2019年终盘点

end of 2019

目录

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1 急性髓系白血病的诊断分层

AML的预后分层

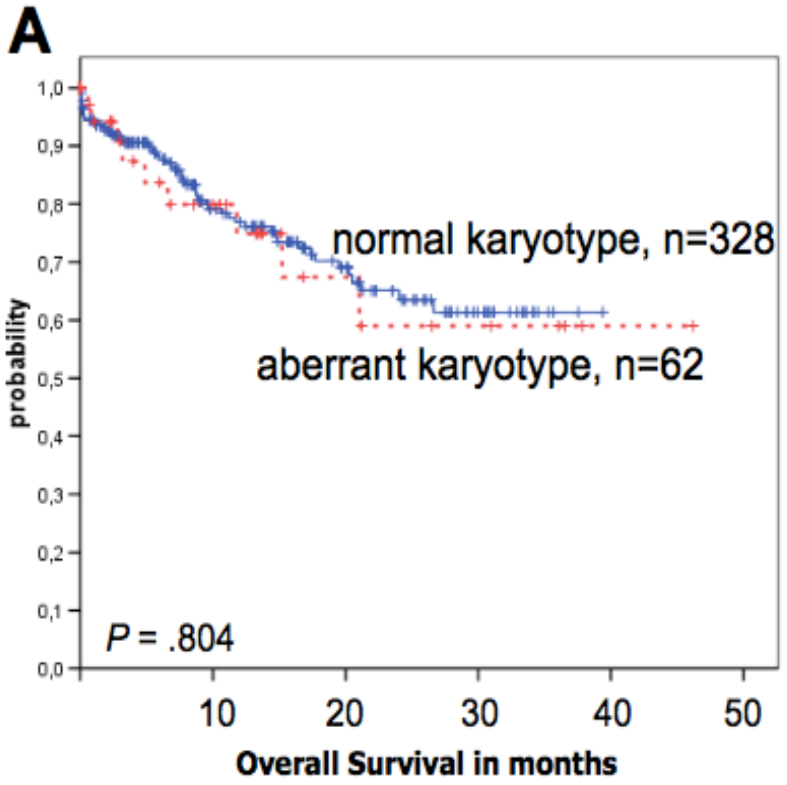
NCCN指南

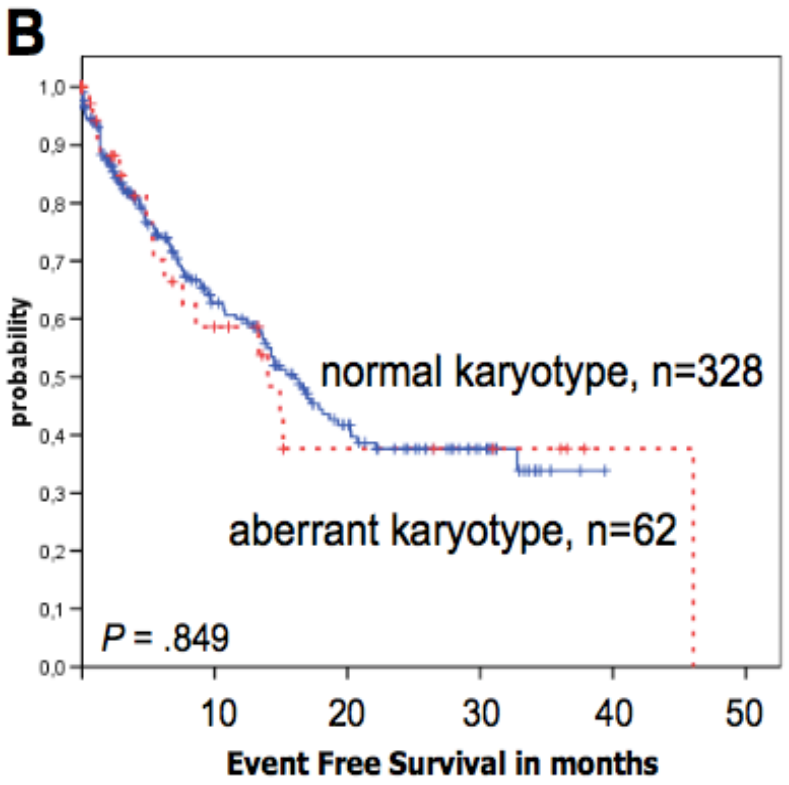
预后分层	细胞遗传学	分子生物学
预后良好	Inv(16)(p13q22)或 t(16;16)(p13;q22)或 t(8;21)(q22;q22)	正常核型： NPM1 突变但不伴有FLT3-ITD突变，或CEBPA双突变
预后中等	正常核型 +8 t(9;11)(p22;q23) 其他异常	Inv(16)(p13q22)或 t(16;16)(p13;q22) 伴有c-Kit突变； t(8;21)(q22;q22)伴有c-Kit突变
预后不良	复杂核型(≥3 种) 单体核型 -5, -7, 5q-, 7q- 11q23 染色体易位，除外t(9;11) inv(3)或t(3;3) t(6;9) t(9;22)	正常核型： 伴有FLT3-ITD突变 TP53突变

预后分层	分子遗传学
预后良好	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) 或 t(16;16)(p13.1;q22); CBFB-MYH11 NPM1突变不伴或低水平FLT3-ITD CEBPA双突变
预后中等	NPM1 突变伴高水平FLT3-ITD 野生型NPM1 不伴或低水平 FLT3-ITD t(9;11)(p21.3;q23.3); MLLT3-KMT2A 无良好或不良的细胞遗传学异常
预后不良	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A 重排 t(9;22)(q34.1;q11.2); BCR-ABL1 inv(3)(q21.3q26.2) 或 t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) -5 或del(5q); -7; -17/abn(17p) 复杂核型或单倍体核型 野生型NPM1 伴高水平FLT3-ITD RUNX1突变 ASXL1突变 TP53突变

ELN指南

AML预后分层：NPM1突变与核型





rather than the previous 4-group system (Table 5). A few other changes have been made. Recent studies have shown that in AML with *NPM1* or biallelic *CEBPA* mutations, the presence of coexisting chromosomal abnormalities does not appear to modify the prognostic effect of the mutations[16,25,115]; prognosis may be more influenced by concurrent gene mutations.[37] Accordingly, and as in CBF-AML, the categorization of these cases is now based on the primary leukemia-defining genetic subsets irrespective of the karyotype. The higher relapse rate and poorer OS associated with *FLT3*-ITD largely depends on the ITD

Blood. 2009;114: 3024-3032
Blood. 2017;129(4):424-447

AML预后分层：Oral-Abstract S1614：伴 $NPM1^{mut}$ 和 $FLT3\text{-}ITD^{neg/low}$ 的AML患者，染色体核型决定临床结局

研究背景：伴 $NPM1^{mut}$ 和 $FLT3\text{-}ITD^{neg/low}$ 的AML患者，是预后较好的分子学异常，且被认为不管细胞遗传学分型如何。此研究验证合并细胞遗传学异常的 $NPM1^{mut}$ 和 $FLT3\text{-}ITD^{neg/low}$ 的AML患者预后情况

研究人群：

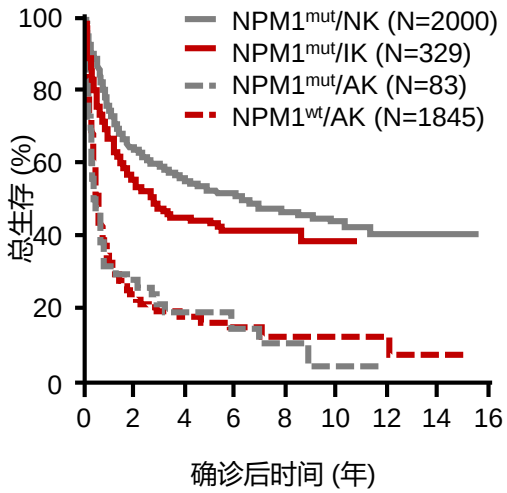
$NPM1^{mut}/FLT3\text{-}ITD^{neg/low}$和染色体核型

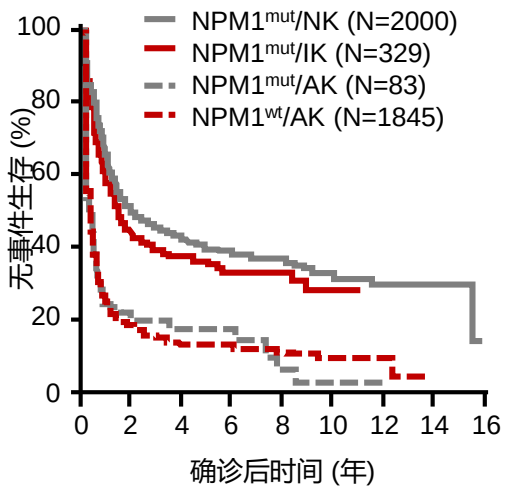
9个国际队列

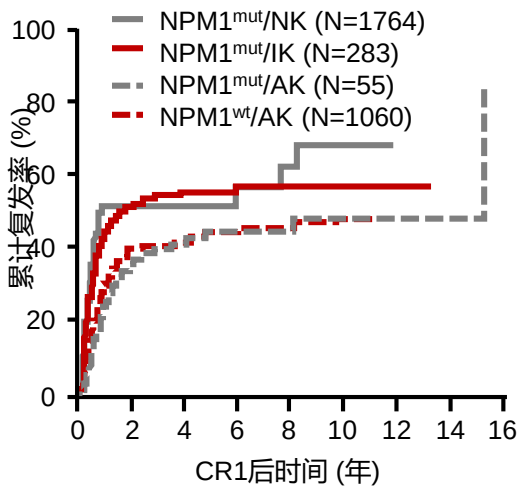
- ≥18岁高强度治疗的AML患者
- 核型根据2017 ELN 进行分类
- **2426例$NPM1^{mut}/FLT3\text{-}ITD^{neg/low}$患者**
  - 2000例正常核型
  - 329例中等异常核型
  - 83例不良核型

