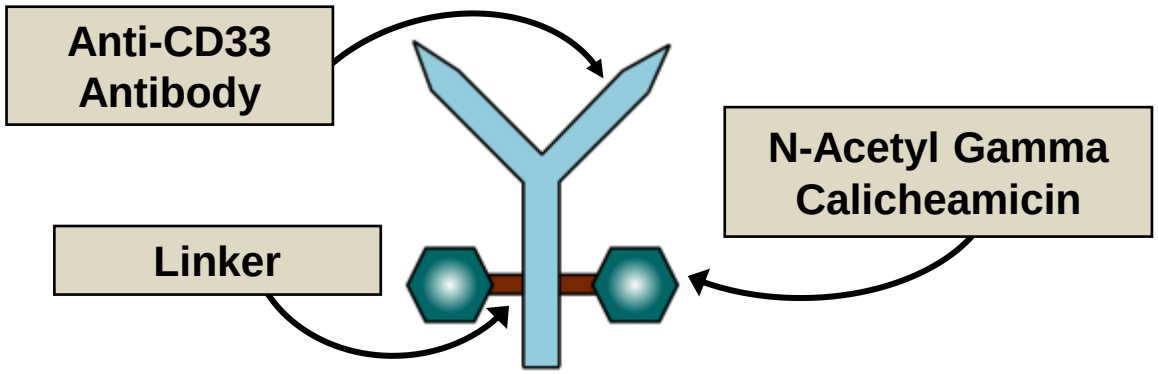
MYLOTARG® (gemtuzumab ozogamicin)

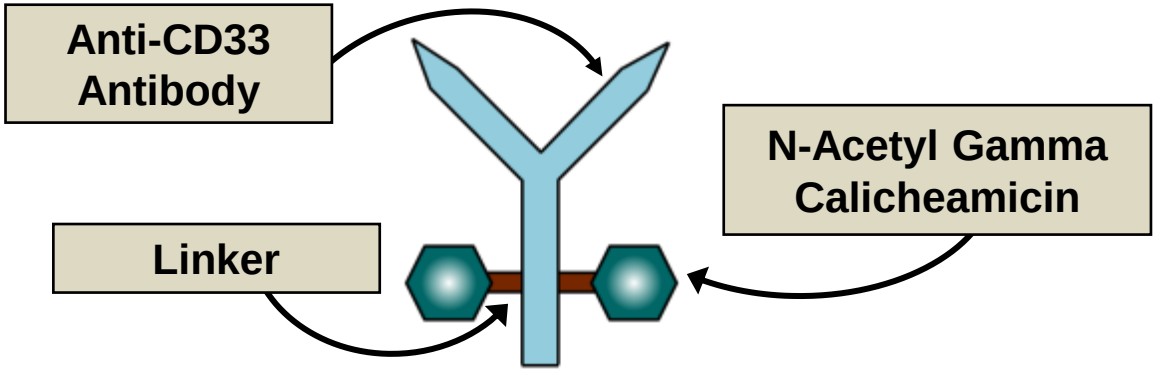
Mace L. Rothenberg, MD
Chief Development Officer, Oncology
Global Product Development
Wyeth Pharmaceuticals Inc, a subsidiary of Pfizer Inc

Oncologic Drugs Advisory Committee Meeting
July 11, 2017
FDA White Oak Campus
Silver Spring, MD

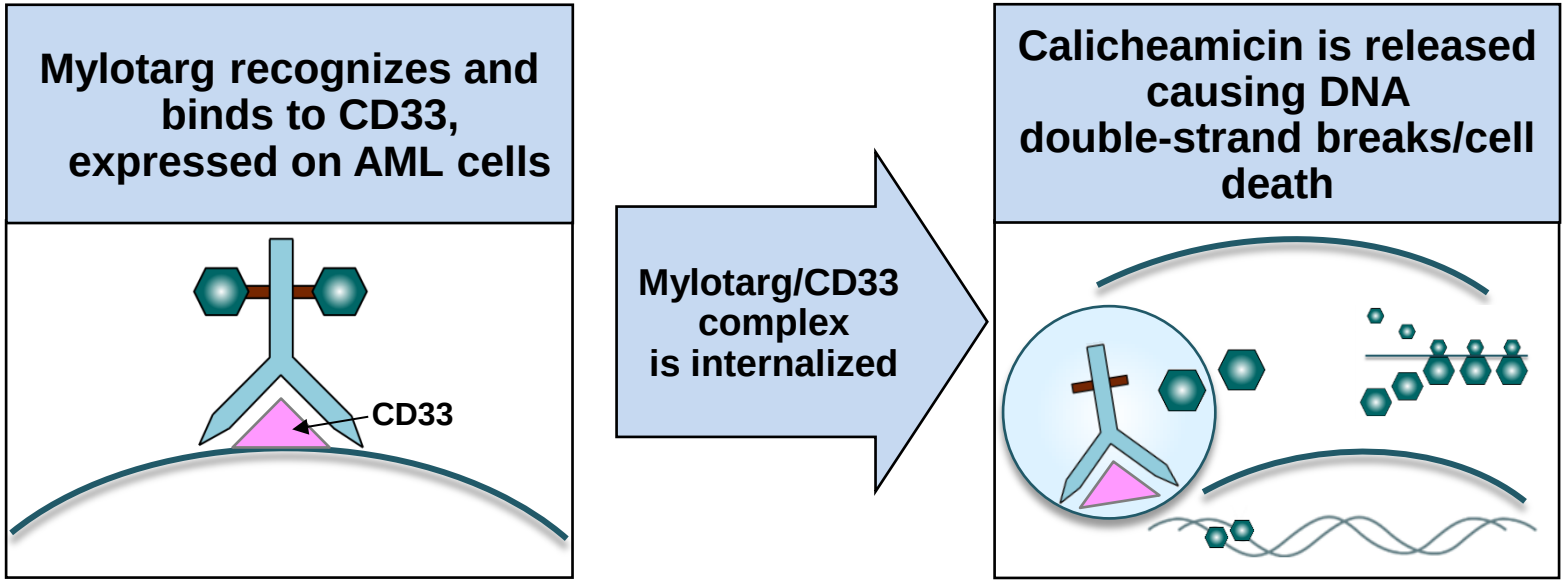
Mylotarg (gemtuzumab ozogamicin)



Mylotarg (gemtuzumab ozogamicin)



Mechanism of Action



AML=Acute Myeloid Leukemia; DNA=Deoxyribonucleic Acid

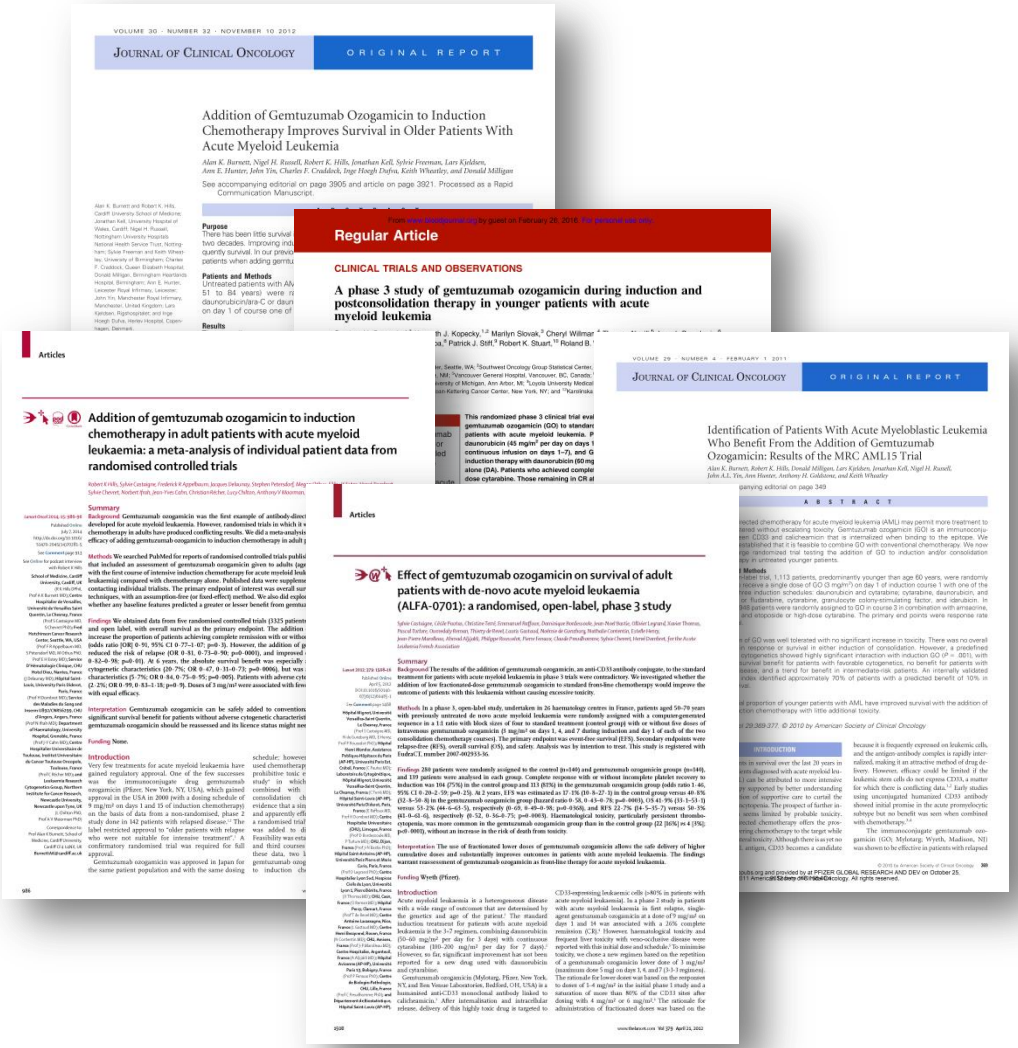
Mylotarg History

- Mylotarg was approved in the US under accelerated approval in May 2000 as monotherapy for patients with CD33+ Acute Myeloid Leukemia (AML) in 1st relapse who were ≥60 years old
- Confirmatory trial – SWOG S0106 failed to confirm the clinical benefit of Mylotarg
- Recognition of increased risk of veno-occlusive disease (VOD) in patients receiving Mylotarg in the post-marketing setting
- Pfizer voluntarily withdrew Mylotarg from the US market in 2010

SWOG=Southwest Oncology Group; US=United States

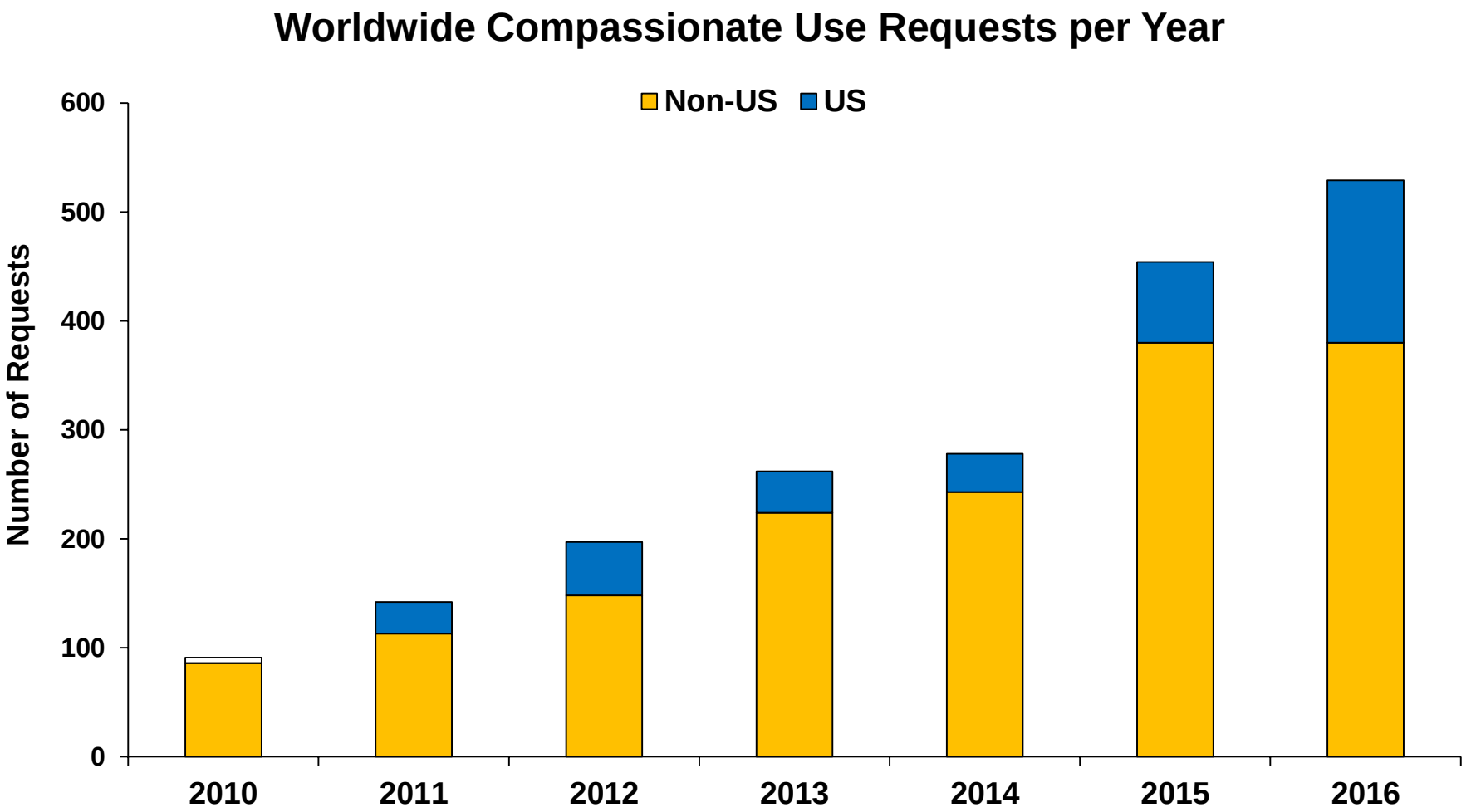
Favorable Clinical Trial Data that Emerged *After* 2010

- Positive data from multiple investigator-designed, cooperative group-run, randomized trials in first line AML
- Suggested significant benefit with Mylotarg when administered in lower total doses and/or a fractionated schedule in conjunction with standard of care chemotherapy



Burnett et al. *J Clin Oncol*. 2011;29(4):369-77.
Burnett et al. *J Clin Oncol*. 2012;30(32):3924-31.
Castaigne et al. *Lancet*. 2012;379(9825):1508-16.
Petersdorf et al. *Blood*. 2013;121(24):4854-60.
Hills et al. *Lancet Oncol*. 2014;15(9):986-96.

AML Community Requests for Mylotarg Continue to Increase



A Unique BLA Submission

A comprehensive clinical data package

- **ALFA-0701 (Pivotal Trial)**
- **Individual Patient Data (IPD) Meta-Analysis from 5 Cooperative Group Trials**
- **Pfizer-Sponsored Trials**

ALFA=Acute Leukemia French Association; BLA=Biologics License Application

Key Elements to this BLA Submission

- Benefit demonstrated across a broad population of AML patients
- IPD meta-analysis and ALFA-0701 are informative in estimating the beneficial effect of Mylotarg in terms of EFS and OS
- A lower dose, fractionated regimen of 3 mg/m^2 on Days 1, 4, and 7 is active and may be associated with an improved safety profile
- Better insight into the safety profile for Mylotarg with identification of factors associated with increased risk of VOD

EFS=Event-Free Survival; mg/m^2=milligrams per meter squared; OS=Overall Survival

Indication Being Sought

Mylotarg is indicated in combination with daunorubicin and cytarabine for the treatment of adult patients with previously untreated, de novo CD33-positive acute myeloid leukemia

Presentation Overview

Topic	Presenter
Introduction	**Mace Rothenberg, MD** Chief Development Officer for Oncology Pfizer Inc
AML Treatment Landscape	**Richard Stone, MD** Chief of Staff and Director of the Adult Acute Leukemia Program Dana-Farber Cancer Institute Harvard Medical School, Boston, MA
Mylotarg in Patients with Previously Untreated De Novo AML	**Iain Webb, MD** Hematologic Malignancies Global Clinical Lead Pfizer Inc
Mylotarg Safety Considerations	**Debbie Chirnomas, MD, MPH** Mylotarg Medical Monitor Pfizer Inc
Mylotarg Benefit/Risk: Clinical Perspective	**Jorge E. Cortes, MD** Deputy Chair in the Department of Leukemia University of Texas MD Anderson Cancer Center Houston, TX

Additional Experts

Expert	Expertise
Herve Dombret, MD, PhD Chair, ALFA Cooperative Group Head of Clinical Adult Hematology Unit Hospital Saint-Louis, Paris	**Clinical Consultant**
James W. Freston, MD, PhD Professor of Medicine Gastroenterology and Clinical Pharmacology University of Connecticut	**Medical Consultant**
Gary Koch, PhD Professor of Biostatistics University of North Carolina	**Statistical Consultant**

