

# **Drug Development in Leukemia: What Have We Learned?**

**John C. Byrd, MD**

**D Warren Brown Chair of Leukemia Research**

**Professor of Medicine and Medicinal Chemistry**

**Associate Director for Translational Research**

**OSU Comprehensive Cancer Center**

**Columbus, Ohio**



## **Goals of Talk**

- **To provide historical background (in detail) of how clinical trials have taken us to where we are at now in CLL**
- **To describe in less detail how clinical trials have improved outcome of patients in other types of leukemia**
  - AML**
  - APL**
  - CML**
  - ALL**
  - MDS**
  - Hairy cell leukemia**
  - PLL**

## **Chronic Lymphocytic Leukemia**

- **The most prevalent type of adult leukemia**
- **Defined by CD5, CD19, CD20, CD23, sIg (dim)+ cells in blood; < 5 x 10<sup>9</sup>/L cells is monoclonal B-cell lymphocytosis (MBL)**
- **Median age of diagnosis of CLL is approximately 72 with only 10% of patients under**
- **CLL treated only when disease becomes symptomatic due to absence of survival advantage with early treatment**
- **For many years, CLL therapy offered no hope of improving survival even when patients were symptomatic**
- **Certain genetic groups progress quickly and do not respond well to all [del(17p13.1)] or a subset of therapies [del(11q22.3)]**

## **History of CLL Therapy 1970-2010**

- **Chlorambucil ± prednisone-historical therapy with response (30-89%) varying upon dose**
- **Fludarabine-higher response and progression time as compared to alkylator therapy in three studies (CALGB 9011)**
- **Fludarabine/Cyclophosphamide Combinations-improved CR, ORR and PFS as compared to fludarabine in three studies (ECOG/CALGB 2097)**
- **Chemoimmunotherapy with addition of rituximab-improved CR, ORR, and PFS as compared to FC (CALGB 9712)**
- **Many additional new agents: Alemtuzumab, bendamustine, ofatumumab, CAL-101, PCI32765, TRU-016, GA-101, flavopiridol, SCH727965, and others**

## **How this has happened?**

**Clinical Trials!!!**

**Now Lets Talk about These a little bit**

## **Available CLL Therapy Prior to 1991**

**Chlorambucil or Cyclophosphamide**

**Patients who stop responding to this have no  
treatment options and short survival**

## **Fludarabine: Background**

- **Fludarabine synthesis late 1970's by Dr. John Montgomery on contract from NCI**
- **Fludarabine monophosphate is soluble & relatively resistant to adenosine deaminase while retaining cytotoxic activity**
- **To get into cell, where it is active F-Ara is phosphorylated by deoxycytidine kinase whose activity is 10 x higher in human BM than dog BM**
- **F-Ara-P is metabolized in part by deamination which occurs in dogs but not in humans**

## **Fludarabine**

- **Preclinical pharmacology did show species differences, but the toxicology studies had not warned of neurotoxicity**
- **Initial knowledge of difference in profound fludarabine metabolism differences not known**
- **Solid tumor phase I DLT was myelosuppression, but in acute leukemia high doses resulted in serious delayed neurotoxicity**
- **Phase I studies of fludarabine at lower doses demonstrated activity in small number of low-grade NHL and CLL pts included**

## **Fludarabine Neurotoxicity**

- **Severe irreversible neurotoxicity was noted in majority of pts treated at doses above 96 mg/m<sup>2</sup> dose**
  - « Cortical blindness
  - « Coma and eventually death
- **Toxicity was usually delayed with early signs and symptoms being subtle or absent**
- **This toxicity resulted in fludarabine development being dropped by Dupont Pharmaceuticals**

## **Fludarabine: On The Respirator**

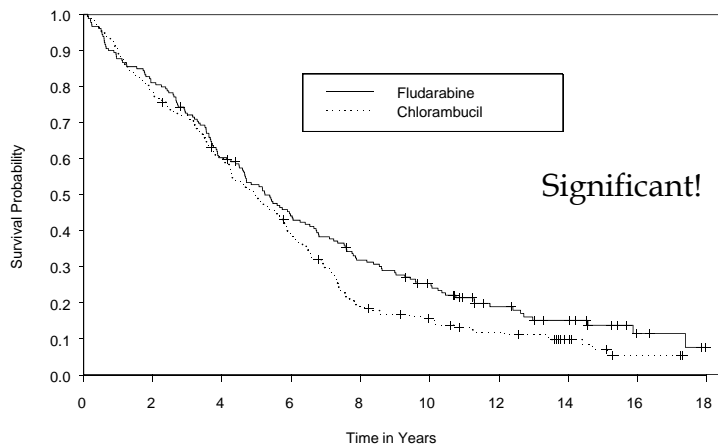
- **Initial activity in low grade lymphoproliferative disorders seen at lower doses where only rare occurrence of neurotoxicity was observed**
- **Small Biotechnology company (Triton Biotechnology) purchased right to develop fludarabine**
- **Subsequent successful phase II studies in alkylator-refractory CLL (SWOG-MR Grever and MDACC-M Keating) resulted in accelerated approval in 1991**
- **Success of fludarabine demonstrated ability to do successful clinical research in CLL**

