Impact of the Timing of Complete Remission and Allogeneic Transplantation on Estimates of Event-free Survival in Previously Untreated Acute Myeloid Leukemia (AML)

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Background and Objective

- Lag in new drug development in AML in the past 3 years, despite drug approval in other types of leukemia.
- End points other than overall survival may facilitate drug development and approvals in AML.

Question: would EFS be a reasonable alternative endpoint to OS?

Background: EFS definition

A composite endpoint including **failure to obtain complete remission (CR)**, **relapse from CR**, and **death**

Advantage	Disadvantage
• Quicker endpoint • Not influenced by subsequent therapy after induction failure or relapse.	• Uncertainties in determining when induction failure occurs • Lack of a consistent consideration of HCT

Goal: examine the impact of the timing of induction failure and censoring of HCT in EFS estimation.

Methods: Induction Failure definition

Definition 1 (D1)	• no CR by 60 days
Definition 2 (D2)	• no CR by the end of all protocol induction courses
Definition 3 (D3)	• no CR by the end of all protocol treatment

CR was defined as <5% blasts in a cellular marrow with recovery of >1000 neutrophils/ul (>1500 neutrophils/ul for C10201), >100,000 platelets/ul, and no red cell transfusion requirement.

Methods: EFS definition

- Time from registration to the first evidence of induction failure (using D1, D2, or D3), relapse, or death from any cause.
- Consider censoring or no censoring for alloHCT.
- In total, **6 different definitions of EFS**, estimated by Kaplan Meier methods.
- Pooled arms for randomized trials.
- Patients last known to be alive without relapse were censored at the date of last contact.

Trial Identification

Inclusion Criteria: untreated pts with AML in prospective trials conducted through the Alliance, using anthracycline and cytarabine chemotherapy

Exclusion Criteria: trials whose primary endpoint data has not been reported yet

Trial	N	Phase	Period of Accrual	Treatment	Max. # of Induction	Population
C10201	506	3	2003-2006	(7+3, HiDAC) ± Oblimersen	2	Older AML
C10503	546	2	2007-2011	ADE,HiDAC/chemo+autoHCT /chemo+HiDAC,Decitabine	2	Younger AML
C10603	717	3	2008-2015	(7+3, HiDAC) ± Midostaurin	2	Younger FLT3-mutated AML
C10801	61	2	2011-2014	(7+3, HiDAC) + Dasatinib	2	CBF AML
C11001	54	2	2011-2014	(7+3, IntDAC) + Sorafenib	2	Older FLT3-mutated AML

- Analysis cohort: 1,884 pts from 3 single arm and 2 randomized trials

7+3: cytarabine+daunorubicin; Ara-C: Cytarabine; DNR:Daunorubicin; ADE: cytarabine+daunorubicin+etoposide; HiDAC: high-dose cytarabine; chemo mobilization: Etoposide+HiDAC+G-CSF;

Patient Characteristics

Characteristics, n (%)		C10201 (n=506)	C10503 (n=546)	C10603 (n=717)	C10801 (n=61)	C11001 (n=54)
Median age, years (range)		69 (48-88)*	48 (17-60)	47 (18-60)	50 (19-85)	67 (60-82)
Gender	Male	61	55	44	51	56
	Female	39	45	56	49	44
ECOG PS	0	30	34	43	46	43
	1	55	57	46	41	50
	2	12	7	9	10	7
	>2	2	2	3	2	0

*1 ineligible pt 48 years old, all the others age > 60.

Data Maturity

	C10201 (N=506)
# of Deaths (%)	464 (92%)
Median Follow-up Time in Months for Alive Pts (IQR)	100 (87-105)
EFS Events* (%)	476 (94%)
No CR1 (%)	161 (32%)
Relapsed after CR1 (%)	165 (33%)
Death in CR1 (%)	134 (26%)

*Applied D1 to define induction failure (no CR by 60 days)

