Clinical Activity
Lung Cancer

Andrea Camerini
Ospedale Versilia
The three main objectives in advanced NSCLC

1. In advanced/metastatic cancer, palliation is often the primary treatment goal.

2. Potential strategies to increase treatment duration:
   - Maintenance therapy
   - Metronomic chemotherapy (?)

3. Toxicity and quality of life are important factors when deciding on therapeutic agents and schedules.

Chiefly when talking about patients with special needs as elderly or low PS.
Major clinical trials with metronomic chemotherapy in NSCLC patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Metronomic protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pallis et al. (2011) [23]</td>
<td>Vinorelbine 40–70 mg (oral) three times a week plus cisplatin 70–85 mg/m² (i.v.) on D1</td>
</tr>
<tr>
<td>Briasoulis et al. (2013) [24]</td>
<td>Vinorelbine 50 mg (oral) three times a week</td>
</tr>
<tr>
<td>Gorn et al. (2008) [25]</td>
<td>Docetaxel 25 mg/m² D1, D8, D15 (i.v.) plus trofosfamide 50 mg daily</td>
</tr>
<tr>
<td>Yokoi et al. (2012) [26]</td>
<td>Docetaxel 15 mg/m² (i.v.) weekly</td>
</tr>
<tr>
<td>Correale et al. (2006) [27]</td>
<td>Cisplatin 30 mg/m² D1, D8, D15 (i.v.) plus etoposide 50 mg/m² (oral) D1–21</td>
</tr>
<tr>
<td>Kakolyris et al. (1998) [28]</td>
<td>Oral etoposide 100 mg/day for seven consecutive days and consequently 100 mg every other day for 14 additional days</td>
</tr>
<tr>
<td>Kontopodis et al. (2013) [29]</td>
<td>50 mg p.o. vinorelbine fixed dose three times a week</td>
</tr>
</tbody>
</table>
Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

G. D'Addario1, M. On behalf of the

first-line treatment

• In elderly patients, chemotherapy is generally not indicated, unless survival is expected to be less than 6 months. If treatment is considered, chemotherapy should be offered in the context of a clinical trial.

PS ≥ 2 patients

Chemotherapy prolongs survival and possibly improves QoL in NSCLC patients with a PS of 2, when compared with best supportive care (BSC) [I, B]. Single-agent chemotherapy with gemcitabine, vinorelbine, and taxanes represents an option. Platinum-based combinations may also be considered as an alternative [II, B].

• Poor PS (3–4) patients should be offered best supportive care [II, B] in the absence of tumors with activating (sensitizing) EGFR mutations.

elderly patients

Two randomised phase III trials established single-agent chemotherapy as the standard of care for first-line therapy for clinically unselected elderly advanced NSCLC patients [33, 37]. A recent prospective randomised trial comparing monthly carboplatin plus weekly paclitaxel versus single-agent vinorelbine or gemcitabine in patients aged 70–89 years with PS 0–2 has reported a survival advantage for combination therapy [35].

Benefit was observed across all subgroups, but increased toxicity (notably febrile neutropenia and sepsis-related deaths) was observed. Platinum-based chemotherapy is the preferred option for elderly patients with PS 0–1—as well as selected PS2—and adequate organ function, while a single-agent approach might remain the recommended treatment of unfit or comorbid patients, who are more likely to present with significantly more treatment-related adverse events [I, B].
Tailored treatment is a must!

Molecular portrait…. and clinical portrait: Definition of “Fit for MonoCT”
SUMMARY OF “FIT MonoCT” CHARACTERISTICS

- Elderly (age > 75-80y)
- ECOG PS > 1
- Heart Failure (NYHA > 1)
- Renal Failure (CrCl < 60-45 mL/min)
- Neuropathy/Earing loss (CTCAE v4 > 1)
- Bone Marrow “fragility”

Co-morbidity
CGA arm: median TFFS, 3.1 mo (95% CI, 2.7 to 4.4 mo)
Standard arm: median TFFS, 3.2 mo (95% CI, 2.9 to 4.1 mo)
$P = .32$
# APPROPRIATE TREATMENT AS SINGLE-AGENT CT

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Conditions Influencing Choice Between Oral Versus Intravenous Single-Agent Chemotherapy</th>
</tr>
</thead>
</table>
| Favors oral | - Impaired peripheral venous access.  
- Absence of caregiver to support logistic issues.  
- Personalized scheduling.  
- Patient preference. |
| Favors intravenous | - Esophageal obstructions.  
- Gastrointestinal disorders.  
- Patient preference. |

De Marinis et al, Clin Lung Cancer 2015
mVNR AS SINGLE-AGENT CT: RATIONALE FOR TIW CONTINUOUSLY ORAL NAVELBINE ADMINISTRATION

Elimination half-life: about 40 hours

Bonneterre, Piccart. Annals of Oncology 2001
PHARMACOKINETICS OF mVNR

• Phase IA study in 62 patients who had progressed despite standard treatment.

