Addition of Rituximab to Fludarabine and Cyclophosphamide in Patients with CLL: A Randomized, Open-Label, Phase III Trial

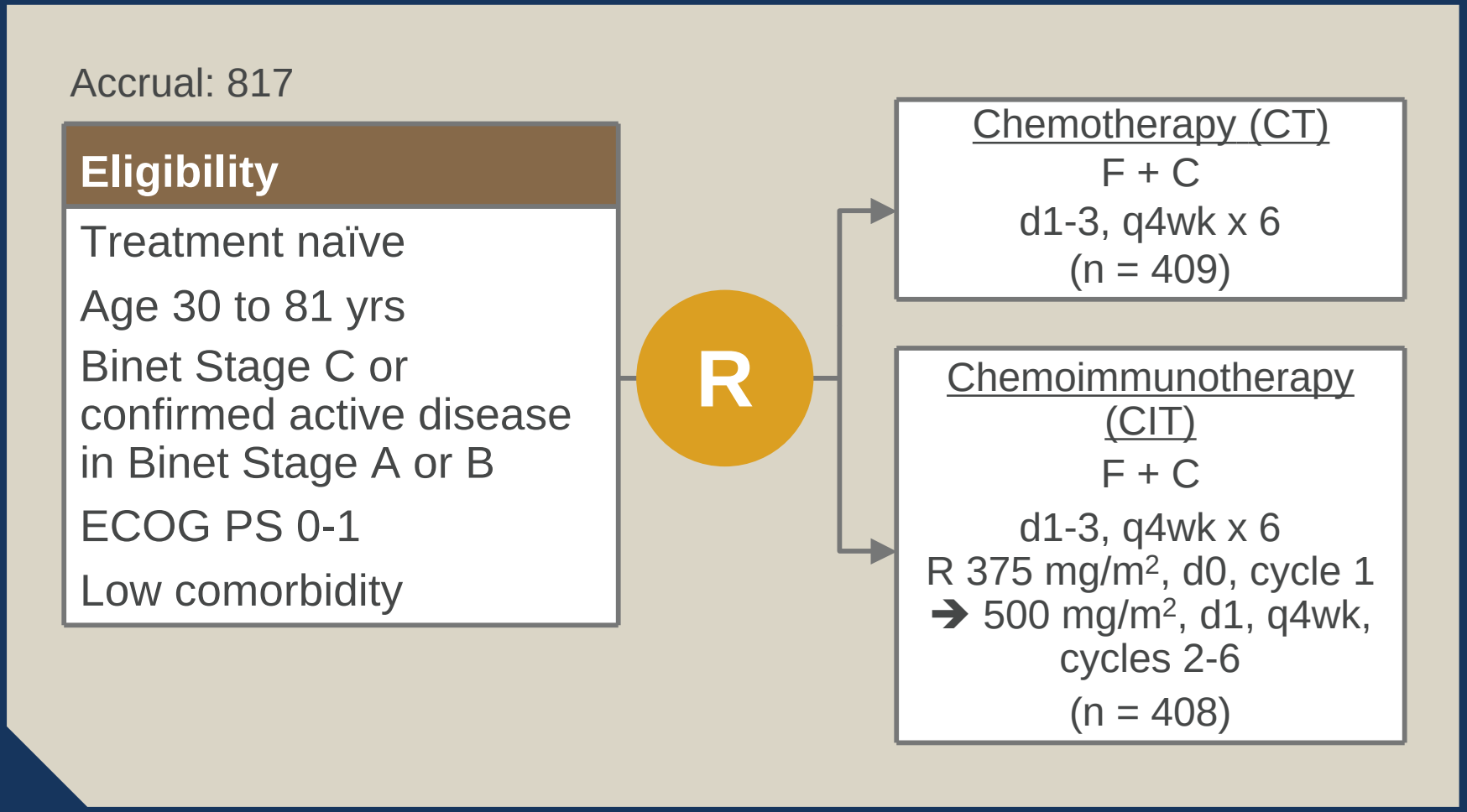
Hallek M et al.
Lancet 2010;376:1164-74.

