Question Posed

Is any other response besides complete remission (CR) acceptable as an endpoint for either full or accelerated approval of a new agent in the treatment of acute leukemia (AML or ALL)?

Response Definitions

	Marrow	Peripheral Blood
CR	< 5% blasts	ANC ≥ 1000/µl and Plts ≥ 100,000/µl
CRi	< 5% blasts	ANC ≤ 1000/µl and/or Plts ≤ 100,000/µl no transfusions
PR	> 5% blasts ≥ 50% decrease from baseline	ANC ≥ 1000 /µl Plts ≥ 100,000 /µl

Information To Be Considered

- Prior MDS, elderly AML
- Length of prior therapy/BMT (ALL)
- Gemtuzumab ozogamicin approval
- MD Anderson database
- Limited published data

Background

- Gemtuzumab ozogamicin (Mylotarg)
- Antibody to CD33 conjugated to calicheamicin
- Only agent approved by FDA for relapsed AML
- 142 patients, first relapse, 3 trials

CR rate 16%

CRp rate 13%

30% OR Rate

Sievers et al, JCO 19(13); 2001, 3244-3254
Bross et al, Clin C Res (7);2001, 1490-1496

Gemtuzumab in Relapsed AML

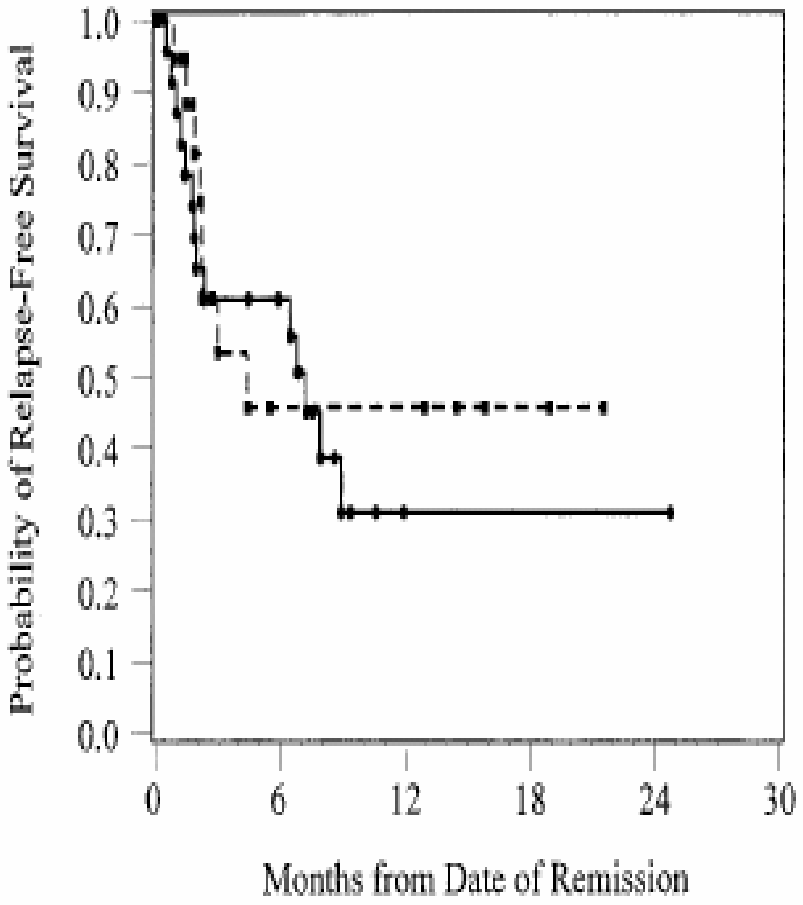


Fig 3. Relapse-free survival for patients with CR (●) and CR_p (■) (log-rank test; $P = .624$). There were 23 CR patients (median, 7.2 months) and 19 CR_p patients (median, 4.4 months).