Primary endpoint: feasibility and safety

Y = 0.0201x + 0.1237
R^2 = 0.9415

STEADY-STATE VNR CONCENTRATIONS FOLLOWING METRONOMIC ORAL DOSING

- Phase IB study in 73 patients who had progressed despite standard treatment.
- Primary endpoint: time to treatment failure

Steady state VRL levels over time (all patients)

VRL concentration (ng/mL)

Weeks

- 30 mg
- 40 mg
- 50 mg

Briasoulis et al. BMC Cancer 2013
CEPs as pharmacodynamic marker of metronomic VNR in mice: characterization of optimal biologic dose (OBD)

MDA-MB-231/LM2-4 human breast cancer treated with oral VNR administered by gavage 3 times a week, at the indicated doses \(^1\)

Black columns represent the optimal therapeutic doses in each case that induce the most significant decline in viable CEP levels and a reduction in tumor volumes, with minimal or no toxicity \(^1\)

9 mg/kg was the OBD for metronomic oral vinorelbine with a demonstrated antiangiogenic effect measured by CEPs, in breast cancer mice model, which corresponds to a human equivalent dose (HED) \(^2\)* of 43.8 mg of oral vinorelbine

2. Reagan-Shaw, et al. FASEB J 2007; *weight: 60 kg, BSA 1.6
Metronomic oral vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer: results of a phase II trial (MOVE trial)

Andrea Camerini*, Cheti Puccetti, Sara Donati, Chiara Valsuani, Maria Cristina Petrella, Gianna Tartarelli, Paolo Puccinelli and Domenico Amoroso
Primary end points:
Clinical Benefit (CR+PR+SD>12wks)
Safety

Secondary end points:
TTP
OS
QoL

Table 1 Baseline study population characteristics (n = 43)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>median (range) 80 (70 – 92)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>36/7</td>
</tr>
<tr>
<td>ECOG PS (0/1/2)</td>
<td>0/16/27</td>
</tr>
<tr>
<td>Stage (IIIB/IV)</td>
<td>16/27</td>
</tr>
<tr>
<td>Smoke (never/past/current)</td>
<td>1/23/19</td>
</tr>
<tr>
<td>Serious co-morbid illnesses</td>
<td>median (range) 3 (0 – 6)</td>
</tr>
</tbody>
</table>
| Histology (n/%)                     | Squamous cell carcinoma 24/43 (55.8%)
|                                     | Adenocarcinoma 11/43 (25.6%)
|                                     | Large-cell carcinoma 4/43 (9.3%)
|                                     | Undifferentiated 4/43 (9.3%)

Camerini et al, BMC Cancer 2015
# EFFICACY RESULTS

## Table 2 Clinical efficacy data at final analysis on 43 patients

<table>
<thead>
<tr>
<th>Number of cycles (median - range)</th>
<th>5 [1 – 21]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment response (n - %)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1/43 - 2.3%</td>
</tr>
<tr>
<td>PR</td>
<td>7/43 - 16.3%</td>
</tr>
<tr>
<td>SD</td>
<td>17/43 - 39.5%</td>
</tr>
<tr>
<td>PD</td>
<td>18/43 - 41.9%</td>
</tr>
<tr>
<td><strong>Clinical benefit</strong></td>
<td>25/43 - 58.1%</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>8/43 - 18.6%</td>
</tr>
<tr>
<td>TTP (median - range)</td>
<td>5 [2 - 21] months</td>
</tr>
<tr>
<td><strong>OS (median - range)</strong></td>
<td>9 [3 - 29] months</td>
</tr>
<tr>
<td>Percentage of alive patients (n - %)</td>
<td></td>
</tr>
<tr>
<td>year 1</td>
<td>16/43 - 37.2%</td>
</tr>
<tr>
<td>year 2</td>
<td>4/43 - 9.3%</td>
</tr>
</tbody>
</table>

CR=complete response; PR=partial response; SD=stable disease; PD=disease progression; ORR=overall response rate; TTP=time to progression; OS=overall survival.
# SAFETY RESULTS

