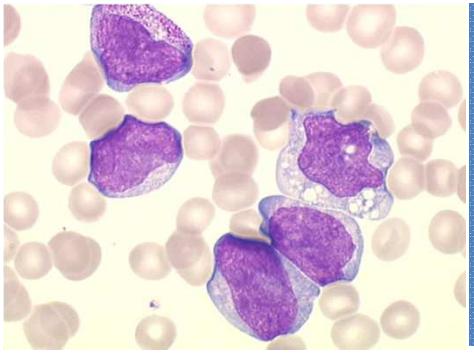
PROSPECTIVE VALIDATION OF A NOVEL CONDITIONING REGIMEN: FLU - MYELOABLATIVE IV BU4(BF), IN 170 PATIENTS (PTS) WITH ACUTE MYELOIDE LEUKEMIA (AML): COMPARATIVE STUDY WITH THE STANDARD CONDITIONING REGIMEN BU-CY2 (BC).

A .Talbi, R .Ahmed Nacer , M .Benakli, F. Mehdid, S. Akhrouf, R. Belhadj, N. Rahmoune, M. Bazizi, H. Bouarab, D. Ait ouali, R.M Hamladji.

Hematology– Bone Marrow transplantation unit. Pierre and Marie Curie Center (CPMC), Algiers, Algeria.

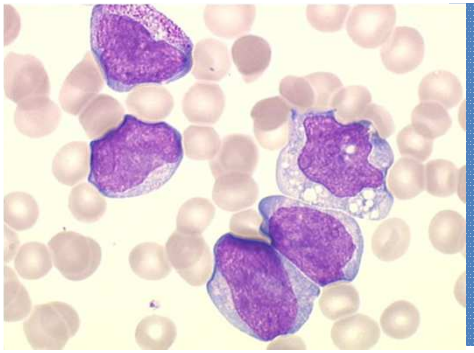


INTRODUCTION

- **The treatment of hematological malignancy notably AML is very challenging because of the poor outcome chemotherapy.**

- **The goal of allogeneic stem cell transplant (HSCT) is inducing a graft versus tumor immune effect, that's why the choice of the conditioning may have an impact on the overall outcome of the transplant. In fact, fully myeloablative conditioning regimens can destroy tumor cells effectively, but can also cause greater morbidity and mortality.**

- **IV Flu-Bu conditioning prior to allo HSCT in adult patients with AML seems an alternative to standard IV BU-CY2 regimen, We compare our results with a retrospective study, about 160 AML pts, undergoing an HSCT, with the standard BU-CY2 or BU-CY2-VP16 regimen.**



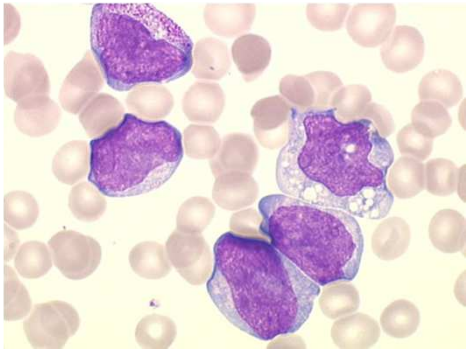
MATERIEL AND METHODS I

- **Number of AML undergoing HSCT : 491 pts (September 1999 to April 2013)**

- **Adult > 15 years conditioning regimen (N = 330):**
  - **BU-CY2 et BU-CY2-VP16 (BC) : 160 pts**
  - **FLU-BU4 (BF): 170 pts**

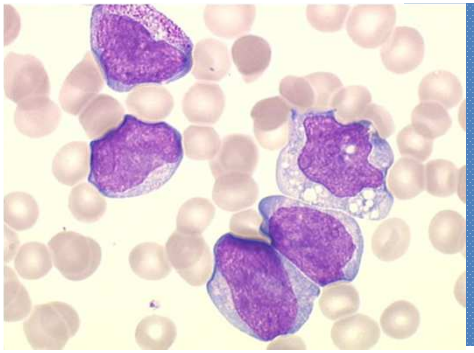
- **At the 30/06/2013**

Condit°	BC	BF
Number (pts)	160	170
Period	09-99 au 04-10	02-08 au 04-13
Follow up (months) Minimal Maximal	 38 165	 2 64