Introduction

- In patients with CLL, the low expression of CD20 antigen on the leukemic cells (*Blood* 2001;98:3383) and poor response rates have raised concern regarding the clinical benefits of R in this particular setting (*Blood* 2001;98:1326).
- The use of higher doses of R has improved response rates in CLL (*JCO* 2001;19:2165), and Phase II trial data suggest that the combined use of R with chemotherapy may provide additive or synergistic effects (*Blood* 2002;100:3115; *JCO* 2005;23:4079).
- Current study objective:
  - Evaluate the safety and efficacy of combined fludarabine (F), cyclophosphamide (C) and R as first-line therapy for advanced, symptomatic CLL.

Hallek M et al. *Lancet* 2010;376:1164-74.

German CLL Study Group Phase III Open-Label Trial



Hallek M et al. *Lancet* 2010;376:1164-74.

Three-Year Progression-Free Survival (PFS) for All Patients and Subgroups

Subgroups	CIT	CT	*p*-value
All (n = 817)	65%	45%	<0.0001
Del(17p) (n = 51)	18%	0%	0.019
Del(11q) (n = 142)	64%	32%	<0.0001
Trisomy 12 (n = 61)	83%	48%	0.01
Del(13q) (n = 224)	76%	52%	0.0002
IgVH mutated (n = 229)	80%	55%	0.0002
IgVH unmutated (n = 390)	55%	35%	0.0003

Median PFS: 51.8 mo (CIT) vs 32.8 mo (CT)

Hallek M et al. *Lancet* 2010;376:1164-74.

Response in All Patients and Subgroups

Subgroups	CR, CIT	CR, CT	*p*-value CR
All (n = 817)	44%	22%	<0.0001
Del(17p) (n = 51)	5%	0%	0.43
Del(11q) (n = 142)	51%	15%	<0.0001
Trisomy 12 (n = 61)	71%	19%	0.0001
Del(13q) (n = 224)	48%	23%	0.0001
IgVH mutated (n = 229)	50%	21%	<0.0001
IgVH unmutated (n = 390)	40%	19%	<0.0001

CR = complete remission

Hallek M et al. *Lancet* 2010;376:1164-74.

Grade 3/4 Hematologic Adverse Events (AEs)

Events	CIT N = 404	CT N = 396	*p*-value
Total hematologic	56%	40%	<0.0001
Neutropenia	34%	21%	<0.0001
Leukocytopenia	24%	12%	<0.0001
Thrombocytopenia	7%	11%	0.07
Anemia	5%	7%	0.42
Autoimmune hemolytic anemia	<1%	1%	0.69

Hallek M et al. *Lancet* 2010;376:1164-74.

Conclusions

- The addition of fludarabine and cyclophosphamide to rituximab was associated with substantial increases in complete remission and progression-free survival at 3 years.
  - CR, 44% (CIT) vs 22% (CT); P<0.0001
  - 3-year PFS, 65% (CIT) vs 45% (CT); P<0.0001
- CIT also improved the 3-year overall survival (data not shown).
  - OS, 87% (CIT) vs 83% (CT); P=0.012
- The incidence of Grade 3/4 adverse events was similar in both groups, with the exception of neutropenia and leukocytopenia (higher with CIT).
- These data may help establish a new treatment model for first-line treatment of CLL in physically fit patients.

Hallek M et al. *Lancet* 2010;376:1164-74.

Faculty Comments

DR FOSS: This is the long-term follow-up of the randomized study evaluating the FCR chemotherapy regimen. The FCR arm remained superior, with higher overall response rates and more complete remissions. The median PFS was 51.8 months for the FCR arm versus 32.8 months for the FC arm.

