Report dei gruppi di lavoro: Linfomi

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Dip. Biotecnologie Cellulari ed Ematologia
Università “Sapienza” Roma
## Disclosures – Maurizio Martelli

<table>
<thead>
<tr>
<th>Category</th>
<th>Disclosures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>Roche, Mundipharma</td>
</tr>
<tr>
<td>Employee</td>
<td>N/A</td>
</tr>
<tr>
<td>Consultant</td>
<td>N/A</td>
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<tr>
<td>Major Stockholder</td>
<td>N/A</td>
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<tr>
<td>Conferences/Educational Activities</td>
<td>Roche, Celgene, Pfizer, Takeda Mundipharma</td>
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<td>Scientific Advisory Board</td>
<td>Janssen, Roche, Celgene, Mundipharma</td>
</tr>
</tbody>
</table>
Grazie a tutti i componenti del panel
A phase III multicenter, randomized study with Lenalidomide (Revlimid®) maintenance versus observation after intensified induction regimen containing rituximab followed by high dose chemotherapy and Autologous Stem Cell Transplantation as first line treatment in adult patients with advanced Mantle Cell Lymphoma

Sergio Cortelazzo, MD on behalf of FIL
Unit of Oncology-Hematology, Humanitas Bergamo, Italy
• Uno schema R-HDS like è ancora considerato nella pratica clinica un regime di chemioterapia di prima linea standard per il paziente giovane affetto da MCL

• La MRD deve essere valutata anche al di fuori di studi prospettici

• Ruolo della terapia di mantenimento post induzione

• ASCT di consolidamento in prima linea in tutti pazienti o solo in casi selezionati
<table>
<thead>
<tr>
<th></th>
<th>No. Pts</th>
<th>CR</th>
<th>Median F-up</th>
<th>PFS</th>
<th>OS</th>
<th>Toxic deaths</th>
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<tbody>
<tr>
<td>R-HCVAD*</td>
<td>97</td>
<td>87%</td>
<td>3.3 yrs (4.8)**</td>
<td>64-73% (48-60%)</td>
<td>82% (65%)</td>
<td>5%</td>
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<tr>
<td>R-HCVAD**</td>
<td>60</td>
<td>72%</td>
<td>3.8 yrs</td>
<td>5-yr FFs 46%</td>
<td>5-yr OS 73%</td>
<td>5%</td>
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<tr>
<td>R-HCVAD***</td>
<td>49</td>
<td>58%</td>
<td>2 years</td>
<td>2-yr PFS 63%</td>
<td>2-yr OS 76%</td>
<td>2%</td>
</tr>
<tr>
<td>R-HDS§</td>
<td>28</td>
<td>100%</td>
<td>2.9 yrs</td>
<td>79%</td>
<td>89%</td>
<td>4%</td>
</tr>
<tr>
<td>NLG#</td>
<td>160</td>
<td>54%</td>
<td>3.8 yrs</td>
<td>66%</td>
<td>70%</td>
<td>5%</td>
</tr>
<tr>
<td>MCL 0208</td>
<td>283</td>
<td>79%</td>
<td>ongoing</td>
<td>2-yr PFS 77%</td>
<td>2-yr OS 88%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

European MCL Network Younger Study: 497 randomized patients

- 4 x R-CHOP
- 2 x R-CHOP

**PR, CR**

- DexaBEAM (stem cell mobilization)
- **PR, CR**
  - Cyclo 120 mg/kg +
  - TBI 12 Gray
  - PBSCT

**R-CHOP/R-DHAP**

- alternating stem cell mobilization
- after course 6

- TBI 10 Gray +
- Ara-C 4 x 1.5 g/m² +
- Melphalan 140 mg/m²
- PBSCT

European MCL Network Younger Study: Time to treatment failure

Hazard Ratio 0.68

<table>
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<tr>
<th></th>
<th>n</th>
<th>events</th>
<th>2-ys</th>
<th>3-ys</th>
<th>4-ys</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-DHAP</td>
<td>223</td>
<td>54</td>
<td>83%</td>
<td>78%</td>
<td>68%</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>227</td>
<td>100</td>
<td>71%</td>
<td>59%</td>
<td>50%</td>
</tr>
</tbody>
</table>

\[ p = 0.0382 \]