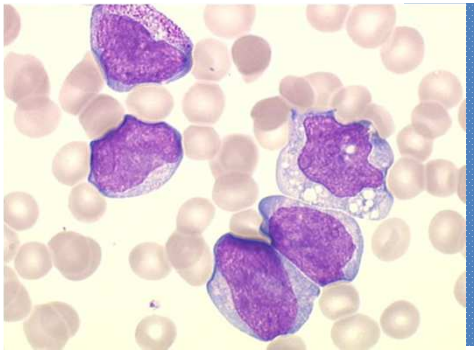
MATERIEL AND METHODS II

Patients characteristics	BC	BF	P
Median age	27 (15 - 47)	35 (18 - 62)	$<10^{-8}$
Sex ratio Male Female	1,2 90 70	1,57 104 66	0,41
Disease Status at HSCT 1st CR 2nd CR Advanced	 146 (91,2%) 11 (6,8%) 3 (1,8%)	 143 (84,1%) 15 (8%) 12 (7%)	 0,75
Median time from diagnosis to transplant	6 (1-52)	4 (2-11)	0,23



MATERIEL AND METHODS III

AML cytologic types	BC	%	BF	%
M0	4	2,5	10	5,8
M1	28	17,5	17	10
M2	70	43,7	79	46,4
M3	12	7,5	3	1,7
M4	21	13,1	36	21,1
M5	16	10	13	7,6
M6	1	0,6	4	3,7
M7	0	0	2	1,1
IND	8	5	6	3,5



MATERIEL AND METHODS IV

Kind of Conditioning:

BF → **FLU - BU: 170 pts**
Fludarabine **IV:200 mg/m²**
Busulfan**IV : 12,8 mg / Kg**

BC

BU – VP – Cy: 140 pts
Busulfan **oral 16 mg/Kg**
Etoposide **IV : 30mg/ Kg**
Cyclophosphamide **IV: 120 mg/m²**

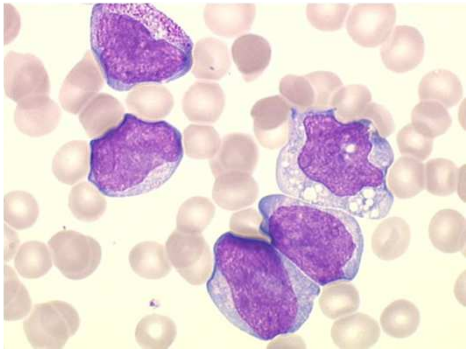
BU - Cy : 20 pts
Busulfan **oral 16 mg/Kg**
Cyclophosphamide **IV: 120 mg/m²**

Transplant (PBSC):

	BC	BF
pts	160	170
$CD34^+$ Cell (10^6 / Kg) extremes	8,92 0,34 – 23,6	7,08 1,25 – 25,3

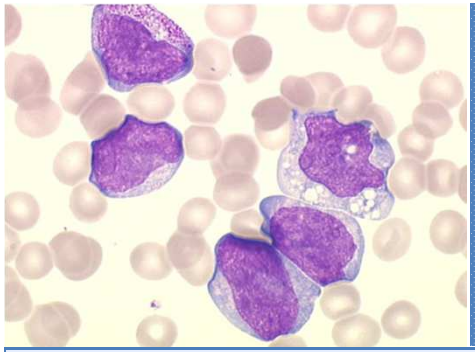
GVHD Prophylaxis:

CA + MTX : Ciclosporine
Methotrexate



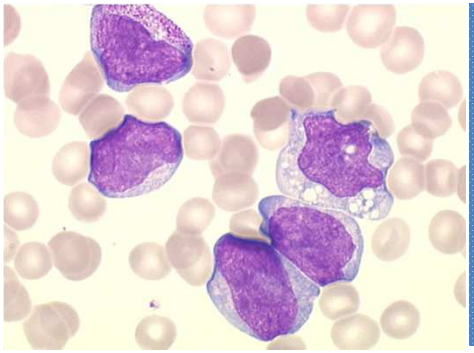
RESULTS I

	BC (N=160)	BF (N=170)	p
Median duration of neutropenia	13 (7 - 26)	8 (4 - 25)	0,084
Day of engraftment (ANC > 500 /mm$^{3)}$)	15 (9-22)	14 (10 -23)	
Transfusion requirements			
•Pts undergoing RBC transfusions	145 (90,6%)	51 (30,4%)	$<10^{-4}$
Blood unit/pt	1,2	0,87	
•Pts undergoing platelet transfusions	151 (94%)	91 (54%)	$<10^{-6}$
Platelet unit/pt	2,1	0,98	