AML Overview and Therapeutic Landscape

Richard M. Stone, MD

Chief of Staff and
Director of the Adult Acute Leukemia Program

Dana-Farber Cancer Institute

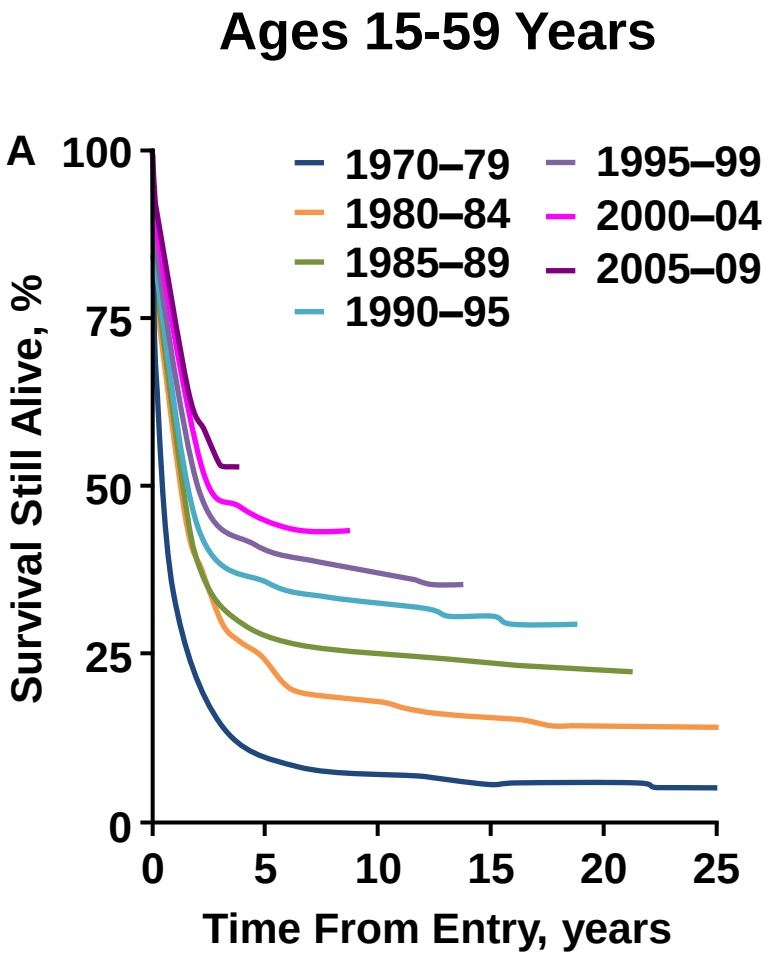
Harvard Medical School, Boston, MA

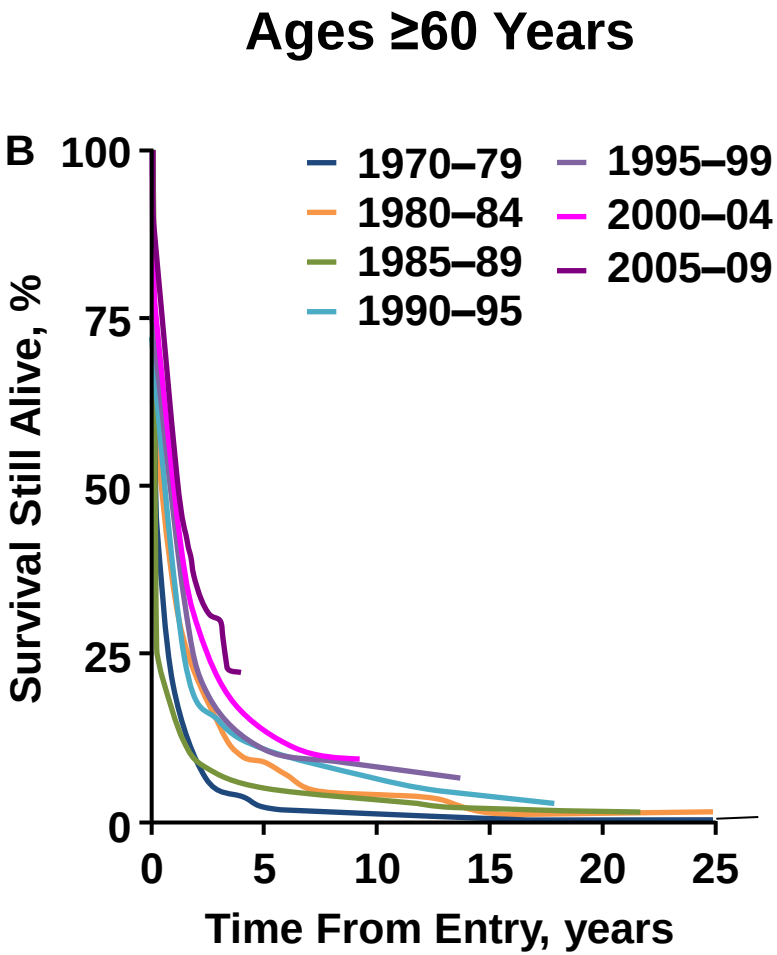
AML is a Deadly Disease with Limited Therapeutic Options

- AML represents a clinically and biologically heterogeneous group of malignancies[1]
  - Accumulation of abnormal myeloid blasts with limited ability to differentiate
- Bone marrow failure, leading to neutropenia and thrombocytopenia, is the main cause of death[1]
- In 2017, 21,380 new cases of AML and 10,590 deaths are expected in the United States[2]
  - Median age at diagnosis is 68 years
- Standard front-line AML treatment has not changed in over 40 years[3]
  - Requires prolonged hospitalization and associated with severe myelosuppression[4]
  - Minimal improvement in outcomes over time, primarily due to advancements in supportive care[5]

1. Estey E. *Am J Hematol*. 2016;91:824-846.
2. SEER Cancer Stat Facts: Acute Myeloid Leukemia. *National Cancer Institute. Bethesda, MD,* April 2017. Available at: http://seer.cancer.gov/statfacts/html/amyl.html. Accessed April 28, 2017.
3. Rowe JM. *Best Pract Res Clin Haematol*. 2013;26:241-244.
4. Walter RB, et al. *Clin Adv Hematol Oncol*. 2013;11:571-577.
5. DiNardo CD, Stone RM, Medeiros BC. *Am Soc Clin Oncol Educ Book*. 2017;37:495-503.

Overall Survival in AML By Age Group





Burnett A, Wetzler M, Löwenberg B. *J Clin Oncol.* 2011;29:487-94.

Initial Goal of AML Therapy: Achieve Complete Remission (CR)

CR Endpoints

CR

- Less than 5% blasts in normocellular marrow
- Complete hematologic recovery

CRp/i

- CRp defined as CR with incomplete platelet recovery[a]
- CRi defined as CR with incomplete hematologic recovery[b]
- Generally allows post-remission therapy, including HSCT

a. Platelets <100,000/µL
b. Absolute neutrophil count <1000/µL or platelets <100,000/µL
Cheson BD, et al. *J Clin Oncol.* 2003;21:4642-4649.
HSCT=Hematopoietic Stem Cell Transplant

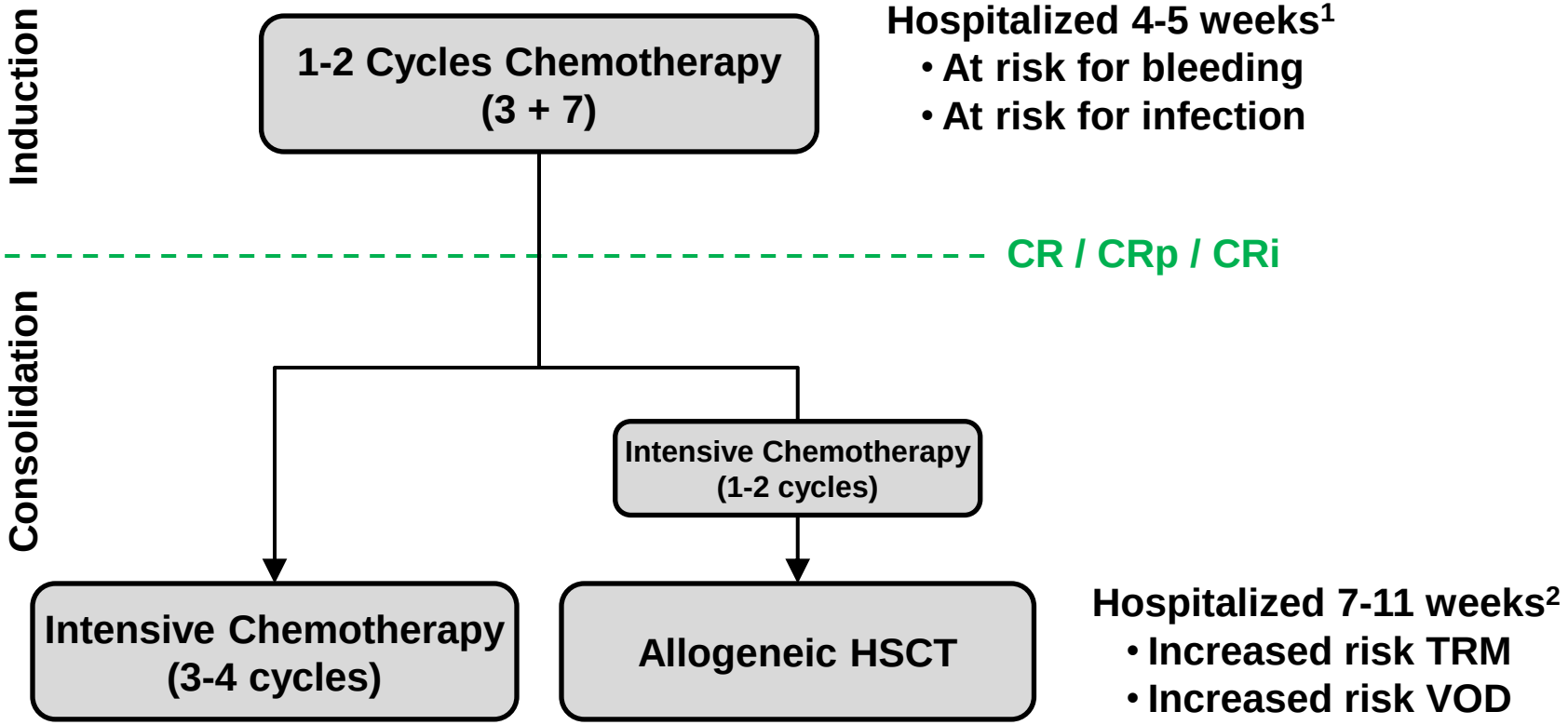
Best Chance at First Remission: Intensive Front-Line Induction Therapy

- Cytarabine-based regimens have remained the standard of care for over 40 years[1]
  - Most common regimen is “3 + 7” → anthracycline on days 1-3 combined with cytarabine on days 1-7
- Treatment considerations: age, performance status, comorbidities[2]
  - Lower intensity treatments recommended for patients ineligible for intensive induction therapy
- Majority of patients achieve CR with intensive front-line induction treatment[2]
  - Rate is higher in younger (<60 years) vs. older (≥60 years) patients

1. Rowe JM. *Best Pract Res Clin Haematol*. 2013;26:241-244.
2. Schlenk RF, Döhner H. *Hematology Am. Soc. Hematol. Educ. Program*. 2013;2013:324-330.

Current Intensive Front-Line Treatment in AML

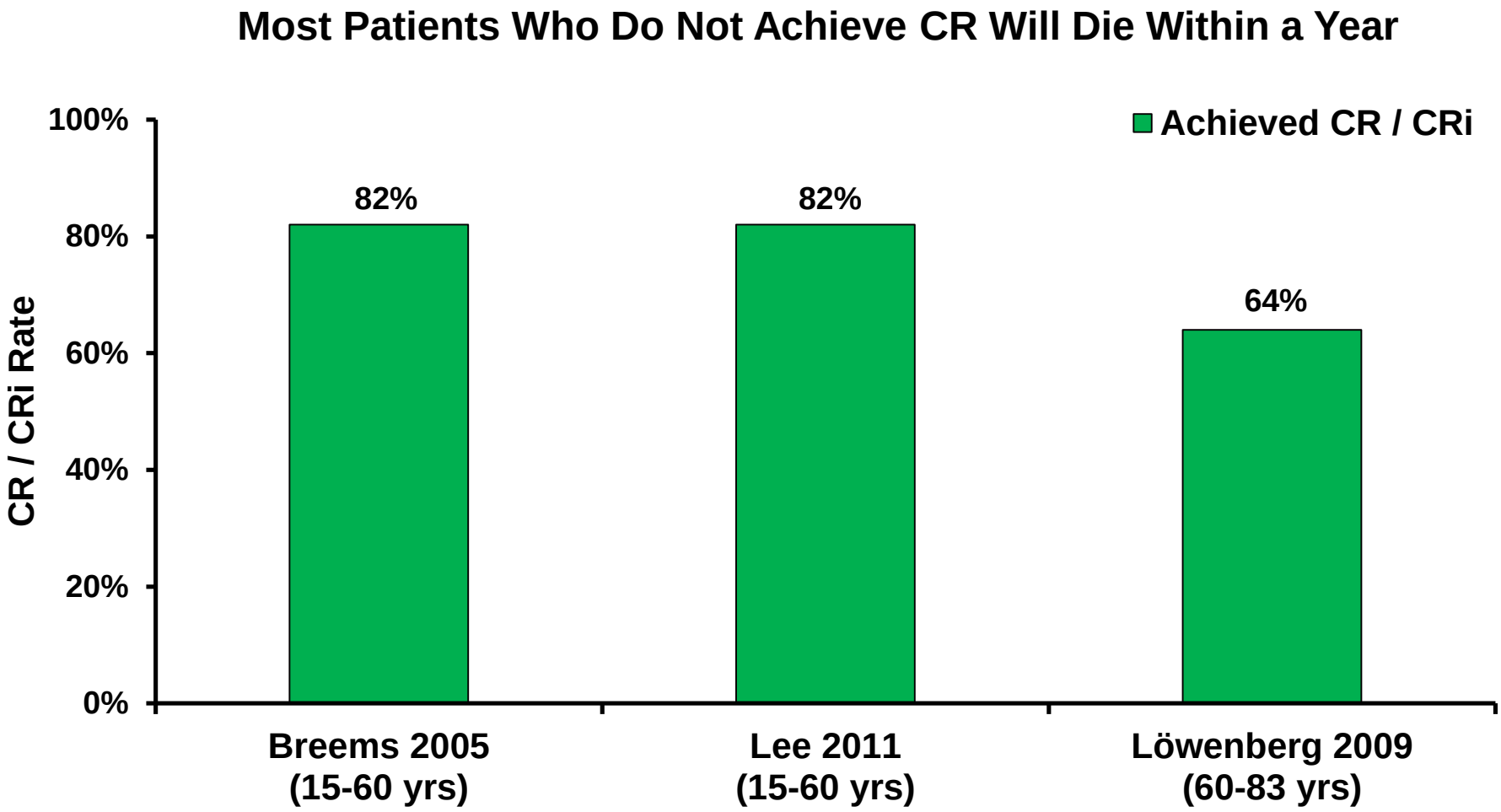
Patient presentation: symptoms associated with myelosuppression (i.e., fever and/or infections or bleeding)[1]



1. Walter RB, et al. *Clin Adv Hematol Oncol*. 2013;11:571-577.
2. Ballen KK, et al. *Biol Blood Marrow Transplant*. 2014;20:1819-1827.

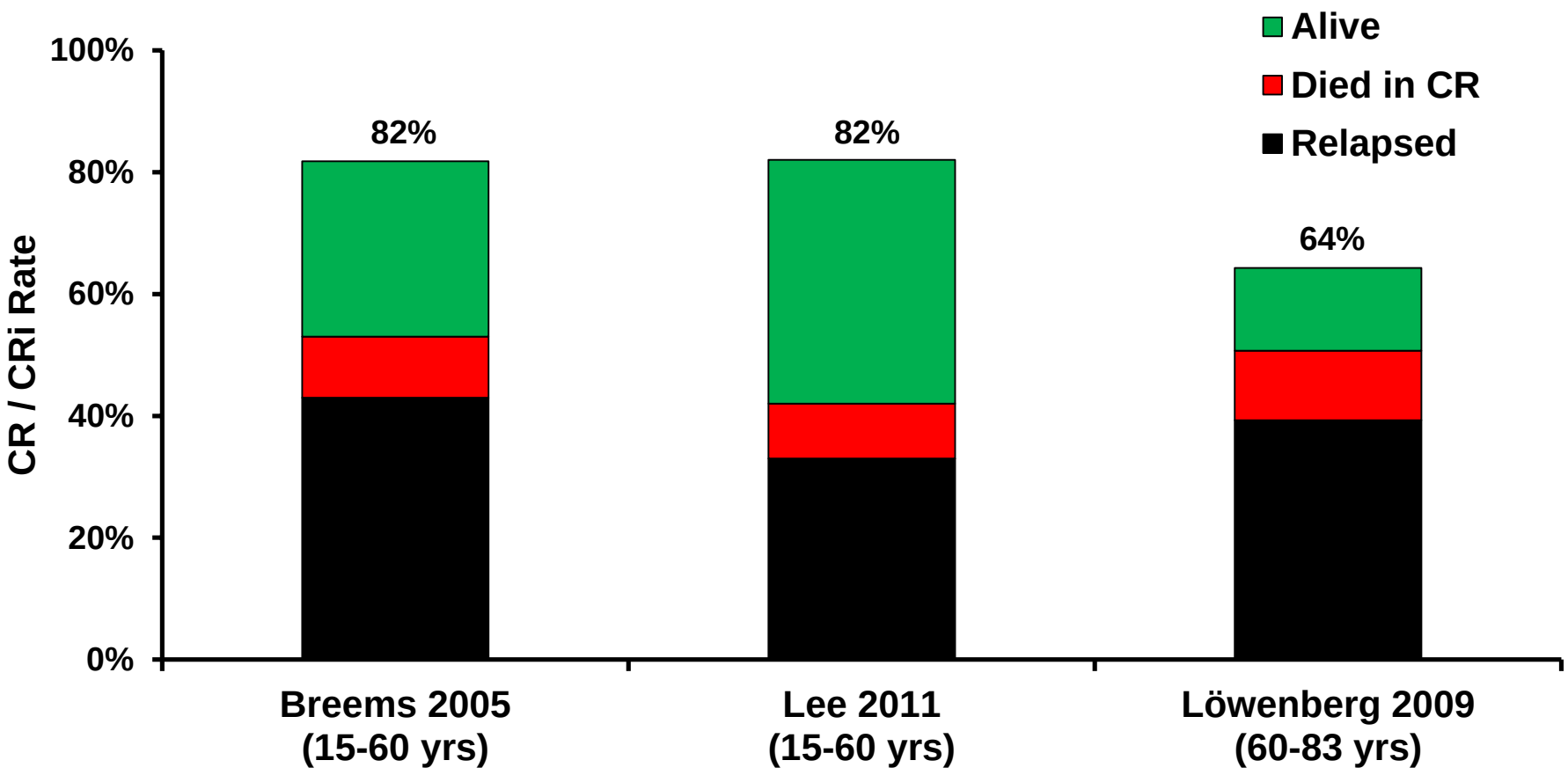
TRM=Treatment-Related Mortality

Challenge of Current AML Treatments: CR Rates Vary with Age



1. Breems DA, et al. *J Clin Oncol*. 2005;23:1969-1978.
2. Lee J-H, et al. *Blood*. 2011;118:3832-3841.
3. Löwenberg B, et al. *N Engl J Med*. 2009;361:1235-1248.