## CALGB 9011 Phase III Study

- **Multi-center, randomized, phase III study**
- **509 patients untreated, symptomatic CLL**
- **Randomized 1:1:1 to 6 (monthly) cycles of**
  - **Fludarabine (F) 25 mg/m<sup>2</sup>/day IV x 5**
  - **Chlorambucil (C) 40 mg/m<sup>2</sup> PO**
  - **Fludarabine + chlorambucil (F+C), 20/20**
- **Primary endpoint: Progression Free Survival**
- **Secondary endpoints: Overall Response (CR+PR)**
- **Third arm (F+C) was closed early due to toxicity**

Rai et al; ASH Abstract 536: Long-term Survival Analysis: CALGB 9011

### C9011: Updated Survival 2009



Number of Patients at Risk

Flu	179	145	107	76	54	39	21	14	4	0
Chlor	193	152	115	73	35	26	18	9	2	0

Rai et al; ASH Abstract 536: Long-term Survival Analysis: CALGB 9011

## Where This Took Us

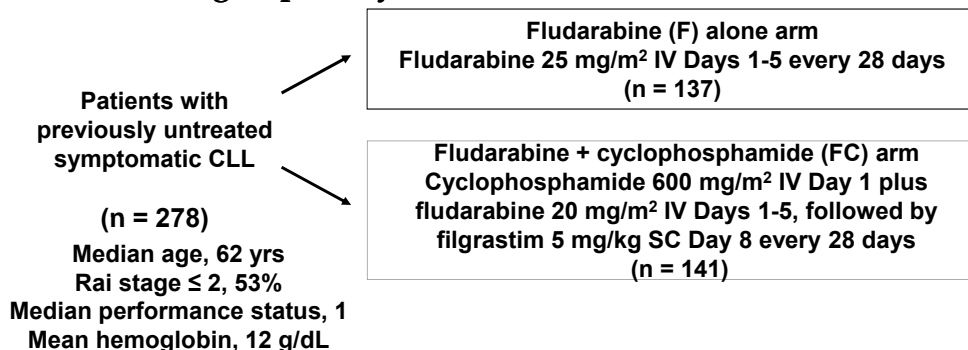
- **Fludarabine a better up-front therapy in CLL as demonstrated by CALGB and three other cooperative groups**
- **Fludarabine has distinct toxicities; some which were identified in CALGB studies**
  - « Immune suppression, bacterial infections, opportunistic infections
  - « Autoimmune complications
  - « Potentially MDS/AML when combined with alkylators but not when given with monotherapy
- **Fludarabine does not work well in del(11q22.3) or del(17p13.1) CLL with shorter PFS and OS**

## Nucleoside Chemotherapy Combinations

- **Biologic Basis for combination**
  - « Combine DNA damaging agent with one that inhibits repair
- **Most promising results seen with cyclophosphamide and fludarabine in symptomatic, untreated CLL**
  - JHU/WRAMC regimen (50% CR) and MD Anderson regimen (35% CR)
- **Prospective concern with these regimens**
  - « Prolonged myelosuppression and infection
  - « Long-term risk of treatment related MDS and AML

## Fludarabine Plus Cyclophosphamide versus Fludarabine

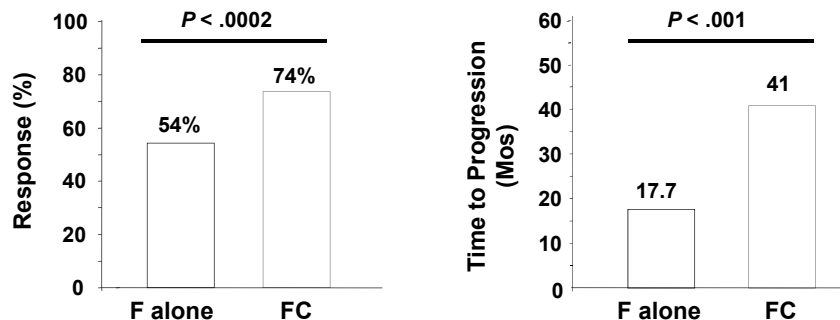
- ECOG 2997/CALGB 2997: A Phase 3, Randomized Intergroup Study



