The 20 most common causes of death from cancer, UK 2008

Lung
Colorectal
Breast
Prostate
Pancreas
Oesophagus
Stomach
Bladder
Non-Hodgkin lymphoma
Ovary
All leukaemias
Kidney
Brain with central nervous system
Liver
Multiple myeloma
Mesothelioma
Malignant melanoma
Oral
Uterus
Bone and connective tissue
Other cancers

Number of deaths

Males
Females

Cancer Research UK
Lung cancer - male mortality by health authority

Lung cancer shows marked geographic variation

2 Age standardised using the European standard population, with 95% confidence interval
cancer survival improves.... but
median survival in trials of advanced NSCLC

survival benefit v. BSC
platinum doublets
3rd-generation doublets
plus targeted
immunotherapy

14
12
10
8
6
4
2
0


BMJ 95
Belani
ECOG 1594
ECOG 4599
Scagliotti
Reck
The lung cancer challenge

- Patients present late
- majority have metastatic spread\(^1\)
- improvements in treatment of advanced disease have had limited effect on 5-year survival
- low percentage resectable\(^2\)
- surgical 5 year survival approximately 40\(^2\)

1. LUCADA 2. ANITA
Clinical rationale for adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Surgical stage (6th ed)</th>
<th>5-yr survival%</th>
<th>relapse % local</th>
<th>relapse % distant</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA T1N0M0</td>
<td>67</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>IB T2N0M0</td>
<td>57</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>IIA T1N1M0</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB T2N1M0 T3N0M0</td>
<td>39 38</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>IIIA T3N1M0 T1-3N2M0</td>
<td>25 23</td>
<td>15</td>
<td>60</td>
</tr>
</tbody>
</table>

- distant failure more common than local relapse
- clinical and pathological evidence of microdissemination at time of surgery
- >80% of recurrences occur within 2 years of surgery

1995 BMJ meta-analysis

Included 14 trials (4357 patients) of adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Hazard ratio</th>
<th>p</th>
<th>5yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>1.15 (1.04-1.27)</td>
<td>0.005</td>
<td>-5%</td>
</tr>
<tr>
<td>‘Other ‘ drugs</td>
<td>0.89 (0.72-1.11)</td>
<td>0.3</td>
<td>4%</td>
</tr>
<tr>
<td>Cisplatin-based</td>
<td>0.87 (0.74-1.02)</td>
<td>0.08</td>
<td>5%</td>
</tr>
</tbody>
</table>

- Alkylating agents detrimental (includes mitomycin C & ifosfamide)
- Cisplatin-based therapy reduced the risk of death by 13% (p = 0.08)
- Absolute benefit of 5% at 5yr – did not reach statistical significance

Meta-analysis of Adjuvant CT in NSCLC (BMJ 311:899, 1995)

- HR = 0.87
- $p = 0.08$

Survival over months:
- Surgery + CT
- Surgery

Graph showing survival rates with surgery and chemotherapy vs. surgery alone, indicating a better outcome for surgery plus chemotherapy with an HR of 0.87 at $p = 0.08$.
Adjuvant Studies - IALT

- Large study (n = 1867; planned 3300)
- Stage I-III (36% stage I)
- Cisplatin based (67% ≥ 300mg/m2)
- Closed early - slow accrual
- Demonstrated a survival benefit (4.1% at 5 years)
- 5yr OS 44.5% vs 40.4% (p<0.003)
- 7 patients died due to chemotherapy

Absolute survival benefit of 4.1% at 5y

JBR10: the study that established adjuvant chemotherapy as a new standard of care

- n=482, stage Ib/II
- Vinorelbine-cisplatin or no chemotherapy
- Designed to detect 10% survival improvement at 3y
- 7 year study (opened July 1994, closed April 2001)

- Absolute survival benefit of 15% at 5y (p<0.011)

Winton et al, NEJM June 2005 352;25 :2589-97
Figure 1. Kaplan-Meier Estimates of Survival among Patients Who Received Adjuvant Vinorelbine plus Cisplatin and Those Who Underwent Observation Alone.

P values are based on two-sided statistical analyses of differences between treatment groups after randomization.