R-DHAP, median not reached
R-CHOP, median = 47

Rituximab maintenance after R-DHAP and ASCT in young untreated MCL: LyMa trial

R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or oxaliplatin or carboplatin)

R-BEAM: Rituximab 500mg/m2 d-8; BCNU 300mg/m2 d-7; Etoposide 400mg/m2/d d-6 to -3; aracytine 400mg/m2/d d-6 to d-3; melphalan 140mg/m2 d-2

Le Gouill et al., ASH 2014; abstract 146 (oral presentation)
Study Flow Chart

Inclusion
- R-DHAP x 4
- R-CHOP x 4
- ASCT (R-BEAM)

Randomization

299

266 (89%)

20 (6.7%)

257 (86%)

239 (80%)

Le Gouill et al., ASH 2014; abstract 146 (oral presentation)
• Uno schema R-HDS like è ancora considerato nella pratica clinica un regime di chemioterapia di prima linea standard per il paziente giovane affetto da MCL

• La MRD deve essere valutata anche al di fuori di studi prospettici

• Ruolo della terapia di mantenimento post induzione

• ASCT di consolidamento in prima linea in tutti pazienti o solo in casi selezionati
Remission Duration according to MRD Status after ASCT - Pooled trials -

\[ n = 182 \]

* \( p = 0.0013 \)

By Courtesy of C Pott

**Hermine O, et al. Lancet Oncology 2013.**
MCL elderly and younger

MRD and remission duration after induction

Pott, Blood 2010
Results of the Intergroup Trials of the European MCL Network

Pott et al., ASH 2014; abstract 147 (oral presentation)
Results of the Intergroup Trials of the European MCL Network

After R-CHOP/R-DHAP/ASCT younger

After induction/maintenance therapy elderly

Cox regression: independent of MIPI, trial and treatment arm
• Uno schema R-HDS like è ancora considerato nella pratica clinica un regime di chemioterapia di prima linea standard per il paziente giovane affetto da MCL.

• La MRD deve essere valutata anche al di fuori di studi prospettici.

• Ruolo della terapia di mantenimento post induzione.

• ASCT di consolidamento in prima linea in tutti pazienti o solo in casi selezionati.
Maintenance therapy: Rituximab vs Interferon α

**B Remission Duration, Patients Assigned to R-CHOP**

- **Rituximab** (median not reached)
- **Interferon alfa** (median, 23 mo)

Median follow-up, 36 mo

P<0.001

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Rituximab</th>
<th>Interferon alfa</th>
</tr>
</thead>
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<tr>
<td>Months</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>72</td>
<td>63</td>
</tr>
<tr>
<td>24</td>
<td>48</td>
<td>29</td>
</tr>
<tr>
<td>36</td>
<td>32</td>
<td>18</td>
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<td>48</td>
<td>17</td>
<td>10</td>
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<tr>
<td>60</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>72</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**D Overall Survival, Patients Assigned to R-CHOP**

- **Rituximab** (median not reached)
- **Interferon alfa** (median, 64 mo)

Median follow-up, 42 mo

P=0.005

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Rituximab</th>
<th>Interferon alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>86</td>
<td>92</td>
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<td>24</td>
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<td>36</td>
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<td>48</td>
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<td>22</td>
</tr>
<tr>
<td>60</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>72</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>96</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Kluin-Nelemans HC et al. NEJM 2012;367:520-31
EFS from time of randomization

- **WW** (95% CI)
  - 24m: 83.1% (75-89)
  - 36m: 73.4% (62.6-81.6)
  - 48m: 61.8% (47.7-73.1)

- **Rituximab** (95% CI)
  - 24m: 93.3% (87-96.6)
  - 36m: 88.1% (79.5-93.2)
  - 48m: 80.4% (67.2-88.7)

$p = 0.0057$
OS from time of randomization

p = 0.7175

**Survival Probability**

<table>
<thead>
<tr>
<th>Observation</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>24m</strong></td>
<td>WW 94.5% (88-97.5) vs Rituximab 93.1% (86.6-96.5)</td>
</tr>
<tr>
<td>36m</td>
<td>WW 85.5% (75.2-91.7) vs Rituximab 93.1% (86.6-96.5)</td>
</tr>
<tr>
<td>48m</td>
<td>WW 83.6% (72.8-90.5) vs Rituximab 83.4% (70.2-91.1)</td>
</tr>
</tbody>
</table>

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**OS (months)**

- Observation: 120, 117, 116, 113, 84, 69, 47, 30, 14, 5, 1, 1, 0
- Rituximab: 119, 117, 115, 110, 92, 72, 53, 36, 22, 13, 3, 0
• Uno schema R-HDS like è ancora considerato nella pratica clinica un regime di chemioterapia di prima linea standard per il paziente giovane affetto da MCL.