Flinn IW, et al J Clin Onc 2007

## Fludarabine Plus Cyclophosphamide in Frontline CLL Therapy

- Superior overall response and longer time to progression when fludarabine combined with cyclophosphamide
- Adverse events manageable and similar in both arms



Flinn IW, et al J Clin Oncol 2007

## Where This Took Us

- **Fludarabine/Cyclophosphamide a better up-front therapy in CLL as demonstrated by ECOG/CALGB and two other cooperative groups**
- **Fludarabine/Cyclophosphamide more myelosuppressive and difficult to give to elderly CLL**
- **Fludarabine/cyclophosphamide does not work well in patients with del(17p13.1)**
- **Fludarabine/Cyclophosphamide improves outcome of patients with del(11q22.3) to match favorable genetic groups**

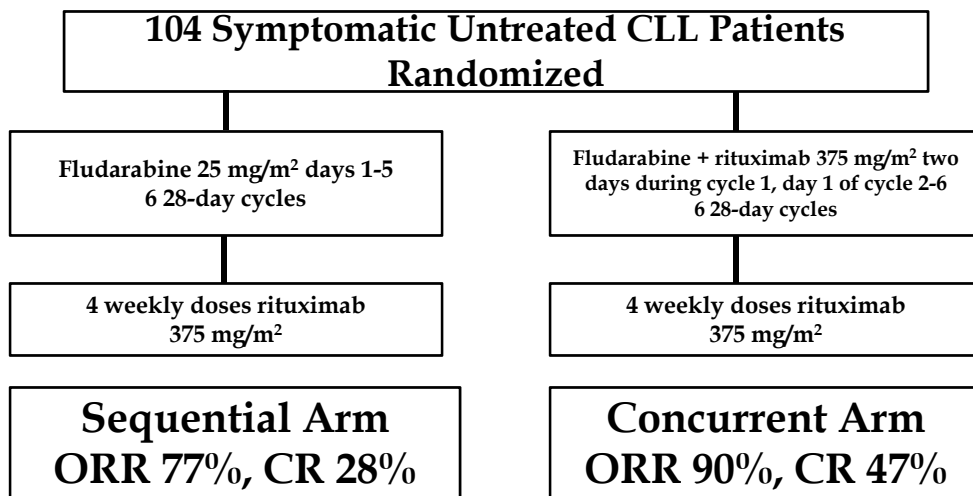
## Antibody Therapy

- **Antibodies are made by B-cells and plasma cells to protect body against infection and cancer**
  - « **Antibody has one target therefore it is the silver bullet**
  - « **Antibody can directly kill**
  - « **Antibody recruit the immune system to kill**
- **Rituximab is a chimeric anti-CD20 antibody**
- **Rituximab first antibody approved for the treatment of relapsed low-grade NHL in December 1997**

## Rituximab in CLL

- Antibody directed at CD20 that is highly active in most type of B-cell malignancies with survival improvement in DLCL, FCL, BL
- Toxicity profile favorable outside of initial infusion toxicity
- Single agent activity in previously un-treated CLL patients although effectiveness against bone marrow disease modest
- Very modest activity in relapsed disease unless given at high total dose (O'Brien S et al, J Clin Oncol 2001) or frequent administration (Byrd JC et al, J Clin Oncol 2001)
- Addition of rituximab to nucleoside analog combinations (FR and FCR) have generated improved PR, CR, PFS and OS as compared to historical controls in phase II studies

### CALGB 9712: A Randomized Phase II Study of Rituximab + Fludarabine



Byrd JC, et al: Blood. 101:6-14, 2003

## Comparison of Older Study with Fludarabine to these Results

Trial	CALGB 9011	CALGB 9712	P=value
No Pts	179	104	
% CR Rate	20	38	0.002
% Overall Response	63	84	0.0003
% 2-year DFS (95%CI)	45 (37,52)	67 (58,76)	<0.0001
% 2-year OS (95%CI)	81 (75,87)	93 (88,98)	0.0009