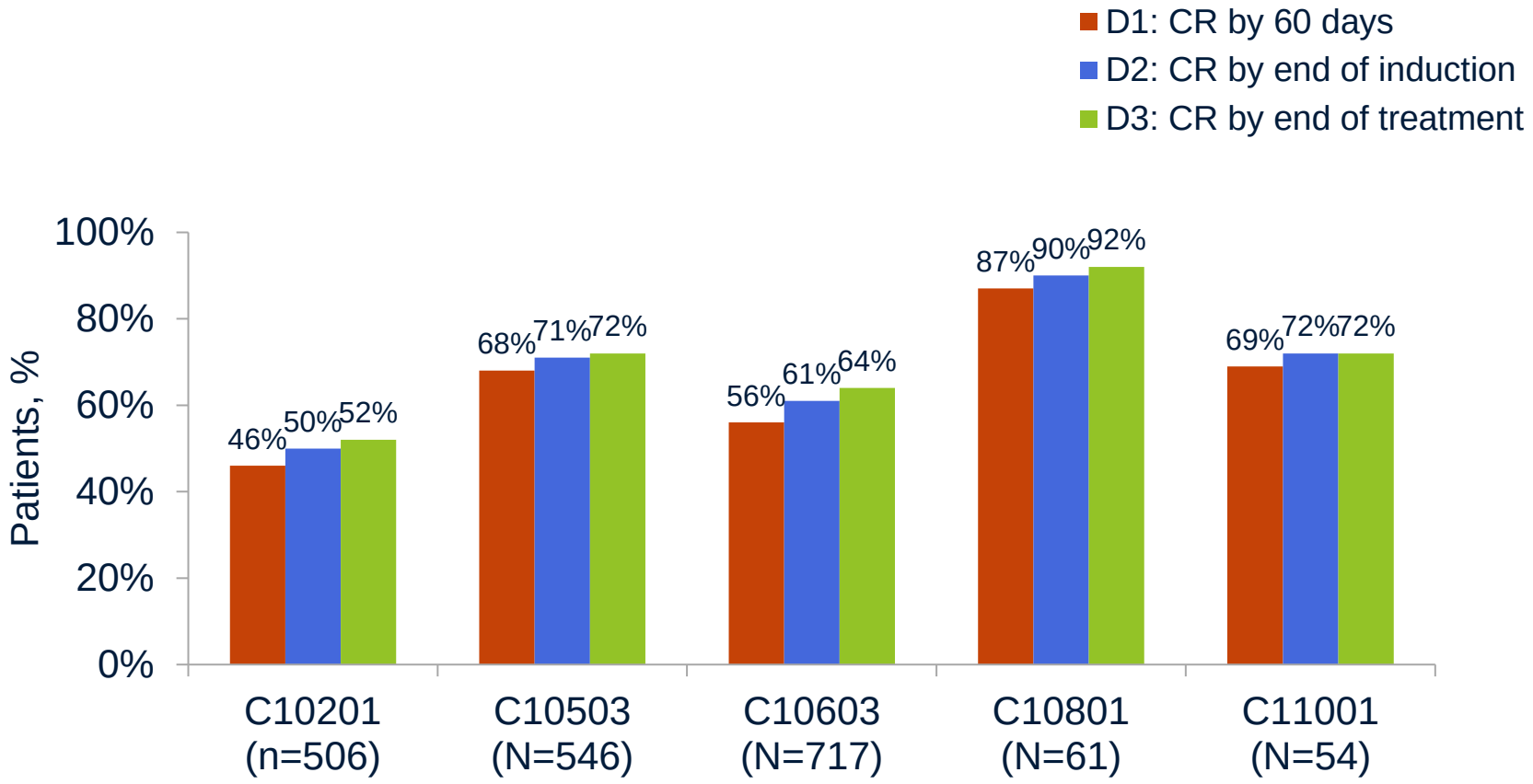
Data Maturity

	C10201 (N=506)	C10503 (N=546)	C10603 (N=717)	C10801 (N=61)	C11001 (N=54)
# of Deaths (%)	464 (92%)	307 (56%)	357 (50%)	13 (21%)	38 (70%)
Median Follow-up Time in Months for Alive Pts (IQR)	100 (87-105)	60 (51-65)	58 (47-67)	34 (26-41)	28 (18-32)
EFS Events* (%)	476 (94%)	395 (72%)	541 (75%)	22 (36%)	43 (80%)
No CR1 (%)	161 (32%)	139 (25%)	278 (39%)	5 (8%)	12 (22%)
Relapsed after CR1 (%)	165 (33%)	181 (33%)	182 (25%)	13 (21%)	20 (37%)
Death in CR1 (%)	134 (26%)	72 (13%)	79 (11%)	4 (7%)	10 (19%)

*Applied D1 to define induction failure (no CR by 60 days)

- Median Follow-up on alive patients: 57 months (range: 1-121 months)
- Overall, 63% of patients have died; 78% of patients had an event.