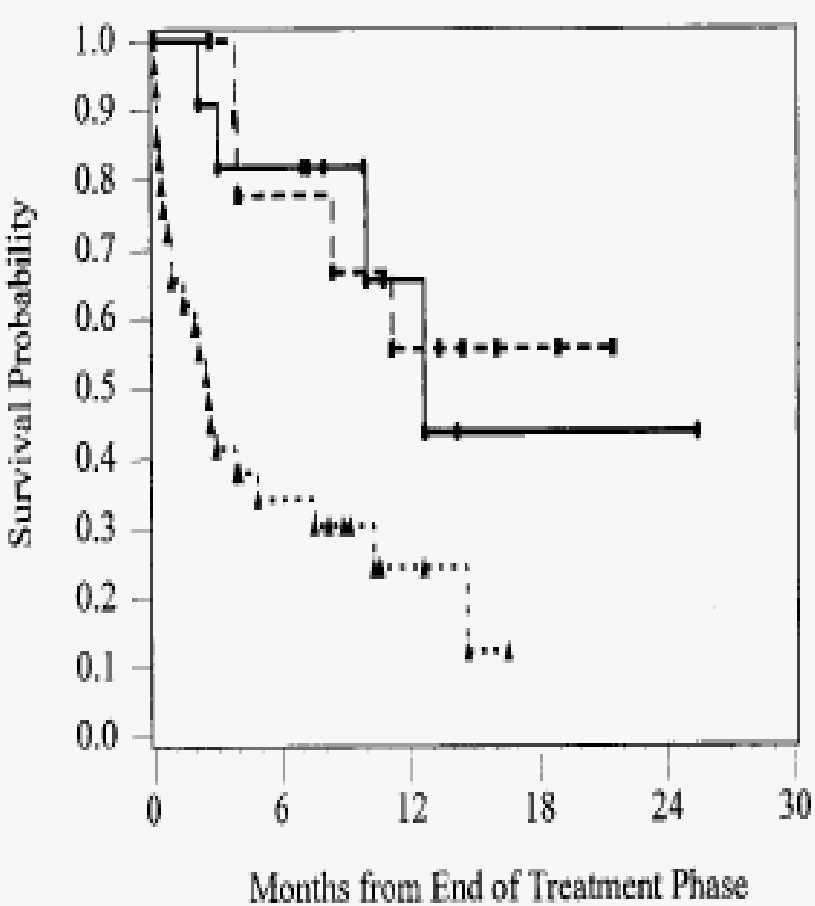


Fig 4. Landmark survival for patients with CR (●), CR_p (■), and NR (▲). There were 23 CR patients (median, 12.6 months), 19 CR_p patients (median, > 11.1 months), and 63 NR patients (median, 2.9 months).

Sievers et al, JCO 19(13):3244-3254, 2001

Issues

- **Does significance of CRi or PR depend on the agent?**
- **Will CRi or PR be more likely in older patients with AML? or patients with prior MDS?**
- **Will CRi or PR have same relevance in ALL?**

Table 1. Chemotherapy Regimen for ALL Patients

Chemotherapy	Dose	Day Number	Administration Route
Induction chemotherapy			
Idarubicin	9 mg/m^2	1, 2, 3, 8	IV
or			
Daunorubicin	30 mg/m^2	1-3, 15, 16	IV
Vincristine	2 mg TD	1, 8, 15, 22	IV
Cyclophosphamide	750 mg/m^2	1, 8	IV
Prednisone	60 mg/m^2	1-7, 15-21	IV or PO
Postinduction chemotherapy			
Arm A (between days 28 and 35; MTZ/IDaraC)			
Cytarabine	1 g/m^2 bid	1, 2, 3, 4	IV
Mitoxantrone	10 mg/m^2	3, 4, 5	IV
or			
Arm B (between days 28 and 35; CPM/araC/MP)			
Cyclophosphamide	1 g/m^2	1, 15, 29	IV
Cytarabine	75 mg/m^2	3-6, 10-13, 17-20	IV
Mercaptopurine	60 mg/m^2	1-28	PO
Maintenance chemotherapy			
MTX/Aspa (on days 75, 90, 220, 304, 388, and months 16, 20, 24, 28)			
Methotrexate*	1,500 mg/m^2	1	IV
L-asparaginase	10,000 U/m^2	2	IV
CPM/araC (on days 105, 262, 346, and months 14, 18, 22, 26, 30)			
Cyclophosphamide	1 g/m^2	1	IV
Cytarabine	500 mg/m^2	1	IV
RT/MP (from day 130 to 145)			
Cranial irradiation	18 Gy		
Mercaptopurine	60 mg/m^2/d	1-15	PO
VAD (on days 160 and 190)			
Vincristine	0.4 mg	1, 2, 3, 4	IV
Doxorubicin	12 mg/m^2	1, 2, 3, 4	IV
Dexamethasone	40 mg	1, 2, 3, 4	IV
MP/MTX (between maintenance courses from day 220 to month 30)			
Mercaptopurine	60 mg/m^2/d		PO
Methotrexate	15 mg/m^2/wk		IM