Winton et al, NEJM June 2005 352;25 :2589-97
## JBR10: Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Observation (95% CI)</th>
<th>Vin-cis (95% CI)</th>
<th>Hazard ratio</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>73m (43-~)</td>
<td>94m (75~)</td>
<td>0.7</td>
<td>0.012</td>
</tr>
<tr>
<td>5yr survival</td>
<td>54% (48-61%)</td>
<td>69% (62-75%)</td>
<td></td>
<td>0.0022</td>
</tr>
</tbody>
</table>
CALGB9633

- n=344, stage Ib (T2N0M0) completely resected patients
- Paclitaxel 200mg/m$^2$ + carboplatin AUC6 d1 q21 for 4 cycles or observation

Absolute survival benefit of 12% at 4y but no significant benefit at 5y
CALGB 9633: Overall Survival, 2004 vs. 2006

ASCO 2004

4 yrs 71% v 59%

HR = 0.62; 90% CI: 0.44-0.89 p = 0.01

ASCO 2006

5 yrs 59% v 57%

HR = 0.80; 90% CI: 0.60-1.07 p = 0.10
CALGB 9633 - long term follow-up

- median follow-up 9 years
- study remains negative overall
- median survival 8.2 versus 6 yrs
- trend to improved OS for all patients but in subgroup analysis no group with significant survival advantage (for tumours >7cm HR 0.53, p=0.051)
ANITA

- Adjuvant Navelbine International Trialists Association study
- 840 patients
- Stage IB (36%) to IIIA
- Observation vs 4 cycles of adjuvant vinorelbine - cisplatin

Douillard et al, Lancet Oncology 2006 Sep; 7(9): 719-27
ANITA confirms NP survival benefit

ASC0 2006

maintained at 7 years (8.4%)

Douillard, ASCO 2006
Adjuvant chemotherapy, survival by stage - ANITA

- Stage I (pT2N0)
- Stage II (pT 1-2, N1)
- Stage III A (pT1-2 N2, pT3 N0-3)

ANITA
Clear benefit in stage II and IIIa
OS by TRIAL

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. deaths</th>
<th>No. entered</th>
<th>Hazard ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>569/1088</td>
<td>569/1088</td>
<td>0.95</td>
<td>0.95 [0.81;1.12]</td>
</tr>
<tr>
<td>ANITA</td>
<td>458/840</td>
<td>458/840</td>
<td>0.82</td>
<td>0.82 [0.68;0.98]</td>
</tr>
<tr>
<td>BLT</td>
<td>152/307</td>
<td>152/307</td>
<td>1.00</td>
<td>1.00 [0.72;1.38]</td>
</tr>
<tr>
<td>IALT</td>
<td>980/1865</td>
<td>980/1865</td>
<td>0.91</td>
<td>0.91 [0.54;1.03]</td>
</tr>
<tr>
<td>JBR10</td>
<td>197/482</td>
<td>197/482</td>
<td>0.71</td>
<td>0.71 [0.54;0.94]</td>
</tr>
<tr>
<td>Total</td>
<td>2356/4584</td>
<td>2356/4584</td>
<td>0.89</td>
<td>0.89 [0.82;0.96]</td>
</tr>
</tbody>
</table>

Test for heterogeneity p=0.34

Chemotherapy effect p = 0.004

Drugs Cisplatin +

ALPI (MTC +VDS) ANITA (NVB) BLT (NVB/VDS/MTC+VNB/MTC+IFM) JBR10 (NVB) IALT (NVB/VDS/VP16)
NSCLC - evidence now conclusive….

after 2 decades of research

meta-analysis  Trial  the results are astonishing”

(Editorial comment on JBR10 study)

New England Journal of Medicine, June, 2005

improvement in OS (%)

<table>
<thead>
<tr>
<th>Trial</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>1995 BMJ</td>
<td>0.08</td>
</tr>
<tr>
<td>IALT</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>JBR10</td>
<td>0.011</td>
</tr>
<tr>
<td>ANITA</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>&lt;0.004</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
IALT: long term follow-up

- OS after median FU 7.5 years HR 0.91; 95% CI 0.81 - 1.02; \( p = 0.1 \)

- OS: F/U before 5 years HR 0.86; 95% CI 0.76 to 0.97 \( p = .01 \)

- OS: F/U after 5 years HR 1.45; 95% CI 1.02 to 2.07 \( p = .04 \)

