Clolar® (clofarabine)

Pediatric Relapsed/Refractory Acute Lymphoblastic Leukemia

Oncologic Drugs Advisory Committee

February 8, 2011

genzyme

Representatives Participating Today

Genzyme

Mark Hayes, PhD, Group Vice President, Regulatory Affairs

Michael Vasconcelles, MD, Group Vice President and Therapeutic Area Head, Transplant/Oncology

Elly Barry, MD, Medical Director, Clofarabine

Children's Oncology Group (COG)

Stephen Hunger, MD, University of Colorado Denver School of Medicine, COG ALL Committee Chair (2008 – present)

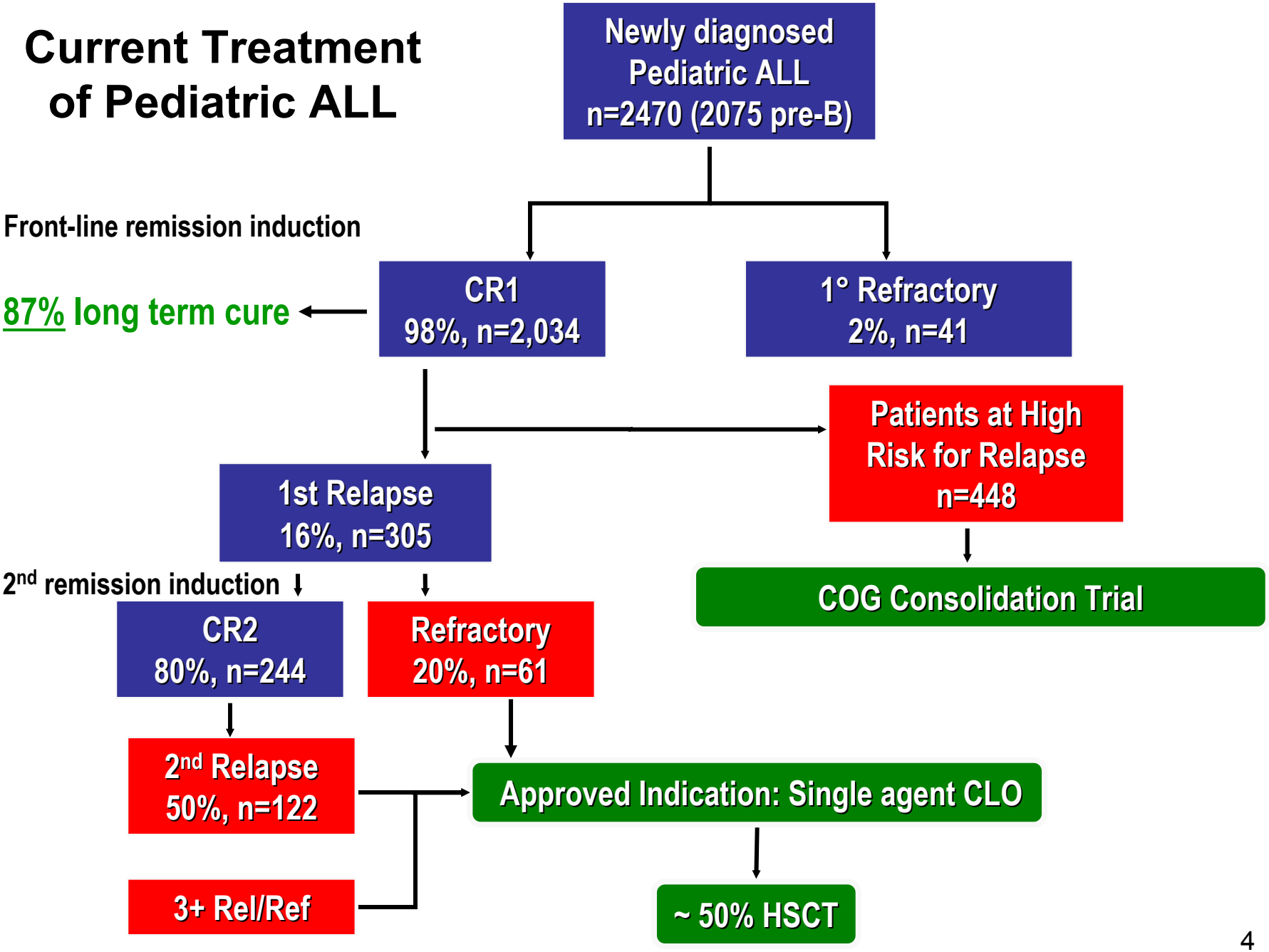
William Carroll, MD, New York University School of Medicine, COG ALL Committee Chair (2001-2007)