Abbreviations: ALL, acute lymphoblastic leukemia; IV, intravenously; TD, total dose; PO, orally; MTZ, mitoxantrone; IDaraC, intermediate-dose cytarabine; CMP, cyclophosphamide; MP, mercaptopurine; araC, cytarabine; RT, radiation therapy; MTX, methotrexate; Aspa, L-asparaginase; VAD, vincristine, doxorubicin, and dexamethasone; IM, intramuscularly.
*Administered over 30 minutes.

Thomas et al JCO 22(20):4075-4086, 2004

Subtypes of Resistant Disease in Patients with AML, RAEBT or RAEB who Fail Initial Induction Chemotherapy

314 patients between 1991 and 2001

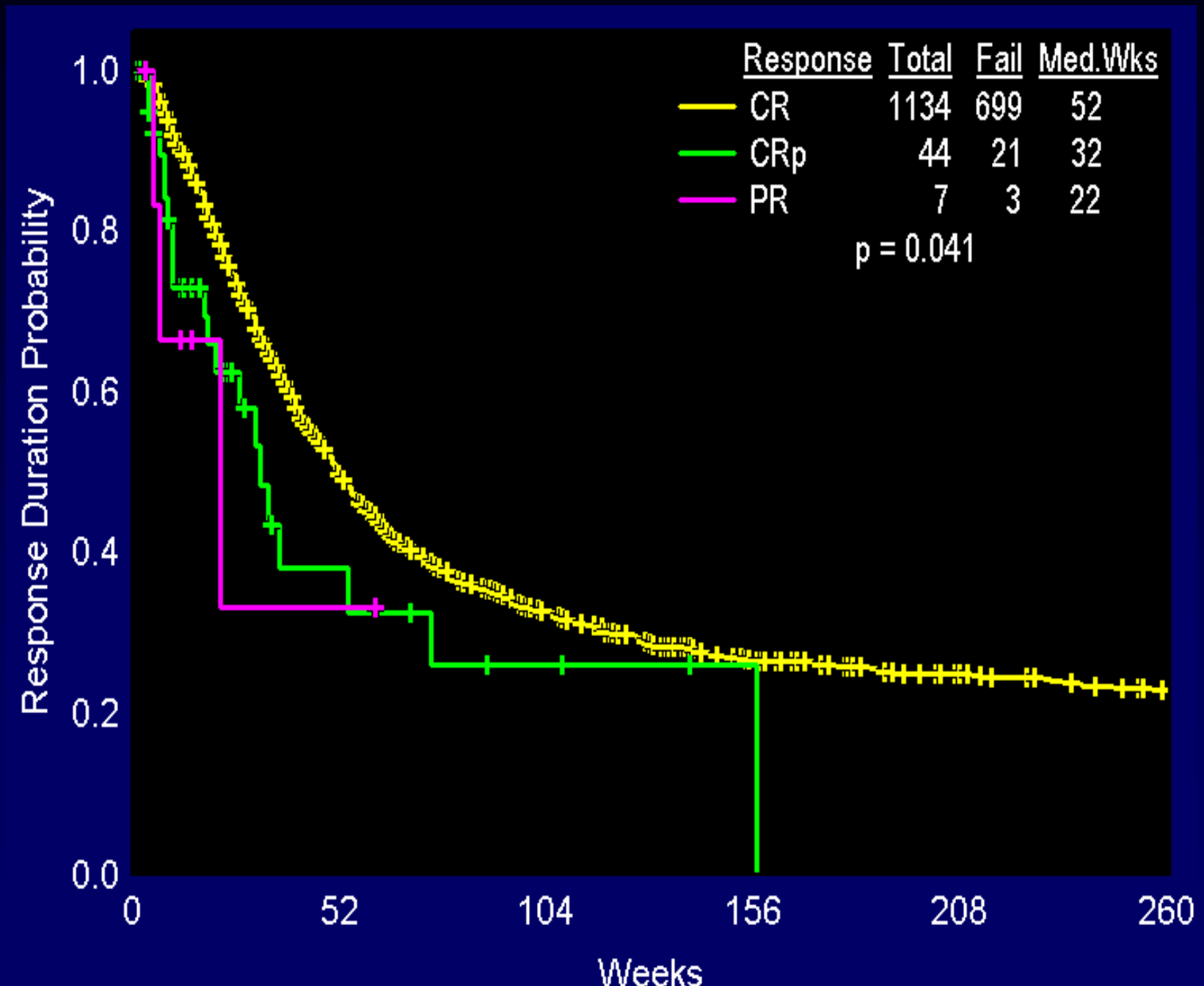
Category	N	Survival (wks)	
< 5% blasts	81	29	p=.008
> 5% blasts	187	18	