Most importantly, the OS rates are also clinically and statistically superior with the FCR regimen. More hematological AEs occurred in the FCR arm. This is the first CLL trial that has clearly demonstrated a survival improvement with up-front therapy.

Bendamustine Combined with Rituximab (BR) in First-Line Therapy of Advanced CLL: A Multicenter Phase II Trial of the German CLL Study Group (GCLLSG)

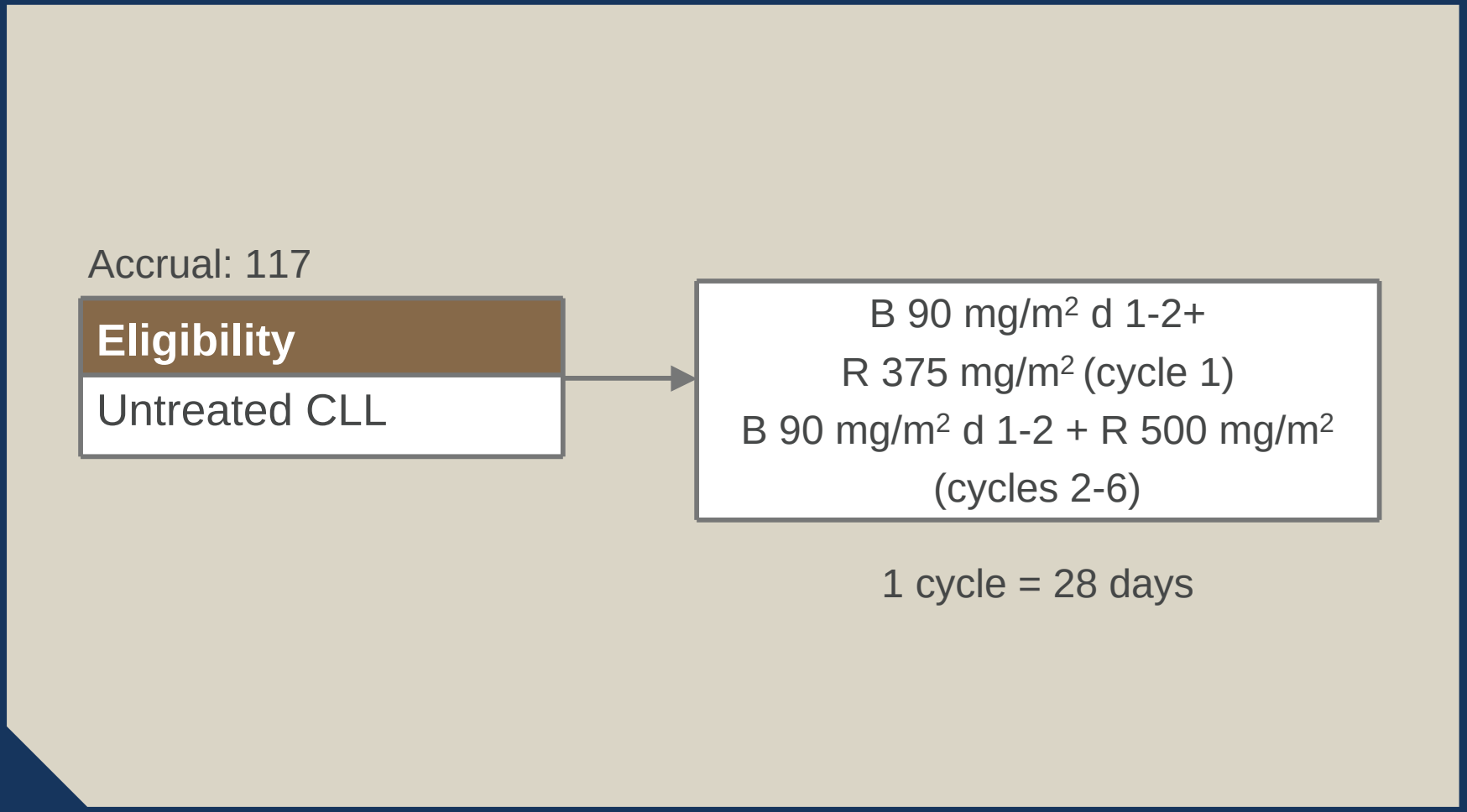
Fischer K et al.
Proc ASH 2009;Abstract 205.

