

- Placebo (156 events)
  Median: 48.2 months
- Erlotinib (254 events)
  Median: 50.5 months

Log-rank test: p=0.3235
HR 0.90 (95% CI 0.74, 1.10)

DFS (del19 and L858R)

- Placebo (32 events)
  Median: 28.5 months
- Erlotinib (39 events)
  Median: 46.4 months

Log-rank test: p=0.0391
HR 0.61 (95% CI 0.384, 0.981)

†Not significant due to hierarchical testing

Kelly et al. J Clin Oncol 2014; 32 (suppl 5; abstr 7501)
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)

Stratification:
- Chemotherapy
- Primary endpoint:
  - DFS

13 IM injections of placebo
  (n=757)

Dec 2007
Start of recruitment
Dec 2011
Stage II CT cohort closure
Mar 2011
Stage IIIA no-CT cohort closure
Oct 2012
Interim analysis
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

Vansteenkiste et al. ESMO 2014
MAGRIT: Phase III Study - MAGE-A3 as Adjuvant Non-Small Cell Lung Cancer Immunotherapy

DFS

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)

Median FU 38.8 months

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
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 1:1**

**Arm A:**
- Chemotherapy x 4 cycles*

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

Followed for Survival/Recurrence
CXR/exam q 3 months x 2 years, then q 6 months through year 5 then annually through year 10

**1501 pts**

*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)

**Primary endpoint: overall survival**
Median follow-up time 41 months

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

Wakelee H.A., 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

The addition of bevacizumab to adjuvant chemotherapy DOES NOT improve survival for patients with surgically resected early stage NSCLC.
1995:
- Controversial (underpowered) RCTs
- LCCG meta-analysis
  - Not-significant trend for Chemo

2005-8
- Powered RCTs
- Several meta-analyses
- LCCG update plus LACE
  - Significant benefit for Chemo

2008-10:
- Long-term concerns for chemo ........?
- LCCG final release

Modified by Kelly K, WCLC 2013
• What do we expect today from adjuvant chemotherapy
• Which data do we have with targeted agents in the adjuvant setting

• **What we (foresee) or we would love to expect with targeted agents**
  - ....according to molecular predictors
EARLY STAGE (OS)

(Quality of)
SURGERY

(Improvement of)

ADJUVANT CHEMOTHERAPY
CUSTOMIZED CHEMOTHERAPY
→ ITACA
→ SCAT
→ BY ADDING A THIRD DRUG, NOT CHEMO, ECOG 1505
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
Overall survival (cut-off March 15th 2015)

HR = 0.86 (0.59-1.27)

OS experimental arm

HR: Low vs High 0.84
HR Inter vs High 0.95
Overall survival and compliance

HR = 0.63 (0.40-0.98)

p = 0.04
**DFS and OS in High-BRCA1**

HR = 1.87 (0.83-4.19)

HR = 1.24 (0.59-2.59)

**DFS and OS Low-BRCA1 levels**

HR = 0.64 (0.38-1.09)

HR = 0.50 (0.28-0.88)

p = 0.016
Preliminary Results of the International Tailored Chemotherapy Adjuvant Trial: the ITACA Trial

Trial Design (stage II-IIIA) n°=761

Stratification Factors:
- stage (IIvsIII)
- smoking habit

ERCC1

High

TS

Low

High

Low

High

Low

Profile 1

Profile 2

Profile 3

Profile 4

Taxanes

Control

Pem

Control

Cis/Gem

Control

Cis/Pem

Primary End Point: OS
Treatment allocation by profile (N=761)

PROFILE 1:
ERCC1 low, TS low

PROFILE 2:
ERCC1 low, TS high

PROFILE 3:
ERCC1 high, TS low

PROFILE 4:
ERCC1 high, TS high

Profile Distribution according to Smoking Habit

p<.001
Conclusions

• Current Treatment Strategy (mainly based upon Stage):
  – To treat 20-25 pts for 1 to benefit (4-5% at 5 yrs)

• Negative results for ‘targeted’ agents in unselected populations?
  – RADIANT, ECOG 1505 and….. MAGRIT!!!!

• Biomarkers for pts selection are required
  – To increase PROGNOSTIC accuracy
  – To increase PREDICTIVE accuracy
Perspectives

• What application for the newest insights from immunotherapy in advanced disease?

  – Different history for anti PD1/PD-L1 MoAbs
    • Advanced SQCC [CheckMate 017]: NIVO improves OS regardless of PD-L1
    • Advanced nonSQCC [CheckMate 057]: NIVO improves OS according to PD-L1
Thank you for your attention!!

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