Bendamustine plus Rituximab versus CHOP plus Rituximab
as First-Line Treatment in Patients with
Indolent and Mantle Cell Lymphomas:
Updated Results from the StiL NHL1 study
on behalf of the StiL (Study Group indolent Lymphomas, Germany)

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H. Ballo, M. Stauch, J. Barth, A. Hinke, and W. Brugger
Objectives: B-R vs CHOP-R

Primary Objective

- To prove a non-inferiority of B-R (261) vs CHOP-R (253): **OK**
- **RR in R-CHOP inferior**

Secondary Objectives.

- RR, TTNT, EFS, OS: **OK**
- Acute and late toxicities, infectious complications: **OK**
- SC mobilization capacity: **OK**
Toxicities BR vs CHOP-R

No Alopecia

Lower paresthesias

More allergenic skin toxicity and (erythema)

No SC mob problem

Cardiac toxicity of anthra: advantage

Similar SPN and transformation risk

PUBLICATION - No diff for OS
Response rates BR vs CHOP-R

Similar RR

but higher CR (10%)
Bendamustine – a rebirth of an old drug

- Jenapharm, Jena, former GDR → East Germany 1963
- Ribosepharm, Munich, Germany → Germany 1992
- Salmedix Inc., San Diego, CA, USA → USA 2002
- Cephalon Inc ¹, Frazer, USA → USA, China 2005
- Symbio ², Tokyo, Japan → Asian countries 2006
- Mundipharma Ltd, Cambridge, UK → Europe 2007
- Astellas ³, Tokyo, Japan → Russia, MENA 2009
- Janssen, USA → Latin America, Australia 2010
- Teva Pharmaceutical Ltd ⁴, Israel → USA, China 2011
- Lundbeck ⁵, Montreal, Canada → Canada 2011

¹) Cephalon took over Salmedix; ²) Cooperation with InnoPharmRX in Taiwan, Eisai in Singapore; ³) Astellas license holder; ⁴) Teva took over Cephalon; ⁵) sub-license from Teva
Thalidomide vs Bendamustine

7235 vs 328 papers
BEACOPP (escalated x4 + baseline x4 cycles) vs. ABVD (x8 cycles) in stage III & IV Hodgkin Lymphoma high-risk (IPS ≥3)

Intergroup study 20012 led by the EORTC Lymphoma Group

## treatment discontinuations (all)

<table>
<thead>
<tr>
<th>reason</th>
<th>ABVD (N=43/272)</th>
<th>BEACOPP (N=49/269)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n   (%)</td>
<td>n   (%)</td>
</tr>
<tr>
<td>relapse/PD</td>
<td>8 (2.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>&lt; PR at C4 or &lt; CRu at C6</td>
<td>9 (3.3)</td>
<td>11 (4.1)</td>
</tr>
<tr>
<td>toxicity (incl. toxic death)</td>
<td>10 (3.7)</td>
<td>28 (10.4)</td>
</tr>
<tr>
<td>death reason unknown</td>
<td>1 (0.4)</td>
<td>-</td>
</tr>
<tr>
<td>patient refusal</td>
<td>7 (2.6)</td>
<td>6 (2.2)</td>
</tr>
<tr>
<td>other</td>
<td>8 (2.9)</td>
<td>3 (1.1)</td>
</tr>
</tbody>
</table>
ABVD vs BEACOPP

Similar RR (82.5 vs 82.8%)
Identical EFS, death rate
More progression and more HL deaths in ABVD (6.6 vs 3.4%)
More toxic death in BEACOPP
PFS little but superior in BEACOPP

Similar SPN (4.7 VS 3.4)
But higher toxicity inc infertility
Similar OS but too early!!!! (90.3 vs 86.7%)

To whom BEACOPP: Worst prognostic,
Guide for physicians

- Treatment burden & cost,
- Fertility issues,
- Risk of salvage,
- Immediate & late morbidities
- IPS
R-CVP vs R-CHOP vs R-FM as first line therapy for Advanced Stage Follicular Lymphoma. Final results of FOLL05 trial from the Fondazione Italiana Linfomi.


On behalf of the FOLL05 Team
Grade 3-4 Neutropenia by Arm and Cycle

PRESENTED BY: M. Federico
Conclusions

Similar RRs with R-CHOP and R-FM

Better PFS with R-CHOP and R-FM

Similar OS

More toxic deaths with R-FM (17 vs 9 vs 4): re-think for first line treatment

*Due to rounding total percentages may not be 100
Results of E4402 (RESORT): A Randomized Phase III Study Comparing Two Different Rituximab Dosing Strategies for Low Tumor Burden Indolent B-Cell Lymphoma

Michael Williams, Fangxin Hong, Brad Kahl, Randy Gascoyne, Lynne Wagner, John Krauss, Sandra Horning
TTF: FL vs non FL

Kahl et al, ASH 2011 LBA #6; ASCO/ASH Joint Session 2012
Time to First Cytotoxic CT: FL vs non FL

