# Addition of the mammalian target of rapamycin inhibitor, everolimus, to consolidation therapy in acute myeloid leukemia: experience from the UK NCRI AML17 trial

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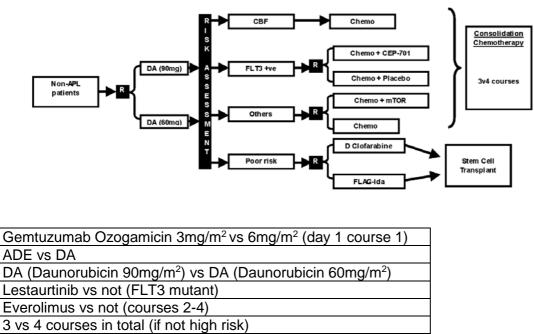
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Received: January 24, 2018. Accepted: July 4, 2018. Pre-published: July 5 2018. Correspondence: akburnett719@gmail.com

#### Supplemental Figure 1: Randomizations Addressed in AML17

#### **Protocol Version 7**

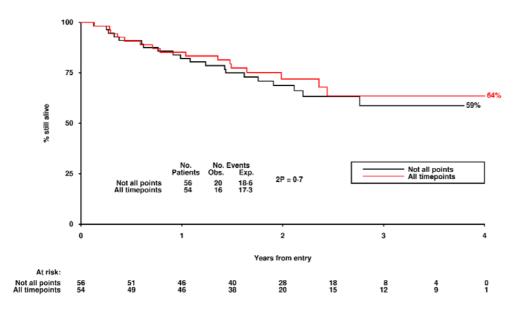


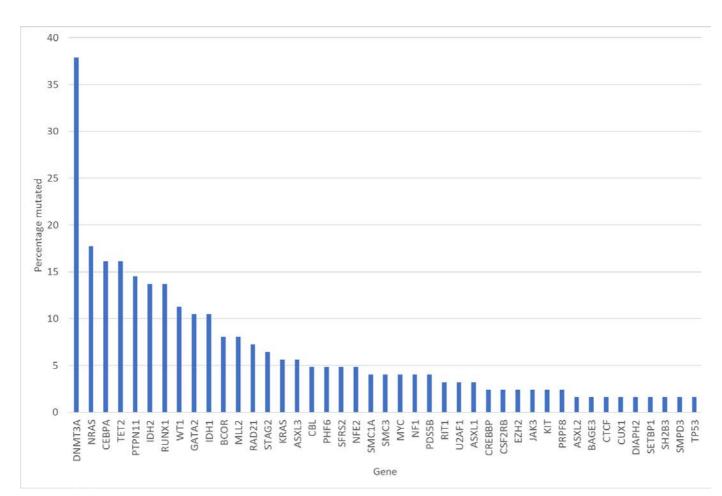
FLAG-Ida vs Daunorubicin/Clofarabine

#### Supplementary Figure 2: Plasma Inhibitory activity (PIA) Measurement.

The protocol requested, with patient agreement, the collection of blood samples pre-dose on day 14 of each course of everolimus treatment. To assess mTOR inhibitory activity, 400µl patient plasma was incubated in triplicate with 5x10<sup>5</sup> HEL cells for 1h at 37°C in a humidified incubator with 5%CO<sub>2</sub>. The approach was similar to those reported for other inhibitory assays.<sup>18</sup> A standard curve of phospho-S6 ribosomal protein (pS6-RP) PIA versus everolimus concentration was generated by spiking healthy volunteer plasma with everolimus that produce clinically-relevant concentrations ranging from 1 to 200ng/ml. In this context an estimate of plasma inhibition of phospho-S6 ribosomal protein (p S6-RP) in response to patient plasma was measured in cell lysates by immunoblotting and ELISA. The results were expressed as a percentage reduction of pS6-RP inhibitory activity compared to the maximum inhibition achieved by a 200ng/ml everolimus concentration which was run in parallel along with a no drug control.

## Overall survival from Everolimus randomization: Inhibition at all vs not at all timepoints (1+ timepoints measured)





## Supplementary Figure 3: Resolution of Sanger data with AML17 mTOR randomisation (n=124)

Mutations in the following genes were found in only one patient and are not shown in the graph:

ATRX	ERCC2	KIAA1267	PTEN	SMG1
CBFB	FBXW7	LUC7L2	PTPRF	STAG1
CBLB	GATA1	MED12	SF1	U2AF2
CBLC	KDM6A	MYH11	SF3B1	ZRSR2
CSF3R	1	1		1

### Supplementary Figure 4: Stratified analysis of Relapse Free Survival. A) Demographics; B) Mutation status (minimum 10 mutant patients with RFS data)

A)