Clolar (clofarabine) Subpart H Approval December 28, 2004

Clolar® is indicated for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least 2 prior regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.

- Pivotal efficacy from Phase 2 single arm trial in R/R pediatric ALL (n=61)
  - Heavily pre-treated (2-6 prior Tx) patients with no options
  - 20% CR/CRp
    - 40% received post-remission HSCT
    - Remission duration for CR/CRp patients not receiving HSCT = 32-160+ days
- FDA/ODAC assessment: complete remissions are reasonably likely to predict clinical benefit in ALL
  - Ability to assess remission duration attributable to Clolar confounded due to frequency of post-induction therapy, particularly HSCT

Current Treatment of Pediatric ALL



Two Original Post-Marketing Commitments at Approval: PMC #1 to Define a Useful Combination

1. Completion of Phase 1/2 Study of Clofarabine Plus Ara-C and L-Asp in R/R pALL, showing that an **acceptable and potentially useful regimen** has been developed for study in a Phase 3 study.

   If either the Phase 1 or 2 components fail to identify a useful and tolerated regimen, you have agreed to promptly **develop an alternative plan** to verify and describe clinical benefit.

PMC #2: Controlled Clinical Study Not Yet Defined

2. Completion of a controlled clinical study to verify and describe the clinical benefit of clofarabine in pediatric ALL

   FDA: Proposed COG Phase 3 study [1st relapse pALL] "does not appear to have a realistic chance of showing a clinical benefit of clofarabine"

   Submit a new protocol for a study to show clofarabine clinical benefit in children with ALL within 2 months of the date of this letter