Challenge of Current AML Treatments:
Most of Patients Who Achieve CR / CRi Will Relapse or Die



1. Breems DA, et al. *J Clin Oncol*. 2005;23:1969-1978.
2. Lee J-H, et al. *Blood*. 2011;118:3832-3841.
3. Löwenberg B, et al. *N Engl J Med*. 2009;361:1235-1248.

Clinical Assessment of Response to Therapy

- Clinically relevant events in AML
  1. Death
  2. Failure to achieve remission or relapse, which are generally associated with bone marrow failure and increased risk for bleeding/infection

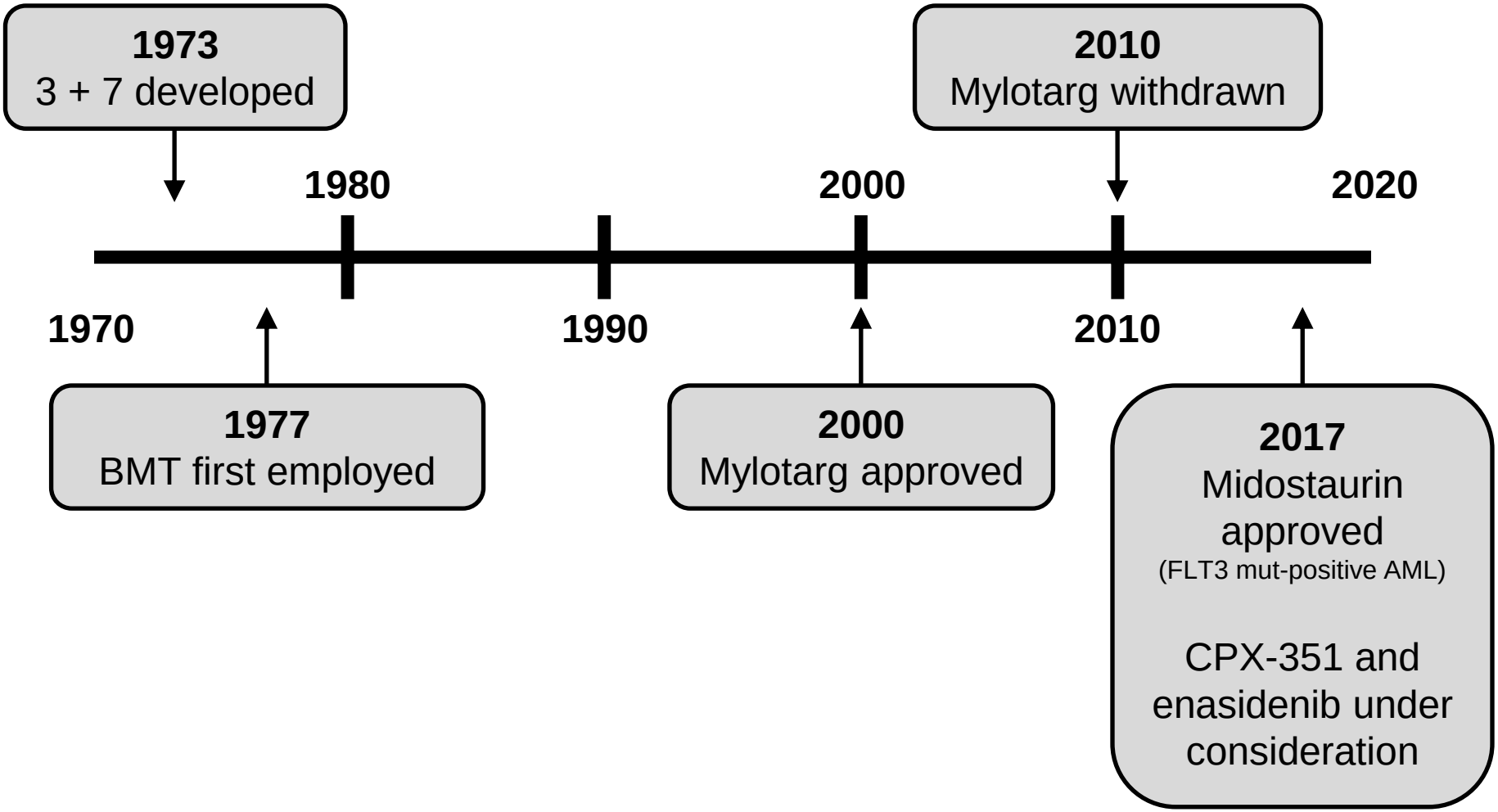
Endpoint	Definition
EFS Event-Free Survival	Time from date of randomization/diagnosis to the date of an event of induction failure, relapse, or death from any cause, whichever came first
DFS/RFS Disease-Free Survival Relapse-Free Survival	Time from response to relapse or death from any cause
OS Overall Survival	Time from randomization/diagnosis to death due to any cause

The Value of EFS as an Endpoint in AML

- Long duration (i.e., ≥12 months) of first remission increases likelihood of achieving a second remission after relapse[1-4]
- Moderate level of positive correlation with OS[5-8]
  - Confounded by salvage therapy (i.e., treatment(s) received after induction failure or relapse)
- Delay or avoid the burdens and toxicities associated with additional chemotherapy, hospitalizations, as well as transfusions[9]
- Delay the emotional distress that patients and their families experience when the disease relapses[10,11]

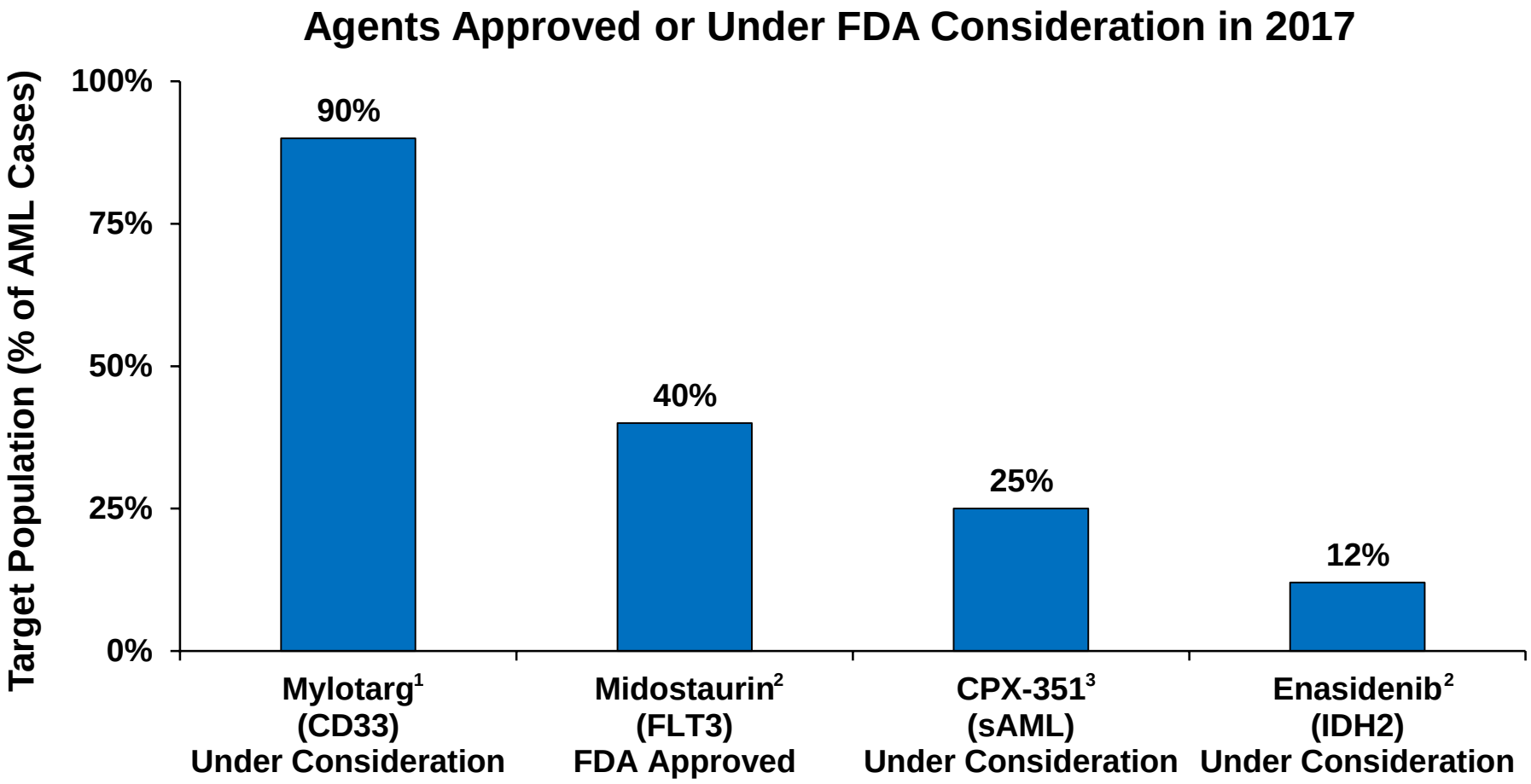
1. Keating MJ, et al. *J Clin Oncol*. 1989;7:1071-1080.
2. Angelov L, et al. *Leuk Lymphoma*. 1991;6:15-24.
3. Ravandi F, et al. *Lancet Oncol*. 2015; 16:1025-1036.
4. Sarkozy C, et al. *Am J Hematol*. 2013;88:758-764.
5. Othus M, et al. *Haematologica*. 2016;101:e284-286.
6. Buyse M, et al. *Haematologica*. 2011;96:1106-1112.
7. Luskin MR, et al. *Blood*. 2014;124:2599.
8. Schlenk RF, et al. *Blood*. 2015;126:3744.
9. Sekeres MA, et al. *Leukemia*. 2004;18:809-816.
10. Tomaszewski EL, et al. *Oncol Ther*. 2016;4:225-238.
11. Cheng MJ, et al. *J Palliat Med*. 2017 May 24. [Epub ahead of print]

AML Treatment Landscape Timeline



BMT=Bone Marrow Transplant; FLT-3=FMS-Like Tyrosine Kinase-3

Proportion of Patients with AML in Which Newer Agents Are Applicable



1. Ehninger A, et al. *Blood Cancer J.* 2014;4:e218.
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Acute Myeloid Leukemia. Version 3. 2017. June 6, 2017. NCCN.org
3. Østgård L et al. *Eur J Haematol*. 2010;85(3):217-226.

sAML=secondary AML; IDH2=Isocitrate Dehydrogenase 2

Summary

- AML is a serious, rapidly progressing, life-threatening hematologic malignancy with a front-line standard of care that has changed little in over 40 years
- More agents are needed to achieve deeper and, therefore, longer remissions
  - Longer remissions are reflected in event-free survival, which is beneficial to patients
- Mylotarg combined with standard induction chemotherapy provides clinical benefit, including prolonged event-free and overall survival

Mylotarg in Patients with Previously Untreated De Novo AML

Iain Webb, MD

Global Clinical Lead, Hematologic Malignancies

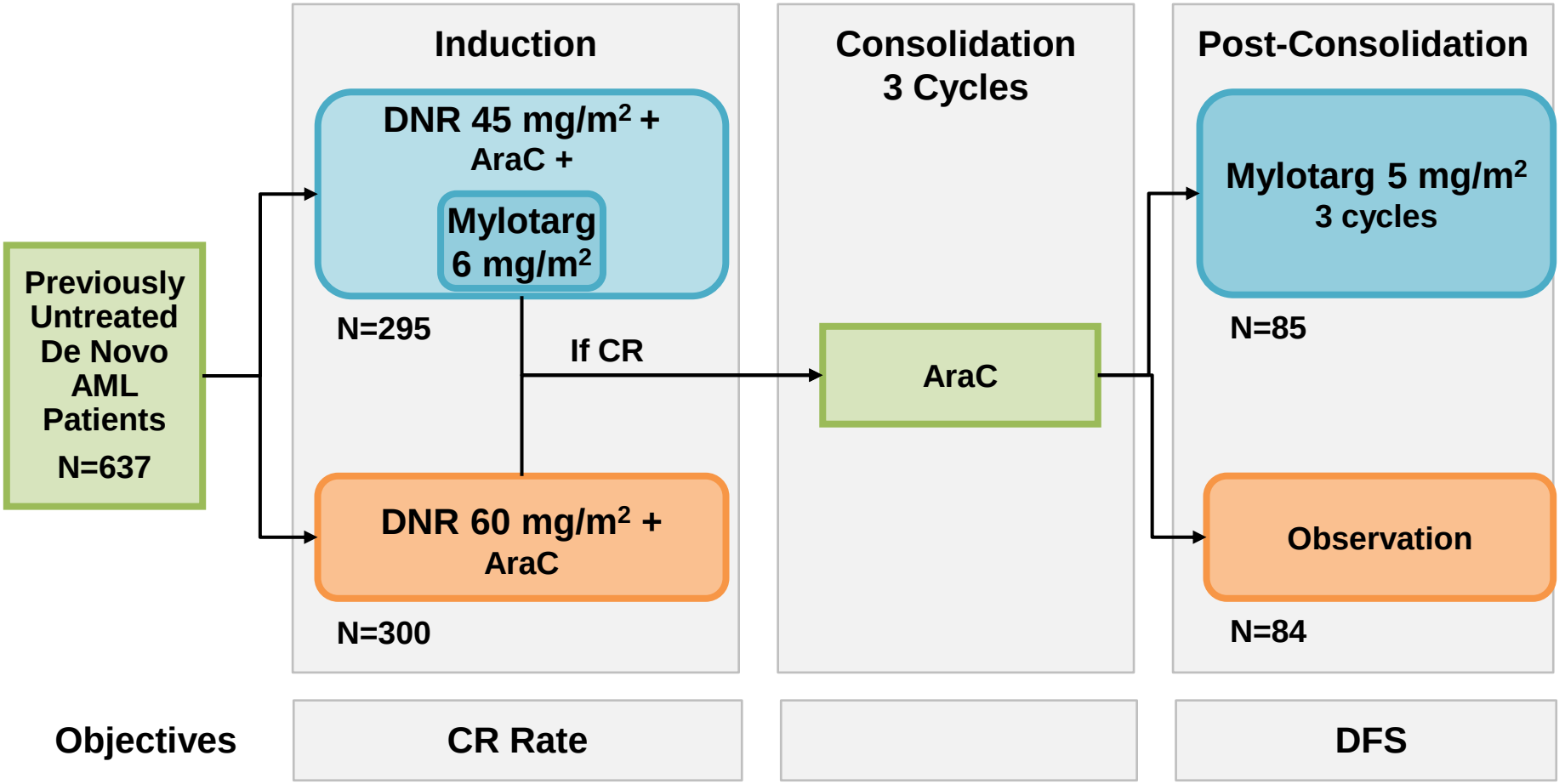
Pfizer Inc

Mylotarg Clinical Trial Experience in Previously Untreated AML, N=3331

Protocol	Patient Population	Mylotarg Dosing	N
Primary Study for BLA Submission			
ALFA-0701	50-70 years	3 mg/m^2 x 3	271
Supportive Studies			
SWOG S0106	18-60 years	6 mg/m^2 x 1	595
MRC AML15	<60 years	3 mg/m^2 x 1	1099
NCRI AML16	>60 years	3 mg/m^2 x 1	1115
GOELAMS AML2006IR	18-60 years	6 mg/m^2 x 1	251

GOELAMS=Groupe Ouest Est d'Etude des Leucemies aigues et Autres Maladies du Sang; MRC=Medical Research Council; NCRI=National Cancer Research Institute

SWOG S0106: Study Design



Petersdorf SH, et al. *Blood*. 2013;121(24):4854-4860.
AraC=Cytarabine; DNR=Daunorubicin; g/m²/12h=grams per square meter per 12 hours