		Events/I Everolimus	Patients Control	Stati (O-E)	stics Var.	O.R. & 95% CI (Everolimus : Control)	
By age:				-			
Age 15-29		16/33	8/15	0.2	5.4		
Age 30-39		23/34	11/17	-0.7	7.1		1.04 (0.45, 2.42)
Age 40–49		38/58	13/31	7.8	11.9		0.90 (0.43, 1.88)
Age 50–59		56/73	25/37	4.2	18·5		1.92 (1.09, 3.40)
Age 60-69		10/20	9/11	-2.5	4.2		1.25 (0.79, 1.98)
· _							0.55 (0.21, 1.44)
-	Subtotal:	<b>143/218</b> ubgroups: $\chi_4^2 = 5.9$ ; P = 0.	66/111	8-9	47.1		1.21 (0.91, 1.61) 2P = 0⋅2; NS
Test for trend	d between subgroups	s: $\chi_1^2 = 0.1$ ; P = 0.8; NS	2; N5				
By sex:							
emale		72/116	43/69	-0.1	26.8		1.00 (0.68, 1.45)
Male		71/102	23/42	8.7	20.8	┝╼╋╌╴	1.52 (0.99, 2.33)
	Subtotal:	143/218	66/111	8-6	47.6		1.20 (0.90, 1.59)
Fest for hete	erogeneity between su	ubgroups: $\chi_1^2 = 2.1$ ; P = 0	1; NS				2P = 0·2; NS
By WBC:							
WBC 0-9.9		95/136	40/64	7.3	30.2	∔∰⊸	1.27 (0.89, 1.82)
NBC 10-49.	.9	34/61	17/34	2.4	12.0		
NBC 50-99.		8/15	6/9	-1.4	3.1	<b>_</b> <sup>_</sup>	1.23 (0.70, 2.16)
NBC 100+		6/6	3/4	1.2	2.2		0.63 (0.21, 1.95) 1.73 (0.46, 6.51)
-	Subtotal:	143/218	66/111	9.5	47.5		1.22 (0.92, 1.63)
_				5-5	47.5		2P = 0.2; NS
lest for hete Test for trend	erogeneity between su d between subgroups	ubgroups: $\chi_3^2 = 1.6$ ; P = 0 s: $\chi_1^2 = 0.1$ ; P = 0.8; NS	7; NS				
By WHO PS							
Performance	e Status 0	112/176	51/87	6.5	37.1		1.19 (0.86, 1.64)
	Status 1	27/37	12/19	2.0	8.7		
		=			1.1 -		1.26 (0.65, 2.45)
Peformance		3/4	2/3				
Peformance Performance	e Status 2	3/4 1/1	2/3 1/2	-0·1 0·2	0.5		0.93 (0.15, 5.78)
Peformance Performance Performance	e Status 2 e Status 3+ Subtotal: erogeneity between su	1/1 <b>143/218</b> ubgroups: $\chi_3^2 = 0.1$ ; P = 1-	1/2 <b>66/111</b>			₽	1.42 (0.08, 24.66)
Peformance Performance Performance	e Status 2 e Status 3+ Subtotal: rrogeneity between su d between subgroups	1/1 <b>143/218</b>	1/2 <b>66/111</b>	0.5	0.5	Ø	1.42 (0.08, 24.66) <b>1.20 (0.90, 1.59</b> )
Peformance Performance Performance Test for hete Test for hete Test for trend By diagnosi	e Status 2 e Status 3+ Subtotal: rrogeneity between su d between subgroups	1/1 <b>143/218</b> ubgroups: $\chi_3^2 = 0.1$ ; P = 1-	1/2 <b>66/111</b>	0.5	0.5	<	1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS
Peformance Performance Performance Test for hete Test for trend By diagnosi de Novo	e Status 2 e Status 3+ Subtotal: rrogeneity between su d between subgroups	1/1 <b>143/218</b> ubgroups: $\chi_3^2 = 0.1$ ; P = 1- s: $\chi_1^2 = 0.0$ ; P = 1-0; NS	1/2 66/111	0∙2 8•6	0·5 47·5		1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS 1.18 (0.88, 1.59)
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Peformance Performance Performance Test for hete Test for hete Test for trend By diagnosi de Novo Secondary High risk MD Test for hete By induction ADE alone (r ADE alone (r ADE alone (r ADE + GO 3m DA + GO 6m DA + GO 6m DA + GO 6m DA (90mg) – DA (90mg) –	e Status 2 e Status 3+ Subtotal: erogeneity between subgroups is: Subtotal: erogeneity between su n therapy: not rand) mg ig 19 9	1/1 143/218 ubgroups: $\chi_3^2 = 0.1$ ; P = 1: s: $\chi_1^2 = 0.0$ ; P = 1:0; NS 130/202 4/5 9/11 143/218 ubgroups: $\chi_2^2 = 0.4$ ; P = 0: 7/13 19/29 17/26 19/24 18/22 19/26 20/37	1/2 66/111 0; NS 60/102 1/3 5/6 66/111 8; NS 4/7 8/14 7/14 8/14 3/10 7/12 13/19	0.2 8.6 7.2 0.9 0.3 8.4 0.2 1.1 2.2 3.2 5.4 1.5 -2.4	0.5 47.5 43.3 1.2 3.2 47.7 2.6 6.0 5.2 6.4 4.8 5.7 7.2		1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS 1.18 (0.88, 1.59) 2.17 (0.35, 13.52) 1.10 (0.37, 3.26) 1.19 (0.90, 1.59) 2P = 0.2; NS 1.07 (0.31, 3.62) 1.20 (0.54, 2.66) 1.53 (0.65, 3.61) 1.65 (0.76, 3.58) 3.05 (1.25, 7.43) 1.29 (0.57, 2.94) 0.72 (0.35, 1.50) 0.74 (0.38, 1.44) 1.20 (0.90, 1.60)
Peformance Performance Performance Test for hete Test for trend By diagnosi de Novo Secondary High risk MD Est for hete By induction ADE alone (r ADE alone (r ADE alone (r ADE + GO 3m ADE + GO 3m DA + GO 6m DA + GO 6m DA (60mg) – DA (90mg) –	e Status 2 e Status 3+ Subtotal: erogeneity between subgroups is: SS Subtotal: erogeneity between su n therapy: not rand) mg ing ig ig ig ig ig ig ig ig ig ig ig ig ig	1/1 143/218 ubgroups: $\chi_3^2 = 0.1$ ; P = 1. s: $\chi_1^2 = 0.0$ ; P = 1.0; NS 130/202 4/5 9/11 143/218 ubgroups: $\chi_2^2 = 0.4$ ; P = 0 7/13 19/29 17/26 19/24 18/22 19/26 20/37 24/41	1/2 66/111 0; NS 60/102 1/3 5/6 66/111 8; NS 4/7 8/14 7/14 8/14 3/10 7/12 13/19 16/21 66/111	0.2 8.6 7.2 0.9 0.3 8.4 0.2 1.1 2.2 3.2 5.4 1.5 -2.4 -2.6	0.5 47.5 43.3 1.2 3.2 47.7 2.6 6.0 5.2 6.4 4.8 5.7 7.2 8.8		1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS 1.18 (0.86, 1.59) 2.17 (0.35, 13.52) 1.10 (0.37, 326) 1.19 (0.90, 1.59) 2P = 0.2; NS 1.07 (0.31, 3.62) 1.20 (0.54, 2.66) 1.53 (0.65, 3.61) 1.65 (0.76, 0.58) 3.05 (1.26, 7.43) 1.29 (0.57, 2.94) 0.72 (0.35, 1.50) 0.74 (0.36, 1.44)
Peformance Performance Performance Test for hete Test for hete Test for trend By diagnosi de Novo Secondary High risk MD Im Test for hete By induction ADE alone (r ADE alone (r ADE alone (r ADE alone (r ADE 4 GO 3m DA + GO 6m DA + GO 7m DA +	e Status 2 e Status 3+ Subtotal: erogeneity between su d between subgroups is: DS Subtotal: erogeneity between su n therapy: not rand) mg ing ig - protocol 7 Subtotal: erogeneity between su	1/1 143/218 ubgroups: $\chi_3^2 = 0.1$ ; P = 1: s: $\chi_1^2 = 0.0$ ; P = 1:0; NS 130/202 4/5 9/11 143/218 ubgroups: $\chi_2^2 = 0.4$ ; P = 0: 7/13 19/29 17/26 19/24 18/22 19/26 20/37 24/41 143/218	1/2 66/111 0; NS 60/102 1/3 5/6 66/111 8; NS 4/7 8/14 7/14 8/14 3/10 7/12 13/19 16/21 66/111	0.2 8.6 7.2 0.9 0.3 8.4 0.2 1.1 2.2 3.2 5.4 1.5 -2.4 -2.6	0.5 47.5 43.3 1.2 3.2 47.7 2.6 6.0 5.2 6.4 4.8 5.7 7.2 8.8		1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS 1.18 (0.88, 1.59) 2.17 (0.35, 13.52) 1.10 (0.37, 3.26) 1.19 (0.90, 1.59) 2P = 0.2; NS 1.07 (0.31, 3.62) 1.20 (0.54, 2.66) 1.53 (0.65, 3.61) 1.65 (0.76, 3.58) 3.05 (1.25, 7.43) 1.29 (0.57, 2.94) 0.72 (0.35, 1.50) 0.74 (0.38, 1.44) 1.20 (0.90, 1.60)