   Request a meeting to discuss this protocol

Two Options for Demonstration of Clinical Benefit

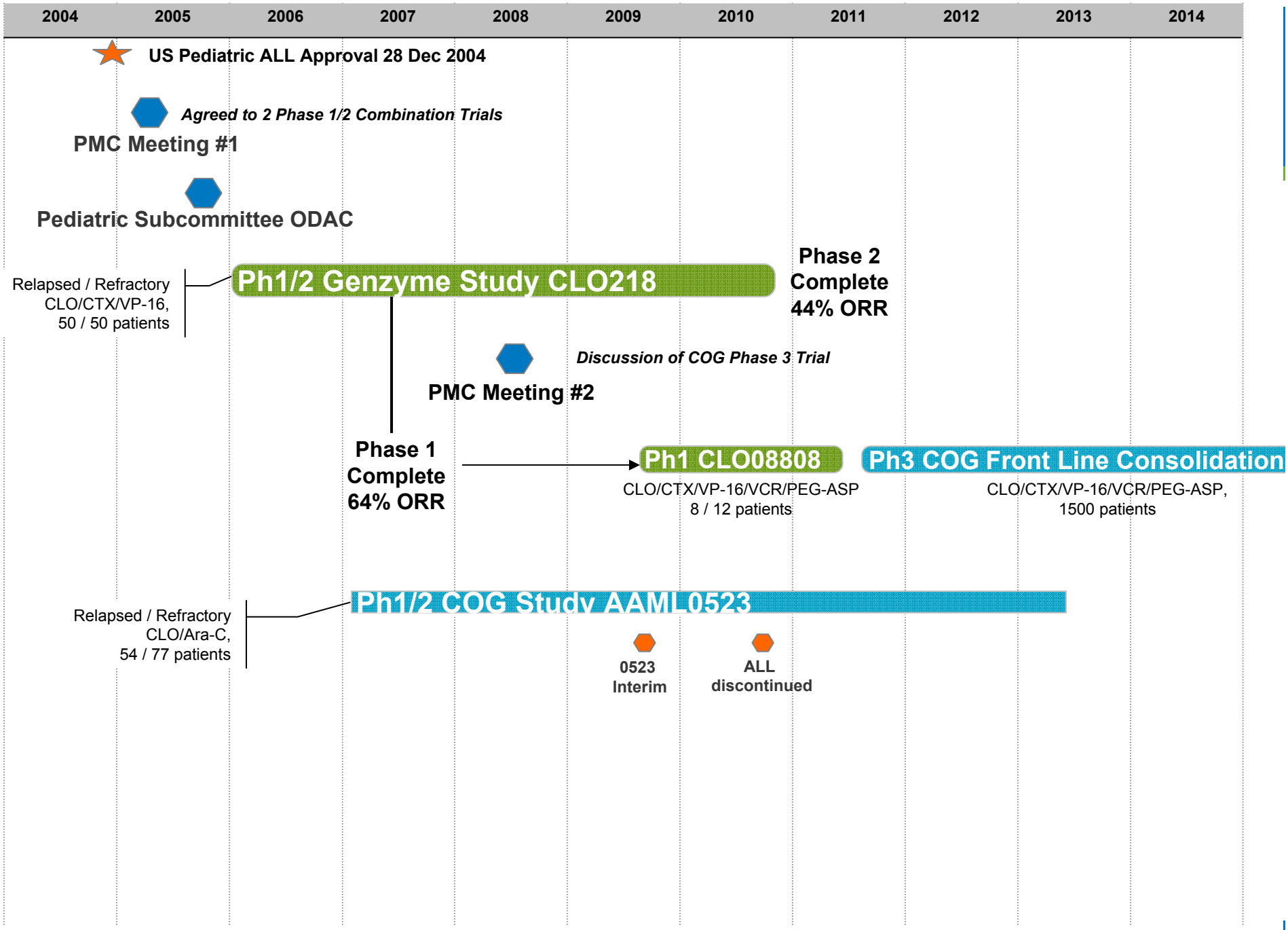
- Achievement of durable remission in R/R patients
  - Interpretation of remission duration attributable to Clolar from pivotal trial complicated by HSCT
- Improvement in time-to-event endpoint in randomized trial
  - Requires evaluation of optimal combinations with Clolar
  - Requires investigation in earlier line of therapy
    - Complexity of earlier line therapies creates challenges in isolating the effect of any new agent
  - Randomized trial accrual timelines are long

Sponsor-FDA PMC Meeting #1: 19 April 2005

- Agreement on stepwise approach
- Genzyme proposed two Phase 1/2 trials to evaluate MTD and activity of Clolar in combination with
  - cytarabine (COG AAML0532)
  - etoposide/cyclophosphamide (CLO-218)
- Results to inform Phase 3 trial
- Too early to commit to a Phase 3 study design
- Anticipated timelines (5 year accrual) for Phase 3 are long
  - "It is unlikely that investigators will be interested in entering patients over such a long time period (something new is bound to arise)"

Pediatric Subcommittee of ODAC
October 20, 2005

- Discussion of how to identify optimal combinations for use with clofarabine
- Recommend subsequent clinical development in pediatric ALL in earlier lines of therapy (versus multiply R/R patients)
- Consider primary endpoint of either CR rate or minimal residual disease status (vs. 4-month event-free survival) in this patient population
- Questioned the relevance of demonstration of clinical benefit in adult AML to pediatric ALL