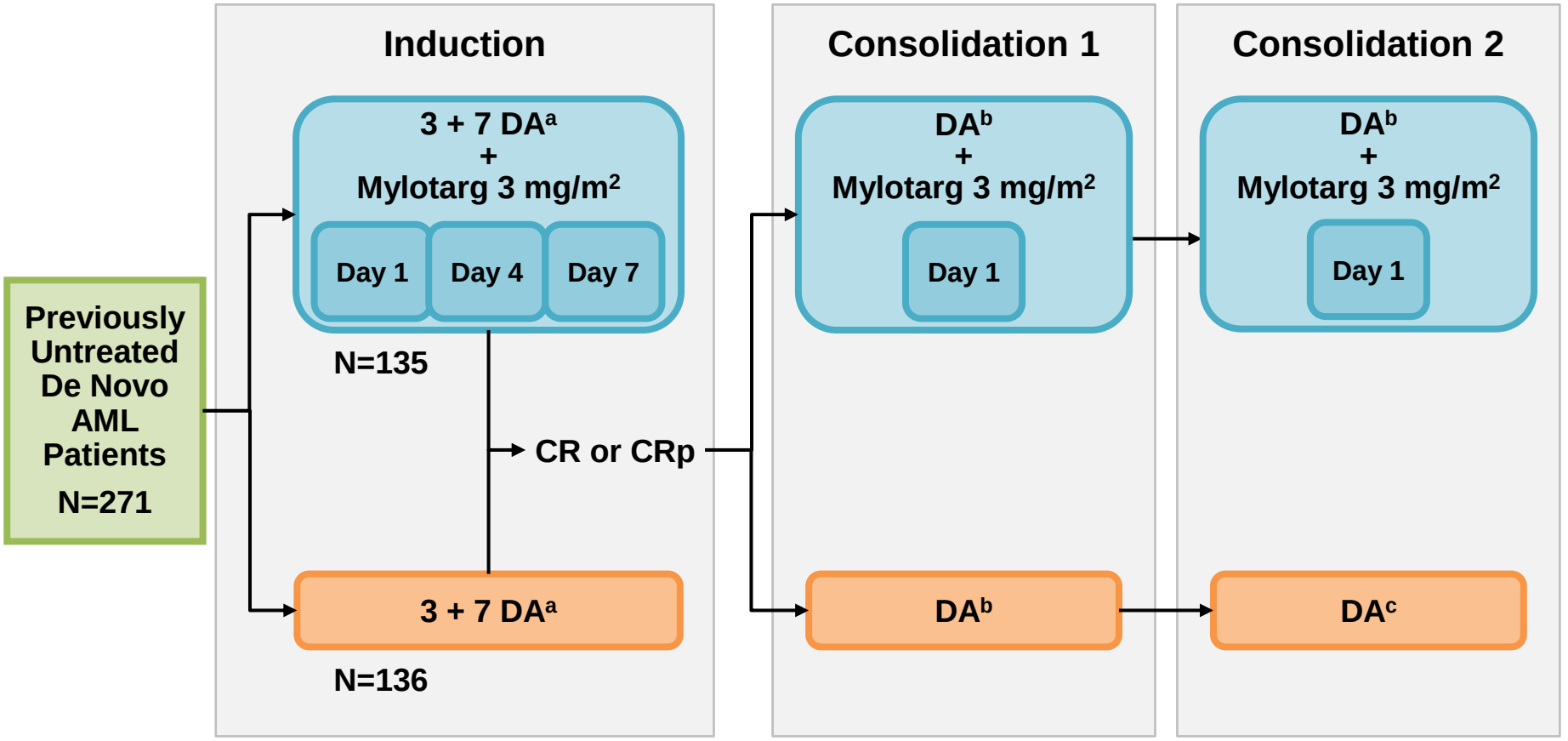
SWOG S0106: Interim Analysis August 2009

	Mylotarg	Control	p-value
Complete Remission Rate, %	69	70	0.59
Median DFS, months	14	NR	-
Hazard Ratio (95% CI)	1.48 (0.99, 2.22)		0.97
Induction deaths	5.5	1.4	0.0062

- Conclusion
  - SWOG DSMC recommended early closure of both the induction and post-consolidation randomization

CI=Confidence Interval; DSMC=Data and Safety Monitoring Committee; NR=Not Reached

ALFA-0701 (MF3): Phase 3 Study Design

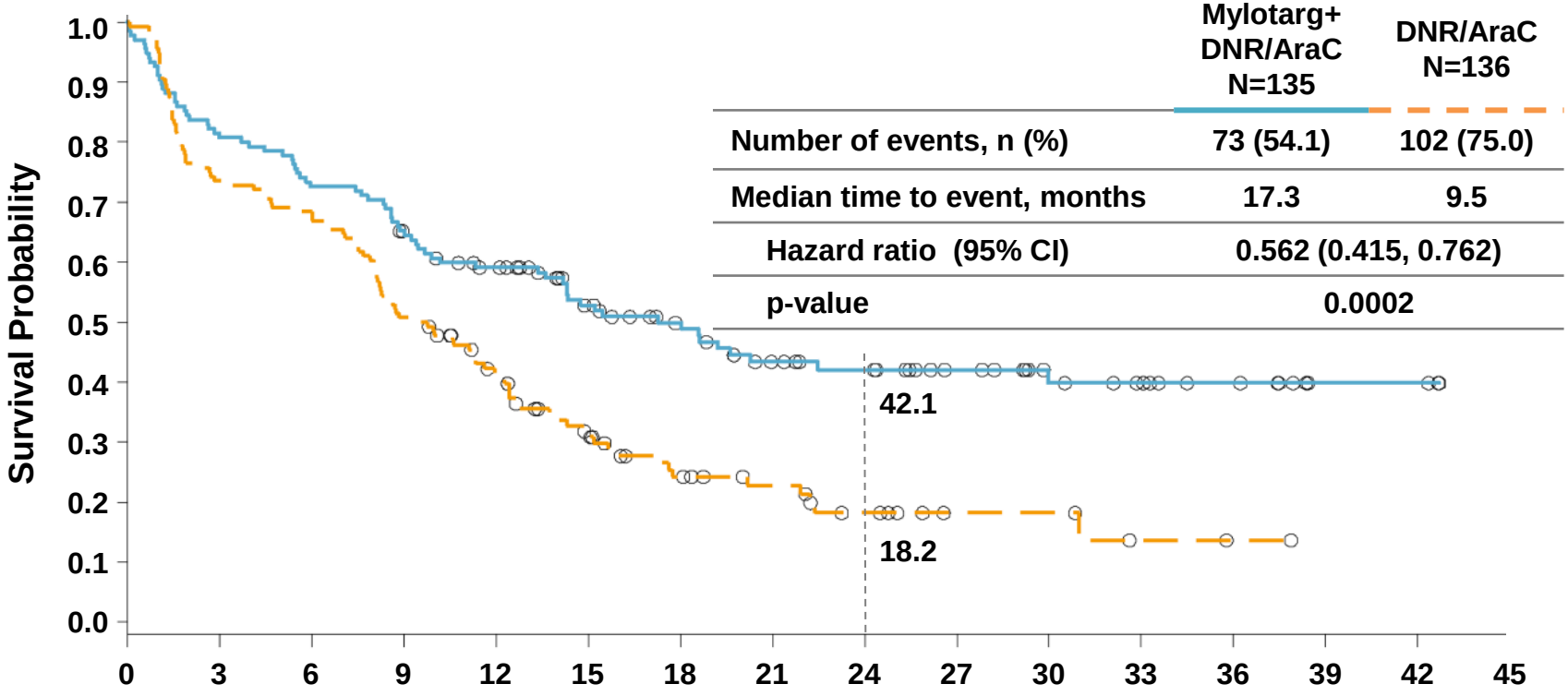


a. 3+7 DA=Daunorubicin 60 mg/m^2 Days 1 to 3 + Cytarabine 200 mg/m^2 Days 1 to 7
b. Daunorubicin 60 mg/m^2 Day 1 + Cytarabine 1 g/m^2/12h Days 1 to 4
c. Daunorubicin 60 mg/m^2 Day 1 and 2 + Cytarabine 1 g/m^2/12h Days 1 to 4
DA=Daunorubicin+Cytarabine; MF3=MyloFrance 3

ALFA-0701:
Patient Baseline Characteristics

Baseline Parameter		Mylotarg+DNR/AraC N=135	DNR/AraC N=136
Age, median (range)	Years	62.0 (50-70)	61.0 (50-70)
Gender, n (%)	Male	74 (54.8)	60 (44.1)
	Female	61 (45.2)	76 (55.9)
CD33 positivity, n (%)	N	100	94
	<30%	17 (12.6)	20 (14.7)
	≥30%	83 (61.5)	74 (54.4)
	<70%	37 (27.4)	31 (22.8)
	≥70%	63 (46.7)	63 (46.3)
Cytogenetics, n (%)	Favorable	3 (2.2)	6 (4.4)
	Intermediate	91 (67.4)	89 (65.4)
	Adverse	27 (20.0)	30 (22.1)
	Unknown	14 (10.4)	11 (8.1)

ALFA-0701:
Event-Free Survival – Primary Analysis

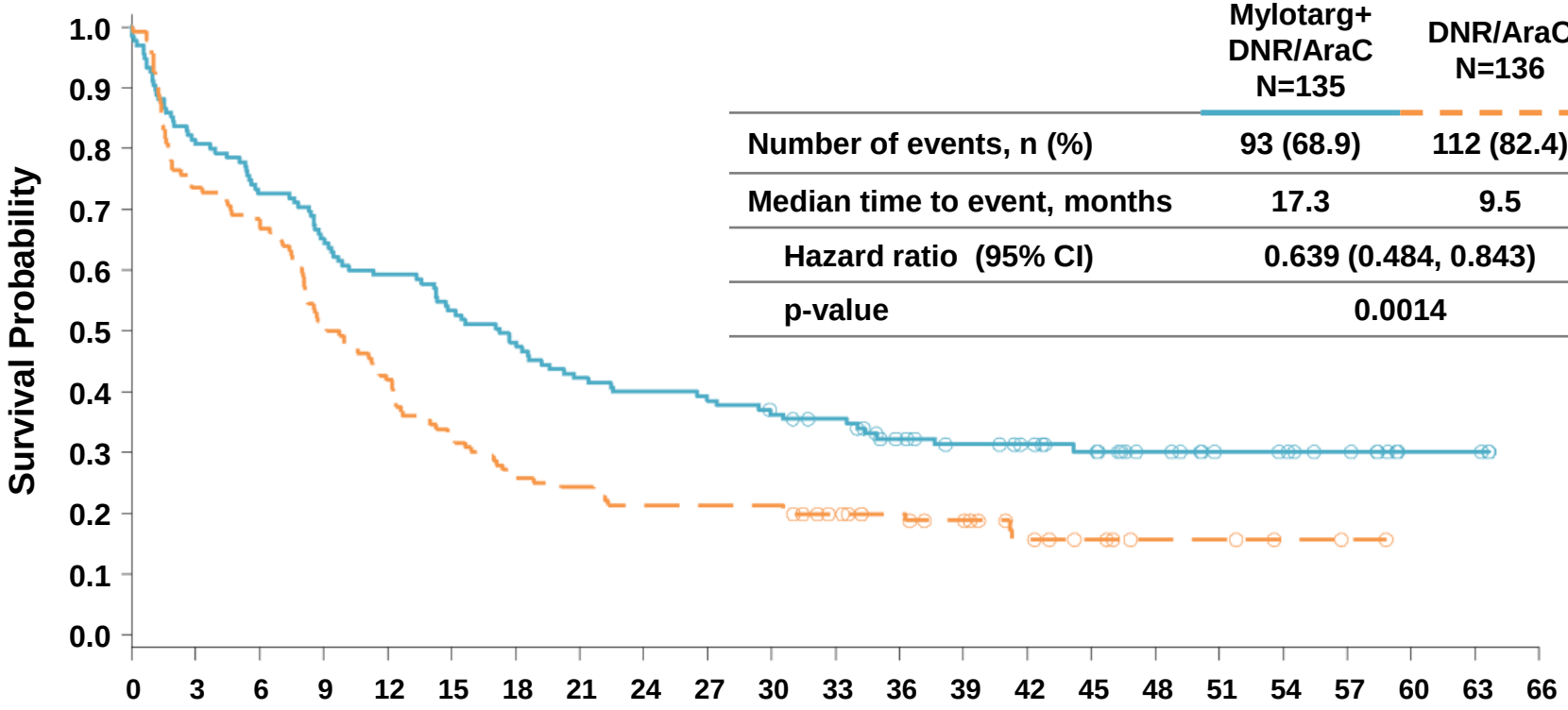


	Mylotarg+ DNR/AraC N=135	DNR/AraC N=136
Number of events, n (%)	73 (54.1)	102 (75.0)
Median time to event, months	17.3	9.5
Hazard ratio (95% CI)	0.562 (0.415, 0.762)	
p-value	0.0002	

Number at Risk																
Mylotarg+ DNR/AraC	135	109	98	86	74	57	47	36	32	25	18	15	10	3	3	0
DNR/AraC	136	100	93	69	51	32	21	16	10	5	5	2	1	0		

mITT population; Data cutoff date: August 1, 2011
mITT=modified Intention-To-Treat

ALFA-0701:
Event-Free Survival – Longer Follow-Up



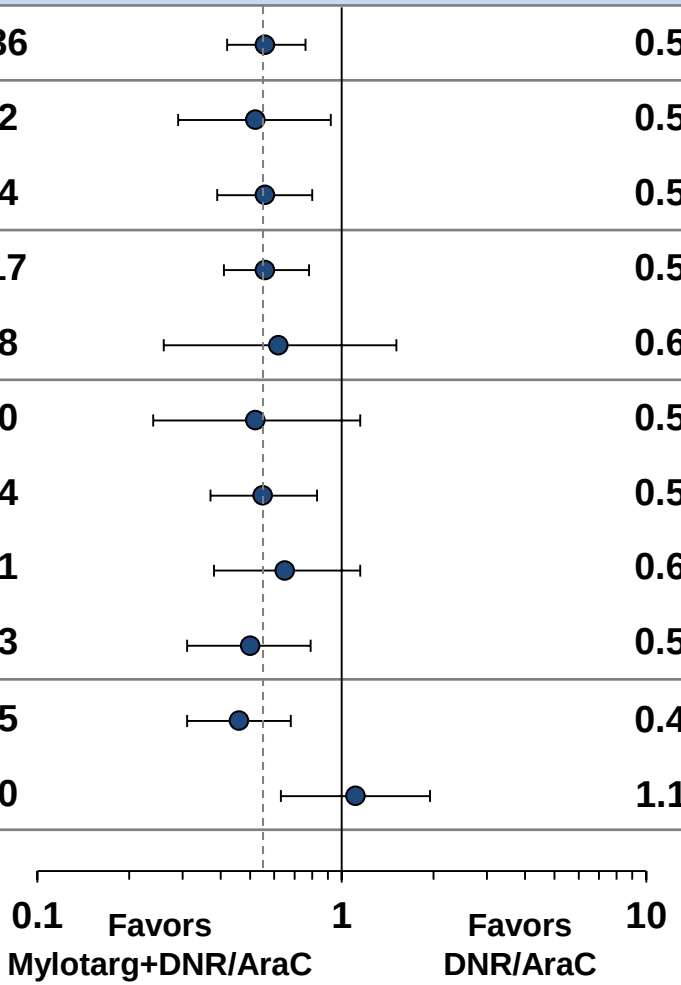
	Mylotarg+ DNR/AraC N=135	DNR/AraC N=136
Number of events, n (%)	93 (68.9)	112 (82.4)
Median time to event, months	17.3	9.5
Hazard ratio (95% CI)	0.639 (0.484, 0.843)	
p-value	0.0014	

Number at Risk																							
Mylotarg+ DNR/AraC	135	109	98	88	80	72	65	57	54	53	48	45	36	32	29	25	19	14	13	10	3	3	0
DNR/AraC	136	100	93	69	57	44	35	33	29	29	29	23	19	16	10	7	4	4	2	1	0		

mITT population; Data cutoff date: April 30, 2013

ALFA-0701:
Event-Free Survival – Subgroup Analysis

Subgroup		n Mylotarg+ DNR/AraC	n DNR/AraC	Hazard Ratio (95% CI)
Overall		135	136	0.56 (0.42, 0.76)
Age	<60	38	52	0.52 (0.29, 0.92)
	≥60	97	84	0.56 (0.39, 0.80)
ECOG PS	0,1	121	117	0.56 (0.41, 0.78)
	≥2	14	18	0.62 (0.26, 1.51)
CD33 Positivity	<30%	17	20	0.52 (0.24, 1.15)
	≥30%	83	74	0.55 (0.37, 0.83)
	<70%	37	31	0.65 (0.38, 1.15)
	≥70%	63	63	0.50 (0.31, 0.79)
Cytogenetics	Favorable/ Intermediate	94	95	0.46 (0.31, 0.68)
	Adverse	27	30	1.11 (0.63, 1.95)

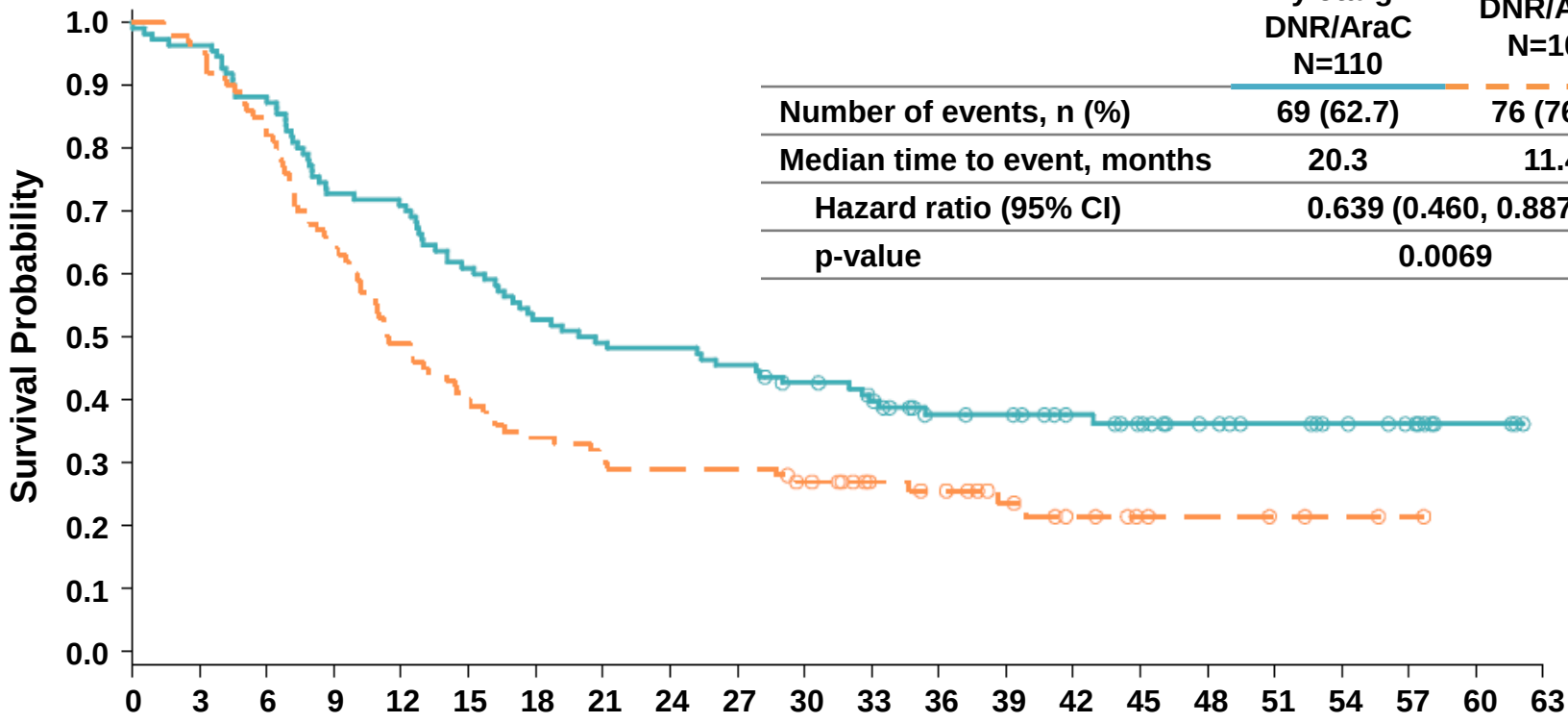


mITT population; Data cutoff date: August 1, 2011
ECOG PS=Eastern Cooperative Oncology Group Performance Status