Results: CR Rates by Induction Failure Definition D1-3

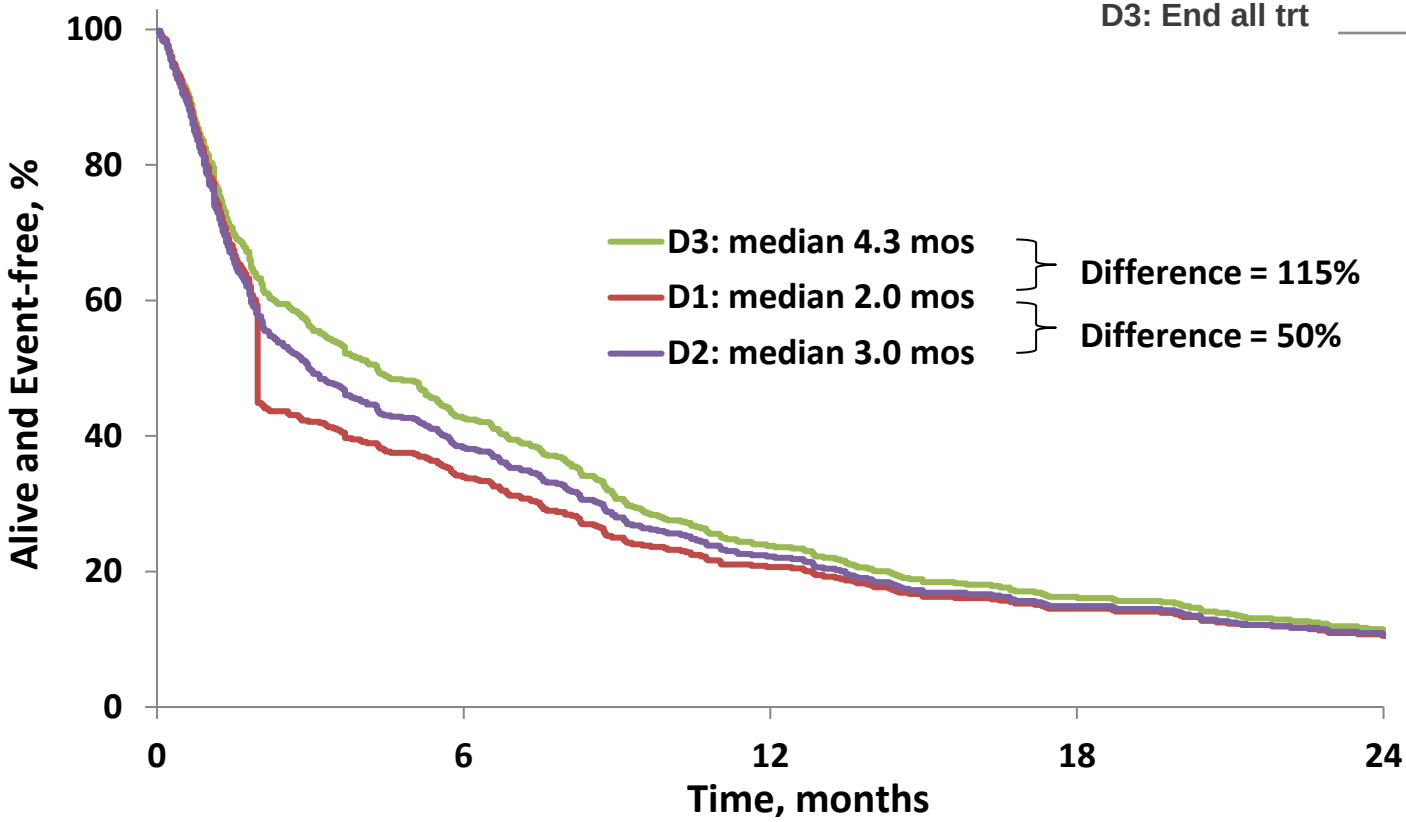


- **Slight difference in the CR rate between different induction failure definitions.**

Results: EFS Estimates by Induction Failure Definition D1-3, No Censoring at AlloHCT