Peformance Performance Performance Test for hete Test for trend By diagnosi de Novo Secondary High risk MD Im Test for hete By induction ADE 4 GO 3m DA 4 GO 6m DA 4 GO 7m A 100 A 1	e Status 2 e Status 3+ Subtotal: erogeneity between su d between subgroups is: DS Subtotal: erogeneity between su n therapy: not rand) mg ng ng ng ng ng ng ng ng ng subtotal: e protocol 7 Subtotal: erogeneity between su status:	1/1 143/218 ubgroups: $\chi_3^2 = 0.1$ ; P = 1: s: $\chi_1^2 = 0.0$ ; P = 1:0; NS 130/202 4/5 9/11 143/218 ubgroups: $\chi_2^2 = 0.4$ ; P = 0: 7/13 19/29 17/26 19/24 18/22 19/26 20/37 24/41 143/218	1/2 66/111 0; NS 60/102 1/3 5/6 66/111 8; NS 4/7 8/14 7/14 8/14 3/10 7/12 13/19 16/21 66/111	0.2 8.6 7.2 0.9 0.3 8.4 0.2 1.1 2.2 3.2 5.4 1.5 -2.4 -2.6	0.5 47.5 43.3 1.2 3.2 47.7 2.6 6.0 5.2 6.4 4.8 5.7 7.2 8.8		1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS 1.18 (0.88, 1.59) 2.17 (0.35, 13.52) 1.10 (0.37, 326) 1.9 (0.90, 1.59) 2P = 0.2; NS 1.07 (0.31, 3.62) 1.20 (0.54, 2.66) 1.53 (0.65, 3.61) 1.65 (0.76, 3.58) 3.05 (1.26, 7.43) 1.28 (0.57, 2.94) 0.72 (0.35, 1.50) 0.74 (0.36, 1.44) 1.20 (0.90, 1.60) 2P = 0.2; NS
Peformance Performance Performance Performance Test for hete Test for hete Test for hete By induction ADE alone (n ADE alone (n ADE alone (n ADE 4 GO 3m DA + GO 6m DA + GO 7m DA + GO 7m DA + GO 7m DA + GO 7m DA + GO 7m D	e Status 2 e Status 3+ Subtotal: erogeneity between su d between subgroups is: OS Subtotal: erogeneity between su n therapy: not rand) mg ing - protocol 7 Subtotal: erogeneity between su status: is: MRD-	1/1 143/218 ubgroups: $\chi_3^2 = 0.1$ ; P = 1. s: $\chi_1^2 = 0.0$ ; P = 1.0; NS 130/202 4/5 9/11 143/218 ubgroups: $\chi_2^2 = 0.4$ ; P = 0. 7/13 19/29 17/26 19/24 18/22 19/26 20/37 24/41 143/218 ubgroups: $\chi_7^2 = 9.2$ ; P = 0.	1/2 66/111 0; NS 60/102 1/3 5/6 66/111 8; NS 4/7 8/14 7/14 8/14 3/10 7/12 13/19 16/21 66/111 2; NS	0.2 8.6 7.2 0.9 0.3 8.4 0.2 1.1 2.2 3.2 5.4 1.5 -2.4 -2.6 8.6	0.5 47.5 43.3 1.2 3.2 47.7 2.6 6.0 5.2 6.4 4.8 5.7 7.2 8.8 46.8		1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS 1.18 (0.86, 1.59) 2.17 (0.35, 13.52) 1.10 (0.37, 326) 1.09 (0.90, 1.59) 2P = 0.2; NS 1.07 (0.31, 3.62) 1.20 (0.54, 2.66) 1.53 (0.65, 3.61) 1.65 (0.76, 3.58) 3.05 (1.25, 7.43) 1.29 (0.57, 2.94) 0.72 (0.35, 1.50) 0.74 (0.38, 1.44) 1.20 (0.90, 1.60) 2P = 0.2; NS 1.10 (0.56, 2.15)
Performance Performance Performance Performance Test for hete Fest for hete Fest for hete By diagnosi de Novo Secondary High risk MD Fest for hete By induction ADE alone (r ADE alone (r ADE alone (r ADE alone (r ADE 4 GO 3r ADE 4 GO 3	e Status 2 e Status 3+ Subtotal: progeneity between su d between subgroups is: DS Subtotal: progeneity between su n therapy: not rand) mg ng pg - protocol 7 Subtotal: protocol 7 Subtotal:	1/1 143/218 ubgroups: $\chi_3^2 = 0.1$ ; P = 1: s: $\chi_1^2 = 0.0$ ; P = 1:0; NS 130/202 4/5 9/11 143/218 ubgroups: $\chi_2^2 = 0.4$ ; P = 0: 7/13 19/29 17/26 19/24 18/22 19/26 20/37 24/41 143/218 ubgroups: $\chi_7^2 = 9.2$ ; P = 0: 24/43	1/2 66/111 0; NS 60/102 1/3 5/6 66/111 8; NS 4/7 8/14 7/14 8/14 3/10 7/12 13/19 16/21 66/111 2; NS 14/24	0.2 8.6 7.2 0.9 0.3 8.4 0.2 1.1 2.2 3.2 5.4 1.5 -2.4 -2.6 8.6 8.6	0.5 47.5 43.3 1.2 3.2 47.7 2.6 6.0 5.2 6.4 4.8 5.7 7.2 8.8 46.8 8.6		1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS 1.18 (0.86, 1.59) 2.17 (0.35, 13.52) 1.10 (0.37, 326) 1.07 (0.31, 3.62) 1.20 (0.54, 2.66) 1.53 (0.65, 3.61) 1.65 (0.76, 3.58) 3.05 (1.25, 7.43) 1.29 (0.57, 2.94) 0.72 (0.35, 1.50) 0.74 (0.38, 1.44) 1.20 (0.90, 1.60) 2P = 0.2; NS 1.10 (0.56, 2.15) 1.65 (0.97, 2.82)
