CARE at ASH 2015: CLL review

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Suggested abstracts

1. 495 Results from the International, Randomized Phase 3 Study of Ibrutinib Versus Chlorambucil in Patients 65 Years and Older with Treatment-Naïve CLL/SLL (RESONATE-2™)

2. 830 Deep and Durable Responses Following Venetoclax (ABT-199 / GDC-0199) Combined with Rituximab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Results from a Phase 1b Study

3. 494 Safety and Efficacy of a Combination of Venetoclax (GDC-0199/ABT-199) and Obinutuzumab in Patients with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia - Results from a Phase 1b Study (GP28331)

4. 719 Favorable Outcomes in CLL Pts with Alternate Kinase Inhibitors Following Ibrutinib or Idelalisib Discontinuation: Results from a Large Multi-Center Study

5. 497 Idelalisib Given Front-Line for the Treatment of Chronic Lymphocytic Leukemia Results in Frequent and Severe Immune-Mediated Toxicities
First-line treatment of CLL
Standard of care – firstline CLL tx

- Young fit: GCLLSG CLL8 study – FCR
- Fit (mostly young): GCLLSG CLL10 study – FCR but BR for age > 65 years
- Older, unfit: GCLLSG CLL11: CLB-obinutuzumab
- MaBle study: unfit BR better than CLB-R

- Over 65yrs, not fit for fludarabine – RESONATE-2: ibrutinib?
CLL5: Overall survival CLB vs F

CLL5: PFS CLB vs Fludarabine

As in younger patients, F vs CLB resulted in higher ORR (72% vs 51%), CR (7% vs 0%) rates and longer TTF (11mo vs 18mo) but did not lead to longer PFS (19mo vs 18 mo) or OS (46mo vs 64mo)

More toxicity with F and better response to second line therapy with CLB

Firstline therapy with F does not result in major clinical benefit in elderly CLL patients, compared to chlorambucil

Similar results from the UK CLL4 study who also showed that survival after 2nd line therapy was much better for patients treated with monotherapy with CLB or F vs FC

Catovsky et al Lancet 2007; 370: 230
CLL11: Overall survival advantage with addition of OBINUTUZUMAB to chemo (CLB) in first-line tx of CLL

Overall survival

Time (months)

Stratified HR: 0.41
95% CI, 0.23-0.74
P=0.0022

No. at risk

G-Clb: 238 226 223 221 215 211 170 144 115 71 34 14 2 0
Clb: 118 109 105 103 102 94 70 56 44 29 15 5 0 0

Total number of deaths: G-Clb, 22 (9%); Clb, 24 (20%)

Goede V et al NEJM 2014; 370:1101
RITUXIMAB to chemo (CLB) in first line tx of CLL

Total number of deaths: R-Clb, 44/233 (19%); Clb, 34/118 (29%)

Goede et al, Leukemia 2015. Letter to the editor; 1-3
CLL11: Progression-free survival comparing CLB-R to CLB-obinutuzumab

Median PFS for CLB monotherapy group = 11 months

Stratified HR: 0.39
95% CI, 0.31-0.49
P<0.0001

Goede V et al NEJM 2014
(MaBLe) BR versus R-Clb

Rituximab in combination with bendamustine or chlorambucil for the treatment of chronic lymphocytic leukaemia: Primary results from the randomised phase IIIb MaBLe study

- Included both frontline and second line patients
- Considered “unfit” for fludarabine
- Bendamustine 90mg/m2 for frontline, CLB 10mg/m2 daily x 7 days

<table>
<thead>
<tr>
<th>Group</th>
<th>BR (n = 121)</th>
<th>R-Clb (n = 120)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (%)</td>
<td>24</td>
<td>9</td>
<td>0.002</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>91</td>
<td>86</td>
<td>0.304</td>
</tr>
<tr>
<td>median PFS (months)</td>
<td>40</td>
<td>30</td>
<td>0.003*</td>
</tr>
<tr>
<td>median OS (months)</td>
<td>44</td>
<td>NC</td>
<td>0.939†</td>
</tr>
</tbody>
</table>

Michallet, et al. IwCLL 2015
RESONATE-2

- Patients ≥ 65 years with previously untreated CLL
- Ibrutinib vs CLB 0.5-0.8mg/kg D1 and D15 for 6-12 cycles
- Del(17p) excluded
- Primary endpoint = PFS
- Median age 73, 69% had comorbidities including CIRS > 6 in 69%, reduced creat or ECOG 2
- CLB group: 40% completed 12 cycles (mean dose 0.6mg/kg)
- Median f/u 18.4 months, PFS ibrutinib not reached, CLB=18.9 months
- OS ibrutinib vs CLB = NR for both but HR=0.16, p=0.001