1845例$NPM1^{wt}/FLT3\text{-}ITD^{neg/low}$不良核型患者

研究结果：合并不良细胞遗传学分型的患者CR率更低、OS更差、EFS短，CIR更高

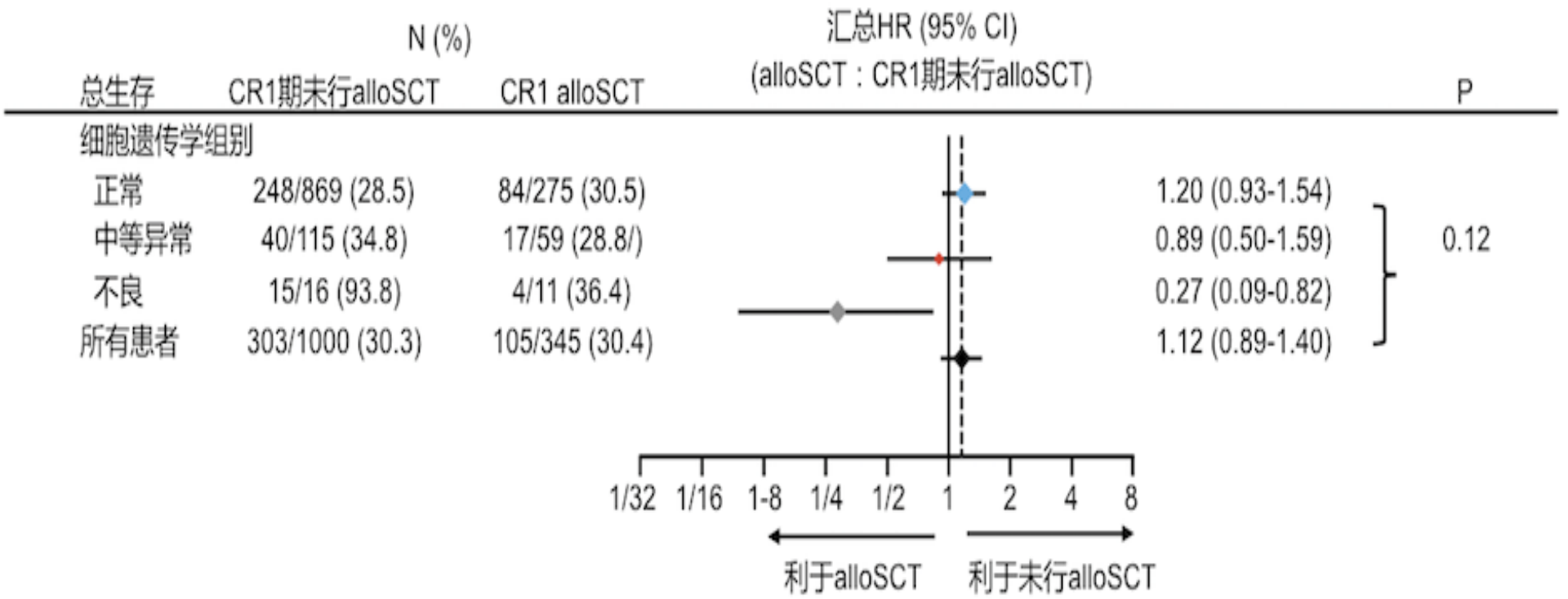






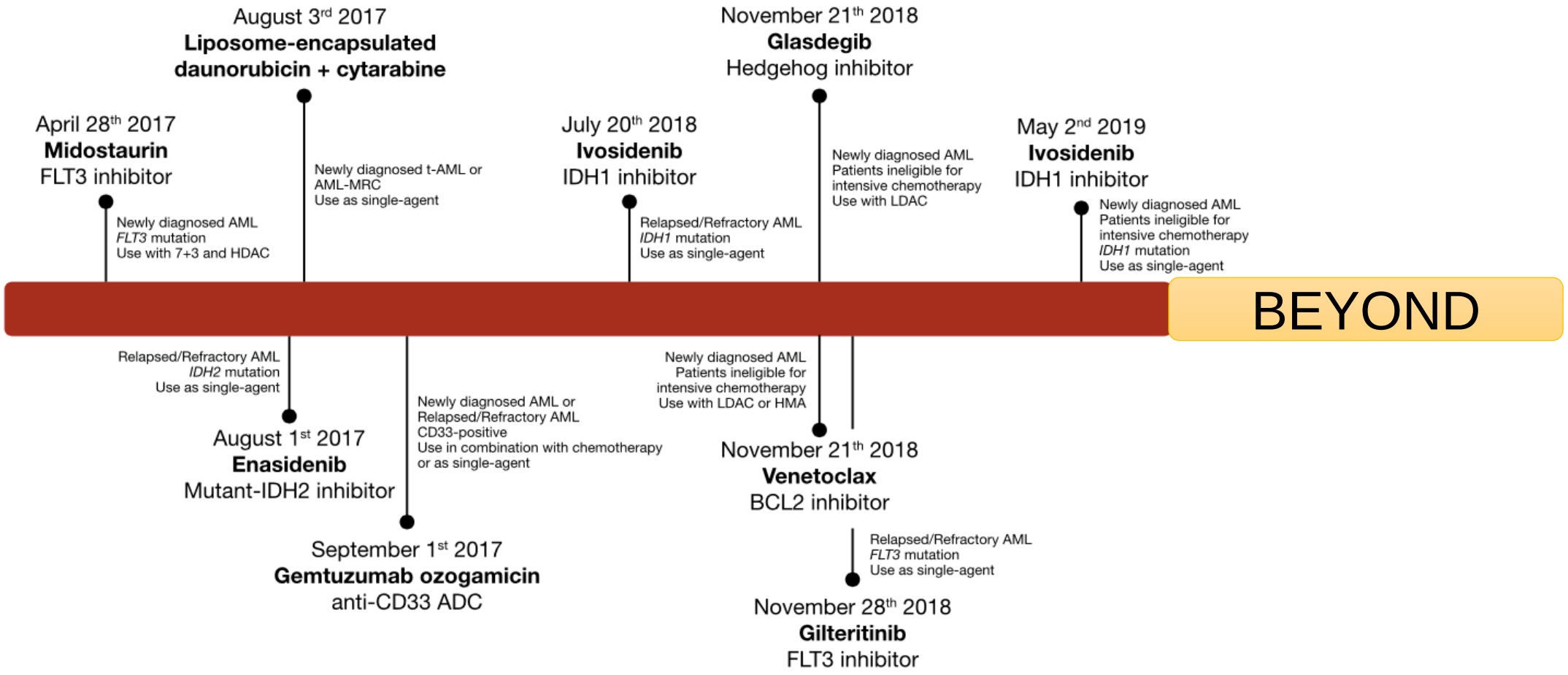
多变量	CR	OS	EFS	CIR
不良核型 vs 正常核型	0.29 (0.17-0.48) P<0.0001	2.97 (2.29-3.87) P<0.0001	2.63 (2.05-3.38) P<0.0001	2.52 (1.75-3.62) P<0.0001
中等异常核型 vs 正常核型	0.84 (0.59-1.19) P=0.33	1.27 (1.07-1.50) P=0.0060	1.21 (1.04-1.41) P=0.014	1.18 (0.97-1.44) P=0.10

研究结果：细胞遗传学良好或一般患者，CR1后移植与否不影响OS，而细胞遗传学不良患者CR1后行移植明显改善OS



2 急性髓系白血病的诱导、巩固及维持治疗

AML的治疗靶向进展



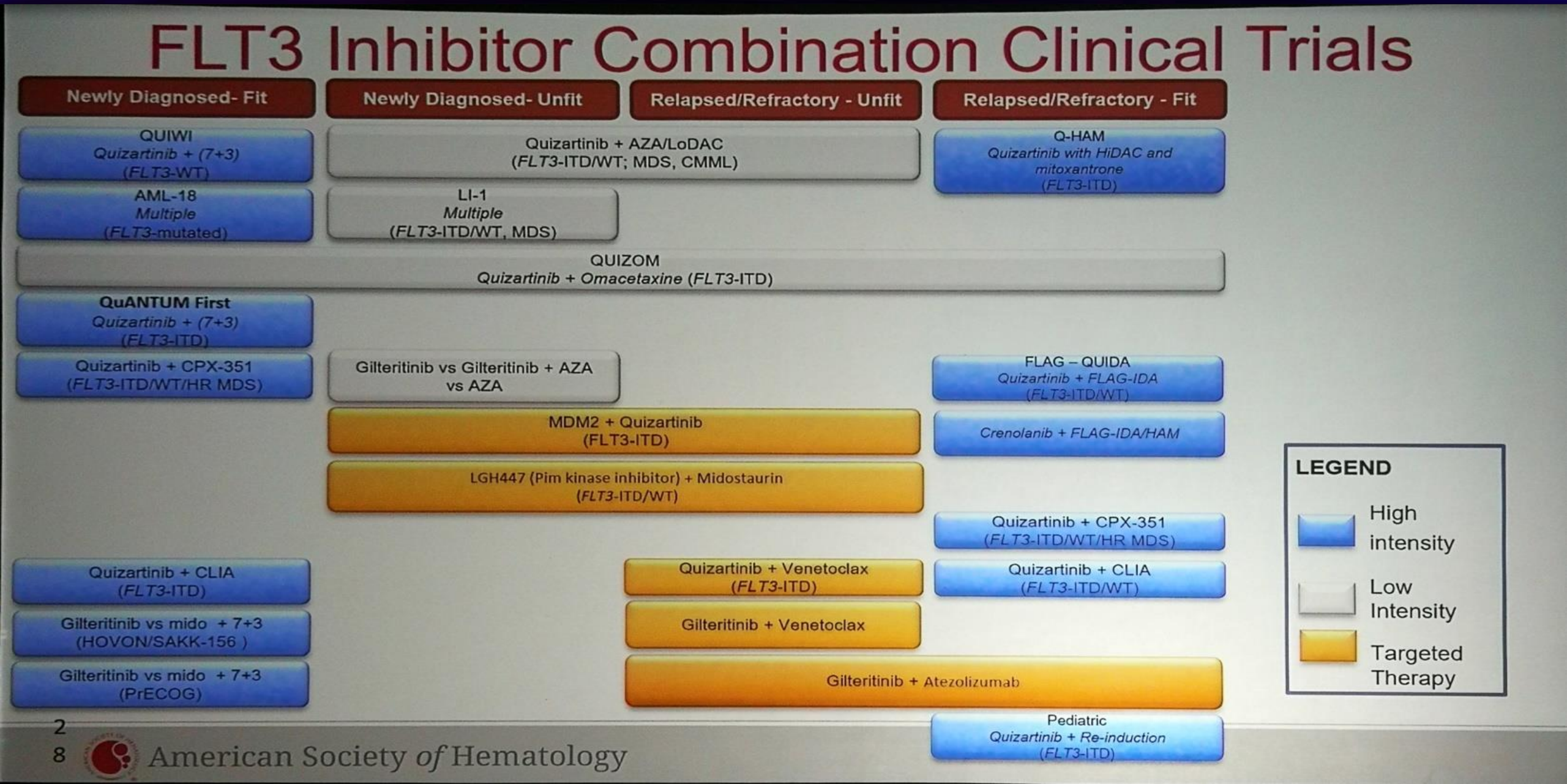
Hematology Am Soc Hematol Educ Program. 2019 Dec 6;2019(1):548-556.