Peformance Performance Performance Performance Test for hete Test for trend By diagnosi de Novo Secondary High risk MD Im Test for hete By induction ADE alone (r ADE alone (r ADE alone (r ADE alone (r ADE 4 GO 3m DA + GO 6m DA (90mg) – Im Test for hete By course 1 Confirmed C Confirmed C	e Status 2 e Status 3+ Subtotal: progeneity between su d between subgroups is: DS Subtotal: progeneity between su n therapy: not rand) mg ng pg - protocol 7 Subtotal: protocol 7 Subtotal:	1/1 143/218 ubgroups: $\chi_3^2 = 0.1$ ; P = 1: s: $\chi_1^2 = 0.0$ ; P = 1:0; NS 130/202 4/5 9/11 143/218 ubgroups: $\chi_2^2 = 0.4$ ; P = 0: 7/13 19/29 17/26 19/24 18/22 19/26 20/37 24/41 143/218 ubgroups: $\chi_7^2 = 9.2$ ; P = 0: 24/43 47/63	1/2 66/111 60; NS 60/102 1/3 5/6 66/111 8; NS 4/7 8/14 7/14 8/14 3/10 7/12 13/19 16/21 66/111 2; NS 14/24 14/24	0.2 8.6 7.2 0.9 0.3 8.4 0.2 1.1 2.2 3.2 5.4 1.5 -2.4 -2.6 8.6 8.6	0.5 47.5 43.3 1.2 3.2 47.7 2.6 6.0 5.2 6.4 4.8 5.7 7.2 8.8 46.8 8.6 13.6		1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS 1.18 (0.88, 1.59) 2.17 (0.35, 13.52) 1.10 (0.37, 3.26) 1.19 (0.90, 1.59) 2P = 0.2; NS 1.07 (0.31, 3.62) 1.20 (0.54, 2.66) 1.53 (0.65, 3.61) 1.65 (0.76, 3.58) 3.05 (1.25, 7.43) 1.29 (0.57, 2.94) 0.72 (0.35, 1.50) 0.74 (0.38, 1.44) 1.20 (0.90, 1.60) 2P = 0.2; NS 1.10 (0.56, 2.15) 1.65 (0.97, 2.82) 0.67 (0.23, 3.22) 1.35 (0.91, 2.01)
Peformance Performance Performance Performance Test for hete Test for hete Test for hete By diagnosi de Novo Secondary High risk MD Test for hete By induction ADE + GO 3m ADE + GO 6m DA + GO 6m CAE + GO	e Status 2 e Status 3+ Subtotal: progeneity between subgroups is: DS Subtotal: progeneity between subgroups is: DS Subtotal: progeneity between subgroups is: not rand) mg ig ig - protocol 7 Subtotal: progeneity between subgroups is: Subtotal: progeneity between subgroups is: Subtotal: progeneity between subgroups is: Subtotal: Subtotal:	1/1 143/218 ubgroups: $\chi_3^2 = 0.1$ ; P = 1. s: $\chi_1^2 = 0.0$ ; P = 1.0; NS 130/202 4/5 9/11 143/218 ubgroups: $\chi_2^2 = 0.4$ ; P = 0 7/13 19/29 17/26 19/24 18/22 19/26 20/37 24/41 143/218 ubgroups: $\chi_7^2 = 9.2$ ; P = 0 24/43 47/63 4/8 75/114 ubgroups: $\chi_2^2 = 1.3$ ; P = 0	1/2 66/111 0; NS 60/102 1/3 5/6 66/111 8; NS 4/7 8/14 7/14 8/14 3/10 7/12 13/19 16/21 66/111 2; NS 14/24 14/24 5/9 33/57	0.2 8.6 7.2 0.9 0.3 8.4 0.2 1.1 2.2 3.2 5.4 1.5 -2.4 -2.6 8.6 8.6 0.8 6.8 -0.3	0.5 47.5 43.3 1.2 3.2 47.7 2.6 6.0 5.2 6.4 4.8 5.7 7.2 8.8 46.8 8.6 13.6 2.2		1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS 1.18 (0.86, 1.59) 2.17 (0.35, 13.52) 1.10 (0.37, 326) 1.19 (0.90, 1.59) 2P = 0.2; NS 1.07 (0.31, 3.62) 1.20 (0.54, 2.66) 1.53 (0.65, 3.61) 1.65 (0.76, 3.58) 3.05 (1.26, 7.43) 1.29 (0.57, 2.94) 0.72 (0.35, 1.50) 0.74 (0.36, 1.44) 1.20 (0.90, 1.60) 2P = 0.2; NS 1.10 (0.56, 2.15) 1.65 (0.97, 2.82) 0.87 (0.23, 3.22)