Lopez et al, Blood 98(11); 2001, 329a

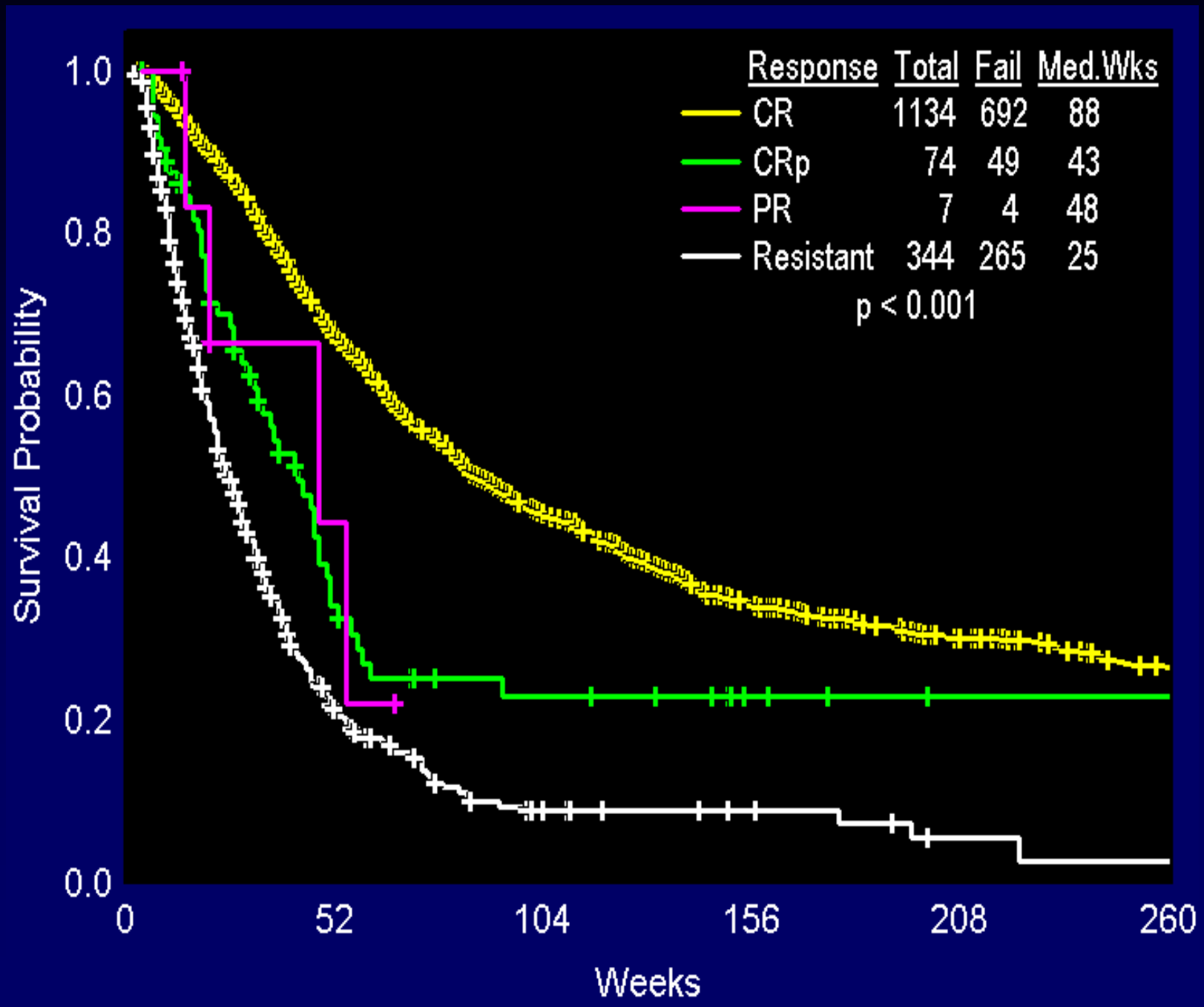
Update on Patients Not Achieving CR with Induction Therapy 1990-2005 (N = 425)