2004
2005
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US Pediatric ALL Approval 28 Dec 2004
Agreed to 2 Phase 1/2 Combination Trials
PMC Meeting #1
Pediatric Subcommittee ODAC
Relapsed / Refractory
CLO/CTX/VP-16,
50 / 50 patients
Ph1/2 Genzyme Study CLO218
Phase 2
Complete
44% ORR
Discussion of COG Phase 3 Trial
PMC Meeting #2
Phase 1
Complete
64% ORR
Ph1 CLO08808
CLO/CTX/VP-16/VCR/PEG-ASP
8 / 12 patients
Ph3 COG Front Line Consolidation
CLO/CTX/VP-16/VCR/PEG-ASP,
1500 patients
Relapsed / Refractory
CLO/Ara-C,
54 / 77 patients
Ph1/2 COG Study AAML0523
0523
Interim
ALL
discontinued

Sponsor-FDA PMC Meeting #2: 16 July 2008

- Genzyme proposed COG Ph 3 front line consolidation in high risk pts
  - CLO/CTX/VP-16 (CLO218 regimen) + VCR/PEG-ASP versus Ara-C/CTX/6-TG + VCR/PEG-ASP
- Agreement on pilot study CLO08808 to establish safety of CLO218 regimen when augmented with VCR/PEG-ASP
- FDA feedback: proposed COG Ph 3 trial of interest
  - timelines are long
  - trial will not isolate effect of Clolar
- FDA suggested consideration of a PMC package combining COG data + adult AML data for possible submission for conversion to full approval

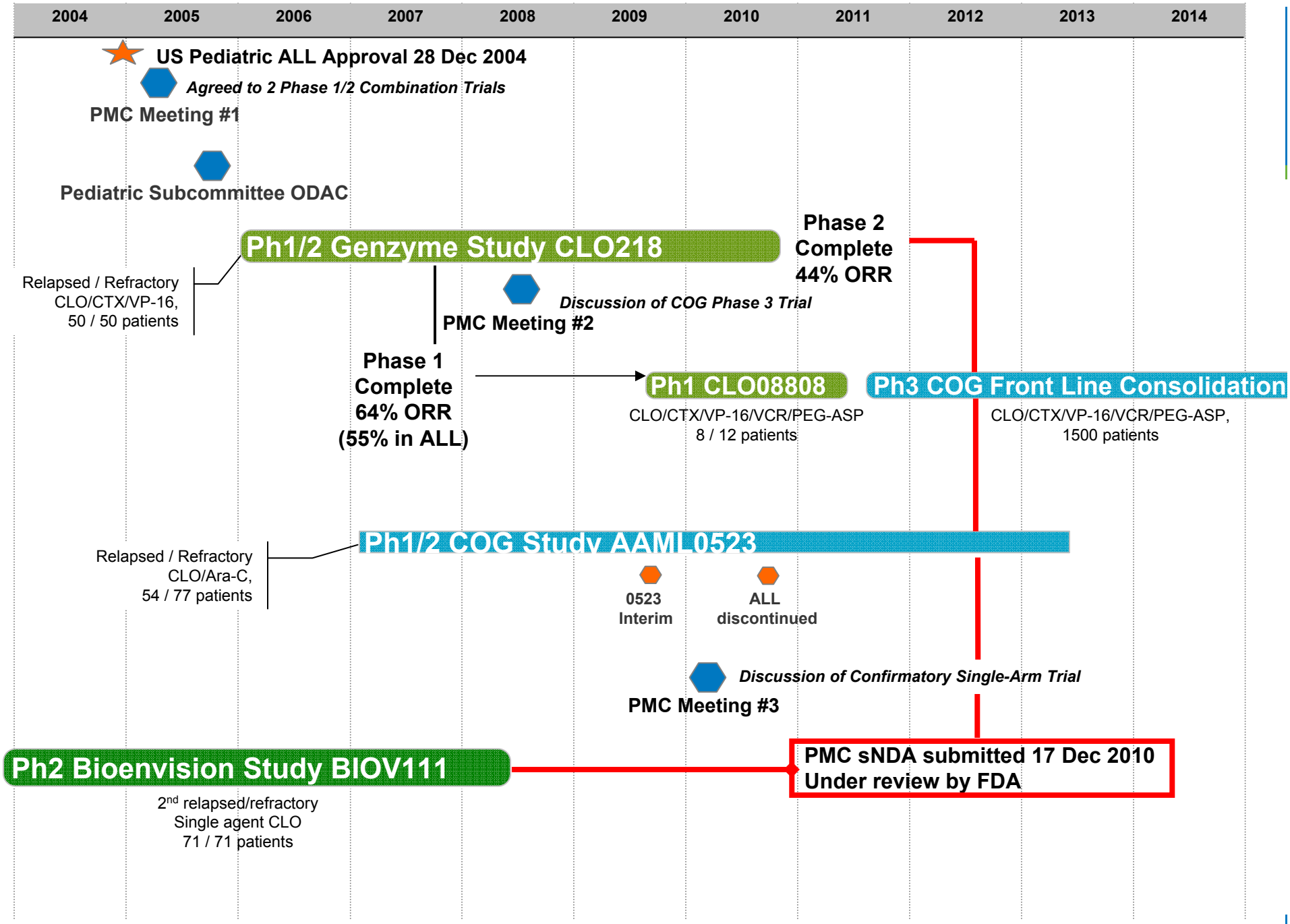
Sponsor-FDA PMC Meeting #3: 14 January 2010