Table 3 All grade (left column) and grade 3/4 (right column) Treatment-related toxicities at final analysis (n = 43)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>All grade</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-hematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>32.4%</td>
<td>0.1%*</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.0%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5.0%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.5%</td>
<td>0.1%*</td>
</tr>
<tr>
<td>Mucositis</td>
<td>4.5%</td>
<td>0.1%*</td>
</tr>
<tr>
<td>Sensorial neuropathy</td>
<td>2.4%</td>
<td>0%</td>
</tr>
<tr>
<td>hematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>44.0%</td>
<td>0.1%*</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4.0%</td>
<td>0.1%*</td>
</tr>
</tbody>
</table>

*Rounded to 0.1%
FIRST-LINE “Fit for MonoCT” PTS: WHAT ELSE mVNR CAN OFFER?

- **MILES ’03**
  - GEM+VNR=VNR/GEM
  - Age 74
  - PS2 23%
  - MS 28 wks.
  - Cycles 4
  - G3/4 neutr. 25%

- **GRIDELLI ’04**
  - oral VNR
  - Age 74
  - PS2 19%
  - MS 36 wks.
  - Cycles 4
  - G3/4 neutr. 50%

- **MOVE ’15**
  - oral mVNR
  - Age 80
  - PS2 63%
  - MS 38.7 wks.
  - Cycles 5
  - G3 neutr. 1

- **ELVIS ’99**
  - VNR > BSC
  - Age 74
  - PS2 23%
  - MS 28 wks.
  - Cycles 4

MTD (up to 6 cy)

**ELVIS ’99**
- VNR > BSC
- Age 74
- PS2 23%
- MS 28 wks.
- Cycles 4
- G3/4 neutr. 25%

**MILES ’03**
- GEM+VNR=VNR/GEM
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- Cycles 4
- G3/4 neutr. 50%

**MOVE ’15**
- oral mVNR
- Age 80
- PS2 63%
- MS 38.7 wks.
- Cycles 5
- G3 neutr. 1

136 mg/week

150 mg/week
## Differences in toxicities among treatments*

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>MTD CT</th>
<th>Targeted</th>
<th>Immuno</th>
<th>Metronomic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia / thrombocytopenia</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Anaemia</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhoea / constipation</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Rash</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Nausea</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vomiting</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alopecia</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

*Adapted from IASLC update: Immunotherapy for Lung Cancer 2016 (M. O’Brien) 2016, 01, 13
FUTURE PERSPECTIVES (MTD vs mCT)

mVNR in unfit* NSCLC - TEMPO LUNG Trial

• ARM A:
  • NAVELBINE 60 mg/m² weekly, for cycle 1, then 80 mg/m² weekly for subsequent cycles according to haematological tolerance and investigator’s decision.
  • Until disease progression

• ARM B:
  • NAVELBINE Oral 50 mg total dose 3 days/week
  • Until disease progression

*Appropriate previous adjuvant platinum-based chemotherapy for resected NSCLC within 6-12 months; Creatinine Clearance < 60 ml/min; Heart Failure NYHA class II-III; Hearing Loss > Grade 2; Medical condition impairing platinum-based chemotherapy according to physician’s opinion

Pierre Fabre Study Code: PM 0259 CA 232 J1
EudraCT Number: 2014-003859-61
FUTURE PERSPECTIVES (MTD vs mCT)

mVNR in very*elderly NSCLC - MOON Trial

**ARM A:**
- NAVELBINE 60 mg/m2 weekly, for cycle 1, then 80 mg/m2 weekly for subsequent cycles according to haematological tolerance and investigator’s decision.
- Until disease progression

**ARM B:**
- NAVELBINE Oral 50 mg total dose 3 days/week
- Until disease progression

*Age >=75 yrs
Feasibility of metronomic oral VRL + RT, with/without CDDP in stage III NSCLC

- Dosing/schedule:
  - Phase 1: cohorts of increasing oral VRL tiw (60–180 mg/week)
  - Phase 2: cohorts of increasing oral VRL tiw (130–150 mg/week) + cisplatin 80 mg/m² every 3 weeks
  - Both phases: radiotherapy (60 Gy total, in 2-Gy/day fractions, 5 days per week)
- Duration: not specified