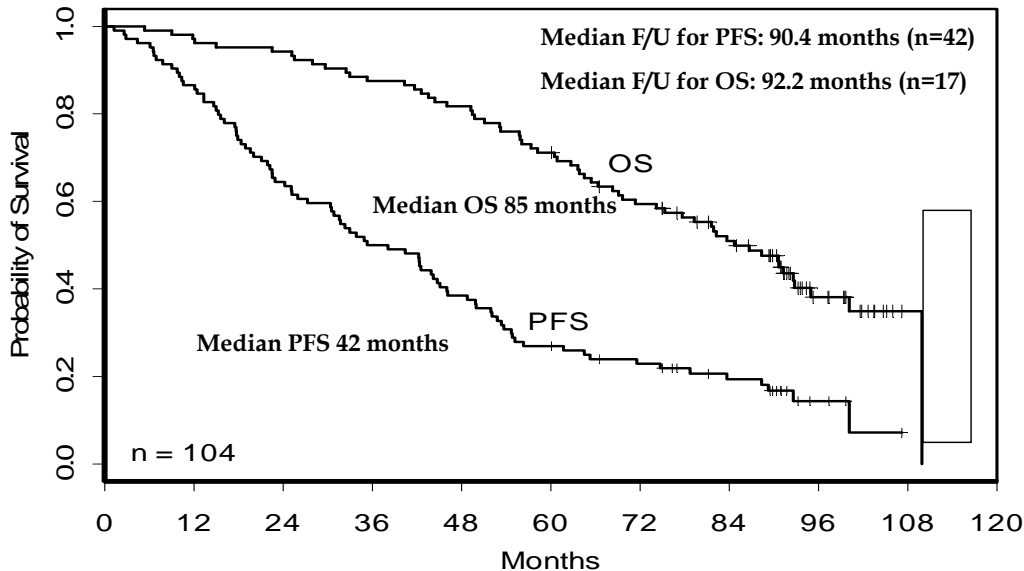
Byrd JC, et al: Blood 105:49-53, 2005

## Long-Term Outcome of CALGB 9712

- **Extended remission duration and overall survival as compared to historic results with fludarabine monotherapy**
- **Less optimal results in high risk genomic patients**
  - « IgV<sub>H</sub> un-mutated patients
  - « del(11q22.3) and del(17p13.1) patients
- **Complications with this regimen minimal**
  - « No unusual infections
  - « No secondary MDS or AML during follow up
  - « No increased risk of Richter's transformation
- **Very reasonable therapy for low risk CLL patients**

Woyach J, et al: ASH 2009

## Long-Term Outcome CALGB 9712



## Fludarabine, Cyclophosphamide, and Rituximab In Previously Untreated CLL

- Three day MDA FC regimen with addition of rituximab repeated q 28 days for 6 cycles of therapy
- 300 patients enrolled with 36% being Rai stage III/IV
- Well tolerated with 75% of patients finishing therapy and low frequency of infectious morbidity (2.6% of courses)
- Responses noted in 95% of patients, including 70% CR rate and extended PFS as compared to historical FC controls
- del(11q22.3) patients have favorable outcome with FCR

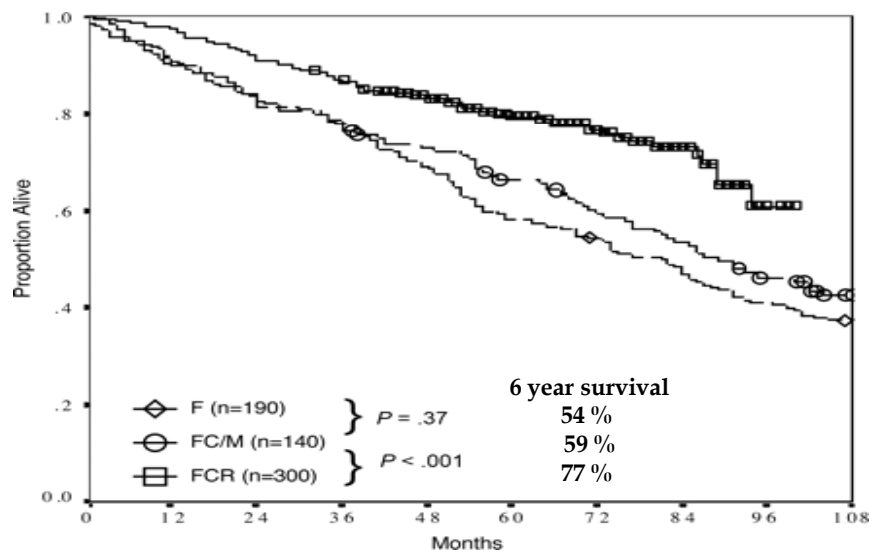
M Keating et al JCO 2005

## FCR Long Term Outcome

- At a median F/U of 72 months actuarial 6-year OS is 77% and whereas PFS is 51%
- Recurrent late cytopenias occurred in 69 (28%) pts usually in first year remission and did not require growth factor support
- Opportunistic infections 10% year 1; 4% year 2; majority of these varicella zoster infections
- Secondary MDS and AML in 8 patients (3%)