- Based on recommendation from July 2008 meeting, Genzyme proposed package that combines adult AML data with data from COG Phase 3 front-line trial in high risk pediatric ALL patients
- FDA did not support utility of adult data
- FDA reiterated concerns around timelines and ability to isolate effect of Clolar in COG trial

Sponsor-FDA PMC Meeting #3: 14 Jan 2010 (cont.)

- As an alternative to COG trial, FDA recommended sponsor consider single-arm trial in R/R pediatric ALL patients who have failed HSCT with primary endpoint of durable CR rate
  - However, remission duration in post-HSCT patients still likely to be confounded by second HSCT

- Genzyme proposed to provide final results from BIOV-111 study completed as specific obligation for EMA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0523
Interim
ALL
discontinued
Discussion of Confirmatory Single-Arm Trial
PMC Meeting #3
Ph2 Bioenvision Study BIOV111
2nd relapsed/refractory
Single agent CLO
71 / 71 patients
PMC sNDA submitted 17 Dec 2010
Under review by FDA

Perspectives on FDA Questions to ODAC

- In heavily pre-treated R/R pediatric ALL patients, accelerated approval based on single arm data has provided earlier access to a new agent where there was no acceptable option
  - Durable CR in R/R ALL represents clinical benefit
  - No acceptable comparators in pivotal patient population

- Randomized trials in rare cancers such as pediatric ALL obligate long accrual time lines, assuming a reasonable expected treatment effect

Perspectives on FDA Questions to ODAC

- Accelerated approval of Clolar resulted in:
  - Access to R/R patients with no acceptable options
  - Continued development, including cooperative group interest
- Because 70% of pediatric ALL patients are enrolled in COG trials, collaboration is imperative
  - Support efforts by OEWG (NCI)
  - Encourage early collaboration between: FDA, cooperative groups, CTEP, and industry sponsors

Backup Slides

CLO21800205: Dose Scheme

Dose-Escalation Scheme				
PHASE I – Completed				
Cohort	Actual Accrual	Clolar	Etoposide	Cyclophosphamide
1	3	20 mg/m²	75 mg/m²	340 mg/m²
2	3	20 mg/m²	75 mg/m²	440 mg/m²
3	3	20 mg/m²	100 mg/m²	440 mg/m²
4	10	30 mg/m²	100 mg/m²	440 mg/m²
5 **RP2D**	6	40 mg/m²	100 mg/m²	440 mg/m²

PHASE II - Completed			
# Pts	Clolar	Etoposide	Cyclophosphamide
25	40 mg/m²	100 mg/m²	440 mg/m²

COG AAML0523: Study Treatment

Dose-Finding Scheme				
PHASE I - Completed				
Cohort	**# Planned Patients**	**# Actual Patients**	**Clolar x 5 days**	**Ara-C x 5 days**
0	10		30 mg/m²	1 gram/m²/day
1 - start	10	10	40 mg/m²	1 gram/m²/day
2	10	10	52 mg/m²	1 gram/m²/day