ALFA-0701: Overall Response

Response Rate	Mylotarg+DNR/AraC N=135 n (%)	DNR/AraC N=136 n (%)	p-value
Overall Response, CR+CRp	110 (81.5)	100 (73.5)	0.1457
(95% CI)	(73.9, 87.6)	(65.3, 80.7)	
By Type of Response			
CR	95 (70.4)	95 (69.9)	
CRp	15 (11.1)	5 (3.7)	
Patients Receiving 2nd Induction Course	19 (14.1)	34 (25.0)	

ALFA-0701:
Relapse-Free Survival – Longer Follow-Up

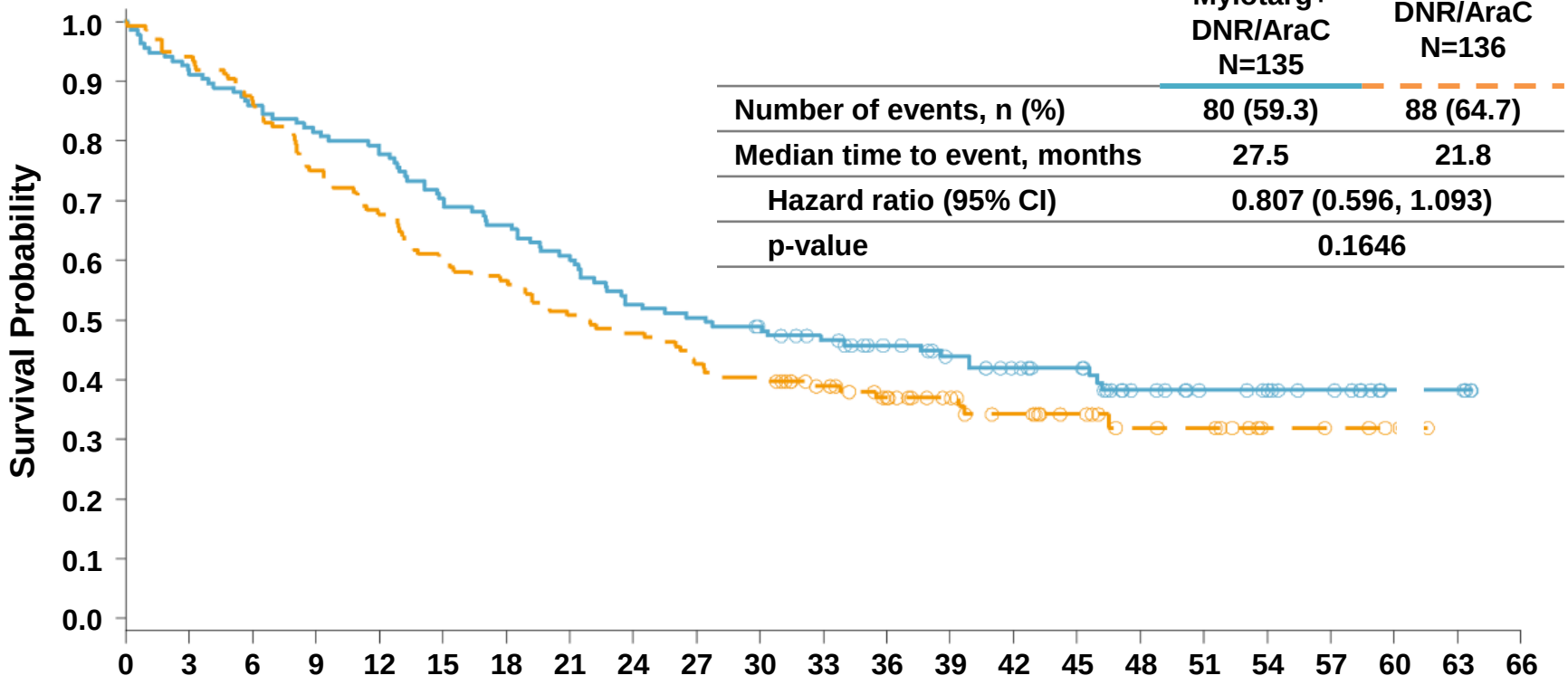


	Mylotarg+ DNR/AraC N=110	DNR/AraC N=100
Number of events, n (%)	69 (62.7)	76 (76.0)
Median time to event, months	20.3	11.4
Hazard ratio (95% CI)	0.639 (0.460, 0.887)	
p-value	0.0069	

Number at Risk																					
Mylotarg+ DNR/AraC	110	106	97	80	78	67	58	54	53	50	45	40	32	31	26	22	17	14	11	8	3	0
DNR/AraC	100	96	83	65	49	40	34	30	29	29	25	19	17	12	8	5	4	3	2	1	0	

mITT population; Data cutoff date: April 30, 2013

ALFA-0701: Overall Survival



	Mylotarg+ DNR/AraC N=135	DNR/AraC N=136
Number of events, n (%)	80 (59.3)	88 (64.7)
Median time to event, months	27.5	21.8
Hazard ratio (95% CI)	0.807 (0.596, 1.093)	
p-value	0.1646	

Number at Risk																							
Mylotarg+ DNR/AraC	135	124	116	110	105	95	89	82	71	68	64	58	51	45	39	36	25	20	18	13	5	4	0
DNR/AraC	136	128	118	102	92	81	77	69	65	58	55	46	36	29	23	18	13	12	6	5	3	0	

mITT population; Data cutoff date: April 30, 2013

Individual Patient Data Meta-Analysis, N=3331

Protocol	Patient Population	Mylotarg Dosing	N
Primary Study for BLA Submission			
ALFA-0701	50-70 years	3 mg/m^2 x 3	271
Supportive Studies			
SWOG S0106	18-60 years	6 mg/m^2 x 1	595
MRC AML15	<60 years	3 mg/m^2 x 1	1099
NCRI AML16	>60 years	3 mg/m^2 x 1	1115
GOELAMS AML2006IR	18-60 years	6 mg/m^2 x 1	251

IPD Meta-Analysis: Endpoints

- Primary Endpoint
  - Overall Survival
- Secondary Endpoints
  - Event-Free Survival
  - Relapse-Free Survival
  - Response Rate
  - Safety

IPD Meta-Analysis: Patient Baseline Characteristics

Baseline Parameter		Mylotarg N=1663 n (%)	No Mylotarg N=1668 n (%)
Age	≥60 years	732 (44.0)	727 (43.6)
Type of AML	De Novo	1464 (88.0)	1469 (88.1)
MRC Cytogenetic Risk Group[a]	Favorable	122 (7.3)	126 (7.6)
	Intermediate	912 (54.8)	915 (54.9)
	Adverse	297 (17.9)	283 (17.0)
Chemotherapy	ADE/DA	1256 (75.5)	1264 (75.8)
	FLAG-Ida	235 (14.1)	234 (14.0)
	DClo	172 (10.3)	170 (10.2)
CD33 Positivity[a]	≥30%	669 (40.2)	648 (38.8)
	≥70%	463 (27.8)	461 (27.6)

a. Based on all patients, including patients with missing data

ADE=Cytarabine, Daunorubicin, and Etoposide; DClo=Daunorubicin+Clofarabine; FLAG-Ida=Fludarabine, Cytarabine, G-CSF and Idarubicin

IPD Meta-Analysis: Overall Efficacy Results

Median Time to, Months	Mylotarg N=1663	No Mylotarg N=1668	Peto Odds Ratio (95% CI)	p-value
Overall Survival	23.6	21.5	0.91 (0.84, 0.99)	0.02

IPD Meta-Analysis: Overall Efficacy Results

Median Time to, Months	Mylotarg N=1663	No Mylotarg N=1668	Peto Odds Ratio (95% CI)	p-value
Overall Survival	23.6	21.5	0.91 (0.84, 0.99)	0.02
Event-Free Survival	9.6	7.6	0.85 (0.78, 0.93)	0.0002
Relapse-Free Survival	18.1	14.5	0.84 (0.77, 0.93)	0.0004

Mylotarg in Patients with Previously Untreated De Novo AML

- Mylotarg in lower fractionated doses added to standard chemotherapy provides
  - Statistically significant and clinically meaningful improvement in EFS and RFS in both ALFA-0701 and the IPD meta-analysis
  - Clinically meaningful improvement in OS in ALFA-0701 confirmed by the IPD meta-analysis, where it was statistically significant

Mylotarg Safety

Debbie Chirnomas, MD, MPH

Mylotarg Medical Monitor

Pfizer Inc

Outline

- Dosing rationale
- Safety profile of Mylotarg in combination with chemotherapy
  - ALFA-0701
  - Individual Patient Data Meta-Analysis
- Topics of special interest
  - Hemorrhage
  - Thrombocytopenia
  - Early death
  - Veno-occlusive disease

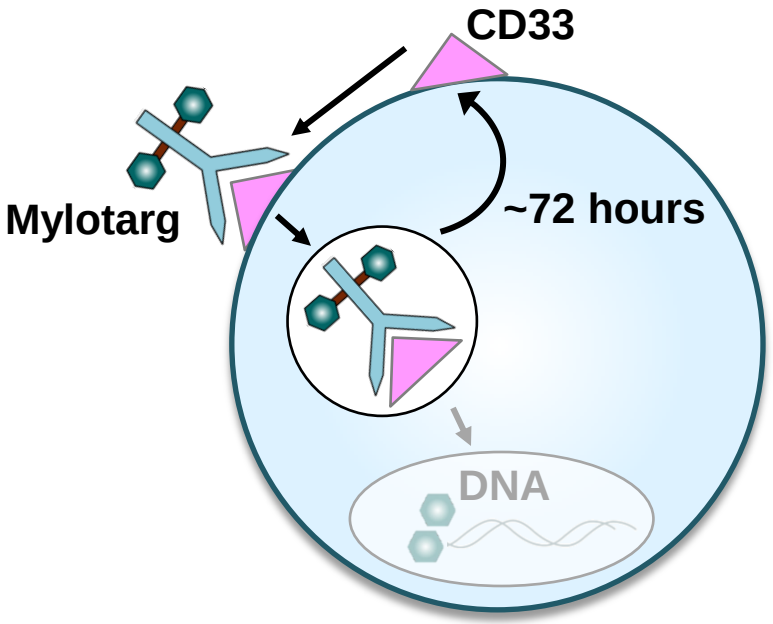
Lower Fractionated Dosing Rationale: Biology

- Initial monotherapy dose:
  9 mg/m^2 x 2
  - VOD
  - Myelosuppression

Van der Velden, et al, *Leukemia*. 2004; 18:983-988.

Lower Fractionated Dosing Rationale: Biology

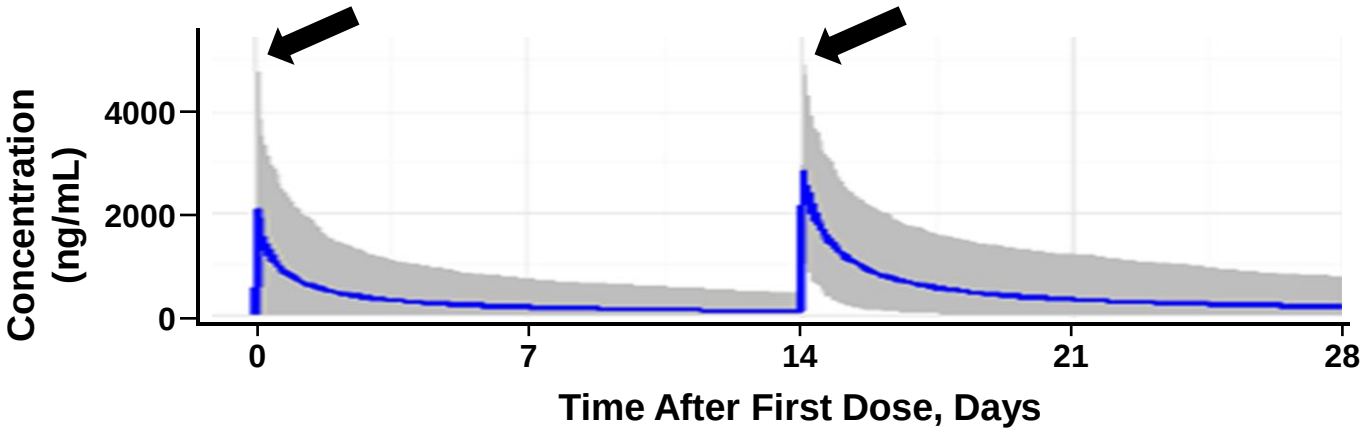
- Initial monotherapy dose:
  9 mg/m^2 x 2
  - VOD
  - Myelosuppression
- Lower fractionated dose:
  3 mg/m^2 every 3 days
  - >90% saturation of CD33
  - Recycling of CD33 in ~72 hours



Van der Velden, et al, *Leukemia*. 2004; 18:983-988.

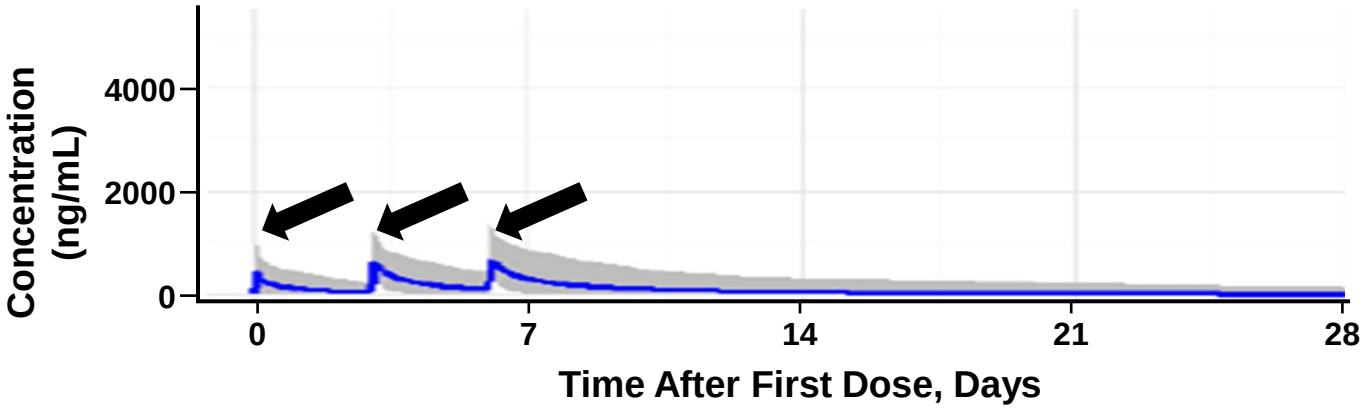
Low Dose Fractionated Regimen: Biology

Original Regimen 9 mg/m^2 x 2



- C_{max} is associated with increased toxicity

New Regimen 3 mg/m^2 x 3

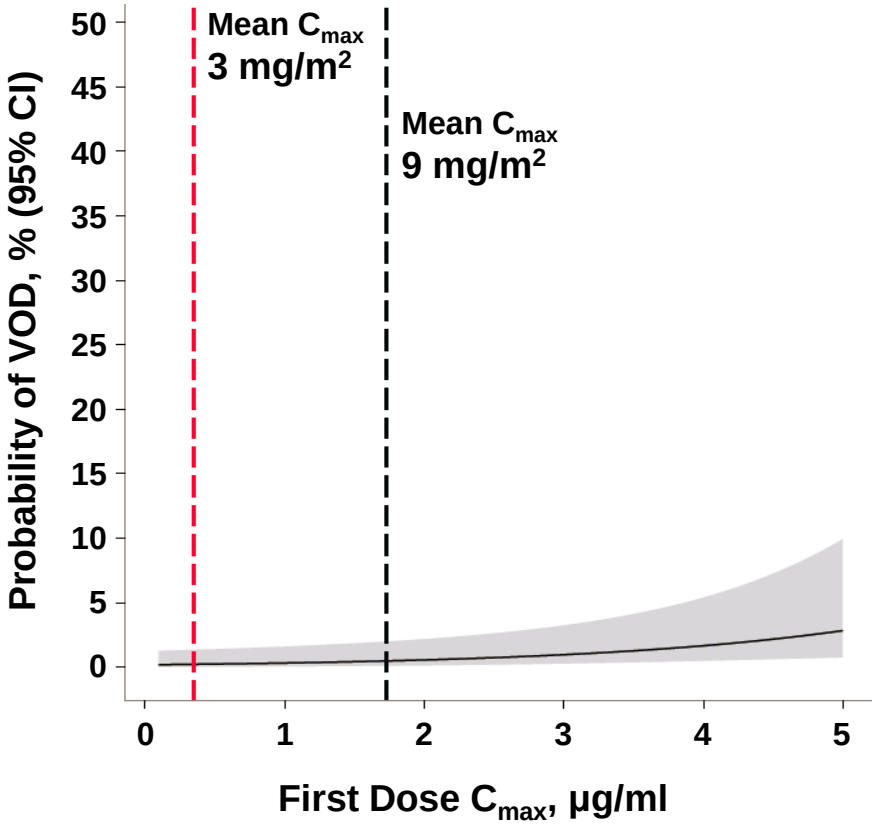


- C_{max} reduced by **~75%**

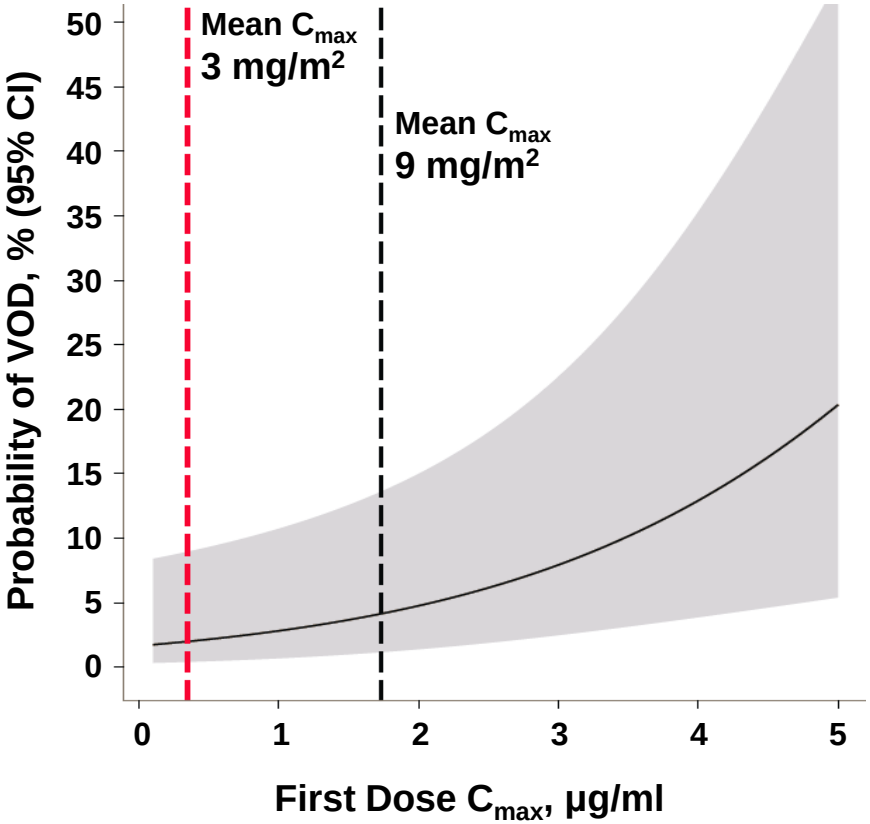
Cmax=maximum Concentration; ng/mL=nanogram/milliliter