Kahl et al, ASH 2011 LBA #6; ASCO/ASH Joint Session 2012
Conclusions

● FL: RR is appropriate strategy in responding cases
● Non-FL: MR is appropriate strategy in responding cases

**Important points:**

- OS –risk of transformation-QOL
- Fc Rec polymorphisms
- Microenvironment analysis via TMAs
- Gene expression profiling

**We need larger studies**
Stringent complete response (sCR) in patients with newly diagnosed multiple myeloma (NDMM) treated with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX)

AJ Jakubowiak,1 K Griffith,2 D Dytfeld,3 DH Vesole,4 S Jagannath,5 T Anderson,2 B Nordgren,2 K Detweiler-Short,2 D Lebovic,2 K Stockerl-Goldstein,6 T Jobkar,2 S Wear,7 A Al-Zoubi,2 A Ahmed,2 M Mietzel,2 D Couriel,2 M Kaminski,2 M Hussein,8 H Yeganegi,9 R Vij6

1University of Chicago, Chicago, IL; 2University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; 3Poznan University of Medical Sciences, Poznan, Poland; 4John Theurer Cancer Center, Hackensack, NJ; 5Mount Sinai Medical Center, New York, NY; 6Washington University School of Medicine, St. Louis, MO; 7Multiple Myeloma Research Consortium, Norwalk, CT; 8Celgene, Inc, Summit, NJ; 9Onyx Pharmaceuticals, South San Francisco, CA
There was no difference by disease stage and cytogenetics.
Responses after Extended Treatment

Overall

- n=53
- Median 12 cycles (range 1–25)
- ≥nCR: 62%
- sCR: 42%

4+ Cycles

- n=49
- Median 13 cycles (range 4–25)
- ≥nCR: 67%
- sCR: 45%

8+ Cycles

- n=36
- Median 16 cycles (range 8–25)
- ≥nCR: 78%
- sCR: 61%
Responses

Initial Response

Change from baseline

M-protein level (% of baseline)

Baseline  C1D15  C2D1  C3D1

51%  67%  81%

Error bars = standard deviation

Best Response

≥PR  ≥VGPR  ≥nCR  sCR

Patients (%)

N = 53; median 12 cycles (range 1–25)
Conclusions

- Good rationale: Combination with IMIDs and NFKB inh
- Lenalidomide + Carfilzomib + LD dex : low toxicity and high RR
- Rapid, high, durable and deep responses: High s CR (61% after 8 cyc)
- Well tolerance: low Gr II-IV tox (PNP), no SC mob problem
- Improved response with time
- No evidence of MRD (91%)

- Immediate vs late SCT
Efficacy of crizotinib in children with relapsed/refractory ALK-driven tumors: A Children’s Oncology Group Phase 1 Study

Yael P Mossé, MD
ASCO Annual Meeting
- June 2, 2012
- Chicago

- Children’s Hospital of Philadelphia
- University of Pennsylvania Perelman School of Medicine
General comments

- ALK mut pts with RR STs and ALCL
- Crizotinib: Oral TKI ($100 – 365 \text{ mg/m}^2/\text{dose BID}$)
  - Recommended phase 2 dose = $280 \text{ mg/m}^2 \text{ BID}$

- **Adult dosage:** $250 \text{ mg BID}$

- Grade 5 CNS hemorrhage
  - Grade 4 transaminitis
  - Grade 4 neutropenia

- **Tolerable drug:** mild side effect and long term use
ALCL: 8 pretreated pts: 7CR- 7-22 cycles
• Molecular monitoring in PB and BM

• IMT: 7 pts: 3 PR 1 prolonged SD >24 mos

• NSCLC: 2 pts: 1 sustained PR >24 mos

NB: 33 pts: ALK (+) 8: 1 CR 1 SD
• 19 pts ALK unknown: 1 CR, 6 SD

• POTENTIAL USE FOR ADULT MESANCYHYMAL TUMORS???
Patient with NB-germline mutation
Dasatinib vs imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: DASISION 3-year follow-up

Andreas Hochhaus, Neil Shah, Jorge Cortes, Michele Baccarani, M. Brigid Bradley-Garelik, David Dejardin, Hagop Kantarjian
**DASISION (CA180-056) Study Design**

- **Primary endpoint**: Confirmed CCyR (cCCyR) by 1 year
- **Randomized**
  - Imatinib 400 mg QD (N=260)
  - Dasatinib 100 mg QD (N=259)

- **Treatment-naïve CML-CP patients (N=519)**
- **108 Centers**
- **26 Countries**

*aStratified by EURO (Hasford) risk score

DASISION (CA180-056): NCT00481247; CCyR = complete cytogenetic response
**Cumulative Incidence of MMR (BCR-ABL ≤0.1%)**

- **Hasford Risk Score**
  - Low
  - Intermediate
  - High
- **MMR 3-y cumulative rates**
  - **Dasatinib**
    - 83%
  - **Imatinib**
    - 65%

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- **P<0.0001**
- 1.6-fold higher likelihood of achieving MMR with dasatinib; HR=1.62 (1.30-2.02)
- By 1 year: 46%
- By 2 years: 64%
- By 3 years: 68%

- By 2 years: 64%
- By 1 year: 46%
- By 3 years: 55%

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- **Dasatinib 100 mg QD**
- **Imatinib 400 mg QD**
Transformation to AP/BP CML by 3 Years

Yearly evaluations after discontinuation are currently stipulated per protocol; additional information on patient status may be provided by investigators at other times.