现有的FLT3抑制剂

Name	Initial name	Type Ⅰ or Ⅱ	Active as monotherapy	Selectivity	Half-life
Midostaurin	PKC412	Ⅰ	No	+	19h
Sorafenib	BAY-43-9006	Ⅱ	Yes	++	25-48h
Quizartinib	AC220	Ⅱ	Yes	+++	~1.5d
Crenolanib	CP-868–596	Ⅰ	Yes	++	6-8h
Gilteritinib	ASP2215	Ⅰ	Yes	++	113h

Hematology Am Soc Hematol Educ Program. 2019 Dec 6;2019(1):539-547

FLT3抑制剂相关临床试验



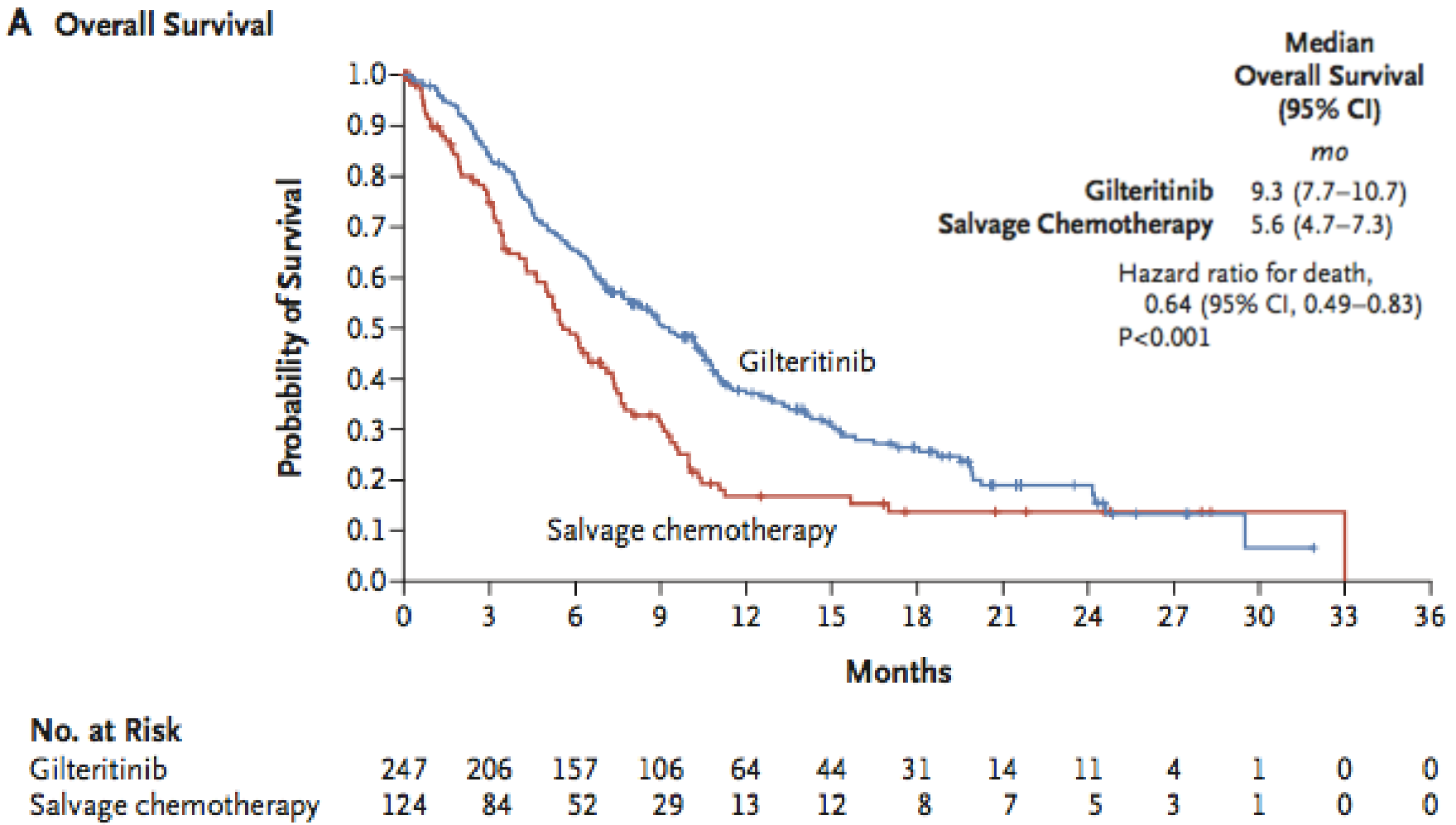
FLT3抑制剂Quizartinib在R/R AML中的疗效

Effect of Co-Mutations and FLT3-ITD Variant Allele Frequency (VAF) on Response to Quizartinib or Salvage Chemotherapy (SC) in Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML)

- Patients with NPM1wt/DNMT3Amut had significantly longer median OS with quizartinib vs SC (39.3 vs 19.6 weeks, respectively; HR, 0.239; P = 0.003) while NPM1mut/DNMT3Amut patients had lower and similar median OS between the 2 arms (23.6 vs 23.4 weeks, respectively).
- Quizartinib treatment showed significantly longer median OS vs SC in patients with high FLT3-ITD VAF (23.9 vs 17 weeks respectively; HR, 0.689, P = 0.0148), while the median OS in patients with low FLT3-ITD VAF was similar (34.1 vs 26.6 weeks, respectively; HR, 0.857, P = 0.535)

ASH2019 Abs737

FLT3抑制剂Gilteritinib治疗R/R AML的生存情况



N Engl J Med 2019;381:1728-40.

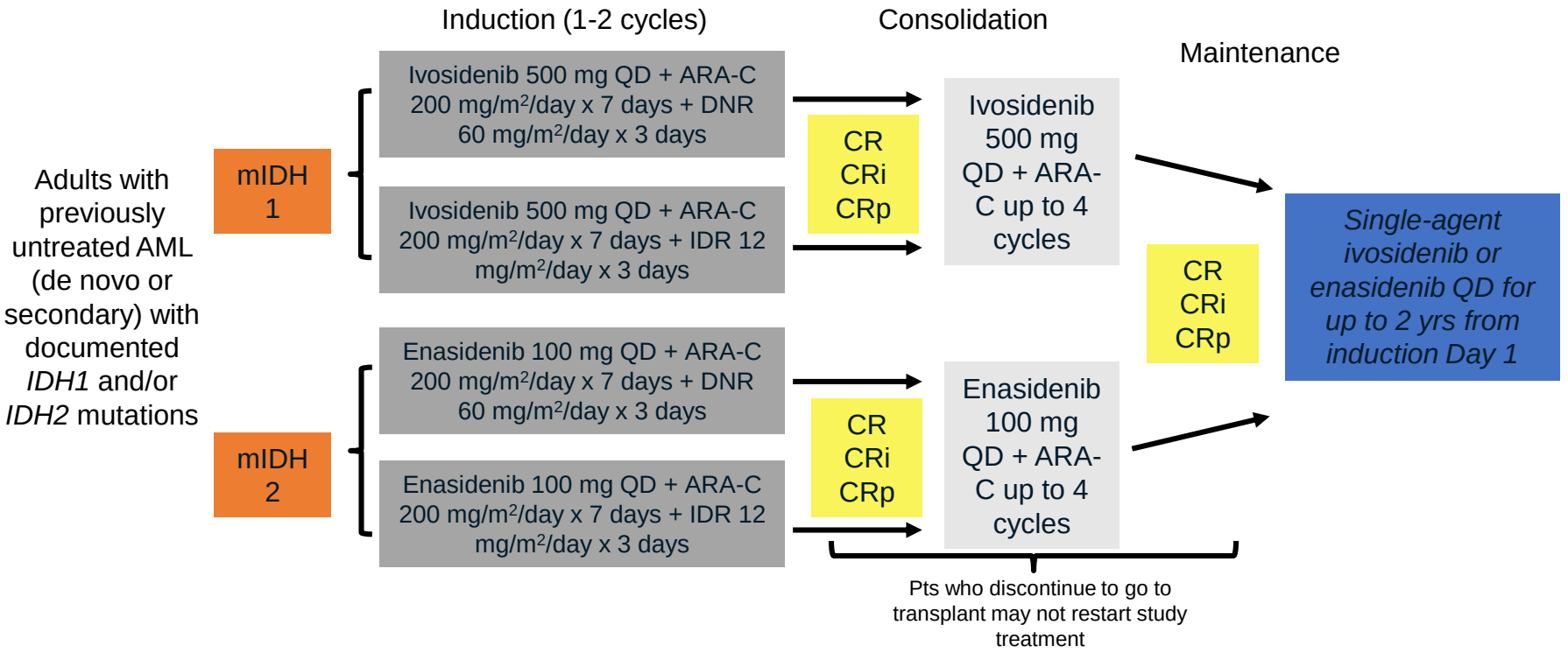
IDH1/2抑制剂在R/R-AML中的疗效

	Enasidenib	Ivosidenib
CR	19.3%	21.6%
ORR	40.3%	41.6%
The median time to a response	1.9 months	1.9 months (range, 0.8 to 4.7)
The median duration of response	5.8 months	6.5 months (95% CI, 4.6 to 9.3)

N Engl J Med 2018;378:2386-98.
Blood. 2017;130:722-731

IDH1/2抑制剂单药在新诊断AML中的疗效

Open-label, phase I dose-escalation and -expansion trial



Primary objectives: safety and tolerability of ivosidenib and enasidenib

BLOOD 2017. 131 726. Blood 2018 132:560

阿扎胞苷联合IVO治疗携带 IDH1 突变的unfit新诊断 AML 患者，安全性良好，ORR达78%

AG221-AML-005（NCT02677922）是一项正在进行中的开放标签、多中心 Ib / II 期研究，主要评估 IVO 或 AG221（enasidenib）联合 AZA 治疗携带 IDH1 或 IDH2 突变的不适合强化治疗的新诊断AML的安全性和有效性 。

此次报告的数据为 IVO + AZA 的数据：中位年龄76岁，继发性 AML（s AML）患者占 26%。细胞遗传学预后中等和预后不良的比例分别为 65% 和 22%，具体用药为 IVO 500mg qd 口服 + **AZA 75mg/m² 皮下 d1-7，28 天一个周期**，直至疾病进展。

	IVO+AZA (n=23)
CR+CRh,%(n)	70(16)
ORR,%(n)	78(18)
CR,%	57
CRi/CRp,%	13
MLFS,%	9
中位至缓解时间，月（范围）	1.8（0.7-3.8）
中位至CR时间，月（范围）	3.5（0.8-6.0）
中位缓解持续时间，月	未达到

All-grade AEs regardless of cause in≥30% its,%	IVO +AZA (n=23)
血小板减少	65
恶心	61
腹泻	57
贫血	52
便秘	52
发热性中粒细胞减少	39
发热	39
呕吐	35
疲乏	35
低钾血症	35
头晕	35
失眠	35
中性粒细胞减少	30