Introduction

- Bendamustine is an alkylating agent that causes cell-cycle inhibition, ultimately resulting in apoptosis (*Am J Health Syst Pharm* 2010;67(9):713).
- Bendamustine monotherapy has shown significant activity in patients with untreated chronic lymphocytic leukemia and is FDA approved in this setting (*JCO* 2009;27:4378).
- In vitro studies have demonstrated a synergistic effect with bendamustine and rituximab (BR) combination therapy (*Proc ASCO* 2005;Abstract 6565).
- Current study objective:
  - Assess the efficacy and toxicity of BR in previously untreated CLL.

Fischer K et al. *Proc ASH* 2009;Abstract 205.

CLL2M: Phase II Study Design



Fischer K et al. *Proc ASH* 2009;Abstract 205.

Efficacy Data (median follow-up 15.4 months)

Clinical Response (n = 110)	N (%)
Overall response rate (ORR)	100 (90.9)
Complete response	36 (32.7)
Nodular partial response	3 (2.7)
Partial response	61 (55.5)
Stable disease	10 (9.1)
Median progression-free survival	Not reached

After 18 months, 75.8% of the patients were still in remission.

Fischer K et al. *Proc ASH* 2009;Abstract 205.

Responses According to Cytogenetics

Characteristic	N	ORR n (%)
FISH Del 17p	7	3 (42.9%)
FISH Del 11q	21	19 (90.5%)
IgVH (unmutated)	63	56 (88.9%)

Fischer K et al. *Proc ASH* 2009;Abstract 205.

Grade 3/4 Adverse Events (n = 114)

Adverse Event*	% of cycles
Leukopenia	14.6
Neutropenia	6.5
Thrombocytopenia	6.1
Anemia	4.9

* Treatment-related mortality occurred in 2.6% of the patients.

Fischer K et al. *Proc ASH* 2009;Abstract 205.

Conclusions

- Bendamustine and rituximab combination therapy is tolerable and effective as first-line treatment for patients with CLL:
  - ORR: 90.9%
  - Median PFS: Not reached
- The major side effects, myelosuppression and infections, were not frequent.
- A Phase III study evaluating bendamustine and rituximab combination therapy in comparison to fludarabine-based immunochemotherapy (FCR) for first-line treatment of CLL is currently under way (NCT00769522).

Fischer K et al. *Proc ASH* 2009;Abstract 205; www.clinicaltrials.gov.

Faculty Comments

DR FOSS: This study investigated up-front bendamustine and rituximab in untreated CLL. The regimen shows good activity with an overall response rate of more than 90 percent, and 75 percent of patients are still in remission at 18 months of follow-up. Among the high-risk genetic subgroups, patients with 11q-minus subtype had a high remission rate, with an ORR of more than 90 percent. These data support up-front bendamustine/rituximab as a reasonable regimen in the setting of untreated CLL.

DR VOSE: The results show bendamustine/rituximab to be an effective and safe first-line treatment for CLL. A randomized trial comparing this regimen to fludarabine-based chemo-immunotherapy is under way.

Ofatumumab Combined with Fludarabine and Cyclophosphamide (O-FC) Shows High Activity in Patients with Previously Untreated CLL

Wierda WG et al.
Proc ASH 2009;Abstract 207.