Response	No.	% of Patients
CR	1134	55
CRp	74	3.6
PR	7	0.3

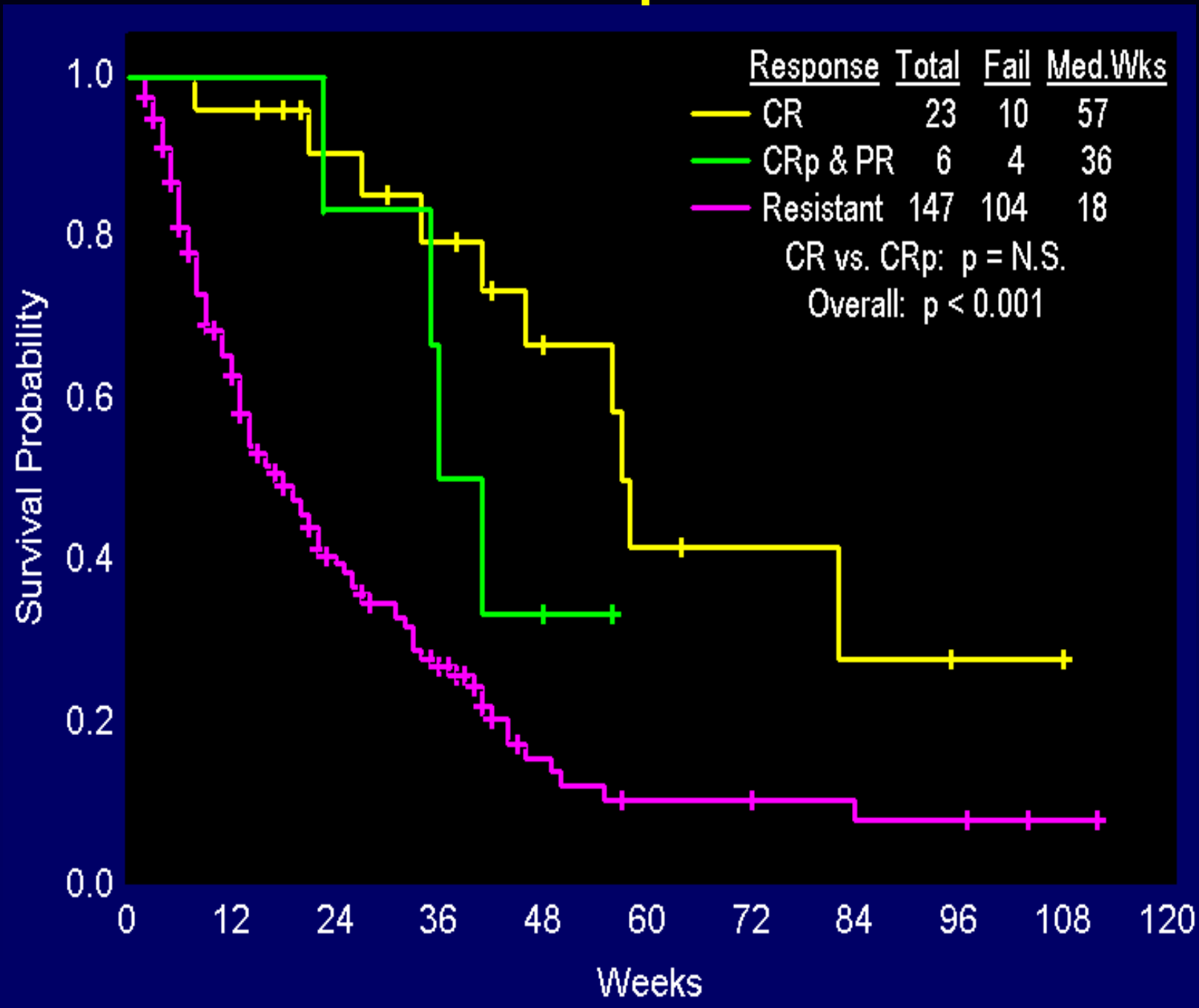
AML Database: Induction Remission Duration