IDH2抑制剂+阿扎胞苷在新诊断AML中的疗效

Enasidenib Plus Azacitidine Significantly Improves Complete Remission and Overall Response Compared with Azacitidine Alone in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) with Isocitrate Dehydrogenase 2 (IDH2) Mutations: Interim Phase II Results from an Ongoing, Randomized Study

ASH2019 Abs643

Table. Clinical efficacy with enasidenib plus azacitidine versus azacitidine monotherapy

	Enasidenib + Azacitidine (N=68)	Azacitidine Monotherapy (N=33)
Overall response rate,*n (%)	**46 (68)**	**14 (42)**
[95%CI]	[55, 79]	[26, 61]
P value	0.0155	
Best response, n (%)		
Complete remission (CR)	34 (50)	4 (12)
[95%CI]	[38, 62]	[3, 28]
P value	0.0002	
CR with incomplete recovery (CRi/CRp)	6 (9)	4 (12)
Partial remission	3 (4)	4 (12)
Morphologic leukemia-free state	3 (4)	2 (6)
Stable disease,† n (%)	15 (22)	13 (39)
Progressive disease, n (%)	2 (3)	1 (3)
Not evaluable, n (%)	1 (2)	0
Missing, n (%)	4 (6)	5 (15)
Time to first response (months), median (range)	1.9 (1–9)	2.0 (1–6)
Duration of response (months), median [95%CI]	NR [11, NR]	10.2 [3, NR]
Time to CR (months), median (range)	5.0 (1–20)	3.7 (3–4)

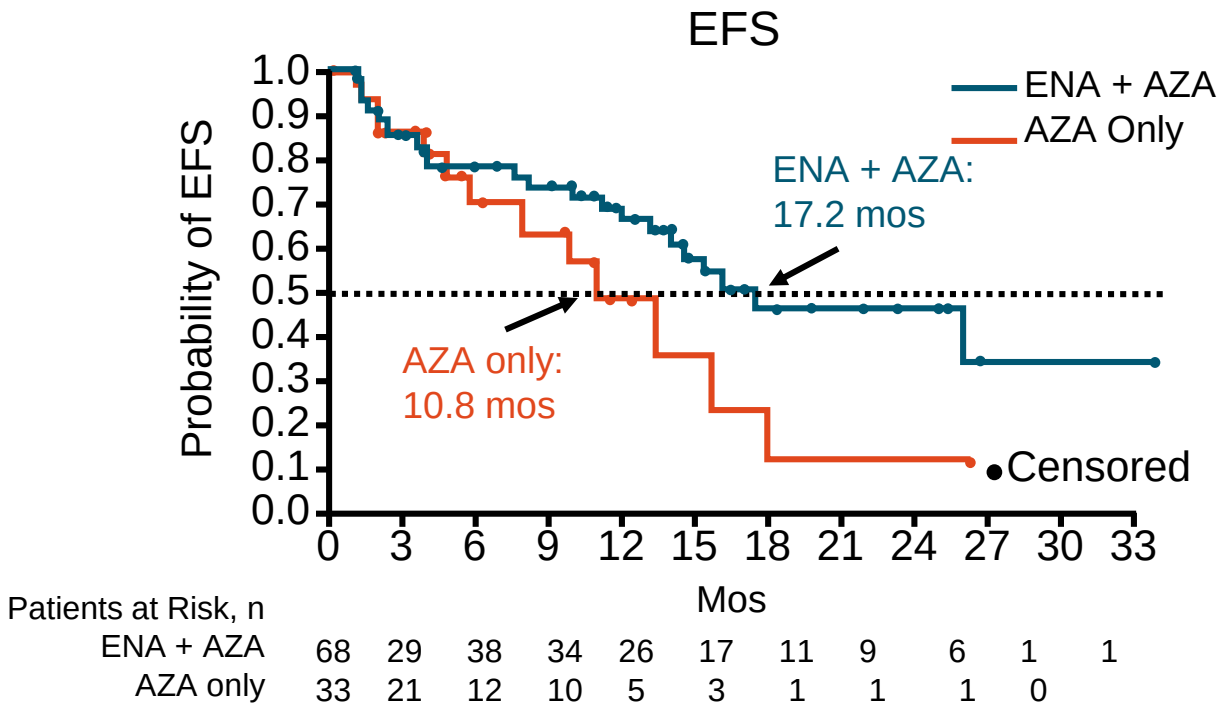
*Overall response comprises complete remission (CR), CR with incomplete hematologic recovery, CR with incomplete platelet recovery, partial remission, or morphologic leukemia-free state, per IWG 2003 AML response criteria.

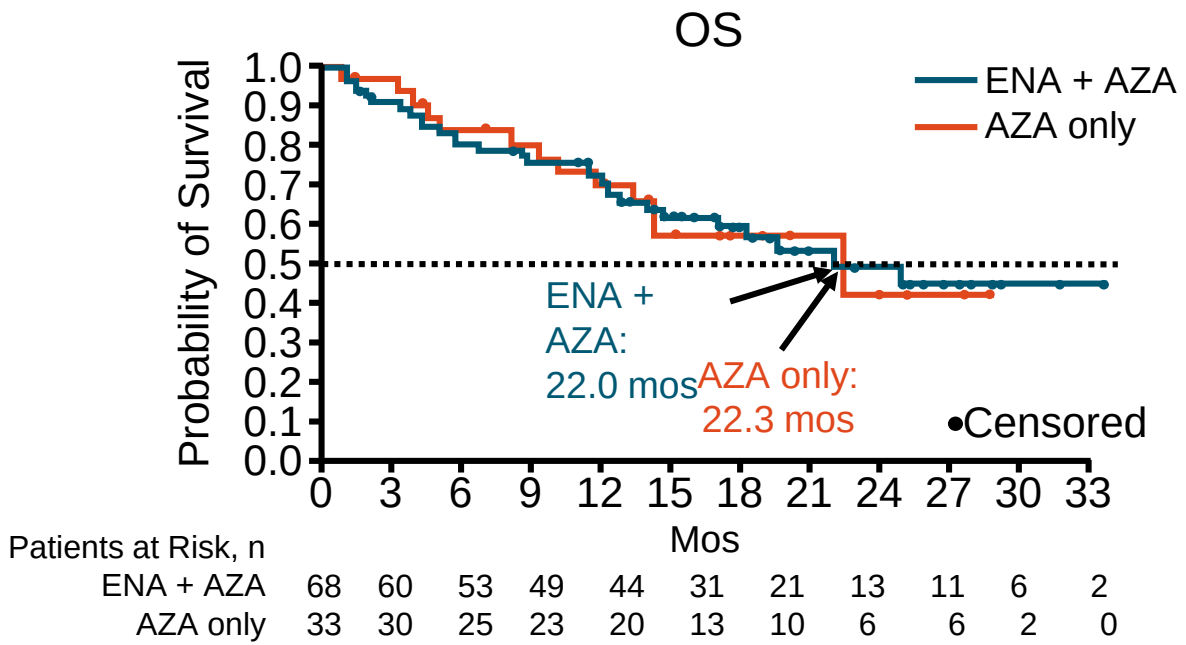
†Absence of hematologic response and not meeting criteria for disease progression, sustained for a period of ≥8 weeks.

P values are from Chi-square test.

95%CI, 95% confidence interval; AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; CRp, CR with incomplete platelet count recovery; IWG, International Working Group; NR, not reached.

IDH2抑制剂+阿扎胞苷治疗新诊断AML的生存情况

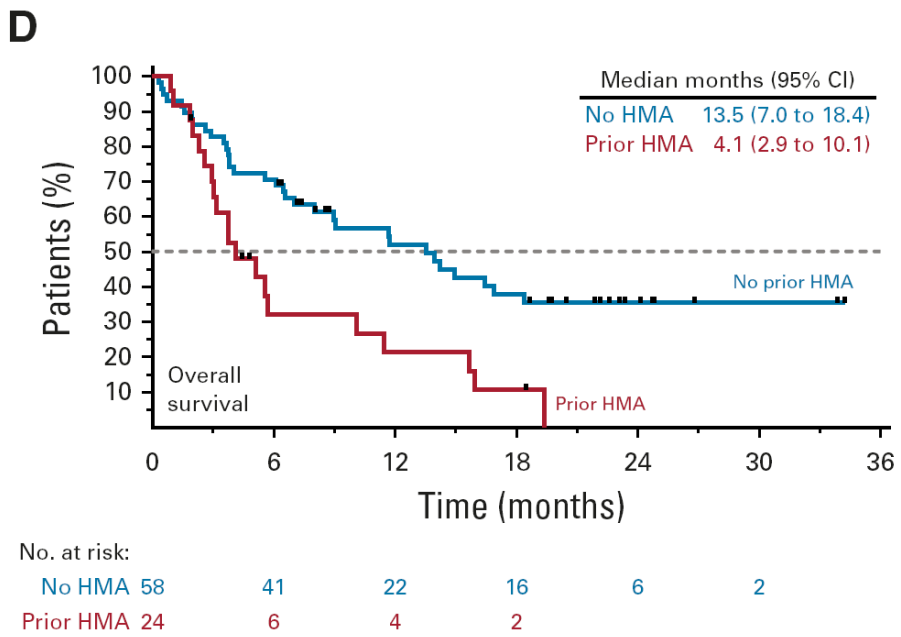




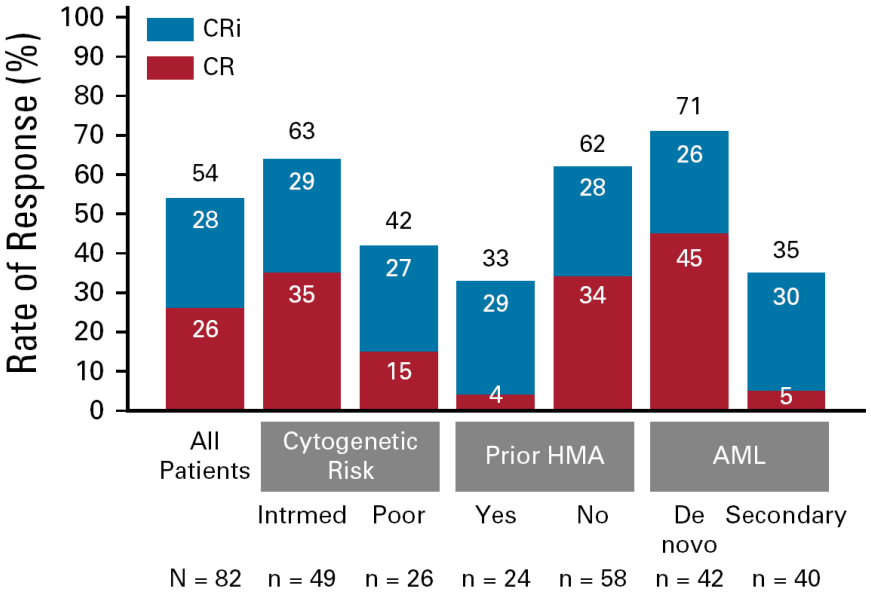
Endpoint	Enasidenib + Azacitidine (n = 68)	Azacitidine Monotherapy (n = 33)	HR (95% CI)	P Value
Median OS, mos	22.0	22.3	0.99 (0.52-1.87)	.9686
Median EFS, mos	17.2	10.8	0.59 (0.30-1.17)	.1278