Introduction

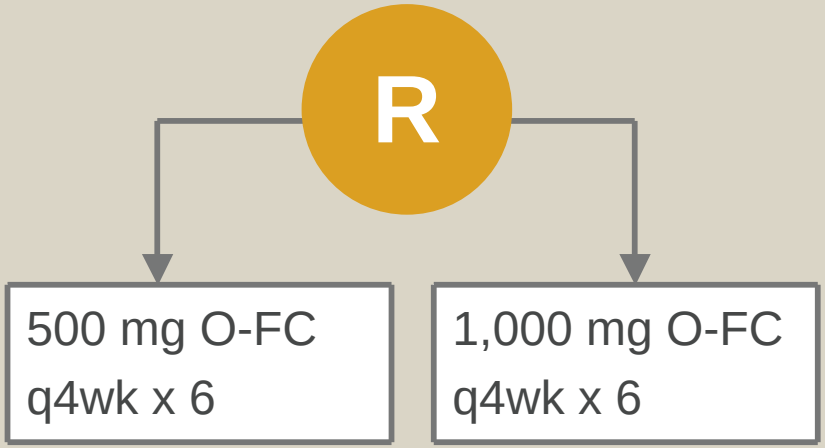
- Chemoimmunotherapy regimens have become standard therapy for patients with chronic lymphocytic leukemia (CLL).
- Ofatumumab, a human monoclonal antibody that targets a unique small loop epitope on CD20 cells, elicits complement-dependent cytotoxicity and antibody cellular-dependent cytotoxicity in vitro.
- Recent studies of single-agent ofatumumab have shown high overall response rates in patients with refractory CLL, and it is FDA approved in this setting (*Blood* 2008;111:1094; *J Clin Oncol* 2010;116:1831).
- Current study objective:
  - Evaluate the efficacy and tolerability of two different doses of O-FC in untreated CLL.

Wierda WG et al. *Proc ASH* 2009;Abstract 207.

Multicenter Phase II Study of O-FC in Previously Untreated CLL

Eligibility (N = 61)

- ≥18 years with previously untreated CLL, $CD5^+/20^+/23^+$
- Active disease
- (1996 NCI-WG criteria)
- Lymphocyte count >5 x 10^9/L
- ECOG PS≤2
- No CLL transformation
- No CNS involvement
- No HIV positivity



Cycle 1: Ofatumumab 300 mg, d1; fludarabine 25 mg/m^2, d2-4; cyclophosphamide 250 mg/m^2, d2-4; Cycles 2-6: Ofatumumab 500 or 1,000 mg, d1; fludarabine 25 mg/m^2, d1-3; cyclophosphamide 250 mg/m^2, d1-3

Wierda WG et al. *Proc ASH* 2009;Abstract 207.

Efficacy Results*

Clinical Parameter	OF-C 500 mg n = 31	OF-C 1,000 mg n = 30
Complete response (CR)	32%	50%
Nodular partial response	3%	3%
Partial response	42%	20%
Overall response rate (ORR)	**77%**	**73%**

* 1996 NCI-WG criteria used

Wierda WG et al. *Proc ASH* 2009;Abstract 207.

Efficacy by Cytogenetic Characteristics and Treatment Received

Patient Characteristic		n	CR	ORR
All patients		61	41%	75%
IgVH genes	Mutated	28	46%	75%
	Unmutated	25	36%	84%
FISH hierarchy	Del13q	25	32%	80%
	Negative	7	71%	100%
	Trisomy 12	9	56%	56%
	Del 11q	10	40%	70%
	Del 17p	8	13%	63%

Wierda WG et al. *Proc ASH* 2009;Abstract 207.

Adverse Events

Grade 3/4 Adverse Events	OF-C 500 mg n = 31	OF-C 1,000 mg n = 30
Neutropenia	35%	60%
Thrombocytopenia	6%	23%
Anemia	6%	20%
Infections	13%	23%
Febrile neutropenia	3%	3%
Sepsis	0%	2%
Herpes virus infection	1%	0%
Respiratory infection	0%	1%
Unspecified infection	0%	1%

Wierda WG et al. *Proc ASH* 2009;Abstract 207.