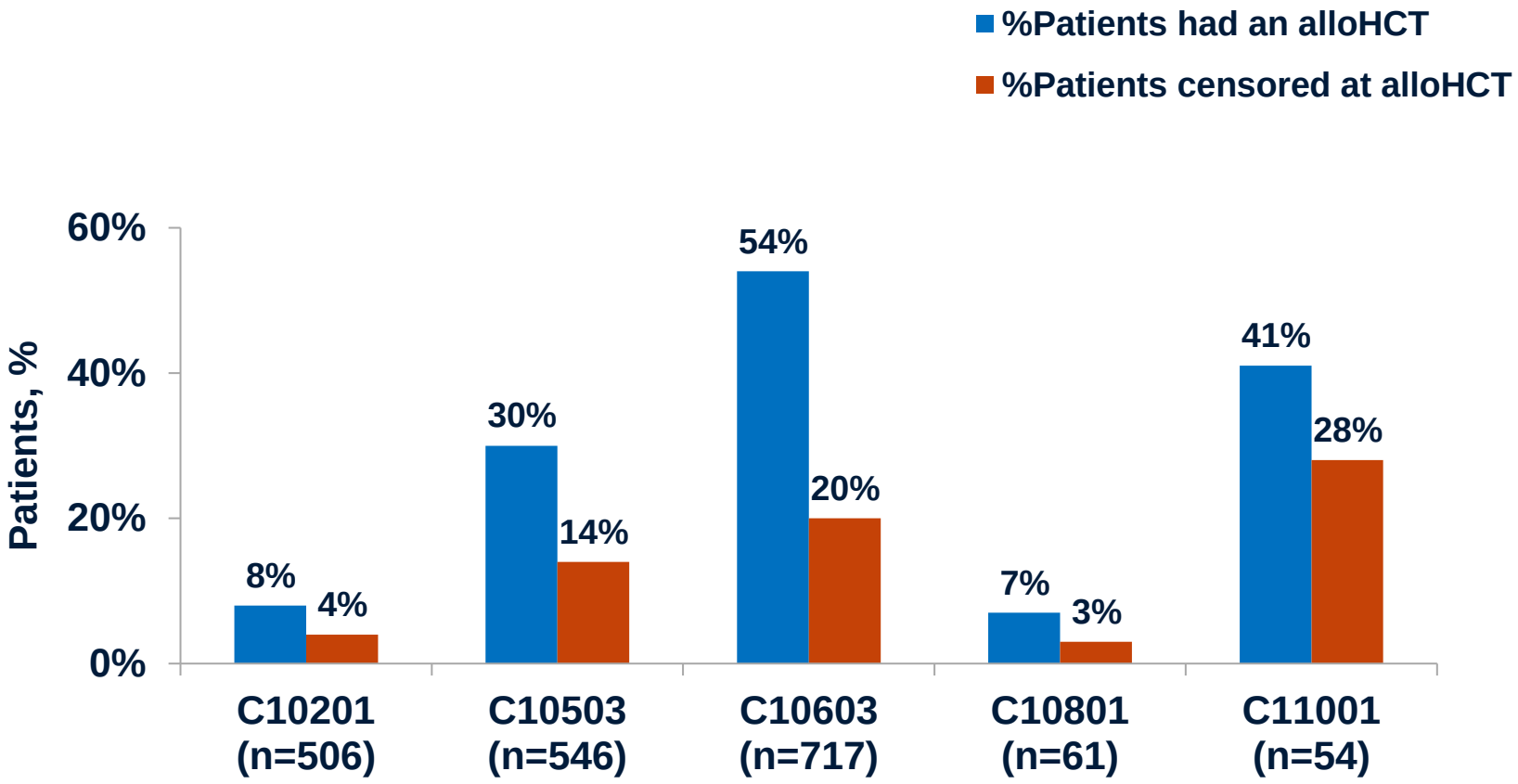
This is as expected- the definition of the longer event free time has better outcome.

Study C10201	Median EFS, months (95% CI)
D1: 60 days	2.0 (NA-NA)
D2: End ind	3.0 (2.3-3.8)
D3: End all trt	4.3 (3.4-5.4)