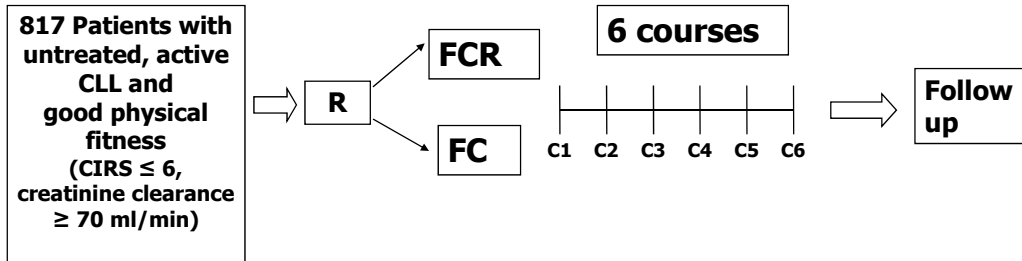
Tam CS & Keating MJ. Blood 2008;112:975–980

## Long-Term Follow Up of F, FC, and FCR OS



Tam CS & Keating MJ. Blood 2008;112:975–980

## CLL8 Study Design



Updated results of the 2nd analysis  
Median observation time 37.7 months.

Hallek et al; ASH Abstract 535: FC vs. FCR (CLL8 trial), 2009

## CLL8: ITT Population (n=817)

	FC (n = 409)	FCR (n = 408)
Female	105 (26%)	105 (26%)
Male	304 (74%)	303 (74%)
Median age	61 (range 36-81)	61 (range 30-80)
Binet A	22 (5.4%)	18 (4.4%)
Binet B	259 (63.6%)	263 (64.6%)
Binet C	126 (31%)	126 (31%)
B symptoms*	197 (48%)	167 (41%)
Median cumulative illness rating scale (CIRS)	1 (range 0-8)	1 (range 0-7)
Trisomy 12	14.4%	9.6%
Del(13q)	59.7%	53.8%
Del(11q23)	22.5%	26.8%
Del(17p13)	9.5%	7.0%

\*P<0.05

Hallek et al; ASH Abstract 535: FC vs. FCR (CLL8 trial), 2009

## CLL8: Adverse Events CTC Grade 3 & 4

	FC	FCR	p
<b>Total number of patients with ≥ 1 grade 3/4 event</b>	<b>248 (62.9%)</b>	<b>309 (76.5%)</b>	<b>&lt; 0.0001</b>
<b>Hematological toxicity</b>	<b>39.6%</b>	<b>55.7 %</b>	<b>&lt; 0.0001</b>
<b>Neutropenia</b>	<b>21.0%</b>	<b>33.7%</b>	<b>&lt; 0.0001</b>
<b>Leukocytopenia</b>	<b>12.1%</b>	<b>24.0%</b>	<b>&lt; 0.0001</b>
<b>Thrombocytopenia</b>	<b>11.1%</b>	<b>7.4%</b>	<b>0.07</b>
<b>Anemia</b>	<b>6.8%</b>	<b>5.4%</b>	<b>0.42</b>
<b>Infection</b>	<b>21.5%</b>	<b>25.5%</b>	<b>0.18</b>
<b>Tumor lysis syndrome</b>	<b>0.5%</b>	<b>0.2%</b>	<b>0.55</b>
<b>Cytokine release syndrome</b>	<b>0.0%</b>	<b>0.2%</b>	<b>0.32</b>

Treatment related mortality 2% for both arms.

Hallek et al; ASH Abstract 535: FC vs. FCR (CLL8 trial), 2009

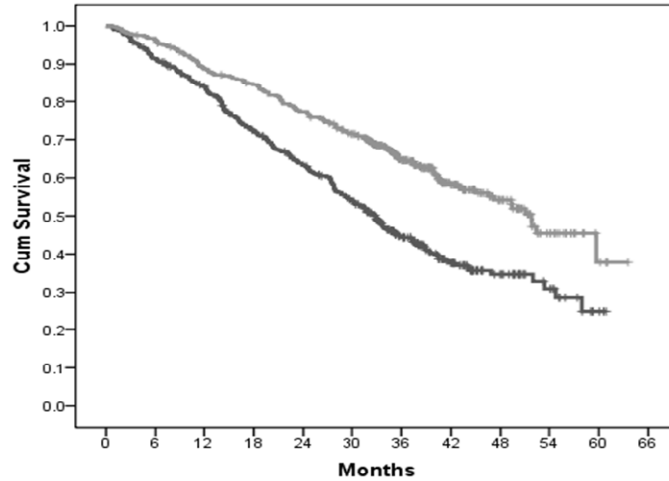
## CLL8: Response to Treatment

	FC	FCR
<b>CR*</b>	<b>21.8%</b>	<b>44.1%</b>
<b>PR</b>	<b>66.6%</b>	<b>51.0%</b>
<b>Overall response rate</b>	<b>88.4%</b>	<b>95.1%</b>