Dasatinib 100 mg QD
Imatinib 400 mg QD
## Overall Survival (OS) and Progression-Free Survival (PFS)

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib 100 mg QD N=259</th>
<th>Imatinib 400 mg QD N=260</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of deaths,(^a) n</strong></td>
<td>17</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td><strong>Estimated 3-year OS, %</strong></td>
<td>93.7 (90.6-96.7)</td>
<td>93.2 (90.1-96.4)</td>
<td>HR=0.86 (0.45-1.65)</td>
</tr>
<tr>
<td><strong>Estimated 3-year PFS, (^b) %</strong></td>
<td>91.0 (87.4-94.7)</td>
<td>90.9 (87.1-94.6)</td>
<td>HR=1.00 (0.55-1.80)</td>
</tr>
</tbody>
</table>

\(^a\) On-study treatment and in follow-up after discontinuation of randomized treatment

\(^b\) Progression was defined as loss of complete hematologic response, loss of major cytogenetic response, accelerated or blast phase CML, death from any cause during treatment and increasing white blood cell count.
Molecular and Cytogenetic Response at 3 Months\textsuperscript{a}

- **≤10% BCR-ABL at 3 Months**
  - Dasatinib 100 mg QD: 84%
  - Imatinib 400 mg QD: 64%
  - Difference: P<0.0001

- **PCyR/CCyR at 3 Months**
  - Dasatinib 100 mg QD: 81%
  - Imatinib 400 mg QD: 67%
  - Difference: P<0.0001

- BCR-ABL of <10% and ≤1% are not fully concordant with ≥PCyR and CCyR, respectively.
- 96% and 83% of dasatinib and imatinib pts with ≥PCyR had <10% BCR-ABL, respectively.
- 68% and 26% of dasatinib and imatinib pts with CCyR had ≤1% BCR-ABL, respectively.

\textsuperscript{a} Calculated from total number of evaluable patients with PCR assessments at 3 months.
Conclusions

- Dasatinib in newly diagnosed CML
  - Deeper and faster responses: Higher PFS
  - Probability: Stop treatment after MMR
  - OS data: immature
  - Fewer transformations to AP/BP
  - Well tolerance, decreasing toxic effects with minimal changes in the number of adverse events from 2 to 3 years
  - Long term follow up is needed
The Bruton’s Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) is Highly Active and Tolerable in Treatment Naïve (TN) Chronic Lymphocytic Leukemia (CLL) Patients: Interim Results of a Phase Ib/II Study

JOHN C. BYRD, MD¹, RICHARD FURMAN, MD², STEVEN COUTRE, MD³, JAN BURGER, MD, PHD⁴, KRISTIE BLUM, MD¹, JEFF SHARMAN, MD⁵, IAN FLINN, MD, PHD⁶, BARBARA GRANT, MD⁷, NYLA HEEREMA, PHD¹, AMY JOHNSON, PHD¹, TASHEDA NAVARRO⁸, DANELLE JAMES, MD, MAS⁸, ERIC HEDRICK, MD⁸, SUSAN O’BRIEN, MD⁴

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⁴Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
⁵US Oncology, Springfield, OR
⁶Sarah Cannon Research Institute, Nashville, TN
⁷Department of Medicine, Vermont Cancer Center, University of Vermont, Burlington, VT
⁸Pharmacyclics, Inc, Sunnyvale, CA
## Best Response

<table>
<thead>
<tr>
<th></th>
<th>420 mg/d (N=26)</th>
<th>Median f/u = 14.4 mos</th>
<th>840 mg/d (N=5)</th>
<th>Median f/u = 7.4 mos</th>
<th>Total (N=31)</th>
<th>Median f/u = 12.8 mos</th>
</tr>
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<tbody>
<tr>
<td></td>
<td># (%)</td>
<td># (%)</td>
<td># (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>3 (12)</td>
<td>0</td>
<td>3 (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>18 (69)</td>
<td>2 (40)</td>
<td>20 (65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR*</td>
<td>81%</td>
<td>40%</td>
<td>74%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal</td>
<td>3 (12)</td>
<td>1 (20)</td>
<td>4 (13)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SD</td>
<td>1 (4)</td>
<td>1 (20)</td>
<td>2 (6)</td>
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<td>0</td>
<td></td>
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</tr>
<tr>
<td>NE</td>
<td>1 (4)</td>
<td>1 (20)</td>
<td>2 (6)</td>
<td></td>
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</tbody>
</table>

*Per IWCLL 2008 criteria
Targeting microenvironment
Compartment shifting
Potential use for other malignancies