Peformance Performance Performance Performance Test for hete Test for hete Test for hete By diagnosi de Novo Secondary High risk MD Test for hete By induction ADE + GO 3m ADE + GO 6m DA + GO 6m CAE + GO	e Status 2 e Status 3+ Subtotal: progeneity between subgroups is: DS Subtotal: progeneity between subgroups is: DS Subtotal: progeneity between subgroups is: not rand) mg ig ig - protocol 7 Subtotal: progeneity between subgroups is: Subtotal: progeneity between subgroups is: Subtotal: progeneity between subgroups is: Subtotal: Subtotal:	1/1 143/218 ubgroups: $\chi_3^2 = 0.1$ ; P = 1. s: $\chi_1^2 = 0.0$ ; P = 1.0; NS 130/202 4/5 9/11 143/218 ubgroups: $\chi_2^2 = 0.4$ ; P = 0. 7/13 19/29 17/26 19/24 18/22 19/26 20/37 24/41 143/218 ubgroups: $\chi_7^2 = 9.2$ ; P = 0. 24/43 47/63 4/8	1/2 66/111 0; NS 60/102 1/3 5/6 66/111 8; NS 4/7 8/14 7/14 8/14 3/10 7/12 13/19 16/21 66/111 2; NS 14/24 14/24 5/9 33/57	0.2 8.6 7.2 0.9 0.3 8.4 0.2 1.1 2.2 3.2 5.4 1.5 -2.4 -2.6 8.6 8.6 0.8 6.8 -0.3	0.5 47.5 43.3 1.2 3.2 47.7 2.6 6.0 5.2 6.4 4.8 5.7 7.2 8.8 46.8 8.6 13.6 2.2		1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS 1.18 (0.88, 1.59) 2.17 (0.35, 13.52) 1.10 (0.37, 3.26) 1.19 (0.90, 1.59) 2P = 0.2; NS 1.07 (0.31, 3.62) 1.20 (0.54, 2.66) 1.53 (0.65, 3.61) 1.65 (0.76, 3.58) 3.05 (1.25, 7.43) 1.29 (0.57, 2.94) 0.77 (0.35, 1.50) 0.74 (0.36, 1.44) 1.20 (0.90, 1.60) 2P = 0.2; NS 1.10 (0.56, 2.15) 1.65 (0.97, 2.82) 0.67 (0.23, 3.22) 1.35 (0.91, 2.01)
Peformance Performance Performance Performance Test for hete Test for hete Test for hete By diagnosi de Novo Secondary High risk MD Test for hete By induction ADE alone (r ADE alone (r ADE alone (r ADE alone (r ADE alone (r ADE 4 GO 3r ADE + GO 6 DA + GO 3r DA + G	e Status 2 e Status 3+ Subtotal: progeneity between subgroups is: DS Subtotal: progeneity between subgroups is: DS Subtotal: progeneity between subgroups is: not rand) mg ig ig - protocol 7 Subtotal: progeneity between subgroups is: Subtotal: progeneity between subgroups is: Subtotal: progeneity between subgroups is: Subtotal: Subtotal:	1/1 143/218 ubgroups: $\chi_3^2 = 0.1$ ; P = 1. s: $\chi_1^2 = 0.0$ ; P = 1.0; NS 130/202 4/5 9/11 143/218 ubgroups: $\chi_2^2 = 0.4$ ; P = 0 7/13 19/29 17/26 19/24 18/22 19/26 20/37 24/41 143/218 ubgroups: $\chi_7^2 = 9.2$ ; P = 0 24/43 47/63 4/8 75/114 ubgroups: $\chi_2^2 = 1.3$ ; P = 0	1/2 66/111 0; NS 60/102 1/3 5/6 66/111 8; NS 4/7 8/14 7/14 8/14 3/10 7/12 13/19 16/21 66/111 2; NS 14/24 14/24 5/9 33/57	0.2 8.6 7.2 0.9 0.3 8.4 0.2 1.1 2.2 3.2 5.4 1.5 -2.4 -2.6 8.6 8.6 0.8 6.8 -0.3	0.5 47.5 43.3 1.2 3.2 47.7 2.6 6.0 5.2 6.4 4.8 5.7 7.2 8.8 46.8 8.6 13.6 2.2		1.42 (0.08, 24.66) 1.20 (0.90, 1.59) 2P = 0.2; NS 1.18 (0.88, 1.59) 2.17 (0.35, 13.52) 1.10 (0.37, 3.26) 1.19 (0.90, 1.59) 2P = 0.2; NS 1.07 (0.31, 3.62) 1.20 (0.54, 2.66) 1.53 (0.65, 3.61) 1.65 (0.76, 3.58) 3.05 (1.25, 7.43) 1.29 (0.57, 2.94) 0.72 (0.35, 1.50) 0.74 (0.38, 1.44) 1.20 (0.90, 1.60) 2P = 0.2; NS 1.10 (0.56, 2.15) 1.65 (0.97, 2.82) 0.87 (0.23, 3.22) 1.35 (0.91, 2.01)