\*According to NCI WG Criteria, confirmatory BM assessment performed up to 6 months after final restaging P < 0.01

Hallek et al; ASH Abstract 535: FC vs. FCR (CLL8 trial), 2009

## CLL8: Progression-free Survival



### Median PFS:

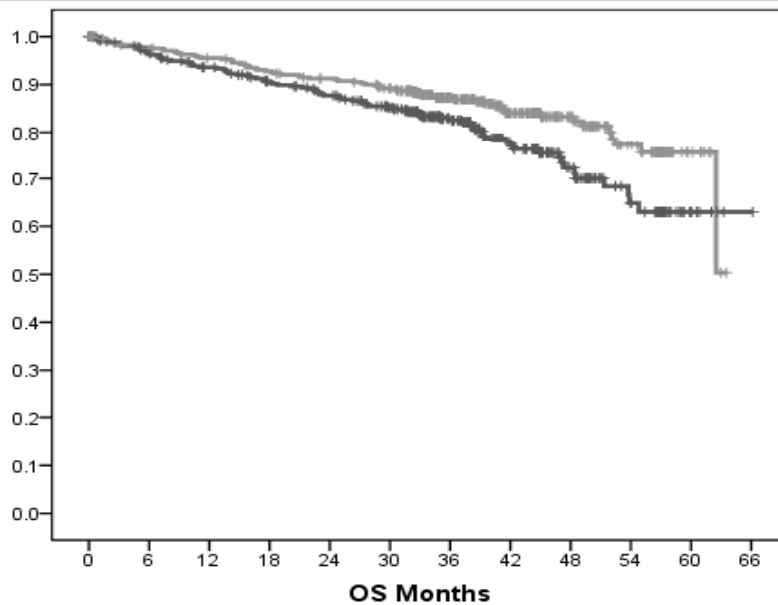
FCR: 51.8 months  
FC: 32.8 months  
(N=790  
Hazard ratio 0.563,  
ranges 0.460-0.689,  
p<0.001)

### PFS rate 3 yrs post randomization:

FCR: 64.9%  
FC: 44.7%

Hallek et al; ASH Abstract 535: FC vs. FCR (CLL8 trial), 2009

## CLL8: Overall Survival



**Overall survival  
3 years post  
randomization:  
FCR: 87.2%  
FC: 82.5%**

**n=817, HR  
0.664, p=0.012**

Hallek et al; ASH Abstract 535: FC vs. FCR (CLL8 trial), 2009

## CLL8: Conclusions

- Addition rituximab to FC first-line therapy improves the outcome of patients with CLL with regard to:
  - « Response rates (CR, ORR, MRD)
  - « Progression-free survival
  - « Overall survival
- Patients with all genetic groups except del(17p13.1) benefit from FCR
- First trial to definitively show a survival advantage with addition of immune therapy in CLL