Dosing Regimen-Based VOD Risk

No Prior Stem Cell Transplant



Prior Stem Cell Transplant



µg/ml=microgram per milliliter

Outline

- Dosing rationale
- Safety profile of Mylotarg in combination with chemotherapy
  - ALFA-0701
  - Individual Patient Data Meta-Analysis
- Topics of special interest
  - Hemorrhage
  - Thrombocytopenia
  - Early death
  - Veno-occlusive disease

ALFA-0701:
Prospective Collection of Predefined AEs >5%

Prospective Predefined Grade 3-4	Mylotarg+DNR/AraC N=131 n (%)			DNR/AraC N=137 n (%)		
	Grade 3	Grade 4	Total Grade 3/4	Grade 3	Grade 4	Total Grade 3/4
Nausea, vomiting, diarrhea	18 (13.7)	4 (3.1)	22 (16.8)	14 (10.2)	0	14 (10.2)
Mucosal toxicity	16 (12.2)	5 (3.8)	21 (16.0)	8 (5.8)	1 (0.7)	9 (6.6)
Pain	16 (12.2)	3 (2.3)	19 (14.5)	5 (3.6)	0	5 (3.6)
Pulmonary toxicity	10 (7.6)	7 (5.3)	17 (13.0)	14 (10.2)	5 (3.6)	19 (13.9)
Skin toxicity	14 (10.7)	0	14 (10.7)	23 (16.8)	0	23 (16.8)
Central neurological toxicity	7 (5.3)	1 (0.8)	8 (6.1)	2 (1.5)	2 (1.5)	4 (2.9)

Grade 1 and 2 were not collected
AE=Adverse Event

ALFA-0701:
Prospective Collection of Predefined AEs >5%

Prospective Predefined Grade 3-4	Mylotarg+DNR/AraC N=131 n (%)			DNR/AraC N=137 n (%)		
	Grade 3	Grade 4	Total Grade 3/4	Grade 3	Grade 4	Total Grade 3/4
Nausea, vomiting, diarrhea	18 (13.7)	4 (3.1)	22 (16.8)	14 (10.2)	0	14 (10.2)
Mucosal toxicity	16 (12.2)	5 (3.8)	21 (16.0)	8 (5.8)	1 (0.7)	9 (6.6)
Pain	16 (12.2)	3 (2.3)	19 (14.5)	5 (3.6)	0	5 (3.6)
Pulmonary toxicity	10 (7.6)	7 (5.3)	17 (13.0)	14 (10.2)	5 (3.6)	19 (13.9)
Skin toxicity	14 (10.7)	0	14 (10.7)	23 (16.8)	0	23 (16.8)
Central neurological toxicity	7 (5.3)	1 (0.8)	8 (6.1)	2 (1.5)	2 (1.5)	4 (2.9)

Grade 1 and 2 were not collected
AE=Adverse Event

ALFA-0701:
Retrospective Collection of Selected AEs

Retrospective Selected AEs	Mylotarg+DNR/AraC N=131 n (%)			DNR/AraC N=137 n (%)		
	Grade ≥3	Grade 5	All Grades	Grade ≥3	Grade 5	All Grades
Infection[a]	102 (77.9)	2 (1.5)	102 (77.9)	106 (77.4)	4 (2.9)	106 (77.4)

	Grade 3	Grade 4	Grade 5	All Grades	Grade 3	Grade 4	Grade 5	All Grades
Hemorrhage	23 (17.6)	4 (3.1)	3 (2.3)	118 (90.1)	12 (8.8)	0	1 (0.7)	107 (78.1)
VOD	2 (1.5)	1 (0.8)	2 (1.5)	6 (4.6)	1 (0.7)	1 (0.7)	0	2 (1.5)

a. Only severe (≥3 Grade) Infection were collected

IPD Meta-Analysis: Selected Adverse Events Grade 3-4

	Mylotarg N=1663		No Mylotarg N=1668	
	Evaluable Patients	n (%)	Evaluable Patients	n (%)
Persistent thrombocytopenia[a]	1075	433 (40.3)	1070	393 (36.7)
Infection	1537	486 (31.6)	1543	505 (32.7)
Persistent neutropenia[a]	965	228 (23.6)	960	247 (25.7)
ALT	1528	185 (12.1)	1533	155 (10.1)
AST	1135	136 (12.0)	1114	88 (7.9)
Bilirubin	1630	144 (8.8)	1630	137 (8.4)
Hemorrhage	1663	114 (6.9)	1668	67 (4.0)
VOD	1661	18 (1.1)	1667	2 (0.1)

a. Persistent is defined as ≥45 days after start of study treatment
ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase

Outline

- Dosing rationale
- Safety profile of Mylotarg in combination with chemotherapy
  - ALFA-0701
  - Individual Patient Data Meta-Analysis
- Topics of special interest
  - Hemorrhage
  - Thrombocytopenia
  - Early death
  - Veno-occlusive disease

Hemorrhage: ALFA-0701

Retrospective Selected AEs	Mylotarg+DNR/AraC N=131 n (%)			DNR/AraC N=137 n (%)		
	Grade ≥3	Grade 5	All Grades	Grade ≥3	Grade 5	All Grades
Infection[a]	102 (77.9)	2 (1.5)	102 (77.9)	106 (77.4)	4 (2.9)	106 (77.4)

	Grade 3	Grade 4	Grade 5	All Grades	Grade 3	Grade 4	Grade 5	All Grades
Hemorrhage	23 (17.6)	4 (3.1)	3 (2.3)	118 (90.1)	12 (8.8)	0	1 (0.7)	107 (78.1)
VOD	2 (1.5)	1 (0.8)	2 (1.5)	6 (4.6)	1 (0.7)	1 (0.7)	0	2 (1.5)

a. Only severe (≥3 Grade) Infection were collected

Study ALFA-0701
Time to Platelet Recovery

	Mylotarg+DNR/AraC			DNR/AraC		
	Induction N=131	Conso. 1 N=97	Conso. 2 N=82	Induction N=137	Conso. 1 N=97	Conso. 2 N=89
Patients Recovered to 50,000/µL, %	83.2	94.8	97.6	86.1	88.7	95.5
Median Time to Recovery, days	34.0	32.0	36.5	29.0	27.0	30.0

Conso=Consolidation

Early Deaths in ALFA-0701

	30-Day Mortality[a]		60-Day Mortality[a]	
	Mylotarg+ DNR/AraC N=131 n (%)	DNR/AraC N=137 n (%)	Mylotarg+ DNR/AraC N=131 n (%)	DNR/AraC N=137 n (%)
Number of Deaths	**5 (3.8)**	**3 (2.2)**	**7 (5.3)**	**7 (5.1)**

Based on As Treated Population

a. Time to death during induction is calculated from date of First Dose regardless of remission status

Early Deaths in ALFA-0701 vs. SWOG S0106

	ALFA-0701 30-Day Mortality		SWOG S0106 Fatal Induction Toxicity	
	Mylotarg+ DNR/AraC N=131 n (%)	DNR/AraC N=137 n (%)	Mylotarg+ DNR/AraC N=292 n (%)	DNR/AraC N=294 n (%)
Number of Deaths	5 (3.8)	3 (2.2)	16 (5.5)	4 (1.4)

VOD/SOS: Clinical Features

- Veno-occlusive disease (sinusoidal obstructive syndrome) is characterized by
  - Rapid weight gain
  - Ascites
  - Painful hepatomegaly
  - Jaundice
- HSCT is the main risk factor for VOD
  - VOD incidence is 10-15% after allogeneic HSCT
  - Variable severity from a mild, reversible disease to a severe syndrome associated with multi-organ failure and death

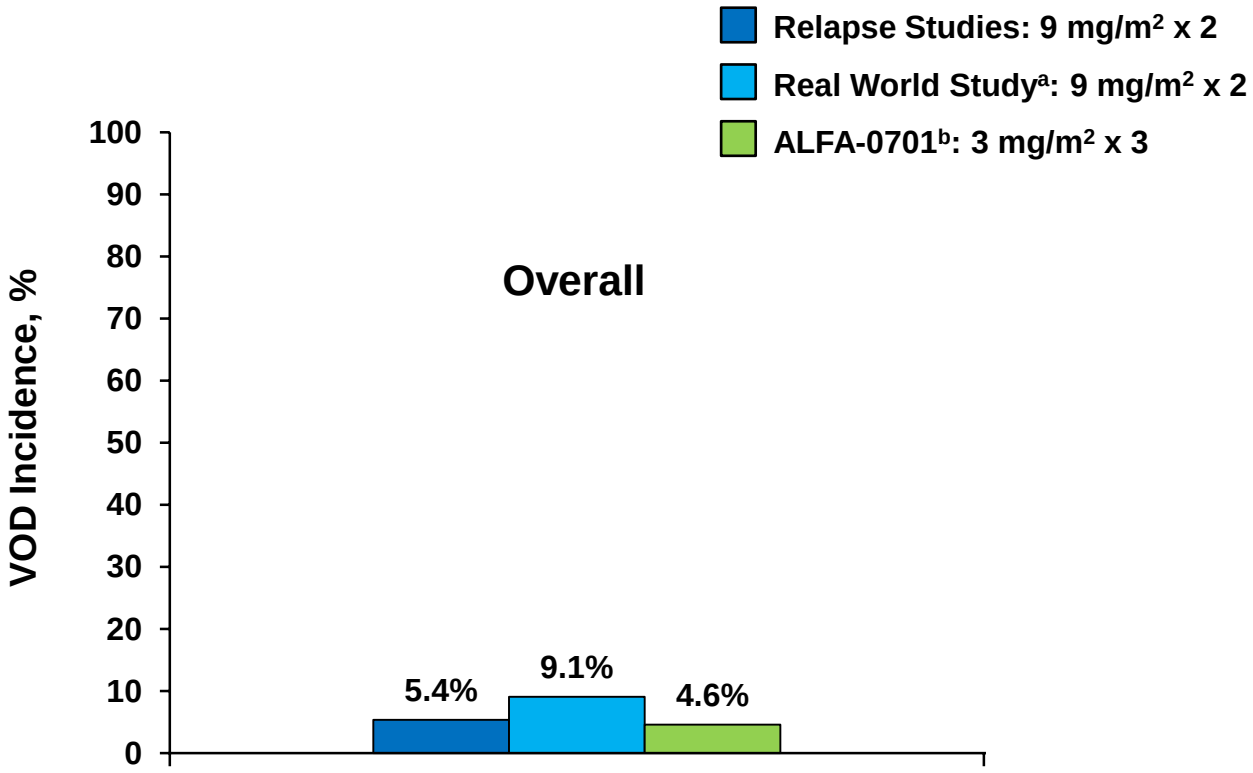
Mohty et al. *Bone Marrow Transplant*. 2015;50:781-789.
SOS=Sinusoidal Obstructive Syndrome

Identification of VOD Risk Factors in AML Patients[a] with Mylotarg Monotherapy, N=669

	Odds Ratio (95% CI)
Moderate/severe hepatic impairment	8.66 (1.88, 39.86)
HSCT after Mylotarg	2.91 (1.50, 5.64)
HSCT prior to study entry	2.63 (1.45, 4.77)

a. >21 years old
Hepatic impairment defined (Per NCI):
Moderate Impairment: 1.5 x ULN < Total Bilirubin ≤ 3 x ULN and AST any level
Severe Impairment: 3 x ULN < Total Bilirubin and AST any level

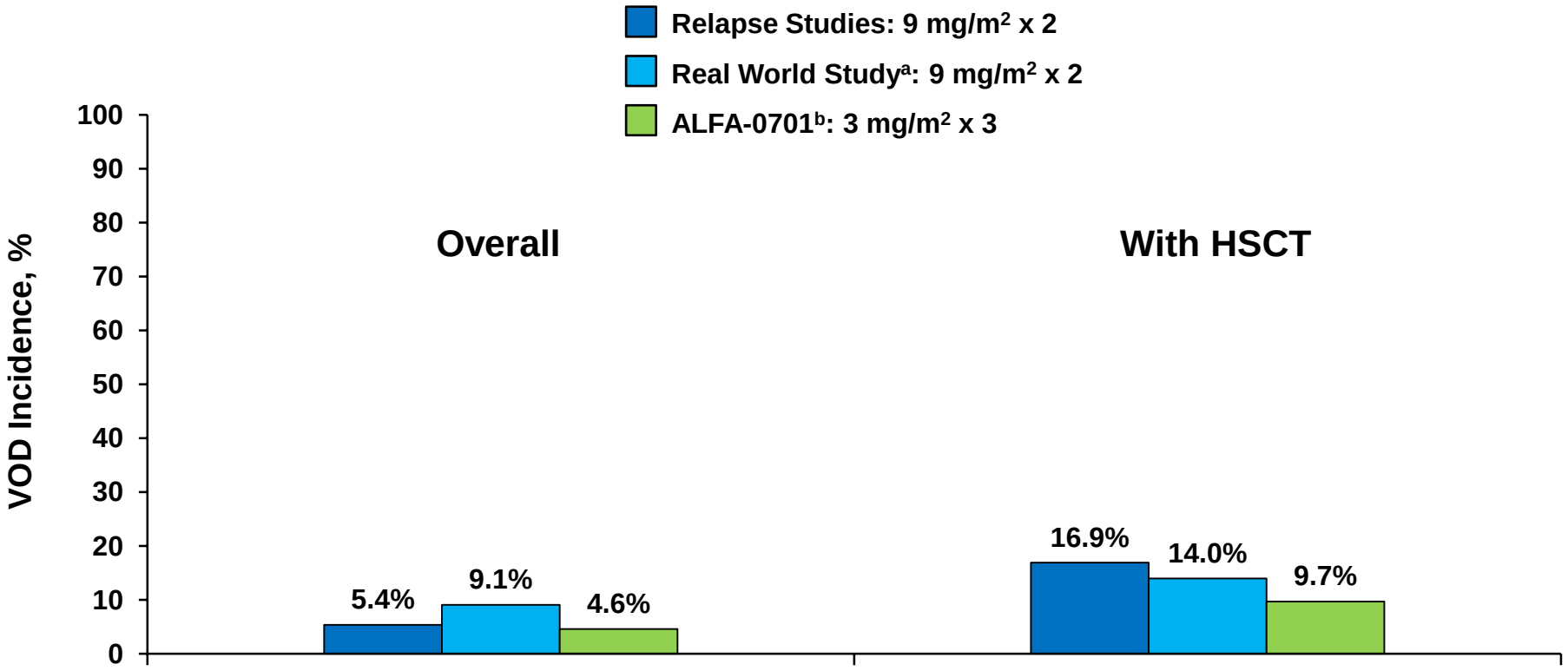
VOD: Incidence and Fatality Rate by Dosing Regimen



N	**277**	**482**	**131**
% Fatal	**3.6**	**1.9**	**1.5**

a. Study 0903X-100847
b. 2 patients in ALFA-0701 Control arm with VOD received Mylotarg in the post-treatment period prior to VOD