AML Database: Induction Survival



AML Database: First Relapse Survival 2002-2005



ALL Induction Database (1990-2005) N=582

Response	No. (%)	Median Survival (wks)
CR	516 (87)	148
PR	5 (1)	45
CRp	2 (<1)	76 + 130
Res.	31 (5)	29
		p < .001

Clofarabine in Pediatric ALL

- **Pivotal Trial N = 49**

  Median 3 prior regimens

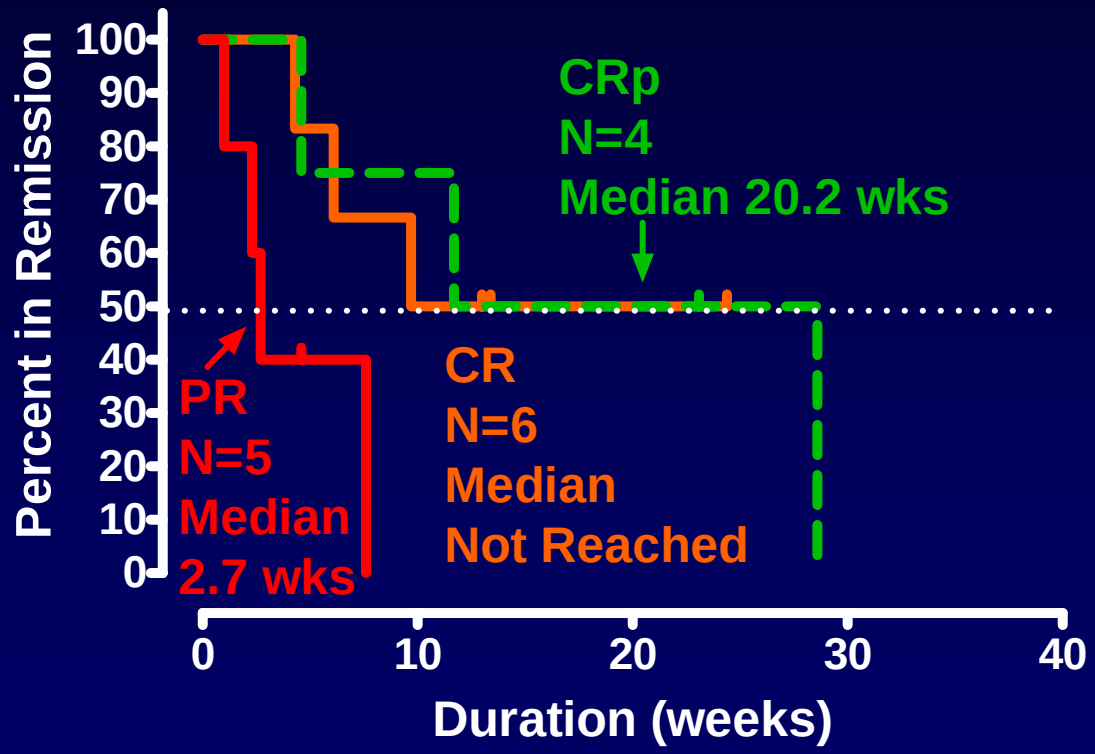
  Prior BMT 31%

  CR 12%

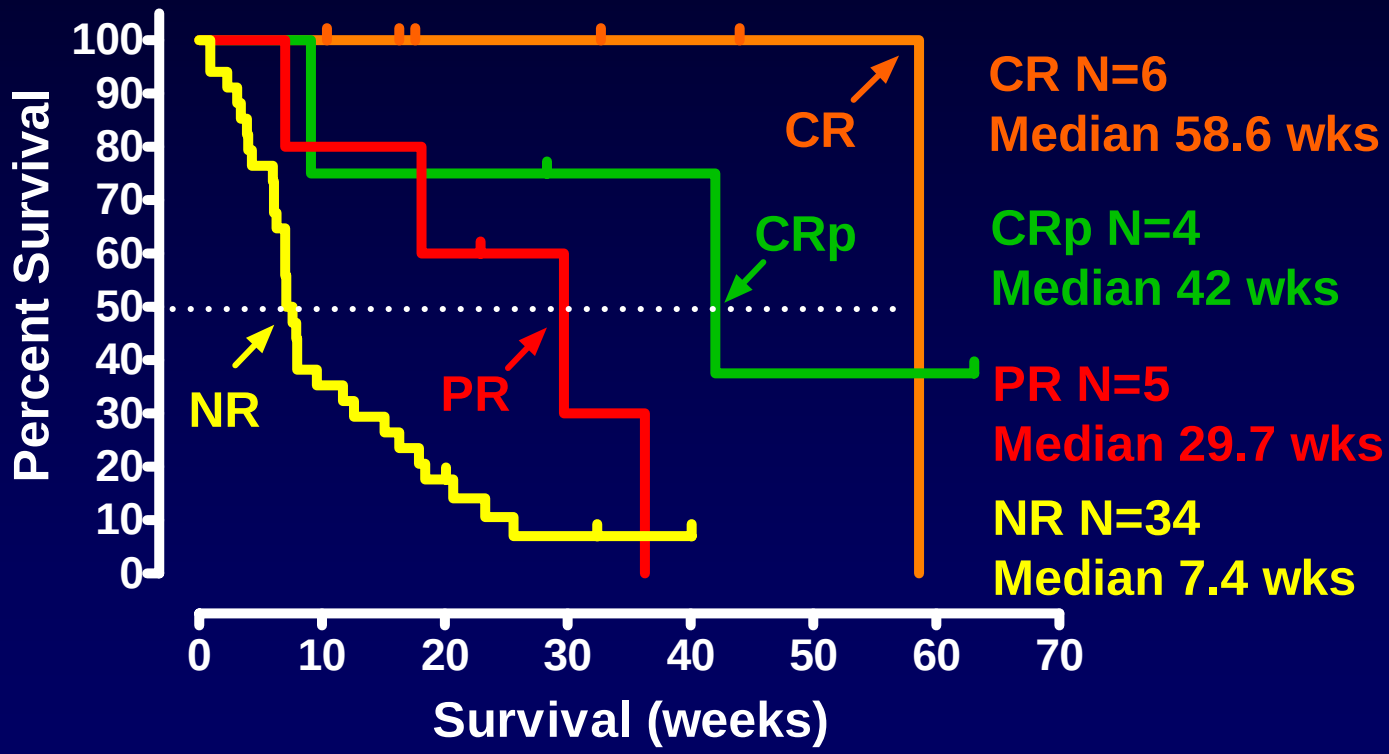
  CRp 8%

  PR 10%

Duration of Remission by Response Pivotal Pediatric ALL