BCL2抑制剂+低甲基化药物在新诊断老年AML中的疗效

Durable Responses



High Response Rate



Venetoclax + LDAC治疗老年新诊断AML

J Clin Oncol. 2019 Mar 20

BCL2抑制剂+ 低甲基化药物在新诊断老年AML中的疗效

Response to venetoclax in combination with LDAC or HMA in untreated patients with AML patients with IDH, FLT3 and other mutations and correlations with BCL2 family expression

Responses to Venetoclax				
	Complete Remission/incomplete Complete Remission Rate, n (%)	Median Overall Survival (mos)	Median Time to First Response (mos)	Duration of Response (mos)
Molecular Marker cohort N = 167	109 (65.3%)	12.5	1.2	15.0
IDH1/IDH2 Detected n= 43	36 (83.7%)	NR	1.1	NR
NPM1 Detected n= 26	22 (84.6%)	NR	1.3	NR
TP53 Detected n= 37	22 (59.5%)	8.9	1.5	5.6
FLT3 Detected n=30	16 (53.3%)	12.4	1.8	19.9

ASH2019 Abstract 546

Venetoclax联合IA诱导及大剂量Ara-C巩固在新诊断AML中的I期临床试验

Pt Age/Gender	Cytogenetics	NGS (VAF%)	Non-Heme Gr 3/4 Adverse events	Outcome (after single induction cycle)
58F	9q-, +10	DNMT3A(40)	DIC after one dose VEN	MRD neg CR
35M	t(1;11), +10	PTPN11 x 5 (3-9)	Mucositis, elevated ALT	MRD neg CR
62F	Abn 9	RUNX1 (4)	None	MRD neg CR
54F	46, XX	DNMT3A (39), NPM1 (31), IDH1 (35), NRAS x 2, (3,20), PTPN11(8)	None	CR
55M	+4, 17q-	DNMT3A (49), NRAS (27), KIT (11), TET2 x 2 (38, 64), U2AF1 (44)	Intracranial hemorrhage/ hemiparesis, B. cereus bacteremia, elevated ALT/AST/bilirubin	CR
73M	92, XXYY	RUNX1 (42), SRSF2 (42)	Typhlitis, heart failure	Early death (day +14, sepsis)
55M	t(X;10), 5q-	CBL (90), ETV6 (43), RUNX1 (49), SETD2 (49)	S. epidermidis and B. cereus bacteremia	MRD neg CR
56F	+8	PTPN11 (18), IDH1 (4), SRSF2 (13)	Asystolic cardiac arrest, typhlitis, resp failure, acute kidney injury, Klebsiella bacteremia	MRD neg CRi
51F	7q-, +8	IDH2 (28), PHF6 (27)	Elevated AST and ALT	MRD pos CR

Blood (2019) 134 (Supplement_1): 3908

- decreasing AraC to 1.5 g/m^2, and administering VEN for 14 days in ind, and 7 days in cons cycles
- Of 23 R/R pts, 17 pts (74%) achieved a best response of CR/CRi (12 CR, 5 CRi: 3 CRh + 2 CRp). 12 (52%) pts attained MRD negative status by flow cytometry.
- Of 11 ND pts, 10 pts (91%) achieved ORR (9 CR, 1 CRh) and all 10 pts became MRD negative by flow cytometry

ASH2019 Abs176

Venetoclax+去甲基化一线治疗后R/R AML的临床特征

Treatment Characteristics	All Patients (N = 41)
VEN + HMA regimen, n (%) ▪ VEN + DEC10 ▪ VEN + DEC5 ▪ VEN + AZA ▪ VEN + DEC10 + FLT3 inhibitor	 18 (44) 18 (44) 4 (10) 1 (2)
Response to VEN + HMA, n (%) ▪ CR ▪ CRi ▪ MLFS ▪ Primary refractory	 19 (46) 11 (27) 3 (7) 8 (20)
Median duration of response, mos (range)	5.3 (0.9-34.1)
Median VEN + HMA cycles, n (range)	4 (1-29)
AlloSCT in CR1, n (%)	4 (10)

Maiti. ASH 2019. Abstr 738.

Venetoclax+去甲基化一线治疗后R/R AML的治疗仍需进一步探讨

- Outcomes poor for R/R AML after first-line VEN + HMA with median OS of 2.4 mos

Patient Population	n	Median OS, Mos
All patients	41	2.4
Subsequent therapy ▪ Yes ▪ No	 24 17	 2.9 1.3
Disease status ▪ Relapse ▪ Refractory	 33 8	 2.3 1.7
Initial diagnosis ▪ de novo AML ▪ Secondary AML ▪ Therapy-related AML	 22 12 7	 2.5 2.8 1.1

Maiti. ASH 2019. Abstr 738.

APR-246+阿扎胞苷在伴TP53突变MDS和AML中的疗效

Parameter	Overall	MDS	AML	MDS-MPN/CMML
Evaluable patients, n	45	33	8	4
ORR, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Median duration of CR, mos	7.3	7.3	7.0	NE
Discontinued for transplant, n (%)	22 (49)	17 (52)	4 (50)	1 (25)

- 45/45 (100%) evaluable patients had ≥ 1 mutation in *TP53* DNA–binding domain on sequencing
- Absence of co-mutations at BL predicted higher CR rate (69% vs 25%; *P* = .0062) and ORR (93% vs 69%; *P* = .08)
- ≥ 10% p53 IHC+ BM-MNCs predicted higher CR rate (66% vs 13%; *P* = .01)
- 20/45 (44%) patients obtained NGS negativity at VAF threshold of 5%, with 5 (11%) achieving MRD negativity (0.1% sensitivity) with median MRD VAF at maximum clearance of 0.63%

Blood (2019) 134 (Supplement_1): 676.

CD47单抗Magrolimab（5F9）+阿扎胞苷治疗MDS及AML有效

CD47, a macrophage immune checkpoint and “don’t eat me” signal on cancers

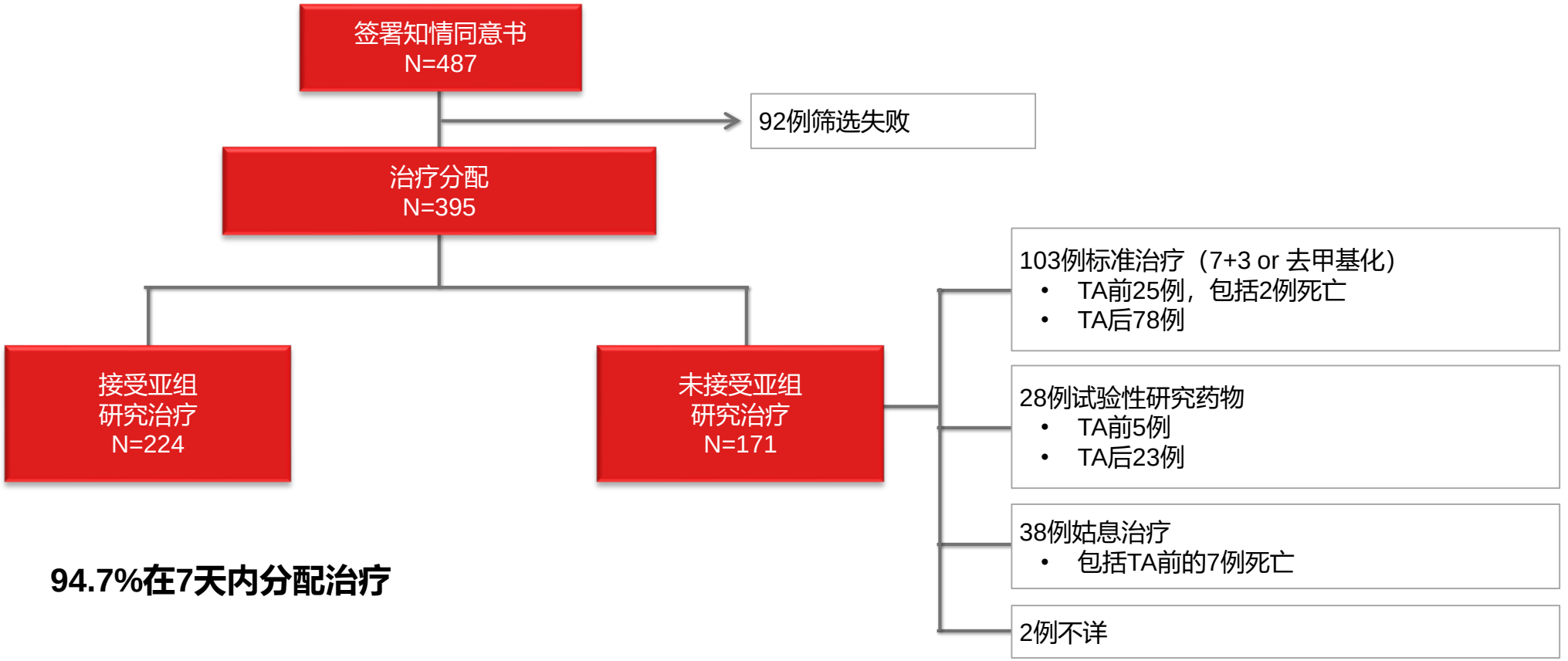
	Magrolimab+AZA (AML: n=16)
ORR, n (%)	11 (69%)
CRi/CR, n (%)	8 (50%)
PR, n (%)	2 (13%)
MLFS, n (%)	1 (6%)
SD, n (%)	5 (31%)

Magrolimab+AZA is a novel immunotherapy regimen that blocks a key macrophage checkpoint.