<table>
<thead>
<tr>
<th>Level</th>
<th>Patients (n)</th>
<th>Total dose (mg) per week</th>
<th>Dose</th>
<th>Patients with a toxicity</th>
<th>dose-limiting toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral VRL single-agent chemotherapy concurrently with radiotherapy (60 Gy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L 1</td>
<td>3</td>
<td>60</td>
<td>20 mg D1, 3, 5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>L 2</td>
<td>3</td>
<td>90</td>
<td>30 mg D1, 3, 5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>L 3</td>
<td>3</td>
<td>100</td>
<td>40 mg D1; 30mg D3, 5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>L 4</td>
<td>3</td>
<td>120</td>
<td>40 mg D1, 3, 5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>L 5</td>
<td>3</td>
<td>130</td>
<td>50 mg D1; 40mg D3, 5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>L 6</td>
<td>6</td>
<td>150</td>
<td>50 mg D1, 3, 5</td>
<td>1 (febrile neutropenia)</td>
<td></td>
</tr>
<tr>
<td>L 7</td>
<td>5</td>
<td>160</td>
<td>60 mg D1; 50 mg D3, 5</td>
<td>4 (3 G3 esophagitis and pneumonia)</td>
<td>1 G3 pneumonia</td>
</tr>
<tr>
<td>L 8</td>
<td>0</td>
<td>160</td>
<td>60 mg D1, 3, 5</td>
<td>NA²</td>
<td></td>
</tr>
<tr>
<td>Oral VRL plus cisplatin concurrently with radiotherapy (60 Gy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L 5 bis</td>
<td>6</td>
<td>130</td>
<td>50 mg D1; 40 mg D3, 5</td>
<td>1 (dehydration + esophagitis)</td>
<td></td>
</tr>
<tr>
<td>L 5 ter</td>
<td>3</td>
<td>140</td>
<td>50 mg D1, 3; 40 mg D3, 5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>L 6 bis</td>
<td>2</td>
<td>150</td>
<td>50 mg D1, 3, 5</td>
<td>1 (febrile neutropenia)</td>
<td></td>
</tr>
</tbody>
</table>

Phase I study in 26 patients with untreated stage III NSCLC. Primary endpoint: MTD and recommended dose

Feasibility of metronomic oral VRL + RT, with/without CDDP in stage III NSCLC

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- Duration: not specified

Phase I study in 26 patients with untreated stage III NSCLC. Primary endpoint: MTD and recommended dose

Ongoing evaluation of metronomic oral VRL as chemo-switch maintenance (ONC-MANILA study)

- Primary endpoint: PFS
- Key secondary endpoints
  - OS
  - ORR
  - Duration of response
  - Duration of post-progression survival
  - Quality of life
  - Safety
- Estimated completion date: Q4/2016 (79 pts at Invest. Meet. On 01/2016)

http://clinicaltrials.gov/show/NCT02176369

Estimated enrolment: 120 patients with stage IIIB/IV NSCLC and stable disease after prior 1st-line platinum-based chemotherapy

Metronomic oral VRL 50 mg tiw

Close observation/best supportive care

Until progression, unacceptable toxicity or death
NS-NSCLC TS+ (mVNR Maintenance)

Open-label, Multicenter, Randomized Phase II Trial of Treatment with Cisplatin and Pemetrexed or Cisplatin and Oral Vinorelbine in Patients affected by stage IIIB-IV Non-Squamous Non-Small Cell Lung Cancer with high Thymidilate Synthase expression

+ NS-NSCLC IIIB-IV
+ First line
+ Nuclear TS > 70

R 1:1

Oral vinorelbine 60-80 mg/m2 on days 1 and 8 (first cycle 60 mg/m2) + Cisplatin 80 mg/m2 on day 1 every 3 weeks x 4 cycles

Pemetrexed, 500 mg/m2, day 1 + Cisplatin, 75 mg/m2, day 1 every 3 weeks x 4 cycles

Metronomic Oral VNR 50mg d 1,3,5 until PD

PEM 500 mg/m2 day 1 every 3 weeks until PD

Primary Objective: DCR (CR+PR+SD)

- N. Centres: 15
- N. planned Pts: 130
- N. enrolled pts: NA
- Start Date: 1Q 2016
- End Date: 3Q 2018
CONCLUSIONS

• Clinical selection is a key point in treatment planning: platinum unfit pts should receive a first-line monoCT (vinorelbine or gemcitabine)

• Global clinical consideration (ClCr is an exclusion criteria and not an inclusion criteria) is a key point

• First line mVNR kept (at least) similar efficacy respect to MTD monoCT with advantages of oral formulation and a good safety profile → increased pts compliance

• Fit for MonoCT, maintenance and concomitant to RT all represent a potential application setting for metronomic oral VNR
So... metronomic CT could be a valid option in advanced NSCLC?