• La MRD deve essere valutata anche al di fuori di studi prospettici.

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Effect of ASCT on MRD Status

By Courtesy of C Pott

Patients with molecular marker: 249/283 (88%)  IGH + 192/283 (69%)  BCL-1 + 101/283 (36%)

1st LK: 152/192 MRD- (79%)  
MRD assessed by ASO nested-PCR

2nd LK: 14/35 MRD- (40%)

MRD by ASO RQ-PCR on 100 patients

BONE MARROW

PERIPHERAL BLOOD
TRIANGLE trial design

A:
- R-CHOP/
  R-DHAP x 6
- ASCT
- Observation

A + I:
- R-CHOP/
  R-DHAP x 6 + I
- ASCT
- 2 yrs I-maintenance
- Observation

I:
- R-CHOP/
  R-DHAP x 6 + I
- 2 yrs I-maintenance
- Observation
R/R MCL (N = 254)
- Pretreatment*
- ECOG PS 0-2
- Cyclin D1 or t(11;14)
- Measurable disease ≥2 cm

Stratification
- <3 or ≥3 years from diagnosis
- <6 vs. ≥6 months from last systemic anti-lymphoma therapy
- Prior SCT

Randomization
- 2:1

Lenalidomide†
25 mg/day PO, days 1-21, q28d
(until PD or toxicity)

Control: Investigator’s choice
Chlorambucil or rituximab until PD or toxicity
Cytarabine, fludarabine, or gemcitabine for ≤6 cycles

If PD
Crossover to lenalidomide
CT scans every 56 days for 6 months, then every 90 days thereafter

Primary endpoint: PFS (per independent central review)
Secondary endpoints: ORR, DOR, OS, safety, and QOL

NCT00875667; data cut-off March 7, 2014.

*≥1 prior combination chemotherapy with an alkylating agent and either an anthracycline and/or cytarabine and/or fludarabine (± rituximab);
≤3 relapses or failure of prior therapy and ineligible for intensified treatment or SCT.
†Prophylaxis for all lenalidomide patients included aspirin or low molecular weight heparin, warfarin, or equivalent prophylaxis for thromboembolic events and allopurinol or equivalent with oral hydration during the first 7 days for tumor lysis syndrome.
At a median follow-up of 15.9 months, lenalidomide-treated patients showed a 39% reduction in the risk of progression or death vs. IC, reflected as an estimated improvement in median PFS of 3.5 months.

ITT patients; data cut-off March 7, 2014.
MCL: new options

Signaling pathway inhibition

- Immunomodulators: lenalidomide
- Proteasome inhibitors: bortezomib
- mTOR inhibitors: everolimus, temsiroliimus
- HDACs inhibitors: Abexinostat
- BCR inhibitors (BTKI: PCI-32765)
- Inhibitors of Syk in B-cell signaling pathway: tamatinib
- PI3K inhibitors: CAL-101
- Pro-apoptotic ABT-199 Bcl-2 family; AT-101 Bcl-2 family

Bortezomib

Lenalidomide

BTKI Ibrutinib

Temsiroliimus
Subcutaneous versus intravenous rituximab in combination with CHOP for previously untreated diffuse large B-cell lymphoma: efficacy and safety results from the phase IIIb MabEase study

Pieternella Lugtenburg, 1 Antonio Rueda, 2 Irit Avivi, 3 Arnon Nagler, 4 Jean Pierre Marolleau, 5 Monica Tani, 6 Henriette Berenschot, 7 Stuart Osborne, 8 Rodney Smith, 8 Michael Pfreundschuh 9

1 Erasmus MC Cancer Institute, Rotterdam, The Netherlands; 2 E.P. Hospital Costa del Sol, Marbella, Spain; 3 Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; 4 Chaim Sheba Medical Center, Tel Hashomer, Israel; 5 University Hospital of Amiens, Amiens, France; 6 S. Maria Delle Croci Hospital, Ravenna, Italy; 7 Albert Schweitzer Hospital, Dordrecht, Netherlands; 8 F. Hoffmann-La Roche Ltd, Basel, Switzerland; 9 University Hospital of Saarland, Homburg, Germany

On behalf of the MabEase investigators
End-of-treatment CR/CRu was comparable between treatment arms

*As determined by investigator
The KM PFS curves were almost identical for rituximab SC (1400 mg) and IV (375 mg/m²).