Effect 2P = 0.2; NS

		Events/P Everolimus	atients Control	(O-E) Statis	tics Var.	O.R. & 95% Cl (Everolimus : Control)	
y FLT3 ITD	):						
fild type		130/197	57/100	9.7	42-7	┼╋╌	1.25 (0.93, 1.69
utant		6/8	1/1	-0-7	0-2		0.03 (0.00, 2.21
	Subtotal:	136/205	58/101	8-9	43-0		1.23 (0.91, 1.6 2P = 0.2; NS
st for heter	rogeneity between subgroup	os: X <sup>2</sup> <sub>1</sub> = 2·9; P = 0·09					
NPM1c:		07400	20.00	10.0	00 F		
fild type utant		97/130 36/70	38/60 19/39	10·0 0·5	30·5 12·6		1.39 (0.97, 1.98 1.04 (0.60, 1.81
	Subtotal:	133/200	57/99	10-6	43.1		1.28 (0.95, 1.
							2P = 0.1; N
st for heter	rogeneity between subgroup	os: $\chi_1^e = 0.7$ ; P = 0.4; NS					
ild type	.D:	133/202	57/99	9.4	43.0	, <b>a</b>	1.25 (0.92, 1.6
utant		3/3	1/2	0.5	0-9		1.71 (0.22, 13.5
	Subtotal:	136/205	58/101	9.9	43-9		1.25 (0.93, 1. 2P = 0.1; N
et for heter	rogeneity between subgroup	$2^{2} - 0.1 \cdot P - 0.8 \cdot NS$					2P = 0.1; N
DNMT3A		55. x <sub>1</sub> = 0.1, P = 0.0, 145					
ild Type	••	31/49	14/29	4.1	10.7		1.47 (0.81, 2.67
utant	<b></b>	21/31	6/15	4.0	6-2		1.92 (0.87, 4.20
-	Subtotal:	52/80	20/44	8-1	16-9		1.62 (1.00, 2. 2P = 0.05
	rogeneity between subgroup	os: $\chi^2_1 = 0.3$ ; P = 0.6; NS					
NRAS: Id Type		44/67	18/36	5.9	14-4	┶━	1 50 10 00 0 5
utant		8/13	2/8	2.6	2.5	+	1.50 (0.90, 2.5) 2.87 (0.82, 9.9)
	Subtotal:	52/80	20/44	8-5	16-9		1.65 (1.02, 2. 2P = 0.04
st for heter	rogeneity between subgroup	os: $\chi^2_1 = 0.9$ ; P = 0.3; NS					21 2 0 0 4
CEBPA:							
ild Type utant		44/69 8/11	17/35 3/9	5·5 2·9	14·1 2·5		1.48 (0.88, 2.4) 3.30 (0.94, 11.5
	Subtotal:	52/80	20/44	8-4	16-6		1.66 (1.03, 2.
st for heter	rogeneity between subgroup	$x_{2}^{2} = 1.3$ ; P = 0.2; NS					2P = 0.04
TET2:							
ild Type		44/69	17/35	5·8 2·4	14-1		1.51 (0.89, 2.54
utant	Subtotal:	8/11 52/80	3/9 20/44	8-2	2·7 16·8		2.41 (0.73, 7.91 1.63 (1.01, 2.
			20/44	0-2	10-0		2P = 0.05
	rogeneity between subgroup	os: $\chi^2_1 = 0.5$ ; P = 0.5; NS					
y PTPN11: ild Type		46/68	17/38	8-9	15-1	<b>_</b> _	1.81 (1.09, 3.00
utant		6/12	3/6	-0.5	1-9		0.91 (0.22, 3.74
	Subtotal:	52/80	20/44	8-7	17-0		1.67 (1.04, 2.) 2P = 0.03
est for heter	rogeneity between subgroup	os: $\chi_1^2 = 0.8$ ; P = 0.4; NS					
IDH2:		11/20	10.00			_	
ild Type utant		44/68 8/12	18/39 2/5	6·8 1·5	14·8 2·2		1.58 (0.95, 2.64
	Subtotal:	52/80	20/44	8-3	17-0		1.63 (1.01, 2. 2P = 0.04
st for hete	rogeneity between subgroup	os: χ <sup>2</sup> = 0·1: P = 0·8: NS					2P = 0.04
RUNX1:		43/69	17/39	7.1	14-3 2-4		1.64 (0.98, 2.7
ild Type				0.7			
ild Type	Subtotol	9/11	3/5	0.7			
ild Type utant	Subtotal:	52/80		0·7 <b>7·8</b>	16-7	A	1.60 (0.99, 2,
ild Type utant est for heter	Subtotal: rogeneity between subgroup	52/80	3/5			Å	1.60 (0.99, 2,
y RUNX1: iild Type utant utant st for heter y WT1: iild Type		52/80	3/5				1.36 (0.39, 4.80 1.60 (0.99, 2.) 2P = 0.06
