First-line Treatment of Chronic Lymphocytic Leukemia

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I never considered a difference of opinion in politics, in religion, in philosophy, as cause for withdrawing from a friend.

-Thomas Jefferson
Untreated, high-risk - watch and wait

First-line therapy
- Del(17p) - Ibrutinib
- Fit CIT-eligible – FCR / BR
- Elderly – chlorambucil+CD20 mAb

Salvage treatments for active disease, incl del(17p)
- BTK-inhibitor (ibrutinib)
- PI3-K-inhibitor (idelalisib) + rituximab
- Rel / Ref del(17p) - venetoclax
- Richter’s trans. – intensive CIT then allo-SCT
CLL10 STUDY: FCR VS BR IN FRONT-LINE

**Design**

Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

**Randomization**

**FCR**
- Fludarabine 25 mg/m² i.v., days 1-3
- Cyclophosphamide 250 mg/m², days 1-3
- Rituximab 375 mg/m² i.v. day 0, cycle 1
- Rituximab 500 mg/m² i.v. day 1, cycle 2-6

**BR**
- Bendamustine 90mg/m² day 1-2
- Rituximab 375 mg/m² day 0, cycle 1
- Rituximab 500 mg/m² day 1, cycle 2-6

**Non-Inferiority of BR in comparison to FCR for PFS:**
- HR (λ BR/FCR) less than 1.388

*Eichhorst et al., ASH 2014, Abstract 19*
CLL10 STUDY: FCR VS BR IN FRONT-LINE

PFS in IGHV matched population (n=398: FCR = 201; BR = 197)

Median PFS
FCR  NR
BR  43.1 months

$P = 0.005$
$HR = 1.565 = > 1.388$

NO difference in overall survival

Eichhorst et al., ASH 2014, Abstract 19
CLL10 STUDY: FCR VS BR IN FRONT-LINE

Progression-free survival by age group

Patients ≤ 65 years:  \( P < 0.001 \)
- FCR 53.6 months
- BR 38.5 months

Patients > 65 years:  \( P = 0.170 \)
- FCR not reached
- BR 48.5 months

Eichhorst et al., ASH 2014, Abstract 19
## CLL10 STUDY: FCR VS BR IN FRONT-LINE

Infections CTC 3-4 in detail

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>FCR (% of pt)</th>
<th>BR (% of pt)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Infections</td>
<td>39.1</td>
<td>26.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infections during therapy only</td>
<td>22.6</td>
<td>17.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Infections during first 5 months after therapy</td>
<td>11.8</td>
<td>3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All infections in patients ≤ 65 years</td>
<td>35.2</td>
<td>27.5</td>
<td>0.1</td>
</tr>
<tr>
<td>All infections in patients &gt; 65 years</td>
<td>47.7</td>
<td>20.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Eichhorst et al., ASH 2014, Abstract 19*
FCR300: Progression-free & Overall Survival

Median follow up time
All - 9.8 yrs
Alive - 11.5 yrs

MDACC Data, IWCLL 2013, Cologne
FCR300: PFS by IGHV Mutation Status

Challenges with First-line Chemoimmunotherapy

- Myelosuppression and risk for infection
- Immune deficiency and risk for infection
- Risk for secondary MDS and AML
- Risk for Richter’s transformation
Ibrutinib 420mg/d cont.
F - 25mg/m² x3
C - 250mg/m² x3
G - 1gm D1,8,15; then D1

C3 Response
CT
BM

C6 Response
CT
BM

<CR or MRD-positive @ C3
Ibrutinib + obinutuzumab – 6mo

CR, MRD-negative @ C3
Ibrutinib -6mo

MRD-positive @ 1yr
Continue Ibrutinib

C12 Response
CT
BM
First-line Therapy – *IGHV*-UM, Older or Unfit

- Fit, *IGHV*-UM can achieve MRD-negative CR with FCR, but virtually all relapse
- New agents / combinations needed for cure
  - Treatment-free interval and avoid resistance
- Delay / avoid chemotherapy
- Better MRD assay needed – DNA; cfDNA
- Consolidation concept
  - Venetoclax; others
- Predictive markers needed
CLL11: Treatment comparisons

- **Randomize 2:1:2**
  - **G-Clb vs. Clb**
    - Obinutuzumab + chlorambucil x 6 cycles
  - **R-Clb vs. Clb**
    - Chlorambucil x 6 cycles (control arm)
    - Rituximab + chlorambucil x 6 cycles
  - **G-Clb vs. R-Clb**
    - Obinutuzumab + chlorambucil x 6 cycles
    - Chlorambucil x 6 cycles (control arm)
    - Rituximab + chlorambucil x 6 cycles

Currently no significant difference in overall survival

Median observation time: G-Clb, 18.8 months; R-Clb, 18.6 months
Type 1 error controlled through closed test procedure; $P$ value of the global test was <0.0001
Independent Review Committee-assessed progression-free survival (PFS) was consistent with investigator-assessed PFS