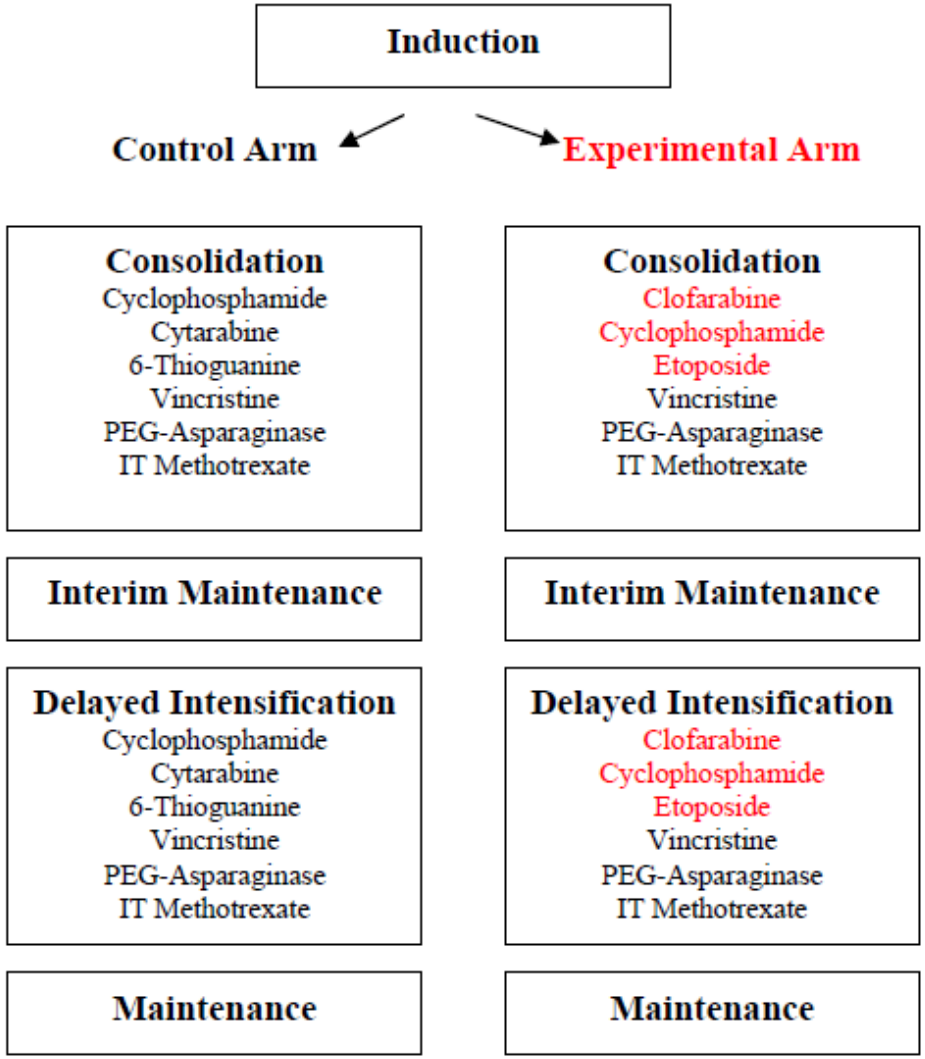
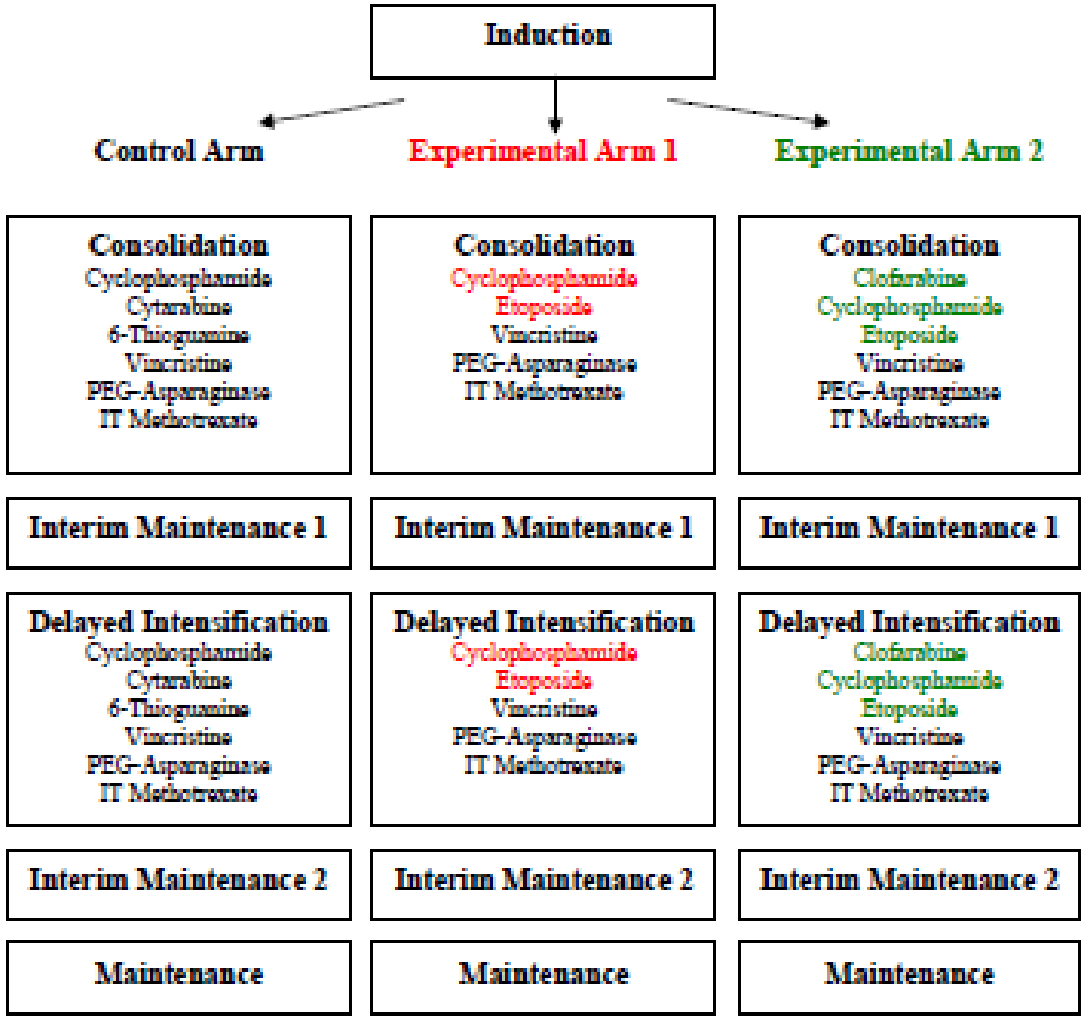
PHASE II – Stage 1 complete; Stage 2 ongoing			
# Planned Patients	**# Actual Patients to date**	**Clolar**	**Ara-C**
50	34	52 mg/m²	1 gram/m²/day

CLO08808: Dose Scheme

PHASE I – Suspended							
Group	Planned Accrual	Actual Accrual	Clolar	Etoposide	Cyclo-phosphamide	VCR*	PEG-Asparaginase **
1	6	6	40 mg/m²	100 mg/m²	440 mg/m²	1.5 mg/m²	2,500 IU/m²
2	3	2	40 mg/m²	100 mg/m²	440 mg/m²	1.5 mg/m²	2,500 IU/m²
3	3		40 mg/m²	100 mg/m²	440 mg/m²	1.5 mg/m²	2,500 IU/m²

** Days 15,22*
*** Day 15*

Original COG Ph. 3 Schema (AALL0831)



Current COG Ph. 3 Schema (AALL1131)