PFS was comparable between treatment arms.

KM, Kaplan-Meier; NR, not reached; PFS, progression-free survival
Administration time was substantially shorter for rituximab SC.
MabEase: Treatment satisfaction at cycle 7

Rituximab Administration Satisfaction Questionnaire

RASQ scores were consistently higher for MabThera SC
• Mab sottocute è normalmente impiegato nella pratica clinica della propria istituzione

• Miglioramento della qualità di vita del paziente

• Miglioramento della gestione clinica del day Hospital
• Primary objective: proportion of patients with a preference for Rituximab SC or Rituximab administered intravenously, to be assessed using a Preference Questionnaire

• Secondary objectives:
  - Safety of Rituximab SC
  - Efficacy (CR including CRu, EFS, DFS, PFS and OS)
  - Comparisons of administration time, patient-assessed satisfaction and convenience using the Cancer Therapy Satisfaction Questionnaire and Rituximab Administration Satisfaction Questionnaire and immunogenicity for Rituximab SC vs Rituximab administered intravenously

Rummel, P467 Hematologica 2014; 99(s1), 157
Nei 190 pazienti che hanno completato il *Patient Preference Questionnaire* al ciclo 6, MabThera SC è stato il trattamento preferito rispetto a MabThera EV\(^1\)

Il “ridotto tempo passato in ospedale” è stato il motivo principale di preferenza per la somministrazione SC, seguito da un “ridotto stress emotivo” e dalla “comodità della via di somministrazione”\(^1\)

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Phase II Study of BEGEV [Bendamustine, Gemcitabine, Vinorelbine] as Induction Regimen Prior to ASCT in R/R HL

R. Mazza, A. Pulsoni, G. Rossi, C. Carlo-Stella, A. Anastasia, M. Bonfichi, C. Rusconi, F. Salvi, S. Luminari, A. Re, M. Gotti, A.M. Liberati, N. Di Renzo, L. Giordano, A. Santoro on behalf of Fondazione Italiana Linfomi (FIL) Hematology & Oncology, Rozzano (Humanitas Cancer Center); Hematology Departments, Rome (Sapienza University), Brescia, Pavia, Milan (Niguarda Hospital), Alessandria, Modena, Terni, Lecce

ClinicalTrials.gov Identifier: NCT01884441
### Response by Patients

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Patients</td>
<td>59</td>
<td>100</td>
</tr>
<tr>
<td>CR</td>
<td>43</td>
<td>73</td>
</tr>
<tr>
<td>PR</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>SD</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>PD</td>
<td>8</td>
<td>13</td>
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<tr>
<td>Drop out</td>
<td>1</td>
<td>2</td>
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### Response by Disease Status

<table>
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<th>Disease Status at Study Entry</th>
<th>CR + PR</th>
<th>SD</th>
<th>PD</th>
<th>P</th>
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<tbody>
<tr>
<td>Relapse</td>
<td>30 (94%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0.033*</td>
</tr>
<tr>
<td>Refractory</td>
<td>19 (70%)</td>
<td>-</td>
<td>8 (30%)</td>
<td></td>
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</tbody>
</table>

* CR-PR vs SD-PD
BEGEV is the new standard salvage therapy in refractory/relapsed Hodgkin’s lymphoma?
Phase I/II Study Design

Eligibility

- Classical HL
- Relapsed or refractory after front-line therapy

Phase I: Safety (n = 10)
Bendamustine IV, 90 mg/m²* d1,2 + B-vedotin IV, d1, 1.8 mg/kg q3wk, up to 6 cycles

Phase II: Expansion (n = 40+)
Bendamustine IV at selected dose + B-vedotin, 1.8 mg/kg

* De-escalated if ≥4/10 patients had dose-limiting toxicity during cycle 1

- ASCT any time after cycle 2
- Post-transplant, B-vedotin monotherapy, up to 16 total doses