ASH Abstract 569

3 老年急性髓系白血病的全程治疗

Beat AML Master Trial



94.7%在7天内分配治疗

ASH2019 Abs 175

Beat AML Master Trial

AML Subtype	Drug
CBF	Samalizumab (CD200 Ab) + induction
NPM1 + FLT3-ITD	Entospletinib (Syk inhibitor) + induction (fit) Entospletinib (Syk inhibitor) monotherapy (unfit)
MLL rearranged	Entospletinib (Syk inhibitor)
IDH2 +	Enasidenib
IDH1 +	Ivosidenib + Aza
TP53+	Entospletinib (Syk inhibitor) + Decitabine
TP53 - Complex Karotype (≥ 3 abn)	Entospletinib (Syk inhibitor) + Decitabine
TP53+	Pevonedistat (Nedd8 inhibitor) + Aza
FLT3-ITD+ or FLT3-TKD +	Gilteritinib monotherapy or + Decitabine
Tet2/WTI	BI 836858 (CD33 Ab) + Aza
Marker Negative	BI 836858 (CD33 Ab) + Aza

ASH2018 Abs559

Beat AML Master Trial

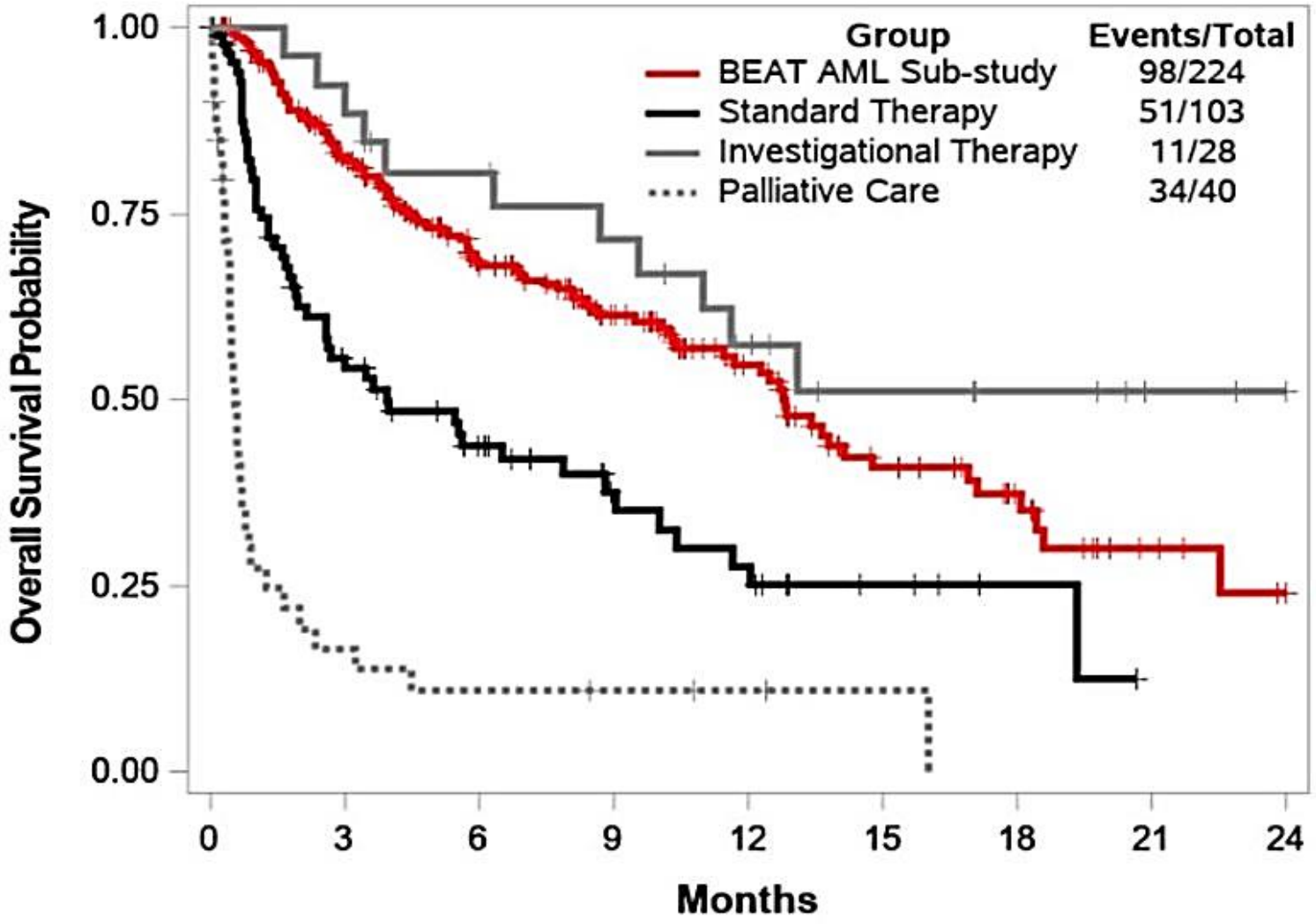
CONCLUSIONS

- Implementation of a rapid treatment assignment umbrella study in elderly AML is feasible with 95% of patients assigned to treatment in ≤ 7 days
- Early death and disease progression prior to treatment assignment is uncommon outside of MLL rearranged AML
- Majority of patients assigned to protocol therapy proceed to trial with increasing frequency as new protocols open
- Promising efficacy observed in several of the treatment arms to date

LEUKEMIA & LYMPHOMA SOCIETY®

ASH2018 Abs559

Beat AML Master Trial中AML的生存情况



HOVON97研究：阿扎胞苷维持治疗可延长老年AML患者DFS

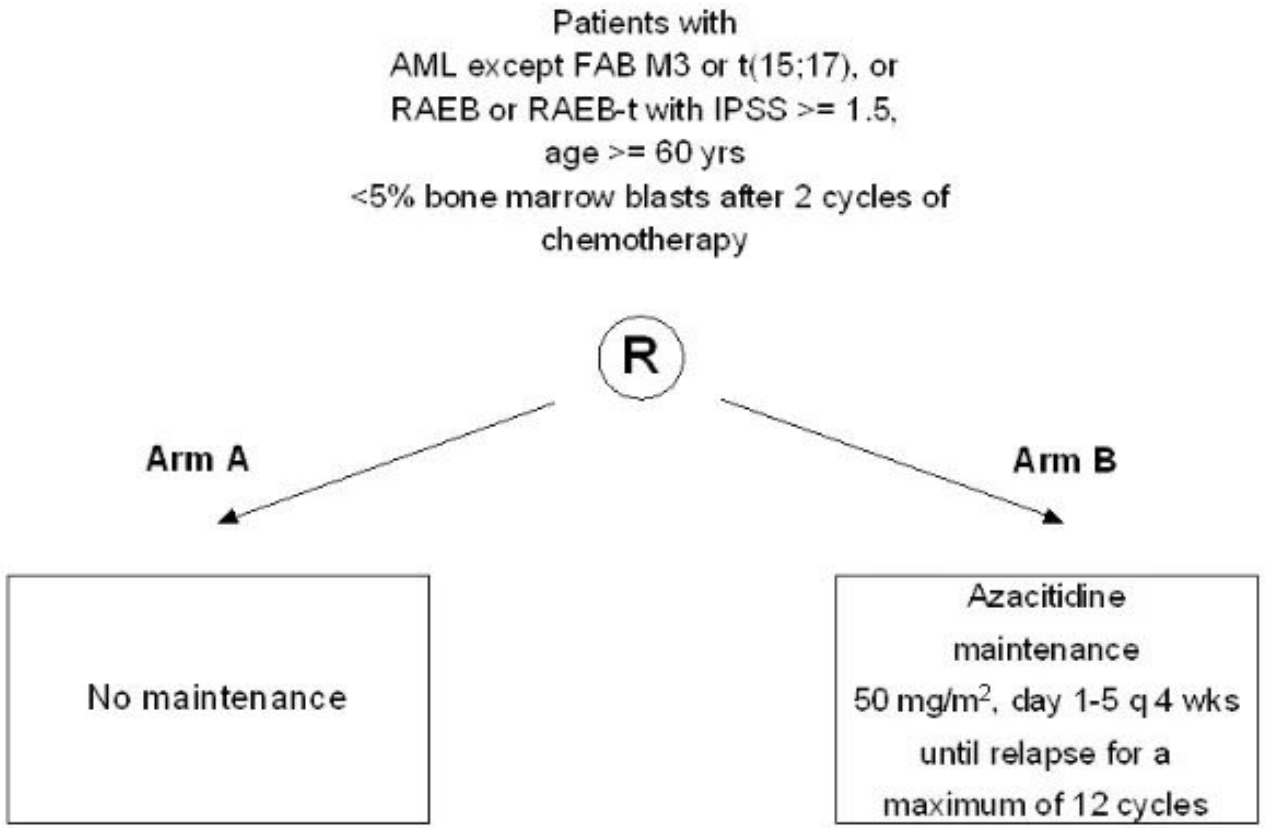
随机性3期临床研究——HOVON-97

N=116，按照1:1分组

A组：观察组

B组：阿扎胞苷组

主要研究终点为DFS，次要研究终点为OS；



Trial design.

Blood (2019) 133 (13)