- benefit of chemotherapy on recurrence maintained

- excess of non-cancer deaths in chemotherapy arm

*Arriagada JCO 2010*
Updated JBR.10

- median F/U 9.3 years

- benefit persists HR 0.78 [0.61-0.99], p = 0.04

- for stage II HR = 0.68 [0.5-0.92], p=0.01

- for stage IB NS

- no difference for 2nd malignancies or non cancer causes of death

**Butts JCO 2009**
updated JBR.10

- for stage IB tumour size was predictive of chemotherapy effect (interaction \( p = 0.02 \) for tumours 4 cm or larger)

- unplanned analysis

- similar HR to stage II but did not reach significance
Which patients?
<table>
<thead>
<tr>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>M1</th>
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</thead>
<tbody>
<tr>
<td>IA</td>
<td>IIA</td>
<td>IIA</td>
<td>IIIB</td>
<td>IV</td>
</tr>
<tr>
<td>IB</td>
<td>IIB</td>
<td>IIA</td>
<td>IIIB</td>
<td>IV</td>
</tr>
<tr>
<td>IIIB</td>
<td>IIIB</td>
<td>IIA</td>
<td>IIIB</td>
<td>IV</td>
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<tr>
<td>IIIB</td>
<td>IIIB</td>
<td>IIIB</td>
<td>IIIB</td>
<td>IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>IALT</td>
<td>JBR10</td>
<td>ANITA</td>
<td>CALGB 9633</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>N1</td>
<td>N2</td>
<td>N3</td>
<td>M1</td>
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<td>----</td>
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</tr>
<tr>
<td>IA</td>
<td>IIA</td>
<td>IIA</td>
<td>IIIB</td>
<td>IV</td>
</tr>
<tr>
<td>IB</td>
<td>IIB</td>
<td>IIA</td>
<td>IIIB</td>
<td>IV</td>
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<tr>
<td>IIIB</td>
<td>IIIB</td>
<td>IIA</td>
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<td>IV</td>
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<tr>
<td>IIIB</td>
<td>IIIB</td>
<td>IIIB</td>
<td>IIIB</td>
<td>IV</td>
</tr>
</tbody>
</table>

6th edition
CT effect & stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard ratio (Chemotherapy / Control)</th>
<th>HR</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>236 / 679</td>
<td></td>
<td>1.01</td>
<td>[0.78;1.31]</td>
</tr>
<tr>
<td>Stage II</td>
<td>369 / 721</td>
<td></td>
<td>0.73</td>
<td>[0.60;0.90]</td>
</tr>
<tr>
<td>Stage III</td>
<td>324 / 488</td>
<td></td>
<td>0.67</td>
<td>[0.54;0.84]</td>
</tr>
</tbody>
</table>

Test for trends

P = 0.02
Elderly also benefit (JBR.10)

Overall Survival
by Treatment Arm, Age >65

H-R = 0.61
Log-Rank, p = 0.04

20% absolute improvement in 5yS
...despite lower dose

**JBR.10 analysis**

<table>
<thead>
<tr>
<th>Dose intensity (mg/m²/wk)</th>
<th>≤65 yrs</th>
<th>&gt;65 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine</td>
<td>13.2</td>
<td>9.9</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>18.0</td>
<td>14.1</td>
</tr>
</tbody>
</table>

No increase in toxicity in elderly patients

*Pepe, Proc ASCO 2006, Abs 7009*
Effect of age

- 4584 patients from LACE meta-analysis (5 trials: ALPI, BLT, IALT, JBR.10, ANITA)
- median age 60 cf. 69 in clinical practice
- upper age limit for ANITA and IALT (both 75), no age limit for other studies
- compared <65 years, 65-69 with ≥ 70 years, benefit for adjuvant chemo in older group despite lower total dose cisplatin
- 10% patients ≥ 70 years, only 61 patients (1.3%) aged over 75 and not analysed separately
- able to generalise to older non-trial population?