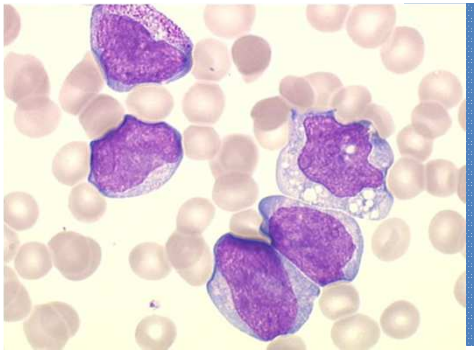
RESULTS II

	BC	BF	p
Early death	30 (19%)	3 (2,9%)	10^{-4}
Failure	-	1	
VOD	14 (9,7%)	0	<0,01
GVHA Appraisable: Nbre of pts: Grade I Grade II-IV	 142 52 (37%) 29 23 (16,1%)	 166 68 (41%) 25 43 (25,9%)	0,3
GVHC Appraisable: Nbre of pts Non Extensive: Extensive:	 141 67 (48,8%) 29 43 (31%)	 89 55 (62,5%) 14 34 (39,2%)	0, 3
CMV	39 (24,3%)	35 (20,5%)	0,4
Relapse	17 (11,8%)	16 (15,8%)	0,13

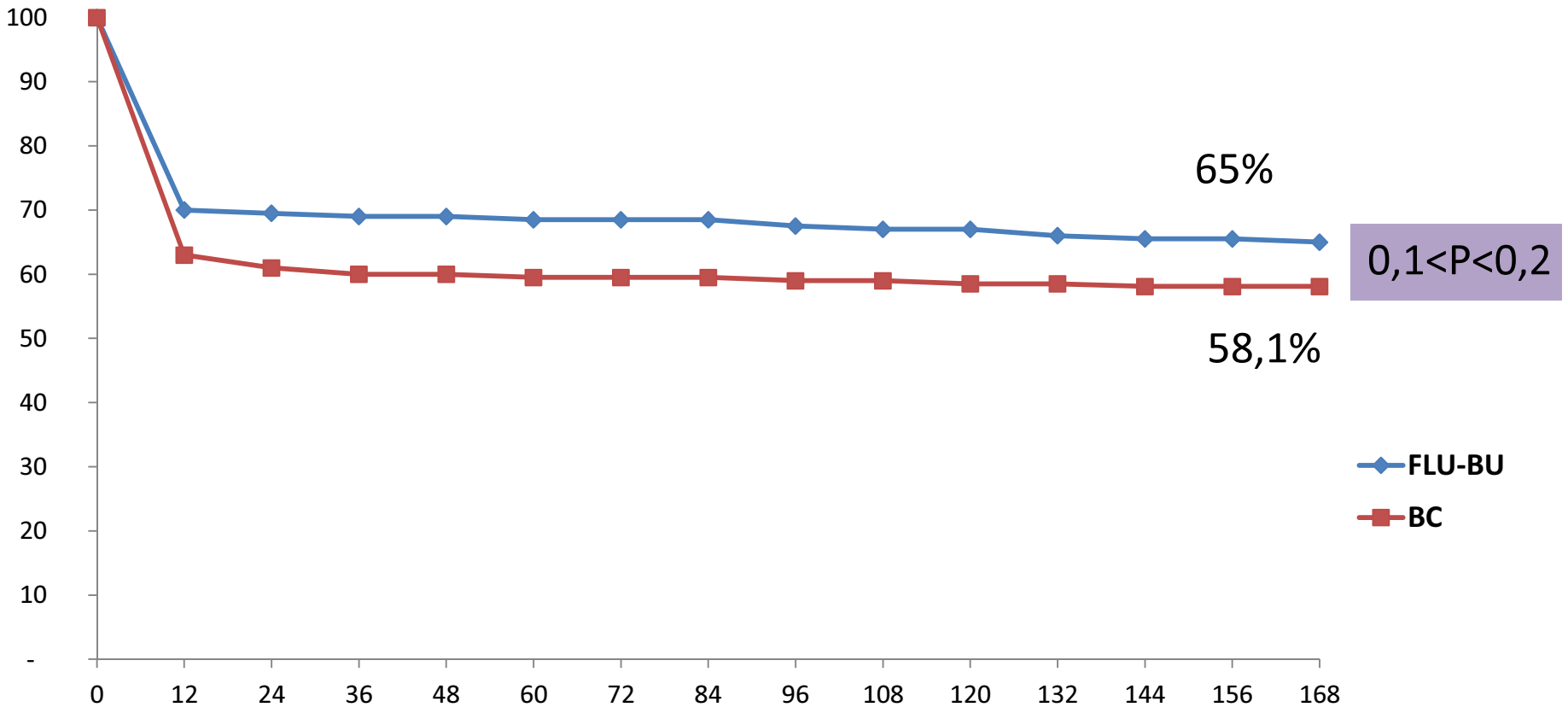


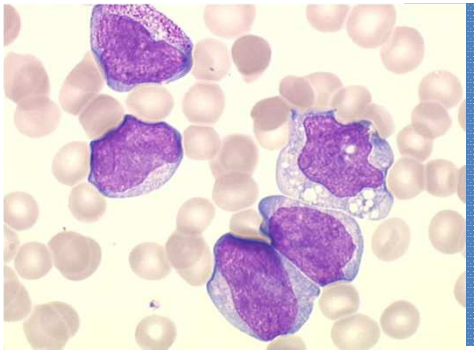
RESULTS III
Causes of death (n = 127)

	BC	BF	p
TRM : • at D100 • At Juin 2013	 43 (26,8%) 52 (32,5%)	 25 (14,7%) 33 (19,4%)	0,0014
a GVHD	13	13	
c GVHD	7	8	
INFECTION	20 (11,8%) dont 2 tardives	7 (4,1%) toutes precoces	
VOD	9	0	
Bleeding	3	0	
Hepatitis toxicity	0	4	
Failure	0	1	
Relapse	19 (11,8%)	22 (12,9%)	0,13
Unknown cause of death	1	0	