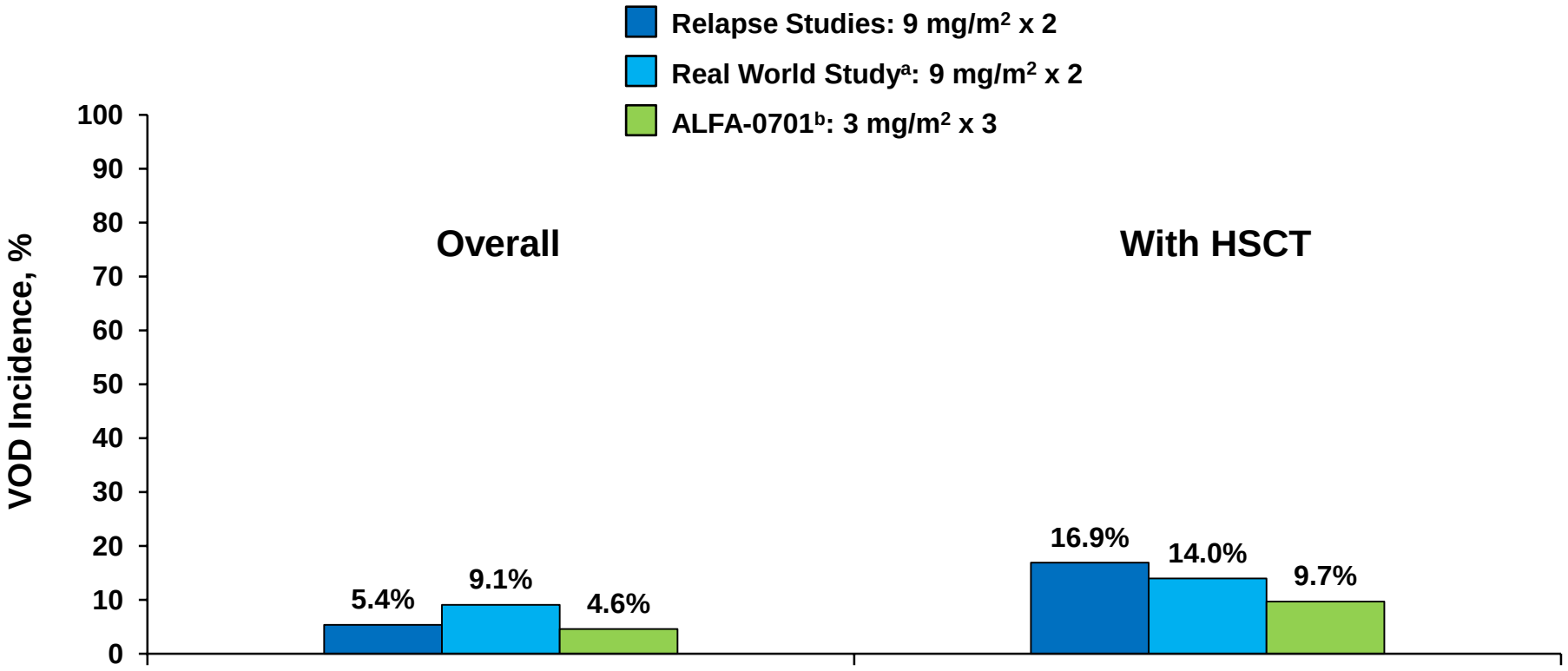
VOD: Incidence and Fatality Rate by Dosing Regimen



N	**277**	**482**	**131**	**77**	**143**	**31**
% Fatal	**3.6**	**1.9**	**1.5**	**10.4**	**3.5**	**0**

a. Study 0903X-100847
b. 2 patients in ALFA-0701 Control arm with VOD received Mylotarg in the post-treatment period prior to VOD

VOD: Incidence and Fatality Rate by Dosing Regimen



N	277	482	131	77	143	31
% Fatal	3.6	1.9	1.5	10.4	3.5	0

a. Study 0903X-100847
b. 2 patients in ALFA-0701 Control arm with VOD received Mylotarg in the post-treatment period prior to VOD

Sponsor's Actions to Address VOD Risk

- Prescribing information
  - Boxed warning
  - Identification of high-risk patients
  - Dosing recommendations

- CIBMTR collaboration
  - Prospective data collection
  - Retrospective case-control analysis

CIBMTR=Center for International Blood and Marrow Transplant Research

Safety Conclusions

- The **lower dose fractionated regimen** improves the tolerability of Mylotarg in combination with chemotherapy
- Clinical data and exposure response modeling indicate the lower dose fractionated regimen decreases the duration of myelosuppression and VOD risk
- Mylotarg has demonstrated a well-characterized and stable safety profile in thousands of AML patients

Benefit/Risk of Mylotarg: Clinical Perspective

Jorge E. Cortes, MD

Deputy Chair in the Department of Leukemia

University of Texas MD Anderson Cancer Center

Houston, TX

Key Challenges in the Management of AML

- Newly diagnosed: majority of patients may respond but high relapse rate, short survival
- Therapeutic status quo for 40+ years despite numerous phase III trials
- Universal myelosuppression from disease and therapy
- High transfusion requirements, frequent hospitalizations for patients not in remission
- HSCT only successful among those who achieve response
- Relapse: no available treatment options, few and short-lived responses, short survival

Majority of Patients Will Die 1 Year After Relapsed/Refractory Disease

Therapy	Data Source	n	Overall Response (CR + CRi)	Median OS, Months
IDAC	Phase 3 study[1]	355	19	6.1
Intensive salvage[a]	Phase 2 study[2]	44	41	6.3
Investigator's choice[b]	Phase 3 study[3]	190	21	3.3
Hypomethylating agents	Multicenter retrospective (2006-2016)[4]	514	18	6.9

1. Ravandi F, et al. *Lancet Oncol*. 2015;16:1025-1036.
2. Cortes JE, et al. *Cancer*. 2015;121:234-242.
3. Roboz GJ, et al. *J Clin Oncol*. 2014;32:1919-1926.
4. Stahl M, et al. *Blood*. 2016;128:1063.

a. Intensive salvage regimens included: MEC (n=23); idarubicin/cytarabine (n=8); cytarabine-based induction + fludarabine ± Mylotarg (n=5); cytarabine-based induction + amsacrine (n=2); cytarabine-based induction + mitoxantrone ± Mylotarg (n=2); cytarabine-based induction + Mylotarg (n=1); cytarabine-based induction + cladribine (n=1); cytarabine alone (n=1); mitoxantrone + etoposide (n=1)

b. Investigator's choice included: high-dose cytarabine (n=22); mitoxantrone, etoposide, cytarabine (MEC; n=44); fludarabine, cytarabine, granulocyte colony-stimulating factor with or without idarubicin (n=65); low-dose cytarabine (n=12); hypomethlyating agents (n=34); hydroxyurea (n=6); or supportive care (n=7)

IDAC=Intermediate-Dose Cytarabine; MEC=Mitoxantrone, Etoposide and intermediate dose Cytarabine

Differences in Study Design of Investigational Arms Between SWOG and ALFA

	SWOG S0106[1] N=595	ALFA-0701[2] N=271
Age, years	18-60	50-70
Primary endpoints	CR, DFS	EFS
Mylotarg	6 mg/m² x 1	3 mg/m² x 3
Daunorubicin	45 mg/m²	60 mg/m²
Mylotarg post induction	Post-Consolidation	Consolidation

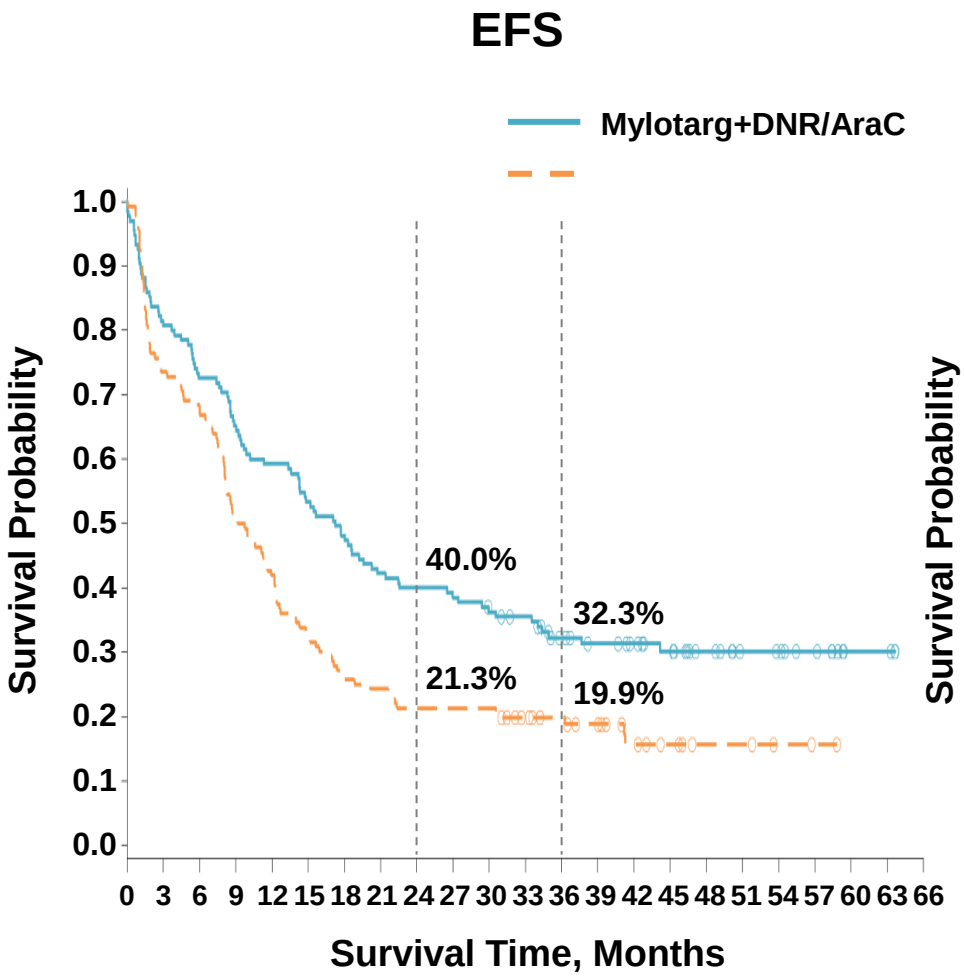
1. Petersdorf SH, et al. *Blood*. 2013;121:4854-4860.
2. Pfizer Data on File

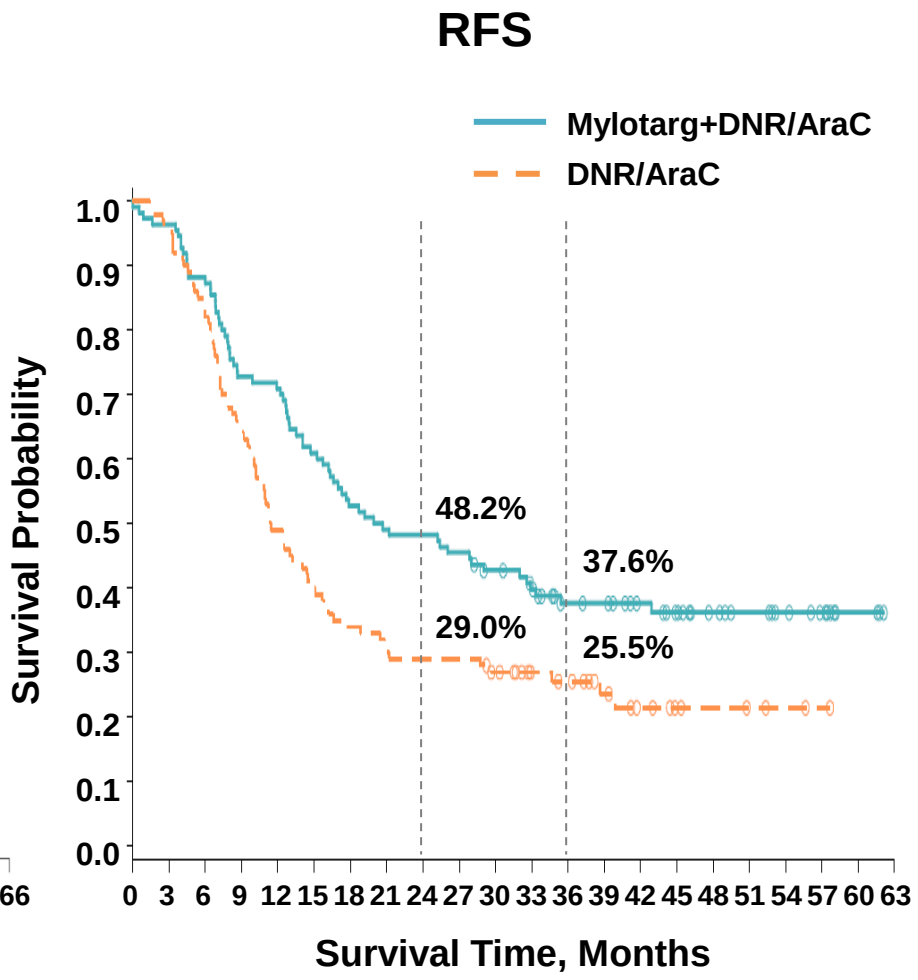
Differences in Study Design of Investigational Arms Between SWOG and ALFA

	SWOG S0106[1] N=595	ALFA-0701[2] N=271
Age, years	18-60	50-70
Primary endpoints	CR, DFS	EFS
Mylotarg	6 mg/m² x 1	3 mg/m² x 3
Daunorubicin	45 mg/m²	60 mg/m²
Mylotarg post induction	Post-Consolidation	Consolidation
Overall response	76% with Mylotarg vs. 74% with No Mylotarg	81.5% with Mylotarg vs. 73.5% with No Mylotarg
EFS	Not reported	0.562
RFS hazard ratio	0.97	0.526
OS hazard ratio	1.13	0.807

1. Petersdorf SH, et al. *Blood*. 2013;121:4854-4860.
2. Pfizer Data on File

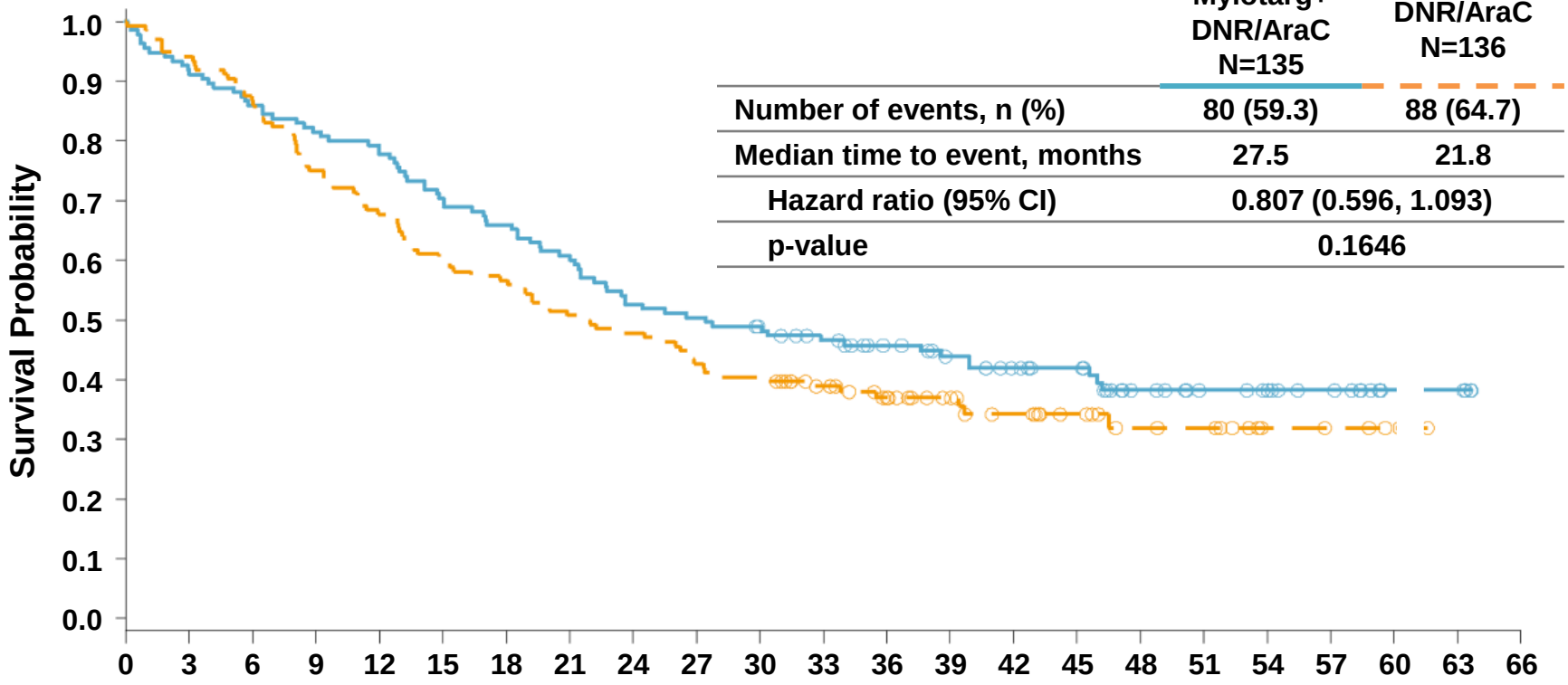
ALFA-0701: Event-Free and Relapse-Free Survival – Longer Follow-Up





mITT population; Data cutoff date: April 30, 2013

ALFA-0701: Trend Towards OS Benefit with Mylotarg



	Mylotarg+ DNR/AraC N=135	DNR/AraC N=136
Number of events, n (%)	80 (59.3)	88 (64.7)
Median time to event, months	27.5	21.8
Hazard ratio (95% CI)	0.807 (0.596, 1.093)	
p-value	0.1646	