Conclusions

- O-FC was highly active at both doses in patients with previously untreated CLL.
  - ORR: 73% (1,000 mg); 77% (500 mg)
  - CR: 32% (500 mg); 50% (1,000 mg)
- Myelosuppression is the most common toxicity.
- Time-to-event endpoint analyses are ongoing.
- Adverse events were manageable with no unexpected toxicities.
- Other studies are under way to evaluate ofatumumab 1,000 mg in combination with chemotherapy in patients with CLL (NCT01125787, NCT01131247).

Wierda WG et al. *Proc ASH* 2009;Abstract 207; www.clinicaltrials.gov.

Faculty Comments

DR FOSS: This Phase II study shows that ofatumumab combined with fludarabine and cyclophosphamide is significantly active in the up-front treatment of CLL. However, the therapy has not been compared to FCR, which is considered the standard treatment for these patients.

DR VOSE: The toxicities were easily managed, with hematological toxicity being the major one. It was believed that the 1,000-mg dose of ofatumumab is perhaps a bit better based on this small study, and that dose is currently going forward in larger trials.

A Phase II Study of Lenalidomide as Initial Treatment of Elderly Patients with Chronic Lymphocytic Leukemia

Badoux X et al.
Proc ASCO 2010;Abstract 6508.

Introduction

- The majority of patients with chronic lymphocytic leukemia (CLL) are older than age 70.
- No standard treatment has been established for elderly patients with CLL.
- Elderly patients with CLL are under-represented in clinical trials and experience increased toxicity from chemoimmunotherapy.
- Lenalidomide is an immunomodulatory drug that is administered orally and is active in patients with relapsed CLL (*JCO* 2006;24:5343, *Blood* 2008;111:5291).
- Current study objective:
  - To evaluate the activity of single-agent lenalidomide as front-line therapy for elderly patients with CLL.

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Phase II Study of Lenalidomide in Elderly Patients with CLL

Eligibility (N = 60)

Untreated and symptomatic CLL

PS 0-2

Age ≥ 65 years

Lenalidomide 5 mg/day x 2 cycles (56 days)

Increase by 5 mg/cycle (28 days) if well tolerated to maximum 25 mg/day

Treatment continued until disease progression

Allopurinol 300 mg PO QD days 1-14 (cycle 1)

No mandated antibiotic, antiviral, DVT or tumor flare prophylaxis

Response assessed at the end of cycle 3 and then every 6 cycles

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Efficacy Results

Clinical Response	N = 60	
Overall response rate (ORR)	62%	
Complete response (CR)/CRi	10%/5%	
Nodular partial response (nPR)/PR	5%/42%	
Response by Baseline Characteristic	**CR/CRi/nPR**	**ORR**
Age, ≥75 years (n = 17)	6%	35%*
IgVH genes, mutated (n = 22)	5%*	50%
FISH hierarchy, deletion 17p (n = 6)	0%	0%

* $p < 0.05$. CRi = CR with incomplete blood count recovery

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Progression-Free and Overall Survival Data

2-Year Survival	Lenalidomide N = 60
Progression-free survival (PFS)	60%
Overall survival (OS)	90%

Median follow-up = 23 months

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Grade 3/4 Adverse Events (N = 60)

Toxicity, % of cycles	Grade 3	Grade 4
Neutropenia	26%	12%
Thrombocytopenia	13%	<1%
Anemia	0%	0%
Tumor flare*	0%	0%
Infections	**Grade ≥3, n (%)**	
All (sepsis, pneumonia/bronchitis, upper respiratory, fever, other)	9 (15%)	

* 50% of patients experienced Grade I/II tumor flare.

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Conclusions

- Lenalidomide as a single agent induces clinical responses in the front-line treatment of elderly patients with CLL.
  - ORR: 62%
  - CR/CRi: 15%
  - 2-year OS: 90%
  - 2-year PFS: 60%
- The most common Grade 3/4 toxicity was myelosuppression.
- No severe tumor flare or tumor lysis syndrome was observed.