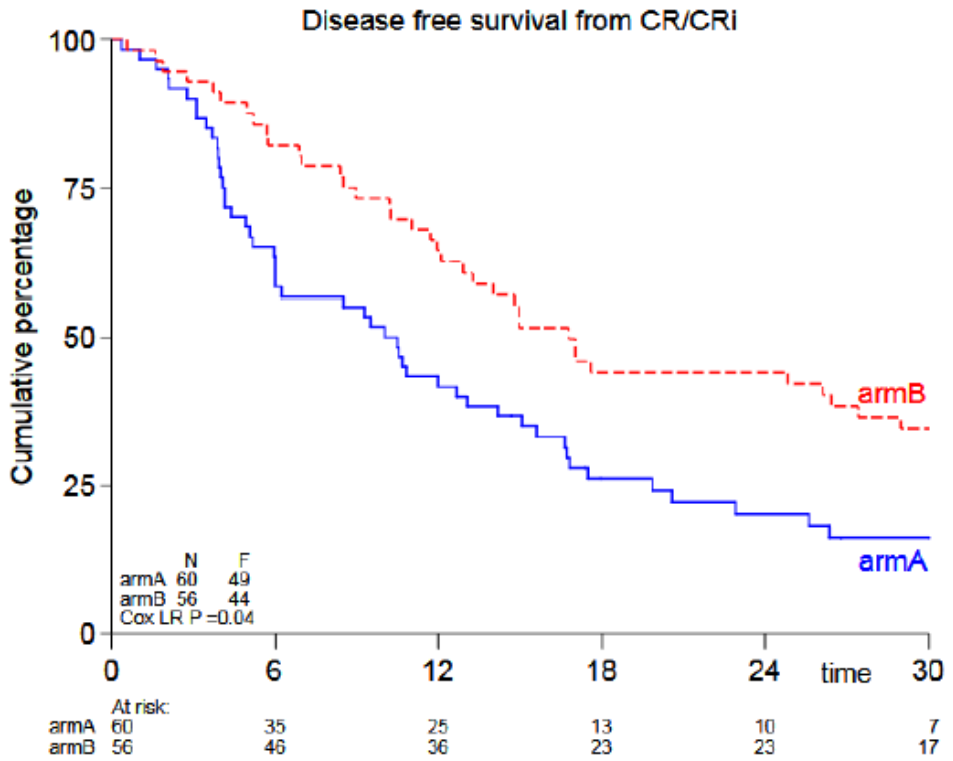
HOVON97研究：阿扎胞苷维持治疗可延长老年AML患者DFS

阿扎胞苷用于这类患者的维持治疗是可行的；

随机化时对诊断时低风险细胞遗传学异常和血小板计数调整后，阿扎胞苷维持治疗组的DFS明显更好

阿扎胞苷组的12个月DFS估计为64%，对照组为42%（P = 0.04）；

24个月和36个月DFS估计为44% vs 20%和32% vs 16%。

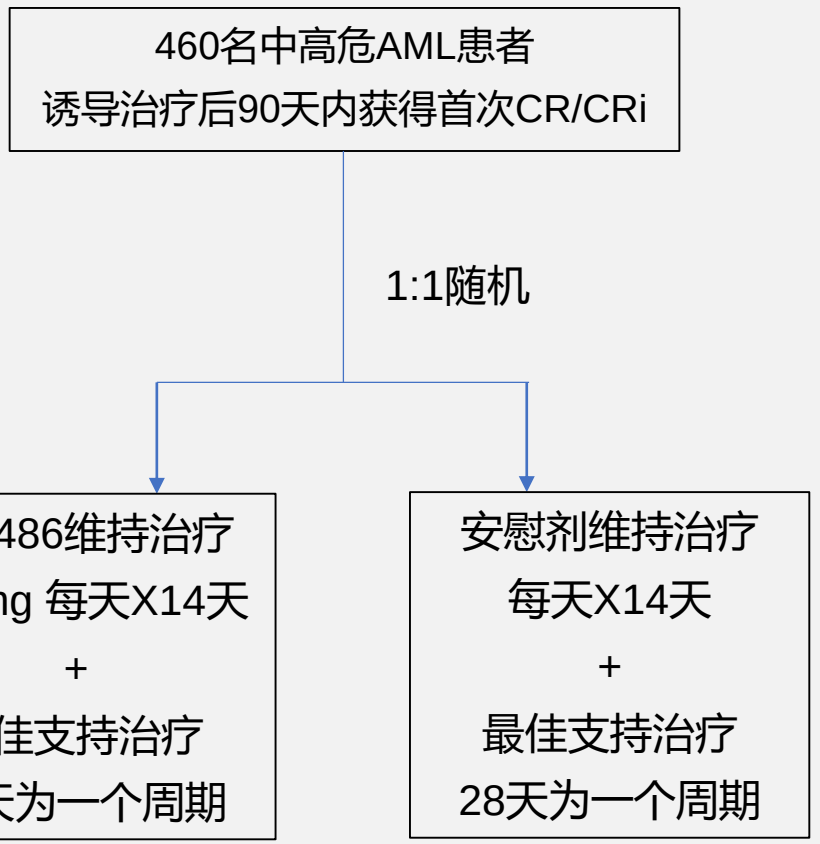


Blood (2019) 133 (13)

QUAZAR AML-001研究是口服AZA用于AML维持治疗

研究设计

1. 含安慰剂对照的III期临床研究，全球13家中心开展。共纳入472名55岁以上中高危AML患者，所有患者均首次通过强烈化疗方案获CR/CRi
2. 患者随机分为CC-486组和安慰剂组，CC-486组接受每周期14天的300mg每天剂量的阿扎胞苷并联合最佳支持治疗，安慰剂组采用同等剂量；每28天为一个周期



研究目的

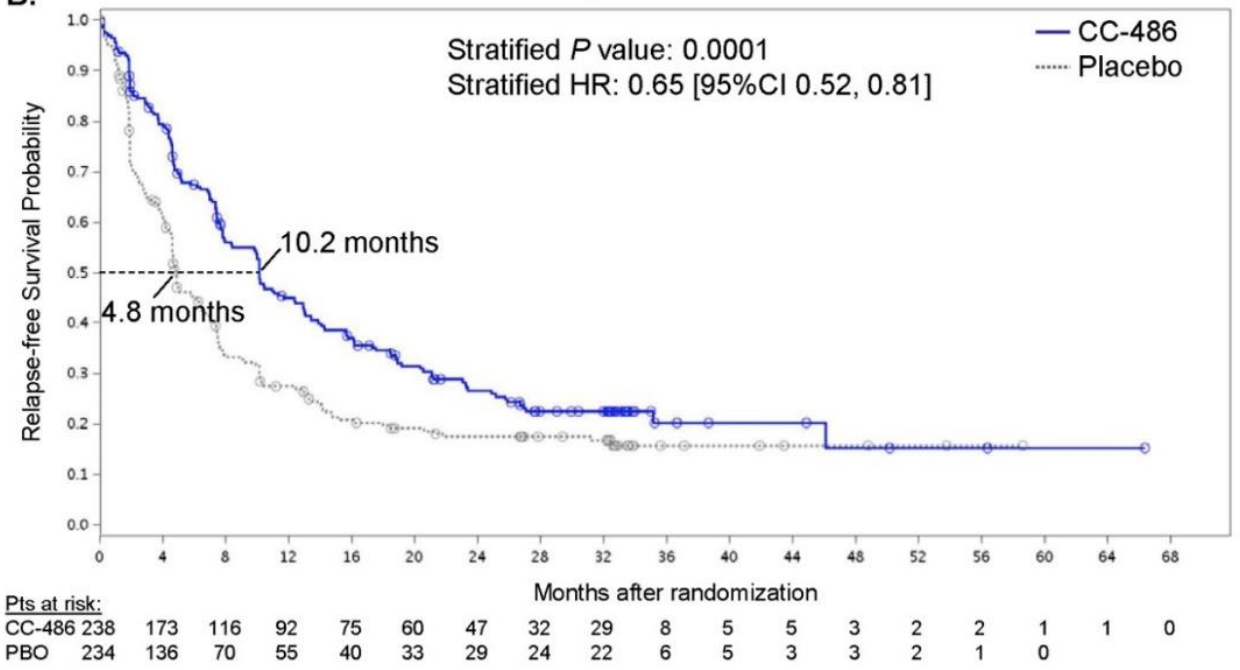
OS、RFS、安全性和耐受性、生活质量评分

Wei. ASH 2019. Abstr LBA_3.

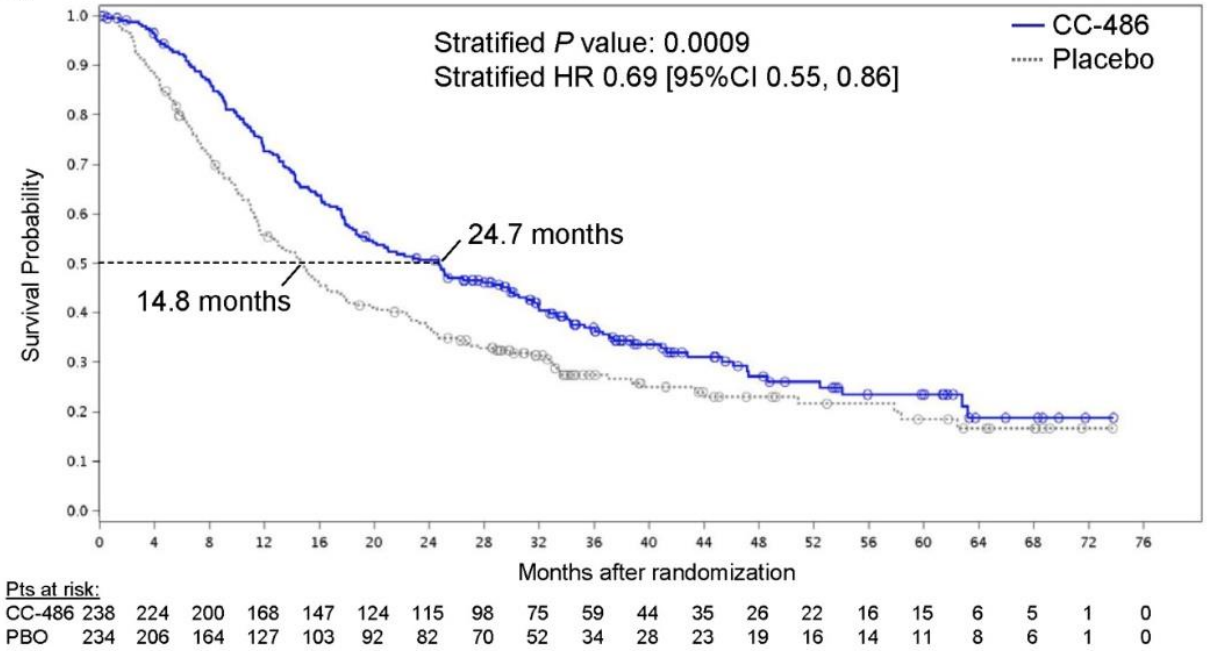
AML的维持治疗：口服阿扎胞苷CC-486用于AML CR1后维持治疗生存获益明显

Figure. Kaplan-Meier plots of (A) overall survival and (B) relapse-free survival, from time of randomization

B.



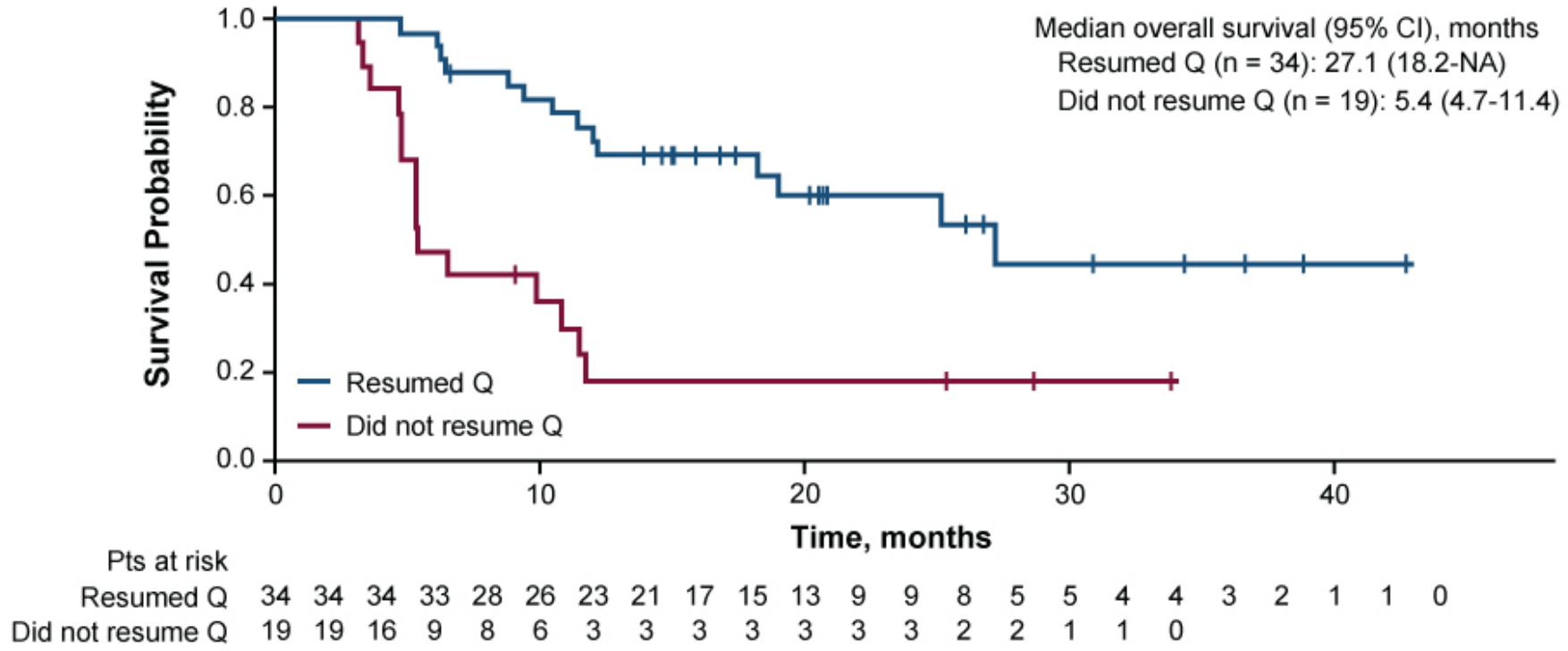
A.