Number at Risk																							
Mylotarg+ DNR/AraC	135	124	116	110	105	95	89	82	71	68	64	58	51	45	39	36	25	20	18	13	5	4	0
DNR/AraC	136	128	118	102	92	81	77	69	65	58	55	46	36	29	23	18	13	12	6	5	3	0	

mITT population; Data cutoff date: April 30, 2013

Mylotarg Addresses an Important Unmet Clinical Need

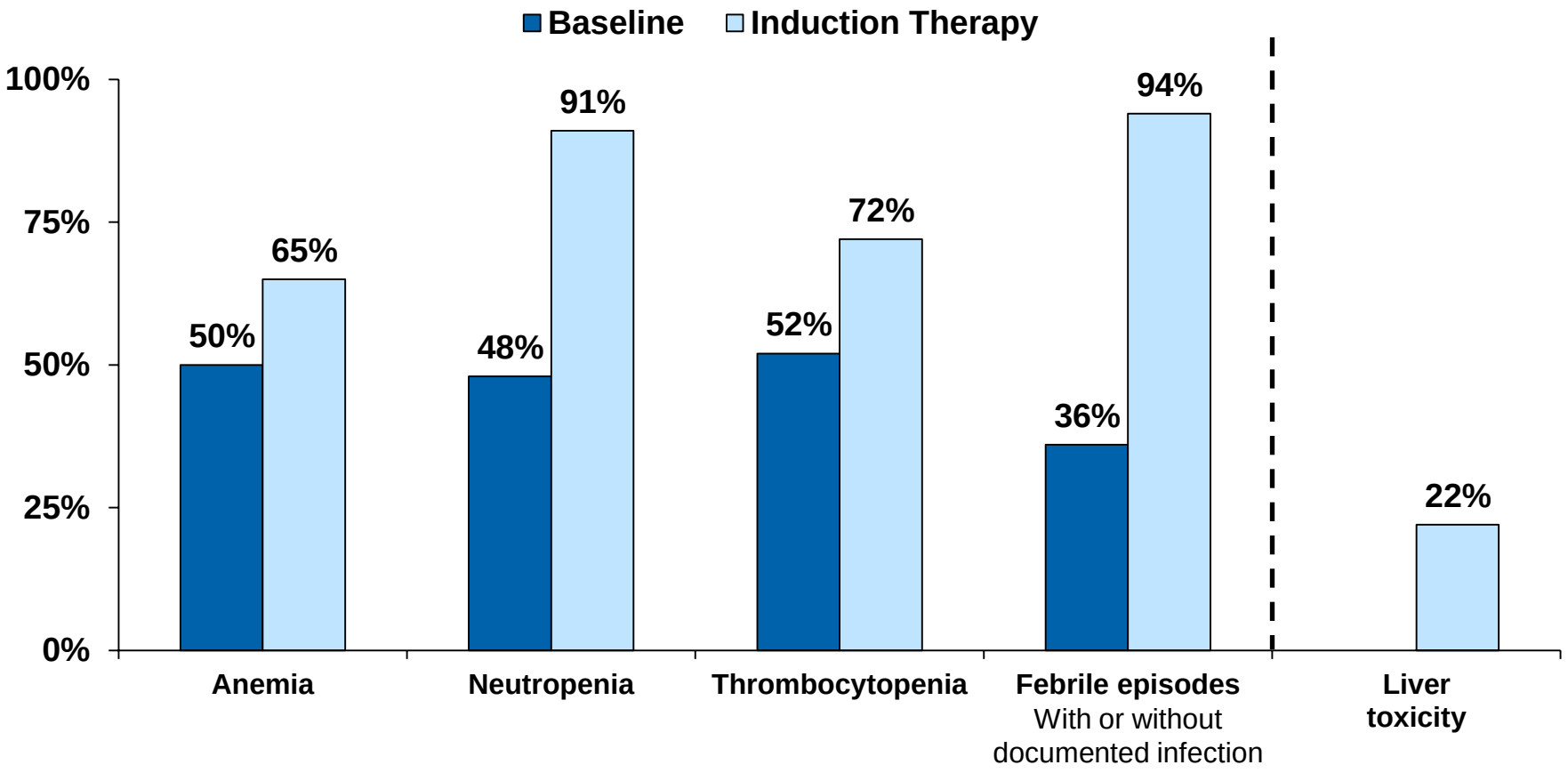
- Significant clinical benefit with addition of Mylotarg to 3 + 7
  - Durable event-free and relapse-free survival benefit with longer follow-up
  - Trend for overall survival benefit in ALFA-0701; confirmed in IPD meta-analysis
- Potential therapeutic option for a majority of patients with AML
  - CD33-positive blasts detected in up to 90% of AML cases

The Safety Profile of Mylotarg is Well-Established and Manageable

- Mylotarg possible safety concerns
  - Prolonged thrombocytopenia
    - Associated hemorrhage
  - Hepatotoxicity, including VOD/SOS

Severe Myelosuppression is Associated with the Disease and Intensive Induction Therapy in AML

Grade 3 or 4 toxicities in 1543 patients treated with standard chemotherapy between 1990 and 2006



Atallah E, et al. *Blood*. 2007;110:3547-3551.

Rates of VOD/SOS in HSCT Patients Across Studies

Therapy	Data Source	Disease	n	VOD Rate %	Fatal VOD Rate %
HSCT	Literature Review (1995-2007)[1]	Any	12,234	14.6	Not Reported
Mylotarg (9 mg/m^2) followed by HSCT	Phase 2 Pooled Analysis (1997-2000)[2]	AML	50	16.0	12.0

1. Coppell JA, et al. *Biol Blood Marrow Transplant*. 2010;16:157-168.
2. Pfizer Data on File.
3. Strouse C, et al. *Blood*. 2016;128:983.
4. Taksin A-L, et al. *Leukemia*. 2007;21:66-71.
5. Battipaglia G, et al. *Bone Marrow Transplantation*. 2017;52:592-599.
6. Chevallier P, et al. *Bone Marrow Transplantation*. 2010;45:165-170.

CIMBTR=Center for International Blood & Marrow Transplant Research; EBMT=European Society for Blood and Marrow Transplantation

Rates of VOD/SOS in HSCT Patients Across Studies

Therapy	Data Source	Disease	n	VOD Rate %	Fatal VOD Rate %
HSCT	Literature Review (1995-2007)[1]	Any	12,234	14.6	Not Reported
Mylotarg (9 mg/m^2) followed by HSCT	Phase 2 Pooled Analysis (1997-2000)[2]	AML	50	16.0	12.0
HSCT	CIBMTR Multicenter Retrospective (2008-2013)[3]	Any	13,097	4.9	Not Reported
Mylotarg (3 mg/m^2×3) followed by HSCT	Phase 2 MyloFrance1 (2005)[4]	AML	7	0	0
Mylotarg followed by Allo-HSCT	EBMT Multicenter Retrospective Study (2002-2012)[5]	AML	146	8.0	2.0
Mylotarg followed by Allo-HSCT	French Multicenter Retrospective Study (2002-2008)[6]	Acute Leukemias	44	7.0	4.5

1. Coppell JA, et al. *Biol Blood Marrow Transplant*. 2010;16:157-168.
2. Pfizer Data on File.
3. Strouse C, et al. *Blood*. 2016;128:983.
4. Taksin A-L, et al. *Leukemia*. 2007;21:66-71.
5. Battipaglia G, et al. *Bone Marrow Transplantation*. 2017;52:592-599.
6. Chevallier P, et al. *Bone Marrow Transplantation*. 2010;45:165-170.

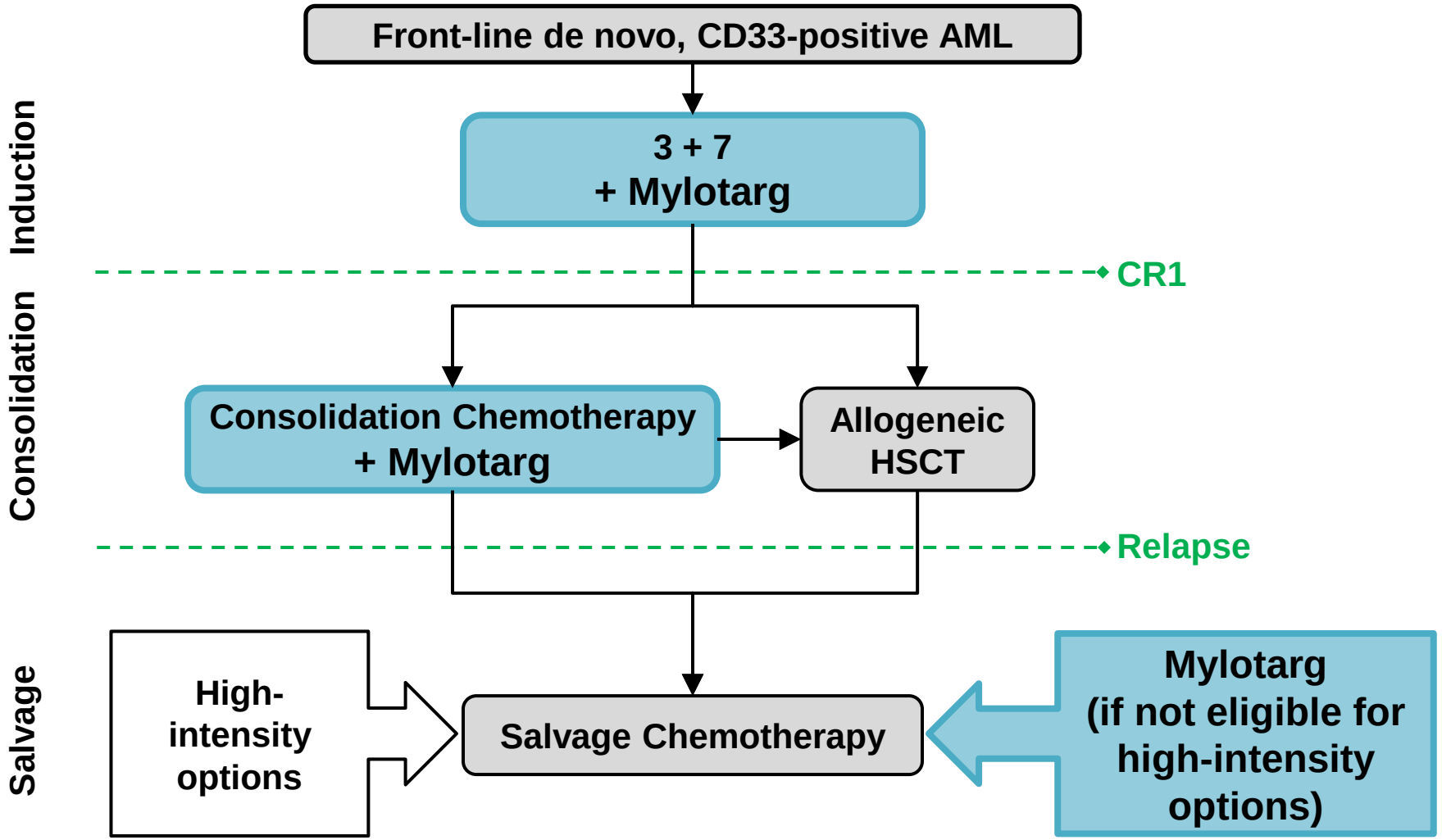
EBMT=European Society for Blood and Marrow Transplantation

Strategies to Mitigate Risk of VOD in Patients Receiving HSCT After Mylotarg

- During HSCT conditioning
  - Avoid use of the following agents: oral busulfan[1], sirolimus[2], dual alkylator regimens[3]
  - Consider a reduced intensity conditioning regimen rather than a myeloblative conditioning regimen in appropriate patients[1]
- During HSCT
  - Meticulous fluid management[1,2]
  - Initiate defibrotide in patients with signs or symptoms of VOD[1,2]

1. Wallhult E, et al. *Eur J Haematol*. 2017;98:322-329.
2. Tewari P, Wallis W, Kebriaei P. *Clin Adv Hematol Oncol*. 2017;15:130-139.
3. Kantarjian HM, et al. *N Engl J Med*. 2016;375:740-753.

Proposed Treatment Algorithm Incorporating Mylotarg in AML



CR1=first Complete Remission; HMA=Hypomethylating Agents; LDAC=Low-Dose Cytarabine

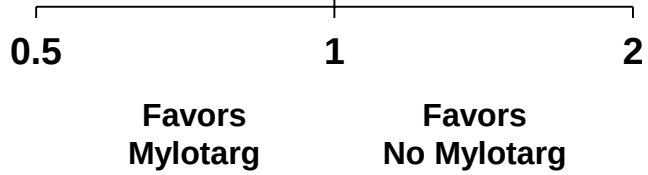
Summary

- Benefit/risk of Mylotarg is favorable in the setting of newly diagnosed AML
- Adding Mylotarg to standard induction chemotherapy led to
  - Significant and durable prolongation of event-free survival
  - Significantly improved relapse-free survival
  - Improvement in OS
- Mylotarg has a well-established safety profile; clinicians are prepared to manage myelosuppression and VOD/SOS
- Mylotarg is a valuable treatment option for the management of previously untreated, de novo AML

Backup Slides Shown

IPD Meta-Analysis: Efficacy Outcomes for Cytogenetics Adverse Risk Patients

	Events/Patients		Mylotarg:No Mylotarg	Peto Odds Ratio (95% CI)	p-value
	Mylotarg	No Mylotarg			
EFS					
Adverse Cytogenetics	275/297	271/283		0.79 (0.64, 0.97)	0.03
RFS					
Adverse Cytogenetics	155/179	145/159		0.84 (0.67, 1.06)	0.1; NS
OS					
Adverse Cytogenetics	268/297	262/283		1.00 (0.84, 1.18)	1.0; NS



NS=Not Significant

ALFA-0701: Early Deaths

	30-Day Mortality[a]		60-Day Mortality[a]	
	Mylotarg+ DNR/AraC N=131 n (%)	DNR/AraC N=137 n (%)	Mylotarg+ DNR/AraC N=131 n (%)	DNR/AraC N=137 n (%)
Number of Deaths[b]				
	5 (3.8)	3 (2.2)	7 (5.3)	7 (5.1)
Primary Cause of Death[b]				
Infection	0	0	0	1 (0.7)
Septic Shock	2 (1.5)	1 (0.7)	2 (1.5)	2 (1.5)
Hemorrhage	3 (2.3)	1 (0.7)	4 (3.1)	1 (0.7)
Liver Toxicity	1 (0.8)	0	1 (0.8)	0
Disease Progression	2 (1.5)	1 (0.7)	2 (1.5)	4 (2.9)
Cardiorespiratory Arrest	0	1 (0.7)	1 (0.8)	1 (0.7)

Based on the as treated population
a. Time to death during induction is calculated from date of First Dose regardless of remission status.
b. More than one cause of death may be selected, therefore, row totals may be larger than the total number of deaths.

VOD
Proposed Risk Minimization Measures

WARNING: HEPATOTOXICITY including severe hepatic veno-occlusive disease (VOD) and sinusoidal obstruction syndrome (SOS), has been reported in association with the use of MYLOTARG. Death from liver failure and from VOD has been reported in patients who received MYLOTARG

Warnings and Precautions:

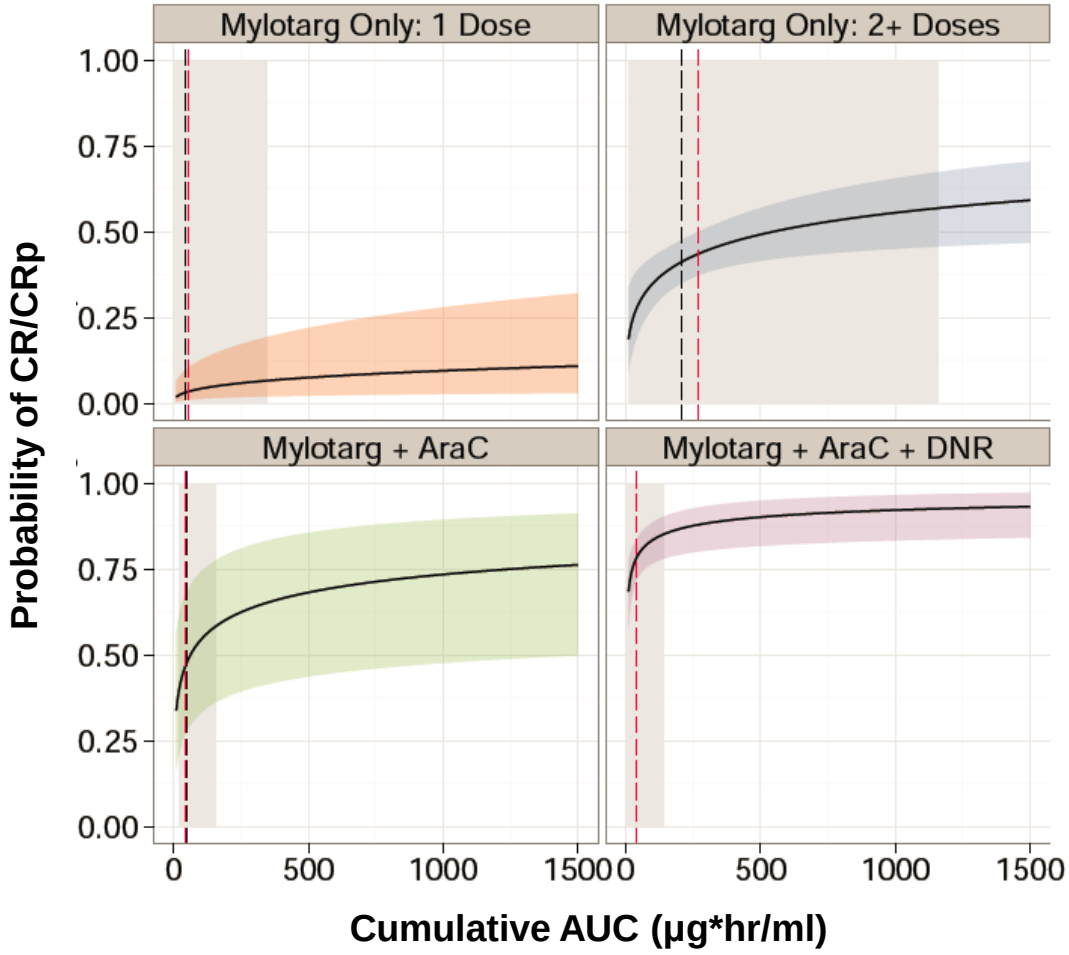
- Patients who receive MYLOTARG, either before or after HSCT, are at increased risk for developing VOD, including severe VOD. A significant exposure-response relationship was observed between the maximum observed concentration (Cmax) of hP67.6 antibody occurring after the first dose of MYLOTARG and hepatic VOD occurring within 28 days after any MYLOTARG dose in clinical studies
- Monitor closely for signs and symptoms of VOD/SOS
- Management of signs or symptoms of hepatic toxicity may require a dose interruption or discontinuation of MYLOTARG
- In patients who experience VOD/SOS, discontinue MYLOTARG and treat according to standard medical practice

Exposure-Response Model Prediction Probabilities for CR/CRp Using Antibody AUC

--- Geometric median of the exposure parameter

--- Geometric mean of the exposure parameter

95% Confidence Interval



AUC=Area Under the antibody concentration-time Curve