LaCasce A et al. Proc ASH 2014;Abstract 293.
## Response

<table>
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<th>Best response</th>
<th>n = 48</th>
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</thead>
<tbody>
<tr>
<td>Objective response rate</td>
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</tr>
<tr>
<td><strong>Complete remission</strong></td>
<td>40 (83%)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

- Majority of complete remissions (34/40) achieved at Cycle 2 restage
- Stem cell mobilization and collection (n = 33)
  - Median CD34+ cell yield (cells/kg): $4.0 \times 10^6$ (range 1.7-11.8) in a median of 2 apheresis sessions (range 1-5)
  - Median time to platelet and neutrophil engraftment <2 weeks

LaCasce A et al. *Proc ASH* 2014;Abstract 293.
Progression-Free Survival (PFS)

- Median PFS not reached
  - 4 progressions and 1 death subsequent to ASCT (8 events overall)
- Medians are not yet estimable for response duration

With permission from LaCasce A et al. *Proc ASH* 2014;Abstract 293.
Adverse Events

- No dose-limiting toxicity in cycle 1
- Main toxicities were infusion-related reactions (IRRs) — dyspnea (15%), chills (13%) and flushing (13%); hypotension requiring vasopressor support also observed
- Delayed hypersensitivity reactions (n = 14, mostly rash) also noted
- Protocol amended to require premedication with corticosteroids and antihistamines
- Premedication decreased severity of IRRs

With permission from LaCasce A et al. Proc ASH 2014;Abstract 293.
## Durability of Response

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>n</th>
<th>ORR</th>
<th>Median Follow-up in weeks</th>
<th>Median Response Duration in weeks</th>
<th>Ongoing Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Myeloma</td>
<td>27</td>
<td>1 (4%)</td>
<td>46</td>
<td>12+</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>DLBCL</td>
<td>11</td>
<td>4 (36%)</td>
<td>23</td>
<td>22 (6 , 77+)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Follicular NHL</td>
<td>10</td>
<td>4 (40%)</td>
<td>91</td>
<td>NR (27+ , 82+)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>CTCL/MF</td>
<td>13</td>
<td>2 (15%)</td>
<td>43</td>
<td>NR (24+ , 50+)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>PTCL</td>
<td>5</td>
<td>2 (40%)</td>
<td>31</td>
<td>NR (11 , 79+)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>23</td>
<td>20 (87%)</td>
<td>86</td>
<td>NR (2 , 91+)</td>
<td>10 (50%)</td>
</tr>
</tbody>
</table>

74 weeks median follow-up
PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin’s Lymphoma

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattray, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.

ABSTRACT
Best Response to Nivolumab (n=23)

- PR (70%)
- CR (17%)
- SD (13%)

Response Duration - Nivolumab

PD-1 Blockade with the Monoclonal Antibody Pembrolizumab in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Preliminary Results from a Phase 1b Study

Ref/Relapsed HD = 19 Pts

ORR = 89%

Moskowitz et al. ASH 2014, abstract 290
Treatment Exposure and Response Duration

- Median time to response: 12 weeks
- 89% (17 of 19) of responses were ongoing as of November 17
- Duration of response
  - Median: not reached
  - Range: 1+ to 185+ days

Moskowitz et al. ASH 2014, abstract 290
PMBCL presents overexpression of PDL1 and PDL2

Patients with Heavily Pretreated Diffuse Large B-Cell Lymphoma (DLBCL) Who Respond to Oral Selinexor Therapy Show Prolonged Survival: Updated Phase I Results


(1) Princess Margaret Cancer Center, Toronto, Canada; (2) Dept. of Oncology, Rigshospitalet, Copenhagen, Denmark; (3) Dana-Farber Cancer Institute, Boston, MA, USA; (4) Washington University St. Louis, MO, USA; (5) The Ohio State University, OH, USA; (6) University of Calgary Calgary, Canada; (7) Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; (8) H. Lee Moffitt Cancer Center & Research Institute Inc., Tampa, FL, USA; (9) MD Anderson Cancer Center, Houston, TX USA; (10) Weil Cornell Medical College, New York, NY, USA; (11) Gabrail Cancer Center, Canton, OH; (12) Karyopharm Therapeutics Inc, Newton, MA, USA; (13) Hackensack University Medical Center, Hackensack, NJ, USA; (14) Ozmosis Research Inc, Toronto, ON, Canada; (15) Vanderbilt University School of Medicine, Nashville, TN, USA
## Patient Characteristics