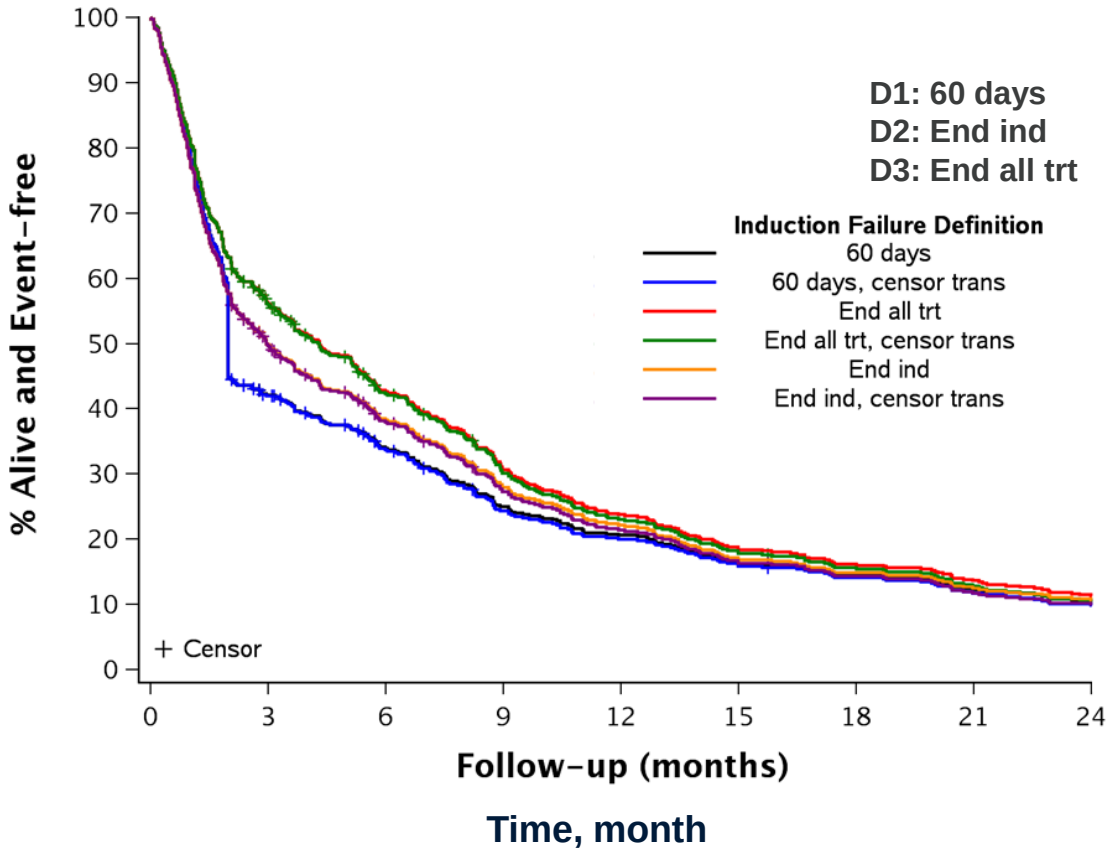
- **Median EFS estimates differed considerably based on the timing of CR used to define induction failure**

Results: Transplant Rate and %Censored due to AlloHCT



- Event of interest (relapse) occurred prior to transplantation in most cases

Results: EFS Estimates by Induction Failure Definition D1-3, Censoring at AlloHCT



	Median EFS, months (95% CI)	
	Not censoring at AlloHCT	Censoring at AlloHCT
D1: 60 days	2.0 (NA-NA)	2.0 (NA-NA)
D2: End ind	3.0 (2.3-3.8)	3.0 (2.2-3.7)
D3: End all trt	4.3 (3.4-5.4)	4.3 (3.3-5.3)

- EFS curves censoring at HCT super-imposed on the curves without censoring at HCT
- The impact of transplantation is minimal compared to the timing of induction failure

Magnitude of the difference caused by using different induction failure definitions

Trial		Induction Failure Definition			%difference in median EFS	
		D1	D2	D3	D2 vs. D1	D3 vs. D1
C10201	Median EFS, months (95% CI)	2.0 (NA-NA)	3.0 (2.3-3.8)	4.3 (3.4-5.4)	50%	115%
	1-year EFS (%)	21 (17-25)	22 (19-26)	24 (20-28)		
C10503	Median EFS, months (95% CI)	9.8 (8.4-11.7)	10.6 (9.3-12.4)	11.2 (9.7-13.8)	8%	14%
	1-year EFS (%)	45 (41-50)	47 (43-51)	48 (44-52)		
C10603	Median EFS, months (95% CI)	5.5 (2.6-6.7)	6.9 (5.7-8.3)	9.7 (8.3-11.7)	25%	76%
	1-year EFS (%)	37 (34-41)	40 (36-43)	46 (42-50)		
C10801	Median EFS, months (95% CI)	NA (20.9-NA)	NA (NA-NA)	NA (NA-NA)	NA	NA
	1-year EFS (%)	78 (68-89)	81 (72-92)	83 (74-93)		
C11001	Median EFS, months (95% CI)	6.9 (3.4-11.5)	8.3 (4.6-11.5)	8.3 (4.6-11.5)	20%	20%
	1-year EFS (%)	35 (25-51)	35 (25-51)	35 (25-51)		