95%CI, 95% confidence interval; HR, hazard ratio; PBO, placebo; Pts, patients

allo-HSCT后Quizartinib维持治疗可带来生存获益

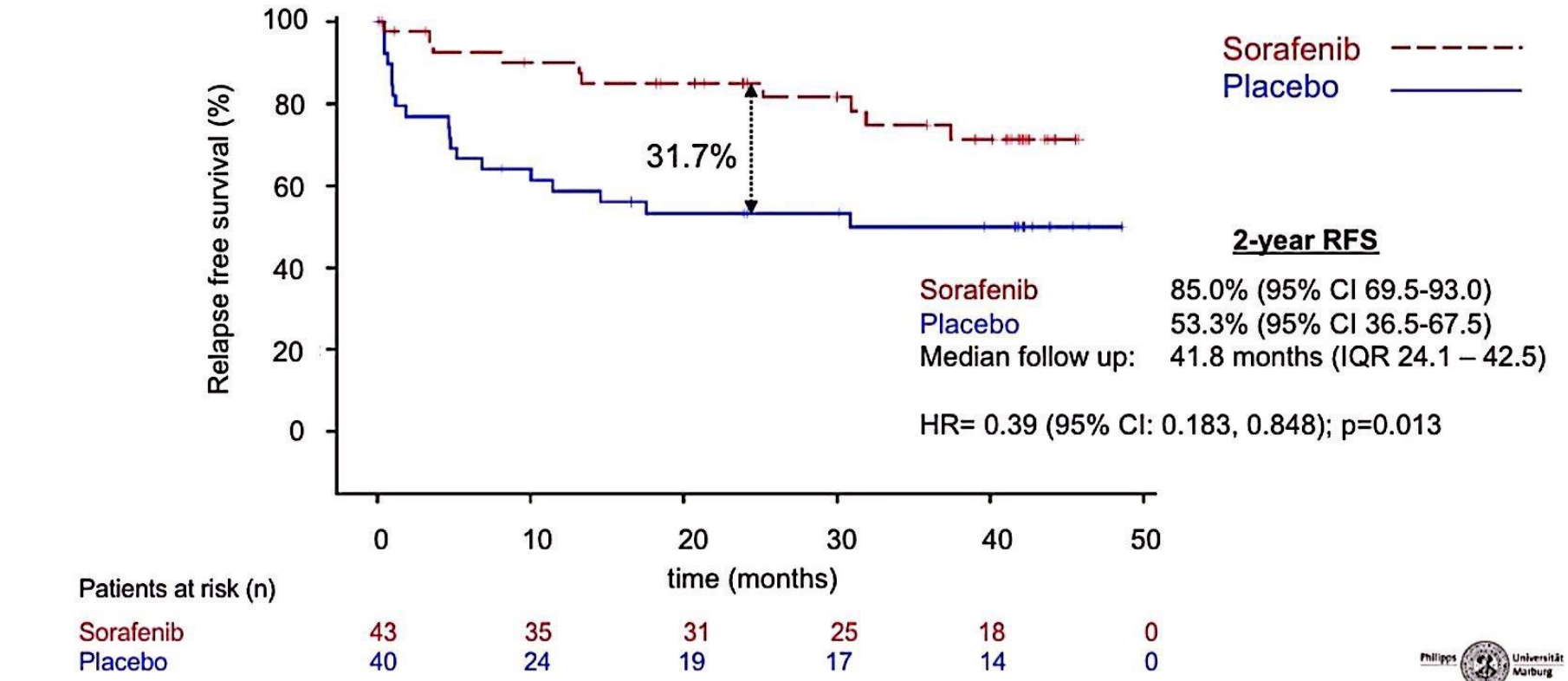
Figure 2. Kaplan-Meier Plot of OS in Pts Who Achieved a Best Overall Response of CRc with Q Who Underwent Allo-HSCT with or without Q Resumption



ASH2019 Abs736

Sorafenib维持治疗可明显延长RFS

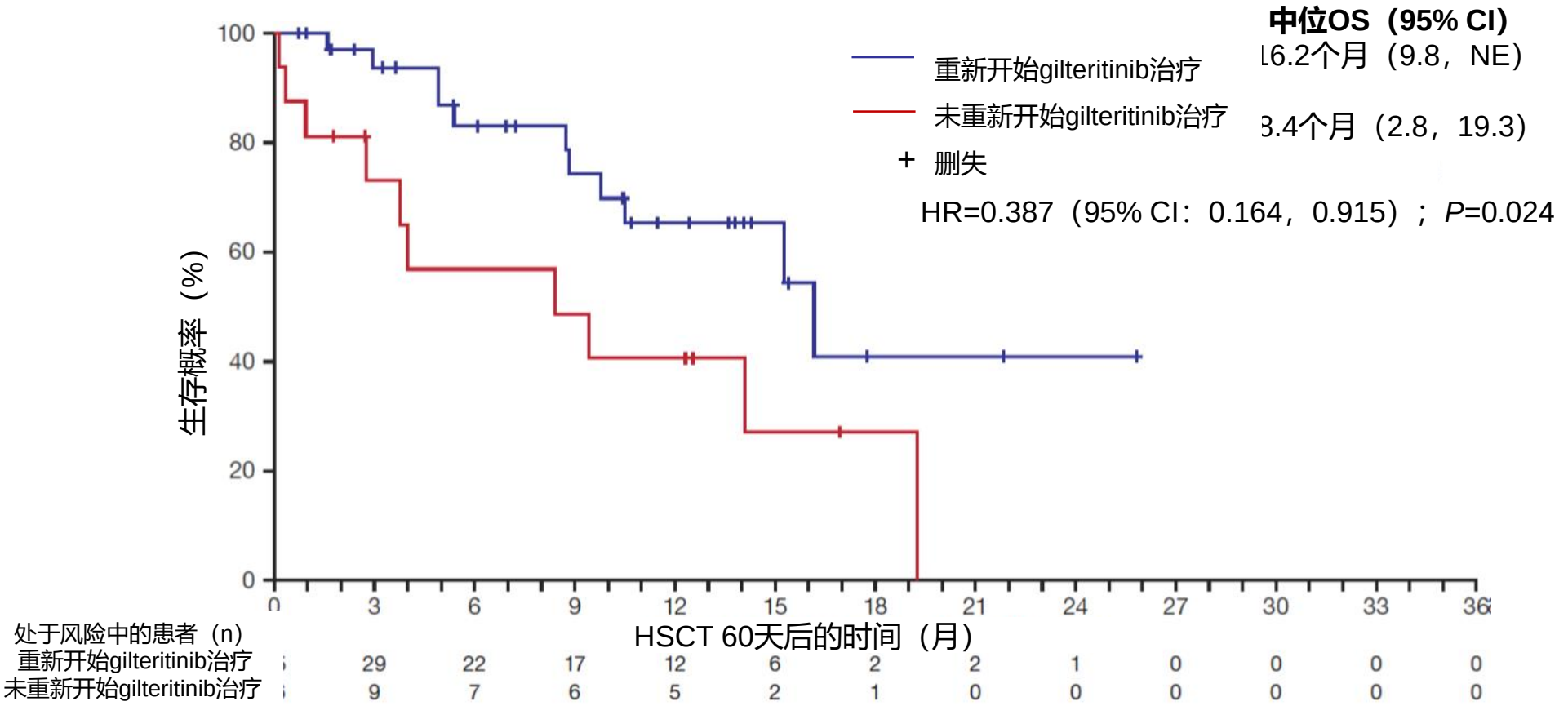
SORMAIN – Results: Relapse free survival



Blood (2018) 132 (Supplement 1): 661.

HSCT后Gilteritinib维持治疗可延长OS

Gilteritinib组的HSCT后生存期：维持治疗的效果
（自HSCT后第60天起的界标分析；n=51）



根据对数秩检验确定双侧*P*值；使用Kaplan-Meier方法结合Greenwood公式确定总生存期和相应的95%置信区间。
缩略语：CI，置信区间；HR，风险比；HSCT，造血干细胞移植；ITT，意向治疗；NE，不可估计； OS，总生存期。

总结

- AML的治疗越来越多的按照遗传学进行分层
- 靶向治疗越来越多的应用于一线、年轻患者
- 更新的药物及治疗方法仍在研究中

New drugs influencing clinical practice in AML

		1st line therapy	Maintenance
Fit for intensive chemo	*FLT3*mut	Intensive chemo + Midostaurin	Midostaurin
	CBF	Intensive chemo + GO	CC-486
	tAML, sAML, AML MRC	CPX-351	
	Alternative non-targeted option	Intensive chemo ± GO	
≥75 or co-morbidities	*FLT3*-ITD	AZA ± FLT3i	
	*IDH1*mut	AZA and/or Ivosidenib	
	*IDH2*mut	AZA and/or Enasidenib	
	*NPM1*mut	HMA or LDAC + Venetoclax	
	Alternative non-targeted option	HMA or LDAC + Venetoclax LDAC + Glasdegib Gemtuzumab ozogomycin	

Relapsed/refractory AML

*IDH1*mut	Ivosidenib
*IDH2*mut	Enasidenib
*FLT3*mut	Gilteritinib
Other	Chemo ± GO