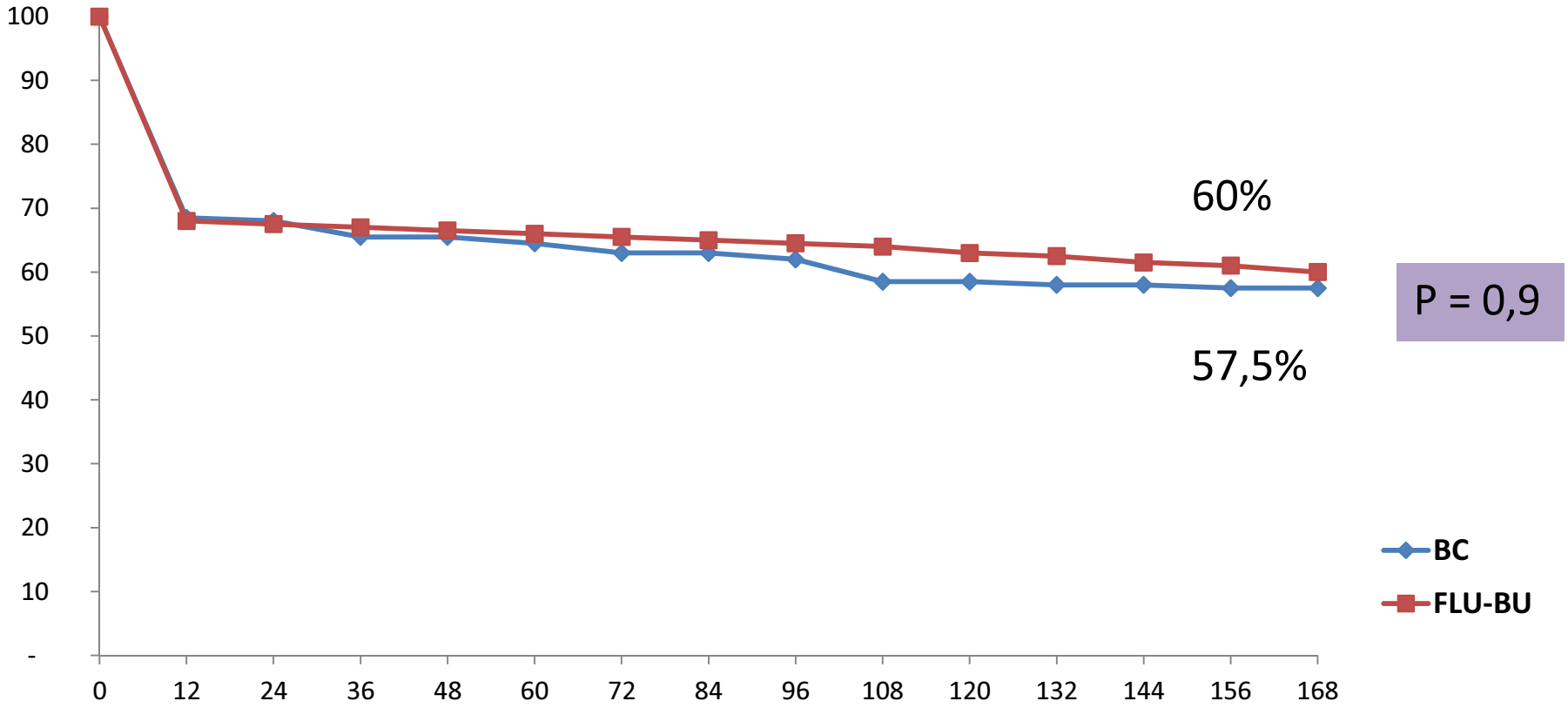


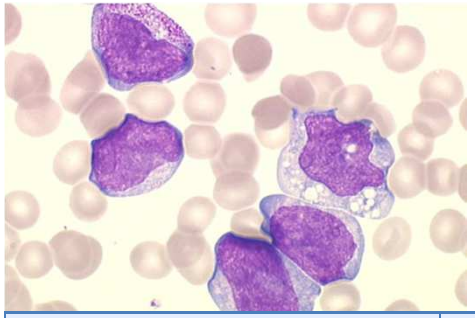
OVERALL SURVIVAL





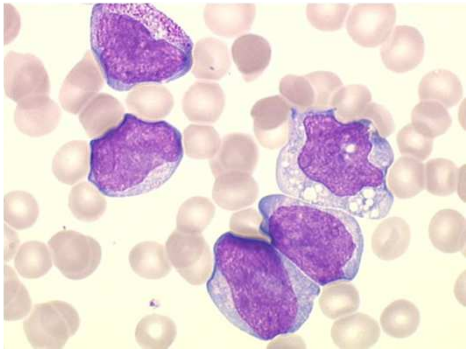
EVENT FREE SURVIVAL





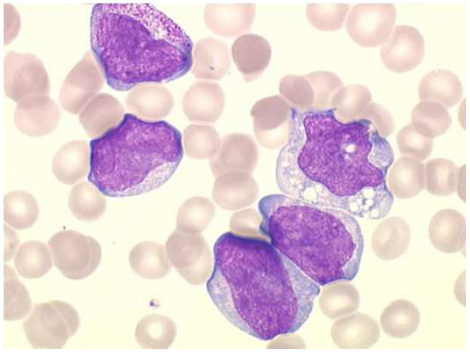
Comparaison: Bu-Cy and F-Bu4

	A.Shimoni Leukemia 2006	B. Anderson Current opinion on oncology 2009	CPMC
Nbre pts: Bu-Cy	45	67	160
Flu-Bu	67	148	170
Os%: Bu-Cy	50%	60%	58,1%
Flu-Bu	49%	79%	65%
DFS% Bu-Cy	47%	45%	57,1%
Flu-Bu	49%	75%	60%
TRM% Bu-Cy	22%	21%	26,8%
Flu-Bu	8% ($P< 10^{-8}$)	6% ($P< 10^{-6}$)	14,7% (P=0,0014)



Comparaison: differents series of F-Bu4

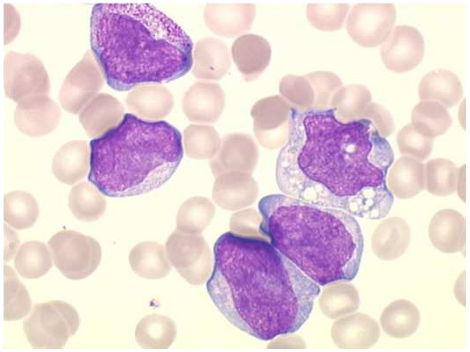
	aGVH %	cGvH %	TRM% at D 100	OS %	DFS %	relapse %
Russel JA Biol blood Marrow Transplant 2002	9%	38%	5%	70%	58%	32%
De Lima M Blood 2004	25%	55%	0%	65%	52%	34%
Iravani M BMT (2007)	15%	60%	17%	71%	64%	29%
Chae YS BMT 2007	12%	44%	14%	83%	77%	17,5%
Cpmc Congres Maghrebin 2014	41%	62,5%	14,7%	65%	60%	15,8%



Conclusion I

- **Flu-B4 is an acceptable regimen because of its low TRM and morbidity; it may well substitute BU-CY2 with the aim of decreasing transplant adverse effects without compromising its efficacy (GVL effect), the rate of relapse attests that.**

- **However we know that our rate of Chronic GVHD is high in this F-BU4 series, we are trying to reduce it, we have newly introduced Thymoglobulin in the conditioning regimen and we are going to evaluate this in a neer future.**



Conclusion II

This regimen help us for increasing the number of the AML patients who can underwent an allogeneic HSCT in an acceptable delay, to reduce the chemotherapy schedules and the toxicity before performing HSCT.