Früh J Clin Oncol 2008
dose intensity for cisplatin / vinorelbine by age (45 patients)

<table>
<thead>
<tr>
<th></th>
<th>&lt; 70 years</th>
<th>≥ 70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean DI</td>
<td>20.2</td>
<td>19.8</td>
</tr>
<tr>
<td>mg/m²/wk</td>
<td>p=NS</td>
<td>p=NS</td>
</tr>
<tr>
<td></td>
<td>UHSM 12.4</td>
<td>ANITA (65yr) 13.2</td>
</tr>
<tr>
<td>vinorelbine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean DI</td>
<td>12.4</td>
<td>11.8</td>
</tr>
<tr>
<td>mg/m²/wk</td>
<td>p=NS</td>
<td>p=NS</td>
</tr>
</tbody>
</table>
4-weekly vinorelbine/cisplatin trial schedule was difficult to deliver

- high incidence of neutropaenia
  - 55% had dose delay, mostly on day 15\(^1\)

- low dose intensity achieved\(^1\)
  - vinorelbine day 1 50%
  - cisplatin day 1 69%

- ANITA authors recommended 3-week schedule\(^2\)

\(^1\) Winton 2005  \(^2\) Douillard 2006
Toxicity

<table>
<thead>
<tr>
<th>G3-4 toxicity</th>
<th>IALT (%)</th>
<th>JBR.10 (%)</th>
<th>ANITA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>neutropaenia</td>
<td>17.5</td>
<td>73</td>
<td>85</td>
</tr>
<tr>
<td>febrile neutropenia</td>
<td>-</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>anaemia</td>
<td>-</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>-</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>asthenia</td>
<td>-</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>peripheral neuropathy</td>
<td>-</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>emesis</td>
<td>3.3</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>constipation</td>
<td>-</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>treatment related deaths</td>
<td>0.8</td>
<td>0.8</td>
<td>2</td>
</tr>
<tr>
<td>courses (median / 4 cycles)</td>
<td>-</td>
<td>3/45%</td>
<td>4/&gt;50%</td>
</tr>
</tbody>
</table>


- QoL returned to baseline and toxicity resolved except for sensory neuropathy and hearing loss
- No impact on pulmonary function
Compliance no longer a major issue

- Early studies
  - Only 48-69% completed planned cycles

- Audit of compliance post - positive studies
  - 80% compliance

- Reflects positive attitude of doctors and patients to adjuvant chemotherapy

*Aljabran, Proc ASCO 2006, Abs 7154*
Regimen

• cisplatin/vinorelbine - most studied, regimen used in the 2 positive studies (JBR10, ANITA)

• carboplatin used when cisplatin contraindicated (consensus)

• E1505 study, 1500 pts with resected NSCLC
  • cisplatin doublet (vinorelbine, docetaxel, gemcitabine or pemetrexed for adenocarinoma histology) with or without bevacizumab
  • each regimen resulted in similar OS (but underpowered to detect differences)
Timing

- JBR10: randomised < 6 weeks post surgery and commenced within 2 days

- IALT < 60 days

- Ontario Registry of Canada: no difference was observed between 2 cohorts (0–10 versus 11–16 weeks): 35% patients initiated chemotherapy > 10 weeks
Guidelines

- ASCO: Adjuvant cisplatin-based chemotherapy is recommended for routine use in patients with stages IIA, IIB, and IIIA disease. Although there has been a statistically significant overall survival benefit seen in several randomized clinical trials (RCTs) enrolling a range of people with completely resected NSCLC, results of subset analyses for patient populations with stage IB disease were not significant, and adjuvant chemotherapy in stage IB disease is not currently recommended for routine use. To date, very few patients with stage IA NSCLC have been enrolled onto RCTs of adjuvant therapy; adjuvant chemotherapy is not recommended in these cases.

- NCCN: adjuvant chemotherapy recommended for IIA - IIIA, for IB chemotherapy considered for high risk (including neuroendocrine, vascular invasion, tumours> 4cm, visceral pleural involvement and incomplete LN sampling)

- NICE (2011): Consider postoperative chemotherapy in patients with good performance status (WHO 0-1) and T2-3 N0 M0 NSCLC with tumours greater then 4cm in diameter. Offer a cisplatin based combination chemotherapy regimen for adjuvant chemotherapy. For patients with NSCLC who are suitable for surgery, do not offer neo-adjuvant chemotherapy outside a clinical trial. Ensure eligible patients have the benefit of detailed discussion of the risks and benefits of adjuvant chemotherapy.
Guidelines: ESMO