CLL11: Overall survival *(Obinutuzumab)*

![Graph showing overall survival over time with median observation times for G-Clb and Clb, and the total number of deaths.](image)

- Median observation time: G-Clb, 23.2 months; Clb, 20.4 months
- No multiplicity adjustment was done for secondary endpoints
- Total number of deaths: G-Clb, 22 (9%); Clb, 24 (20%)

COMPLEMENT 1: Study Design

**Patients with previously untreated CLL**
- Considered inappropriate for F-based therapy
- Active disease (NCI-WG IWCLL 2008)
- ≥18 years
- ECOG ≤ 2
- N=444 (planned)

**Design**
- Randomise 1:1
- Minimum 3 cycles, until best response or PD, maximum 12 cycles
- No cross over allowed

**Follow up:**
1 Month post last dose, Month 3, q3mo thereafter

**O: cycle 1 d1 300 mg, d8 1000 mg, Cycle 2-12 d1 1000 mg every 28 days**

**CHL: 10 mg/m² d1-7 every 28 days**

Dose rationale: evidence of highest ORR and longest PFS with low toxicity compared to any other CHL monotherapy regimen

Hillmen et al. ASH 2013, Abstract 528.
Progression-free Survival
as assessed by an Independent Review Committee
(median [months])

- **CHL**
  - mPFS: 13.1
  - (95% CI: 10.6, 13.8)

- **O+CHL**
  - mPFS: 22.4
  - (95% CI: 19.0, 25.2)

HR 0.57, p<0.001

Median follow-up: 28.9 months

Currently no difference in overall survival

Hillmen et al. ASH 2013, Abstract 528.
Targeting of BCR signaling in CLL

- BCR-associated kinases are targets of new drugs in clinical development
  - Btk (Bruton’s tyrosine kinase) inhibitors: Ibrutinib, CC-292, ACP-196
  - PI3 kinase inhibitors: Isoform-Selective Inhibitor of PI3-Kinases\(^1\), Idelalisib, IPI-145, TGR-1202
  - Syk (spleen tyrosine kinase) inhibitors: GS-9973, Fostamatinib, PRT-2070\(^2\)

From: Nat Rev Immunol 2:945

Patients (N=269)
- Treatment-naïve CLL/SLL with active disease
- Age ≥65 years
- For patients 65-69 years, comorbidity that may preclude FCR
- del17p excluded
- Warfarin use excluded

**Randomize 1:1**

**Phase 3, open-label, multicenter, international study**

**Primary endpoint**: PFS as evaluated by IRC (2008 iwCLL criteria)

**Secondary endpoints**: OS, ORR, hematologic improvement, safety

*Patients with IRC-confirmed PD enrolled into extension Study 1116 for follow-up and second-line treatment per investigator’s choice (including ibrutinib for patients progressing on chlorambucil with iwCLL indication for treatment).
84% reduction in risk of progression or death with ibrutinib

18-month PFS rate: 90% with ibrutinib vs. 52% with chlorambucil

Median follow-up: 18.4 months

Tedeschi A et al. ASH 2015, Abstract 495.
- Median PFS in del11q subgroup: NR with ibrutinib vs. 9 months with chlorambucil (HR=0.02, P<0.0001)
- Median PFS in unmutated IGHV subgroup: NR with ibrutinib vs. 9 months with chlorambucil (HR=0.06, P<0.0001)
- Ibrutinib: 18-month PFS 92% in IGHV mutated, 95% in unmutated subgroup

Tedeschi A et al. ASH 2015, Abstract 495.
84% reduction in risk of death with ibrutinib

24-month OS rate: 98% with ibrutinib and 85% with chlorambucil

3 deaths on ibrutinib arm vs. 17 deaths on chlorambucil arm

Tedeschi A et al. ASH 2015, Abstract 495.
ORR at 8 months: 82% with ibrutinib vs. 30% with chlorambucil
ORR with ibrutinib higher than with chlorambucil at all time points
Weaknesses of RESONATE-2 and Challenges with First-line Ibrutinib

Chlorambucil is an unreasonable comparator as standard of care
Follow up time is short
Population limited to age >65yrs
Ibrutinib approved for relapsed / refractory CLL

Challenges with first-line ibrutinib therapy
- Ibrutinib therapy is continuous and costly
- Associated toxicities, increased in elderly
- Long-term side-effects unknown
- Compliance challenge
CLL Treatment Directions

- Untreated, high-risk – early intervention
- First-line therapy
  - Del(17p) – Ibrutinib-based
  - Fit CIT-eligible – IGHV-Mutated
    - FCR-based with maintenance or Tx for MRD
  - Fit-IGHV-Unmutated & Older
    - BCR- / Bcl-2-inhibitor – sequencing and combinations
- Treatment (consolidation) for persistent disease on BTK-inhibitor (1st and later)
- Salvage therapy for active disease
- Richter’s transformation work-up and “novel treatments” program