Tedeschi et al ASH 2015; abstract 495
RESONATE-2

Tedeschi et al ASH 2015; abstract 495
Relapsed/refractory CLL

830 Deep and Durable Responses Following Venetoclax (ABT-199 / GDC-0199) Combined with Rituximab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Results from a Phase 1b Study

494 Safety and Efficacy of a Combination of Venetoclax (GDC-0199/ABT-199) and Obinutuzumab in Patients with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia - Results from a Phase 1b Study (GP28331)
HC Approved novel agents for r/r CLL


Furman et al NEJM 2014

*Hazard ratio for death, 0.43 (95% CI, 0.24–0.79) P=0.005 by log-rank test*
Ibrutinib best overall response – 16 month f/u data

**RESONATE**

<table>
<thead>
<tr>
<th></th>
<th>ibrutinib</th>
<th>ofatumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to initial response; month (range)</td>
<td>3 (2-17)</td>
<td>3 (2-9)</td>
</tr>
<tr>
<td>Median time to best response; month (range)</td>
<td>5 (2-17)</td>
<td>3 (2-9)</td>
</tr>
<tr>
<td>Median time to CR/CRi; month (range)</td>
<td>11 (6-17)</td>
<td>8 (only 1 pt)</td>
</tr>
</tbody>
</table>

**ORR = CR + CRi + nPR + PR-L + PR.**

*<P<0.0001 for ibrutinib vs. ofatumumab. 15 patients for ibrutinib and 17 for ofatumumab were nonevaluable for response but included in denominator (ITT population).*
Venetoclax + rituximab CR/CRi data

<table>
<thead>
<tr>
<th></th>
<th>All pts n=49</th>
<th>del(17p) n=9</th>
<th>Fludarabine-refractory n=9</th>
<th>IGHV unmutated n=19</th>
<th>Age ≥70 n=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CR/CRi</td>
<td>42 (86)</td>
<td>8 (89)</td>
<td>5 (56)</td>
<td>16 (84)</td>
<td>17 (77)</td>
</tr>
<tr>
<td>nPR</td>
<td>20 (41)</td>
<td>3 (33)</td>
<td>4 (44)</td>
<td>7 (37)</td>
<td>8 (36)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>SD</td>
<td>21 (43)</td>
<td>5 (56)</td>
<td>1 (11)</td>
<td>9 (47)</td>
<td>8 (36)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (8)</td>
<td>0</td>
<td>2 (22)</td>
<td>1 (5)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>d/c before assessment</td>
<td>2 (11)</td>
<td>1 (11)</td>
<td>1 (11)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>PFS rate, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>12-month</td>
<td>87</td>
<td>89</td>
<td>56</td>
<td>83</td>
<td>85</td>
</tr>
<tr>
<td>24-month</td>
<td>84</td>
<td>78</td>
<td>56</td>
<td>83</td>
<td>79</td>
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<tr>
<td>OS rate, %</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>12-month</td>
<td>94</td>
<td>89</td>
<td>89</td>
<td>89</td>
<td>95</td>
</tr>
</tbody>
</table>

*a d/c due to fatal TLS event previously reported; no other fatal TLS events occurred after a May 2013 protocol amendment*
Survival of patients after discontinuation of ibrutinib

Deaths/Total
25/33

Median OS - 3.1 months

Jain et al. Blood 2015;125:2062
Responses to alternate kinase inhibitors after ibrutinib or idealisib d/c

Response rate to non-KI - 40%
Response to idela post ibr – 50%
Response to ibr post idela – 77%
Same outcomes despite reason for d/c
Worse outcome for Richter’s

Mato et al ASH 2015; abstract 719
A word of caution re: novel agents

- Frontline treatment study of idelalisib + ofatumumab
- Grade 3-4 transaminitis – 57%, colitis 14%, pneumonitis 10%
- O’Brien et al ASH 2014; abstract 1194 (frontline study of idelisb + ritux
  - Transaminitis – 23%
  - Colitis – 42%
  - Pneumonitis – 3%
- Furman et al NEJM (r/r CLL) Grade 3-4
  - Transaminitis – 5%
  - Colitis – 4%
  - Pneumonitis - 4% (none listed as Grade 3-4)

Lampson et al; ASH 2015, abstract 497
Other CLL abstracts of interest

1. 493 Safety and efficacy of obinutuzumab plus bendamustine in previously untreated patients with CLL: A subgroup analysis of the Green Study

2. 184 Anti-CD19 chimeric antigen receptor-modified T cell therapy for B cell NHL and CLL: Fludarabine and cyclophosphamide lymphodepletion improves in vivo expansion and persistence of CAR-T cells and clinical outcomes

3. 718 Ristocetin-Induced Platelet Aggregation for monitoring of bleeding tendency in ibrutinib-treated patients with CLL