- Should factors, other than stage, guide the choice of adjuvant therapy?
  - Adjuvant chemotherapy is recommended in stage II and III and should be cisplatin based. The most frequently studied regimen is cisplatin–vinorelbine.
  - The indication should be further discussed in a multidisciplinary tumour board and should consider host factors such as age, comorbidities, performance status (PS), as well as time since surgery and pathology report [V, A].
  - According to data from clinical trials, age per se is not a factor of selection [II, A].
  - Patients with severe comorbidity were excluded from clinical trials. In the Ontario Cancer Registry, a detrimental effect from adjuvant chemotherapy was seen in patients with greater co-morbidity (Charlson score 3+) but still fit for chemotherapy [III, C].
  - Evidence of benefit from adjuvant chemotherapy has been established in patients PS 0, 1 rarely PS 2 [I, A].
  - The precise interval limits to start adjuvant chemotherapy have not been properly addressed in clinical trials. Some trials (IALT) restricted inclusion to patients resected within 60 days before randomisation. The Ontario Registry of Canada looked more carefully at timing and concluded that no difference was observed between 2 cohorts (0–10 versus 11–16 weeks) [III, C].
  - Even if such patients were not included in the RCTs, adjuvant chemotherapy is advised for R1 resection regardless of nodal status [V, A].

Vansteenkiste Annals Oncol  2014
Guidelines: ESMO recommendations

- Adjuvant chemotherapy should be offered to patients with resected stage II and III NSCLC [I, A] and can be considered in patients with resected stage IB disease and a primary tumour >4 cm [II, B]. Pre-existing comorbidity, time from surgery and postoperative recovery need to be taken into account in this decision taken in a multidisciplinary tumour board [V, A].

- For adjuvant chemotherapy, a two-drug combination with cisplatin is preferable [I, A]. In randomised studies, the attempted cumulative cisplatin dose was up to 300 mg/m2, delivered in three to four cycles. The most frequently studied regimen is cisplatin–vinorelbine.

- In the current state of knowledge, the choice of adjuvant therapy should not be guided by molecular analyses such as, e.g. ERCC1 or mutation testing [IV, B]

- In the current state of knowledge, targeted agents should not be used in the adjuvant setting [II, A].

- In view of the equivalence of neo-adjuvant and adjuvant chemotherapy for overall survival, the consistent results and broad evidence base support adjuvant chemotherapy as the timing of choice [I, A]
Absolute risk and benefit

novel adjuvant approaches

- pemetrexed
- targeted therapies with activating mutations
- vaccine therapies
- genomics - stratifying risk
- immunotherapy
- other risk factors - vascular invasion
role of adjuvant pemetrexed in non-squamous NSCLC

- summary of trials

<table>
<thead>
<tr>
<th>Study and Trial Identifier</th>
<th>Study Phase/Treatment Arms</th>
<th>Patients Randomized/Enrolled</th>
<th>Results</th>
<th>Grade 3/4 Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmid-Bindert et al, 2009¹³  NCT00269152</td>
<td>Phase 2/P/Cis (75 mg/m²) vs. P/Carb (AUC, 5) day 1 every 21 days for 4 cycles</td>
<td>118 Patients (P/Cis: 64; P/Carb: 54) Resected stage IB/II NSCLC; ECOG PS 0 to 1</td>
<td>Primary end point Feasibility rate, % (95% CI): P/Cis: 59.4 (46.4-71.5); P/Carb: 50 (36.1-63.9)</td>
<td>P/Cis: neutropenia (14.1%); P/Carb: neutropenia (11.1%); febrile neutropenia (3.7%); thrombocytopenia (5.6%)</td>
</tr>
<tr>
<td>Karapanagiotou et al, 2009¹⁴</td>
<td>Phase 2/P/Carb (AUC, 5) with prophylactic administration of rhG-CSF on days 1 and 14 every 28 days</td>
<td>45 Patients R0 resected stage IB, II, or IIIA NSCLC; ECOG PS ≤ 2</td>
<td>Median time to disease recurrence (mo): 26 (95% CI, 23-29)</td>
<td>No Grade 3/4 toxicities reported</td>
</tr>
<tr>
<td>Charpidou et al, 2009¹⁵</td>
<td>Phase 2/P/Carb (AUC, 5), day 1 of q3 weeks for 3 cycles</td>
<td>43 Patients R0 resected stage IB to IIIA NSCLC</td>
<td>PD: n = 6 (14%); mean time to progression (mo): 20 (95% CI, 18-21)</td>
<td>No Grade 3/4 toxicities reported</td>
</tr>
<tr>
<td>Kreuter et al, 2013¹⁶  NCT00349089 (TREAT)</td>
<td>Phase 2/P/Cis (75 mg/m²), q3 weeks vs. Vincristine (25 mg/m²) on days 1, 8, 15, 22 and Cis (50 mg/m²) on days 1 and 8), q4 weeks</td>
<td>132 Patients R0 resected NSCLC; Stage IB, IIIa, IIIb, and T3N1</td>
<td>Primary end point: clinical feasibility rate, % (95% CI): P/Cis: 95.5 (87.5-99.1) vs. V/Cis: 75.4 (63.1-85.2); P = .001 Secondary end point: dose delivery, % (95% CI): P/Cis: 74.6 (62.5-84.5) vs. V/Cis: 20.0 (11.1-31.8); (P &lt; .0001)</td>
<td>Hematological P/Cis: 10% vs. V/Cis: 74%; P &lt; .001 Nonhematological P/Cis: 33% vs. V/Cis: 31%; P = .798</td>
</tr>
<tr>
<td>Pemetrexed in Elderly Patients</td>
<td>Phase 2/Pem single-agent vs. Docetaxel (75 mg/m²) with Carb (AUC, 5)</td>
<td>42 Patients Resected NSCLC (Pem: n = 19; Doc/Carb: n = 23)</td>
<td>Primary end point: MST (mo): Pem: 23.8; Doc/Carb: 24.13 Secondary end points: 1-year and 2-year survival rates, %: Pem: 94.74 and 73.68; Doc/Carb: 91.30 and 78.26</td>
<td>In 5 patients fever, fatigue, rash, decreased platelets and elevated liver enzymes. Treatment groups not stated</td>
</tr>
</tbody>
</table>