- **Magnitude of difference ranges from:**

  8% to >100%

EFS by Arm for Randomized Phase III Trials

Median EFS, months (95% CI)	Induction Failure Definition		
	D1	D2	D3
C10201 Arm 1 Arm 2	HR=1.03, P=0.77 2.0 (2.0-3.4) 2.0 (NA-NA)	HR=1.02, P=0.85 3.3 (2.4-5.3) 2.7 (1.9-4.3)	HR=1.04, P=0.67 4.5 (3.4-5.7) 3.8 (2.3-5.7)
C10603 Arm 1 Arm 2	HR=0.79, P=0.0051 7.8 (4.7-10.6) 2.8 (2.0-5.9)	HR=0.76, P=0.0016 9.5 (7.3-13.1) 5.5 (3.0-6.7)	HR=0.71, P=0.0002 14.5 (10.6-17.3) 7.2 (6.0-8.9)

*HR, Hazard Ratio; log-rank test p-value

- **Treatment effect does not differ by induction failure definition in randomized trials.**

Conclusion

- The impact of censoring at HCT on EFS estimates was minimal.

- Median EFS estimates differed considerably based on the timing of CR used to define induction failure
  - Magnitude of difference: 14% to >100%
  - Single-arm trial: may lead to incorrect conclusions about efficacy if the ESF definition was not consistent with the historical control.

- The timing of CR should be carefully examined in the historical control data used to guide the design of the next trial.

Discussion

- Defining clinical benefit of therapy in AML is complicated by disease and treatment-specific considerations.

- SWOG[1] and ECOG[2] studies showed a significant correlation between EFS and OS, but the effect size is relatively small.

- Surrogacy:
  - Individual-level: EFS predicts OS with individual patients
  - Trial-level: treatment effect on EFS allows reliable prediction of treatment effect on OS

1. Othus, Megan, et al. *Haematologica* (2016).
2. Luskin, Marlise R., et al. *Blood* 124.21 (2014): 2599-2599.

Other Considerations

- What constitutes induction remission?
  - CR + other types of responses (CRi, CRp)
  - CR + MRD
- Protocol adherence
  - Patients who might have achieved CR with a second induction, but instead received non-protocol therapy

Other Considerations

Induction end date	Last contact date	Transplantation
• last clinical assessment date during all induction treatment • reporting end date of induction	• last clinical assessment date • Last follow-up date	• All types of HCT • AlloHCT only

Example of primary endpoint definition in the SAP for an AML trial

Scenario	EFS Date
Patients who were randomized but never treated; did not officially withdraw; and have virtually no data	Censor on Day 1
Patient withdrawn consent with no treatment	Exclude
Patients who were randomized but have no disease evaluation and are still alive at the time of analysis	Censor on Day 1
Patients who received all induction therapy, were properly evaluated for CR/CRi, and failed to achieve CR/CRi at any time	Event on the last site-reported disease evaluation date during induction.
Patient who didn't receive all induction therapy, and failed to achieve CR/CRi at any time	• If patients went off protocol for alternative therapy, event on the date when patients discontinue the protocol treatment • Else, event on the last site-reported disease evaluation date during induction.
Patents with CR/CRi	• If patients ended treatment during induction 1 or 2 for alternative therapy and they achieved CR/CRi after receiving alternative therapy, event on the date when patients discontinue the protocol treatment • Else, continue to follow for relapse or death

Example of primary endpoint definition in the SAP for an AML trial

Scenario	EFS Date
Patients who relapsed	Event on relapse date
Patients who died in remission	Event on death date
Patients who are alive in remission	Censor at the last site-reported disease evaluation date or the last lab date (whichever is the latest) if during treatment or in CFU, censor at the last contact date if in SFU
Lost of follow-up (or withdrawal of follow-up) without relapse or death	Censor on the last date of site-reported disease evaluation or the last lab date (whichever is the latest) if during treatment or in CFU prior to lost/withdrawal of follow-up; censor on the last contact date if in SFU prior to lost of follow-up/withdrawal of follow-up-up.

Happy Lunar New Year!