ild Type utant est for heter VT1: ild Type		<b>52/80</b> os: $\chi_1^2 = 0.1$ ; P = 0.8; NS	3/5 <b>20/44</b>	7-8	16.7		1.60 (0.99, 2. 2P = 0.06 1.75 (1.05, 2.92 1.33 (0.35, 4.98
ild Type utant est for heter WT1: ild Type		<b>52/80</b> ps: X <sup>2</sup> <sub>1</sub> = 0·1; P = 0·8; NS 47/73	3/5 <b>20/44</b> 16/37	<b>7-8</b> 8-2	16-7 14-7		1.60 (0.99, 2. 2P = 0.06 1.75 (1.05, 2.92 1.33 (0.35, 4.98
IId Type utant est for heter y WT1: IId Type utant	rogeneity between subgraup	52/80 ps: X <sup>2</sup> <sub>1</sub> = 0·1; P = 0·8; NS 47/73 5/7 52/80	3/5 <b>20/44</b> 16/37 4/7	<b>7.8</b> 8.2 0.6	1 <b>6-7</b> 14-7 2-2		1.60 (0.99, 2. 2P = 0.06 1.75 (1.05, 2.9 1.33 (0.35, 4.9
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Id Type utant est for heter y WT1: ild Type utant est for heter	rogeneity between subgroup Subtotal:	52/80 ps: X <sup>2</sup> <sub>1</sub> = 0·1; P = 0·8; NS 47/73 5/7 52/80	3/5 <b>20/44</b> 16/37 4/7	<b>7.8</b> 8.2 0.6	1 <b>6-7</b> 14-7 2-2		1.60 (0.99, 2. 2P = 0.06 1.75 (1.05, 2.96 1.33 (0.25, 4.96 1.69 (1.05, 2. 2P = 0.03
Id Type itant st for heter WT1: Id Type itant st for heter GATA2: Id Type	rogeneity between subgroup Subtotal:	52/80 bs: $\chi_1^2 = 0.1$ ; P = 0.8; NS 47/73 5/7 52/80 bs: $\chi_1^2 = 0.1$ ; P = 0.7; NS 49/74	3/5 20/44 16/37 4/7 20/44 17/37	7-8 8-2 0-6 8-8 7-5	16-7 14-7 2:2 16-9		1.60 (0.99, 2, 2P = 0.06 1.75 (1.05, 2.9 1.33 (0.35, 4.9 1.69 (1.05, 2, 2P = 0.03 1.63 (0.59, 2.6 1.79 (0.31, 10.4
Id Type Jtant st for heter <b>WT1:</b> Id Type Jtant <b>GATA2:</b> Id Type Jtant	rogeneity between subgroup Subtotal: rogeneity between subgroup Subtotal:	52/80 DS: $\chi_1^2 = 0.1$ ; P = 0.8; NS 47/73 5/7 52/80 DS: $\chi_1^2 = 0.1$ ; P = 0.7; NS 49/74 3/6 52/80	3/5 20/44 16/37 4/7 20/44 17/37 3/7	7-8 8-2 0-6 8-8 7-5 0-7	16-7 2-2 16-9 15-3 1-2		1.60 (0.99, 2, 2P = 0.06 1.75 (1.05, 2.9 1.33 (0.35, 4.9 1.69 (1.05, 2, 2P = 0.03 1.63 (0.59, 2.6 1.79 (0.31, 10.4
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Id Type tant  st for heter WT1: Id Type tant  GATA2: Id Type tant  st for heter IDH1: Id Type tant	rogeneity between subgroup Subtotal: rogeneity between subgroup Subtotal: rogeneity between subgroup	52/80 DS: $\chi_1^2 = 0.1$ ; P = 0.8; NS 47/73 5/7 52/80 DS: $\chi_1^2 = 0.1$ ; P = 0.7; NS 49/74 3/6 52/80 DS: $\chi_1^2 = 0.0$ ; P = 0.9; NS 48/71 4/9	3/5 20/44 16/37 4/7 20/44 17/37 3/7 20/44 17/40 3/4	7-8 8-2 0-6 8-8 7-5 0-7 8-2 9-9 -0-9	16-7 2-2 16-9 15-3 1-2 16-5 1-5 1-4		1.60 (0.99, 2 2P = 0.06 1.75 (1.05, 2.9 1.33 (0.35, 4.9 1.69 (1.05, 2, 2P = 0.03 1.63 (0.59, 2.6 1.78 (6.31, 10.4 1.64 (1.10, 1, 2, 2P = 0.04 1.89 (1.15, 3.1) 0.52 (0.10, 2.6
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Supplementary Figure 5: Relapse Free Survival Related to Treatment Compliance. Events within 30 days of course 3 are excluded