Simon Clin Lung Cancer Nov 2013
role of adjuvant pemetrexed in non-squamous NSCLC

• Phase II feasibility studies

  • NCT00269152: pem-cis v pem carbo (n=118), feasibility (4 cycles, >/= 95% planned dose, no grade 3/4 toxicities in >60%) 59 and 50% respectively. OS for both groups 82-83% at 3yr and 80-83% at 5 yr. (Schmid-Bindert 2015)

  • single arm pem-carbo n=45, 38% squamous. No grade III/IV (Kapanagiou 2009)

  • single arm pem-carbo mean TTP 20 months, n=43 (Charpidou 2009)

Mannegold JTO 2009
selected ongoing pemetrexed trials

- UMIN000006737 - ongoing Japanese trial, n=800, non-squamous, vin-cis vs pem cis, stratified for EGFR status, stage, ongoing at last update May 2015

- NVALT 8B - Dutch study, pem cis plus LMWH in high risk (defined by PET - SUVmax \( \geq 7 \)) resected non-squamous. n=600, started 2007

- TASTE: predictive biomarkers (EGFR, ERCC1), phase II/III, phase III cancelled due to ERCC1 unreliability

- ITACA: predictive biomarkers (TS, ERCC1), cisplatin doublet versus tailored treatment ?same issues

- pemetrexed plus immunotherapy

- pemetrexed/cisplatin feasible in adjuvant setting, evidence from 1000+ patients. Feasible to combine with targeted and immunotherapeutic agents
Adjuvant TKi: BR.19 (NCIC CTG BR.19)

- completely resected Stage IB-IIIA
- 2-years of gefitinib (250 mg daily)/placebo
- closed prematurely (ISEL, SWOG 0023), median duration therapy 5-months, n=503, median F/U 4.7 years
- OS and DFS - favoured placebo
- KRAS, EGFR expression (FISH), EGFR mutation status - all favored placebo over gefitinib
- EGFR mutation (+) - HR 1.58 (95% CI: 0.83-3.00) favouring placebo (only 15 (+) tumours, 4%)

Goss JCO 2013
BR.19 (NCIC CTG BR.19)

DFS (L) and OS (R) by treatment arm in patients with EGFR exon 19 and 21 mutations
Adjuvant TKi: TASTE (TAilored post-Surgical Therapy in Early-stage NSCLC)

- Phase II/III French study: feasibility and DFS of pem-cisplatin versus customised therapy in resected II and IIIA (non-N2) non-squamous patients

- known EGFR status, ERCC1 expression status

- experimental arm: EGFR M+ received erlotinib 150mg daily for 1 year, ERCC1 negative pts received four cycles of pem/cis. ERCC1 positive pts were closely monitored

- phase II met feasibility endpoints, phase III component cancelled - reliability of ERCC1 assessment

Soria ASCO 2013
RADIANT Trial: Adjuvant NSCLC with/without Tarceva (Erlotinib)