Hallek et al; ASH Abstract 535: FC vs. FCR (CLL8 trial), 2009

## New Chemoimmunotherapy Regimens

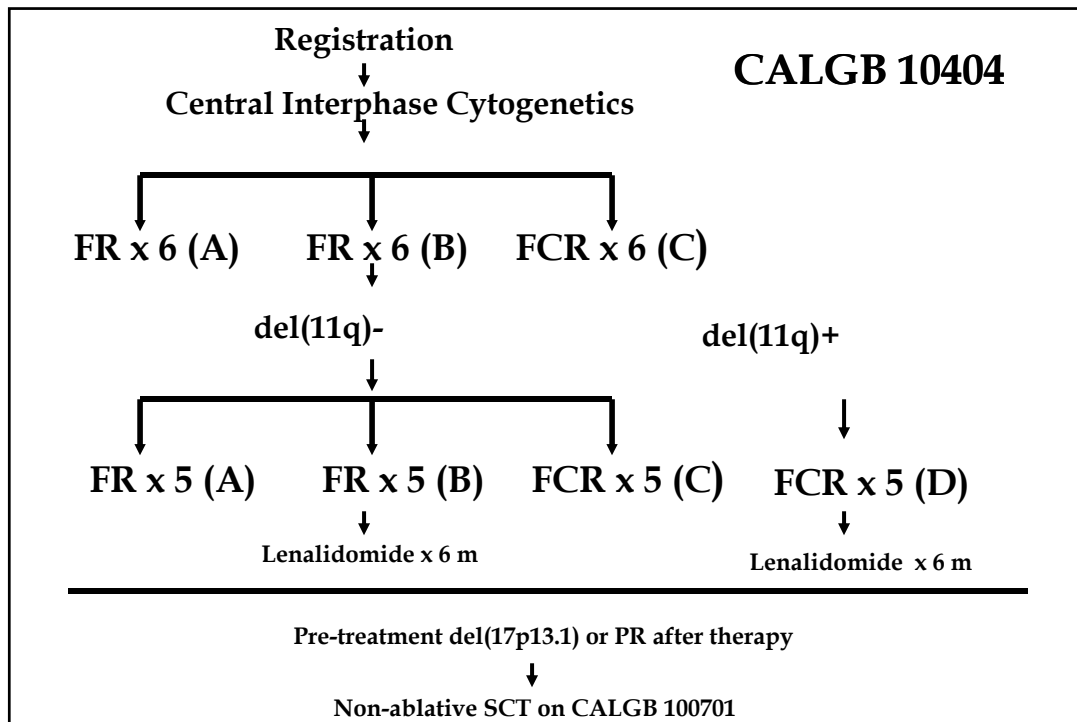
- **Bendamustine/Rituximab (Fischer K, et al: ASH 2009)**
  - 90% ORR, 33% CR
- **Fludarabine, Cyclophosphamide, Ofatumumab (Wierda W, et al: ASH2009)**
  - 73% ORR, 50% CR
- **FCR + Alemtuzumab or FR followed by alemtuzumab tested with no benefit over historical controls and significant infectious morbidity (CALGB 10101)**

## **How Do Genetics Interact with Treatment?**

- **Patients with del(17p13.1) respond but not as well to FR or FCR**
- **Patients with del(11q22.3) have similar response and PFS to FCR or FC and but shorter PFS with F or FR (cyclophosphamide probably important)**
  - These patients should get FCR
- **Patients with IgVH un-mutated disease have shorter remission with all therapies**

## **Is the Winner FCR or FR**

- **No randomized comparative trial available**
- **ORR and CR rate similar to slightly higher with FCR as compared to FR**
- **PFS with much shorter follow-up similar to slightly higher with FCR versus FR**
- **Patients with del(11q22.3) appear to do well with FCR whereas outcome with FR not as good**
- **Less secondary MDS/AML with FR**
- **Patients with IgV<sub>H</sub> un-mutated and del(17p13.1) disease do poorly with FCR or FR**



## Why Lenalidomide in CALGB 10404?

- **Thalidomide derivatives with multiple mechanisms including immune activation, stromal cell interaction, apoptosis**
- **Lenalidomide approved for use in multiple myeloma and MDS**
- **A Chanan-Khan et al (J Clin Oncol 2006)**
  - « 45 pt relapsed phase II study of lenalidomide 25 mg/day x 21 days with 7 days off;
  - « 42% response including 9% CR
  - « Cytopenias, fatigue, and tumor flare observed. Tumor flare treated with motrin
- **A Ferrajoli et al (Blood 2008)**
  - « 42 pt relapsed phase II study of lenalidomide 10 mg day with dose escalation to 25 mg as tolerated (median dose 10 mg);
  - « 32% response (7% CR)
  - « cytopenias and tumor flare observed. Tumor flare treated with corticosteroids
- **Lenalidomide now being tested in up-front and consolidation study (similar to CALGB 10404) in randomized phase III trial**

## **Other Active Novel Agents in CLL**

- **Alemtuzumab** – new CD52 antibody FDA approved
- **Bendamustine** – new chemotherapy drug FDA approved
- **Ofatumumab** – New CD20 antibody FDA approved
- **Flavopiridol** – CDK inhibitor – completing pivotal study
- **ABT 263** – Bcl-2 antagonist
- **SCH727965** – CDK inhibitor
- **GA101** – CD20 antibody
- **TRU-016** – CD37 SMIP
- **PCI-32765** – BTK Inhibitor
- **CAL-101** – PI3K-delta inhibitor