<table>
<thead>
<tr>
<th>DLBCL Patient Characteristics</th>
<th>N* = 42</th>
</tr>
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<tbody>
<tr>
<td>De-Novo Patients Enrolled</td>
<td>31</td>
</tr>
<tr>
<td>Transformed Patients Enrolled</td>
<td>11</td>
</tr>
<tr>
<td>Patients ≥ 1 Month on Study</td>
<td>29</td>
</tr>
<tr>
<td>Median Age (Range)</td>
<td>61 (30 – 82)</td>
</tr>
<tr>
<td>Male : Female</td>
<td>24 : 18</td>
</tr>
<tr>
<td>Median Prior Treatment Regimens (Range)</td>
<td>3 (1 – 9)</td>
</tr>
<tr>
<td>ECOG Performance Status (0:1:2)</td>
<td>12 : 29 : 01</td>
</tr>
<tr>
<td>Neutrophils &gt;1000/µL and Platelets &gt;30,000/µL</td>
<td>31</td>
</tr>
</tbody>
</table>

* As of 1-June-2015

Data are from treatment with doses of 3-80 mg/m²
# Best Responses in DLBCL patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Total Evaluable</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>DCR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong></td>
<td>39*</td>
<td>31%</td>
<td>4 (10%)</td>
<td>8 (21%)</td>
<td>8 (21%)</td>
<td>19 (49%)</td>
<td>51%</td>
</tr>
<tr>
<td><strong>Patients on study ≥ 1 Month</strong></td>
<td>28</td>
<td>43%</td>
<td>4 (14%)</td>
<td>8 (29%)</td>
<td>8 (29%)</td>
<td>8 (29%)</td>
<td>71%</td>
</tr>
<tr>
<td><strong>Origin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>28</td>
<td>25%</td>
<td>3 (11%)</td>
<td>4 (14%)</td>
<td>6 (21%)</td>
<td>15 (54%)</td>
<td>46%</td>
</tr>
<tr>
<td>Transformed</td>
<td>11</td>
<td>45%</td>
<td>1 (9%)</td>
<td>4 (36%)</td>
<td>2 (18%)</td>
<td>4 (36%)</td>
<td>64%</td>
</tr>
<tr>
<td><strong>Subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCB</td>
<td>14</td>
<td>43%</td>
<td>3 (21%)</td>
<td>3 (21%)</td>
<td>5 (36%)</td>
<td>3 (21%)</td>
<td>79%</td>
</tr>
<tr>
<td>non-GCB</td>
<td>4</td>
<td>25%</td>
<td>1 (25%)</td>
<td>--</td>
<td>3 (75%)</td>
<td>--</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Three patients were non-evaluable for response due to consent withdrawal with lack of disease assessment prior to one cycle on study. Responses (as of 1-June-2015) were adjudicated according to the *International Working Group Response Criteria for Non-Hodgkin’s Lymphoma (NHL) 2007* based on interim unaudited data. ORR=Objective Response Rate (CR+PR), CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, DCR=Disease Control Rate (CR+PR+SD) GCB=Germinal Center B Cell.

GCB/non-GCB subtypes were not defined for all patients.

- 31% ORR and 51% DCR for all evaluable DLBCL patients
- 43% ORR and 71% DCR for evaluable DLBCL patients on study ≥ 1 month
- ORR and DCR are equivalent across DLBCL origin or subtype
- Duration of response was >9 months

- Responses were also observed in “double-hit” DLBCL
Novel therapeutic agents may selectively benefit molecular DLBCL subtypes

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>GCB DLBCL</th>
<th>ABC DLBCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF-κB</td>
<td>Bortezomib</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>PI3 kinase</td>
<td>CAL-101</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>PKCB</td>
<td>Enzastaurin</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>BTK</td>
<td>Ibrutinib</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Syk</td>
<td>Fosfamatinib</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Target angiogenesis</td>
<td>Lenalidomide</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>BCL2 family</td>
<td>ABT 199</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>SINE</td>
<td>Selinexor</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>
• Uno schema R-HDS like è ancora considerato nella pratica clinica un regime di chemioterapia di prima linea standard per il paziente giovane affetto da MCL
• La MRD deve essere valutata anche al di fuori di studi prospettici
• Ruolo della terapia di mantenimento post induzione
• ASCT di consolidamento in prima linea in tutti pazienti o solo in casi selezionati