ELIGIBLE:
N=945
Resected I-IIIA
≥ Lobectomy
EGFR IHC/FISH +
Post-operative chemo optional

RANDOMIZE

Tarceva (Erlotinib) 150 mg by mouth daily x 2 yrs

Placebo daily x 2 yrs

2:1 to active drug

Disease-free survival as primary endpoint
RADIANT

• phase III RADIANT (Randomized Double-Blind Trial In Adjuvant NSCLC with Tarceva) trial

• adjuvant erlotinib (E) therapy in resected NSCLC patients who have overexpression of EGFR protein by immunohistochemistry (IHC) or EGFR gene amplification by fluorescence in situ hybridization (FISH)

• rate of EGFR exon 19 and 21 mutations in this unselected patient population is 12%, 973 patients - approximately 113 patients (about 60 patients per treatment arm) with EGFR mutation.

• Overall adjuvant E did not prolong DFS; a trend for E benefit previously observed (ASCO14) in EGFR M+ subgroup is no longer apparent. EGFR mutation status was not a stratification factor in this trial and was not a prognostic factor

O’Brien ASCO 2015
Adjuvant EGFRi

- ongoing trials

- consolidation icotinib - no improvement in DFS, small study

- gefitinib v chemotherapy

- ALCHEMIST, role of erlotinib or crizotinib in mutation positive patients
  - erlotinib 2yrs v placebo in EGFRm+
  - crizotinib v placebo for 2 years in ALK translocations
molecular signatures

• identification of better prognostic and predictive markers

• will need prospective validation

• ERCC1, p27 - neither validated in LACE-Bio project

• prognostic gene expression - 14-gene expression array identified non-squamous patients stage I at high risk relapse. Identified low intermediate and high risk categories in all disease stages in a validation cohort

• cell-cycle progression gene score based on 31 proliferation genes

• commercially available assays

Kratz Lancet 2012
Wistuba Clin Cancer Res 2013
MAGRIT

Resected NSCLC MAGE-A3+

Decision chemo Y/N

Stage IB,II,IIIA MAGE-A3+ (35-50%) complete resection +/- adjuvant chemo

No

Yes

MAGE-A3 ASCI

placebo

up to 4 cycles of chemo

MAGE-A3: 13 administrations over 27m

placebo
MAGRIT

• recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3 positive NSCLC
• IB-IIIA (6th ed)
• did or did not receive adjuvant chemotherapy
• randomised 2:1 to receive immunotherapeutic/placebo over 27 month period
• co-primary endpoints - DFS overall, DFS in no-chemotherapy group, DFS with potentially predictive gene signature

• 13,849 patients screened, 4,210 MAGE-A3 positive, 2,272 randomised and treated - largest clinical trial in NSCLC
• well tolerated, no difference in G3 events
• DFS 60.5m v 57.9m in overall group
  (HR 1.024, 95% CI 0.891-1.177; p = 0.7379), OS not reached
• no predictive gene signature identified
• PRAME

Vansteenkiste Lancet Oncology 2016
Immunotherapy

• PEARLS (ETOP): A randomized, phase III trial with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy

• primary endpoint DFS, secondary -OS, lung ca specific survival, toxicity

http://www.etop-eu.org
Special situations

- multiple ipsilateral tumours (T3, T4): not specifically analysed in the studies

- R1 resection: chemotherapy recommended in ESMO guidelines. Radiotherapy after chemotherapy

- Resected stage IV (oligometastatic) disease: role remains to be determined. Note increasing benefit with increasing stage

- large cell neuroendocrine carcinoma:
conclusions

• adjuvant chemotherapy is established for stage II and III resected NSCLC with sustained benefit

• the regimen with most evidence is cisplatin vinorelbine although the accepted schedule differs from JBR.10 and ANITA trials

• stage IB tumours can be considered for adjuvant chemotherapy if $\geq 4\text{cm}$ although evidence is from unplanned, retrospective analyses (CALGB 9633 and JBR.10)

• selected older patients (70+) tolerate chemotherapy with acceptable toxicity but there is very evidence for the elderly and very elderly (75+, 80+)

• further major improvements with chemotherapy alone are unlikely (pemetrexed?)