Survival by Response
Pivotal Pediatric ALL



NR = No Response

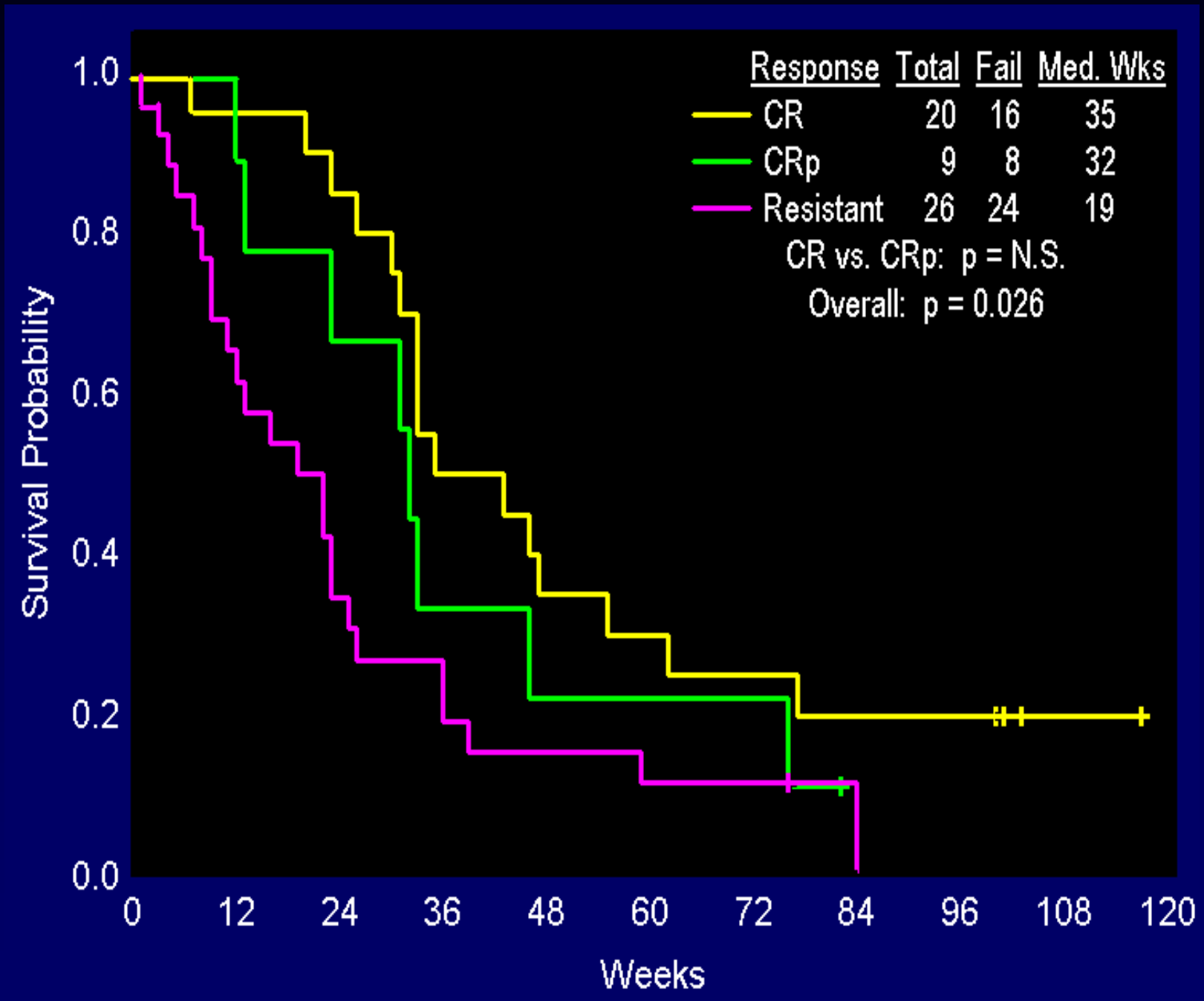
Clofarabine in Adult AML/ALL

- **Phase II trial in relapsed acute leukemia**

Response	No.	(%)
CR	20	(32)
CRp	9	(15)
PR	1	

Kantarjian et al Blood 102(7); 2003, 2379-86

Clofarabine in Relapsed Adult AML/ALL: Survival



AML Induction Database
MDACC (1990-2005) N = 2056

CRp according to prior AHD

CRp	% Pts
Yes	5
No	2.3

$p < .001$

Conclusions - 1

- **MDACC database**

  1^{o} AML: CR > CRp > NR

  ALL: CR > CRp > PR > NR

  Rel. AML: CR = CRp > PR > NR

- **Gemtuzumab**

  CRp = CR

- **Clofarabine**

  Pediatrics CRp = CR

  Adults CRp = CR

Conclusion - 2

- **Relevance of CRi and PR**

  Likely to be important:

  - **in trials testing new agents**
  - **in older patients with AML or those with prior MDS**
  - **in patients with ALL given extensive prior therapy**

Conclusion - 3

- Enough data exists to use CRi / PR as surrogate endpoint for accelerated approval
- Should be validated prospectively before used for full approval