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Faculty Comments

DR VOSE: The study evaluated lenalidomide as initial therapy for older patients with CLL. The overall response rate was approximately 62 percent, with 10 percent complete remissions.

The therapy was fairly well tolerated, and the major complication was hematological toxicity. Authors believed single-agent lenalidomide to be a fairly good potential treatment for older patients with CLL.

Combination Therapy with Lenalidomide and Rituximab in Patients with Relapsed Chronic Lymphocytic Leukemia (CLL)

Ferrajoli A et al.
Proc ASH 2009;Abstract 206.

Introduction

- Lenalidomide (LEN) with rituximab (R) combination therapy has shown clinical responses in a small number of patients with CLL who experienced disease progression while receiving LEN monotherapy (*JCO* 2006;24:5343).
- R monotherapy has modest activity but significantly synergizes with chemotherapy agents when administered to patients with CLL (*JCO* 2010;28:1756, *Lancet* 2010;376:1166).
- Current study objective:
  - Evaluate the safety and efficacy of LEN with R combination therapy in patients with relapsed CLL.

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Phase II Study Design

Accrual: 60

Eligibility

Active CLL

Prior treatment with purine analog-based therapy

→

LEN + R:

LEN: 10 mg/d day 9 (cycle 1) ➔ daily x 28 d (cycles 2-12)

R: 375 mg/m^2 weekly (cycle 1) ➔ q4wk (cycles 3-12)

Median number of prior treatments: 2
All patients received prior treatments of R.

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Efficacy Data

Efficacy After 6 Cycles of Treatment (n = 37)	LEN + R N (%)
Overall response rate	25 (68%)
Nodular partial response	6 (16%)
Partial response	19 (51%)
Stable disease	6 (16%)
Failure to respond*	6 (16%)

* One patient died on day 34 from infectious complications.

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Responses According to CLL Stage and Cytogenetics

Characteristic	N	% nPR	% PR	% ORR
All patients	37	16	51	68
Rai Stage III/IV	15	7	53	60
FISH Del 17p	9	33	33	67
FISH Del 11q	10	10	60	70
IgVH (unmutated)	26	23	46	69

PR = partial response; nPR = nodular PR; ORR = overall response rate

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Common Grade 3/4 Adverse Events

Adverse Event	N (%)
Neutropenia	16 (43)
Fatigue	6 (16)
Thrombocytopenia	4 (11)
Tumor lysis syndrome (Grade 3)	1 (3)
Joint pain (Grade 3)	1 (3)

Grade 1 (22%) and Grade 2 (3%) LEN-associated tumor flare reaction was observed.

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Conclusions

- When compared to historical data with single-agent LEN, R in combination with LEN may have superior activity in relapsed CLL.
- LEN-associated tumor flare reaction was both less frequent and less severe than has been reported with single-agent LEN.
- When compared to baseline, there were significant differences in the distribution of circulating B, T and NK cell populations after three cycles of therapy (data not shown):
  - **B cells:** decreased percentage of $CD19^{+}CD20^{+}$
  - **T cells:** increased percentage of $CD4^{+}$, $CD8^{+}$, $CD4^{+}CD25^{hi}CD127^{-}$
  - **NK cells:** increased percentage of $CD3^{-}CD16^{+}CD56^{+}$
- Research is ongoing to determine the clinical relevance of these immune cell changes.

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Faculty Comments

DR VOSE: This study was designed on the basis of preclinical data indicating that lenalidomide and rituximab have potentially synergistic activity. The patients included in the study had heavily pretreated disease and had received rituximab in prior regimens.

The overall response was 68 percent, with 51 percent PR and 16 percent nodular PR. None of the patients were reported to have achieved CR. The regimen was fairly well tolerated with major toxicities being hematological.

A correlative part of the study examines proportions of different immune cells to see if they might correlate with outcome. That research is still ongoing.