• research will be focused on better discrimination of high versus low risk patients, predictive factors and more targeted therapies
THE END
questions?
ongoing trials of adjuvant pemetrexed

<table>
<thead>
<tr>
<th>Study and Trial Identifier</th>
<th>Study Title</th>
<th>Study Phase/n°</th>
<th>Treatment Arms</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01258127</td>
<td>Pem/Carb (AUC, 6) vs. vinorelbine/Carb (AUC, 6) in patients with completely resected NSCLC</td>
<td>Phase 2/h = 134</td>
<td>Pem and Carb (AUC, 6) and folic acid (350-1000 µg) and dexamethasone vs. Vinorelbine (25 mg/m²) and Carb (AUC, 6) on day 1 every 21 days for 4 cycles</td>
<td>Primary: clinical feasibility</td>
</tr>
<tr>
<td>He et al, 2009^16 NCT00923837</td>
<td>Feasibility of administering adjuvant chemotherapy of Pem followed by Pem/oxaliplatin immediately after VATS in patients with completely resected NSCLC</td>
<td>Phase 2/h = 75</td>
<td>Pem followed by Pem and oxaliplatin (120 mg/m²)</td>
<td>Primary: clinical feasibility</td>
</tr>
<tr>
<td>NCT01209520 (EPRDST-20080779)</td>
<td>Residual hypermethylation in early-stage NSCLC as part of adjuvant therapy and preventive strategy</td>
<td>Phase not provided/h = 20</td>
<td>Completely resected stage IB to IIA NSCLC</td>
<td>Primary: to determine presence of methylated TSGs and degree of demethylation according to 5-azacytidine in tumor tissue/serum of patients with NSCLC Secondary: methylation profile of silenced TSGs after treatment</td>
</tr>
<tr>
<td>Dingemans et al, 2008^19 NVALT BB (2006-002608-16)</td>
<td>A randomized phase II study of adjuvant chemotherapy with or without LMWH in patients with high risk for recurrence and completely resected NSCLC patients</td>
<td>Phase 3/h = 600</td>
<td>Completely resected stage IB to IIA NSCLC</td>
<td>Primary: recurrence-free survival Secondary: OS, dose intensity of subsequent cycles, QoL, toxicity, health economics Exploratory: prognostic markers, germlines/proptoxims</td>
</tr>
<tr>
<td>NCT00775385 TASTE</td>
<td>TaIored Post-Surgical Therapy in Early Stage NSCLC (TASTE)</td>
<td>Phase 2, Phase 3/h = 165</td>
<td>Surgically resected stage II or IIA (non-N2) NSCLC; EOG PS: 0-1</td>
<td>Primary: feasibility Secondary: DFS</td>
</tr>
<tr>
<td>UMIN000006737</td>
<td>Randomized phase 3 study of P/Cis and V/Cis for completely resected nonsquamous NSCLC</td>
<td>Phase 3/h = 800</td>
<td>Completely resected stage II or IIA NSCLC with EGFR mutation</td>
<td>Primary: OS Secondary: DFS, rate of treatment completion, adverse events</td>
</tr>
<tr>
<td>Novelio et al, 2012^20 ITACA</td>
<td>International tailored chemotherapy adjuvant trial</td>
<td>Phase 3/h = 700</td>
<td>Completely resected Stage II to IIA NSCLC</td>
<td>Primary: OS Secondary: recurrence-free survival, therapeutic compliance, toxicity profile</td>
</tr>
<tr>
<td>NCT01533727</td>
<td>OK cell transfusion plus chemotherapy as adjuvant therapy for stage IB-III non–small-cell lung cancer (NSCLC)</td>
<td>Phase 2/h = 222</td>
<td>Pem/vinorelbine and Cis/Carb and OK infusion vs. Pem/vinorelbine and Cis/Carb</td>
<td>Primary: relapse rate</td>
</tr>
<tr>
<td>UMIN00007525</td>
<td>Randomized phase 3 trial of adjuvant chemo-immunotherapy with dendritic cells and activated killer cells in patients with resected primary lung cancer</td>
<td>Phase 3/h = 160</td>
<td>Immunotherapy and chemotherapy vs. Chemotherapy alone</td>
<td>Primary: 2-year and 5-year survival Secondary: recurrence-free survival, safety</td>
</tr>
</tbody>
</table>

Simon Clin Lung Cancer Cancer Nov 2013
Lung cancer incidence - male

High lung cancer incidence in the Northwest

National Statistics

Health Statistics Quarterly Summer 2008