## **Impact of Clinical Trials in AML**

- **Daunorubicin (day 1-3) + cytarabine (day 1-7) therapy followed by standard consolidation present since the 1970's**
- **High dose cytarabine impacts outcome in younger AML pts (Mayer R; NEJM 1994) with greatest impact on t(8:21) and inv(16) AML pts most (Bloomfield CD; Cancer Res 1998)**
- **Cytogenetics and other molecular studies offer opportunity to risk stratify patients to chemotherapy versus allogeneic transplant early**
- **Modest treatment progress since this time outside of non-ablative stem cell transplant (that uses fludarabine)**
- **Many new targeted therapies offer chance to change this including FLT3 inhibitors, other kinase inhibitors, hypomethylating agents, HDAC inhibitors, and lenalidomide**

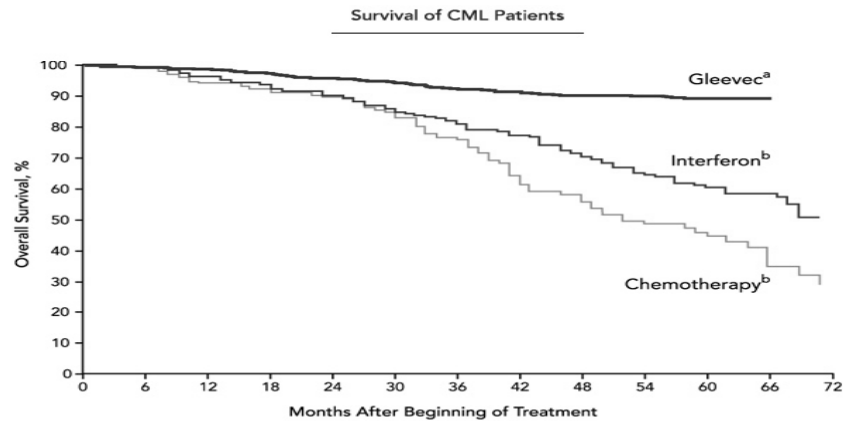
## **Impact of Clinical Trials in APL**

- **Acute promyelocytic leukemia associated with t(15;17) translocation and PML-RAR $\alpha$  rearrangement**
- **Clinical complications include DIC, bleeding and high early mortality rate with chemotherapy with modest long-term outcome**
- **Introduction of ATRA with induction/maintenance dramatically improved PFS and OS but changed toxicity profile observed (ATRA syndrome versus DIC)**
- **Introduction of Arsenic trioxide to ATRA/chemotherapy further improved PFS of APL patients**
- **Outside of high risk patients, most APL patients now cured; dial down of therapy similar to that in Hodgkin's disease now being pursued**

## **Impact of Clinical Trials in CML**

- **Chronic myeloid leukemia in past incurable in absence of allogeneic stem cell transplant**
- **Median survival in absence of transplant 5 years**
- **Standard CML therapy interferon + cytarabine for extended treatment and poor tolerance**
- **Introduction of kinase inhibitor imatinib greatly impacted survival of CML patients**
  - « **Now CML treated initially with oral agent imatinib with deferral of transplant even in young patients**
  - « **Multiple second generation molecules brought forward such as dasatinib and nilotinib that offer small advantage over imatinib**

## Impact of Imatinib in CML



<sup>a</sup> From Druker BJ, Guilhot F, O'Brien SG et al. *N Engl J Med.* (2006) 355:2408-2417.

<sup>b</sup> From The Italian Cooperative Study Group On Chronic Myeloid Leukemia. *N Engl J Med.* (1994) 330:820-825.

## Impact in Of Clinical Trials on ALL

- **Intensive chemotherapy improves outcome for subset of adult ALL (T-lymphoblastic leukemia)**
- **Intensive chemotherapy improves outcome of Burkitt's leukemia and lymphoma (worse to best)**
- **Nelarabine offers opportunity to induce remission in T-cell ALL and T-lymphoblastic lymphoma**
- **Dasatinib improves outcome of adult Ph+ ALL**
- **Rituximab improves outcome in patients with Burkitt's leukemia and lymphoma**
- **Allogeneic transplant improves outcome in high risk adult ALL**

## **Impact of Clinical Trials in Other Types of Leukemia**

- **Pentostatin or Cladribine improve survival of hairy cell leukemia to age matched control population**
- **5-azacytidine improves survival and prevents development of AML in MDS**
- **Lenalidomide highly effective in 5q- MDS**
- **Alemtuzumab highly effective in T-cell prolymphocytic leukemia**

## **Conclusions**

- **What all of you do with respect to work on CALGB clinical trials is important**
- **We have many happy patients with us in the world today because of what you have done**
- **Much progress is to be made yet and at this time we have many new promising therapies that make it possible to hope that all types of leukemia will be a treatable/curable in the future**
- **Thanks for all you do!**