Potential for non-conventional agents in upfront and relapsed APL

APL Rome Sep 2017

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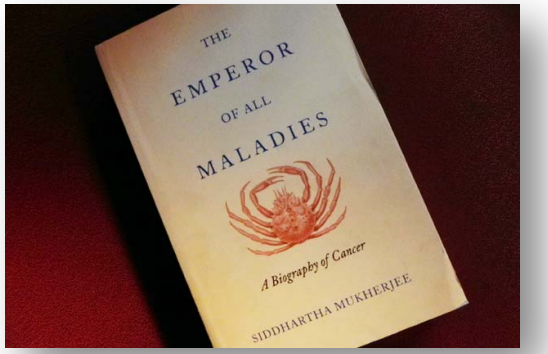
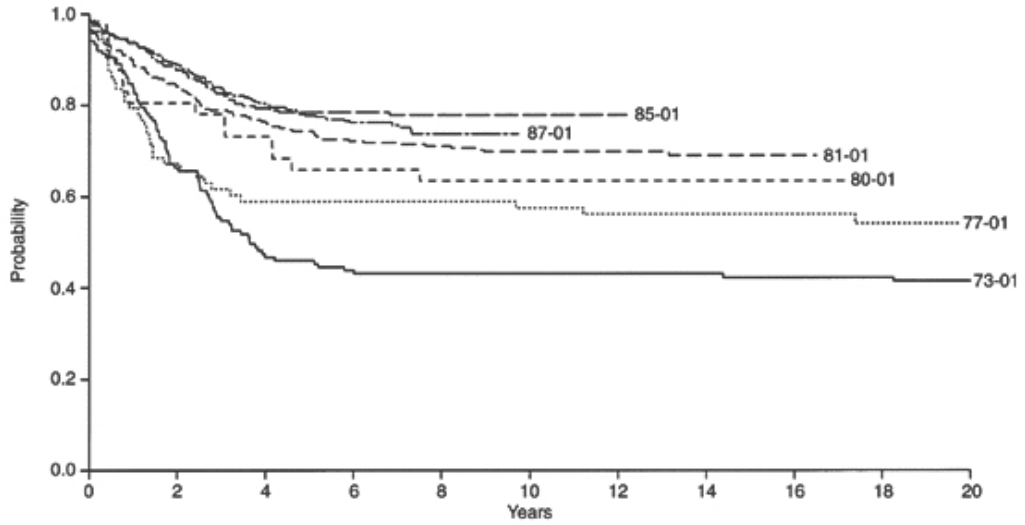
Introduction:

Pediatric Acute Lymphoblastic Leukemia





Re-purposing therapeutic agents

Dexamethasone	1957
Prednisolone	1950
Vincristine	1961
Daunorubicin	1979
Lasparaginase	1978
Cyclophosphamide	1959
Cytosine	1969
Proph-ic cranial RT	1960
Methotrexate	1947
Mercaptopurine	1953
Thioguanine	1951
Etoposide	1983
Adriamycin	1974

- **Optimizing combinations**
- **Optimizing doses**
- **Optimizing schedules**

Potential to re-purpose existing drugs

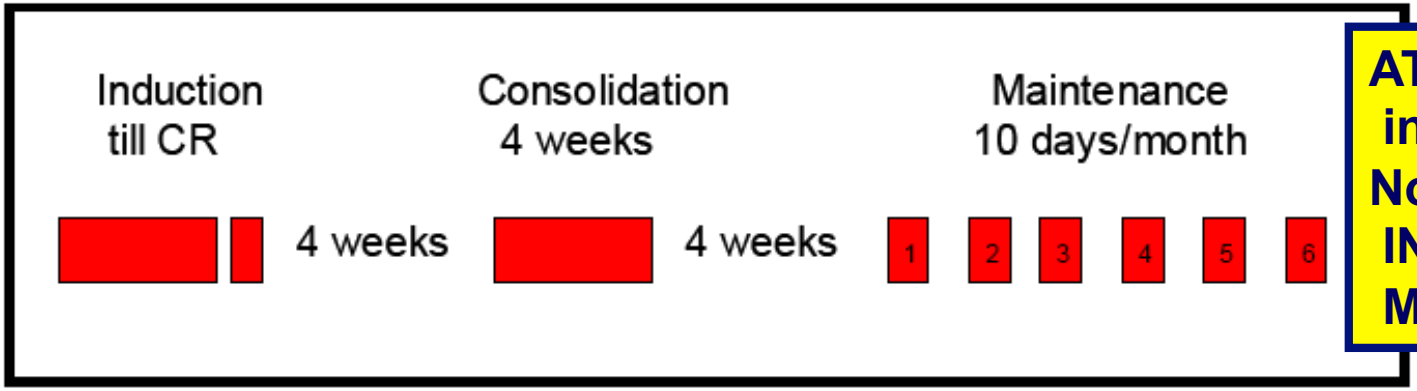
- **anti-cancer**
- **others**

Introduction:

- We have already achieved these goals in APL ! – We did > decade ago
- High risk and relapsed subsets
- Reduced morbidity / toxicity – subsets
- Decreased requirement of supportive care
- Reduced early deaths – non-clinical trial setting
- Reduce cost of treatment / Ease of access
- Gleevec moment!

Single agent ATO based regimen:

Figure 1: Regimen of single agent arsenic trioxide.



ATO till Nov 2003
in-house prepared
Nov 2003 onwards
INTAS pharmaceuticals
Matoda, GU, India

Table 1. Guidelines for administration of hydroxyurea during induction

WBC count, × 10^9/L	Adult patients	Pediatric patients
5 to 10	500 mg once daily	15 mg/kg once daily
10 to 15	500 mg twice daily	15 mg/kg twice daily
15 to 20	500 mg thrice daily	15 mg/kg thrice daily
20 to 50	500 mg 4 times a day	15 mg/kg 4 times a day
More than 50	1.0 g 4 times a day	30 mg/kg 4 times a day

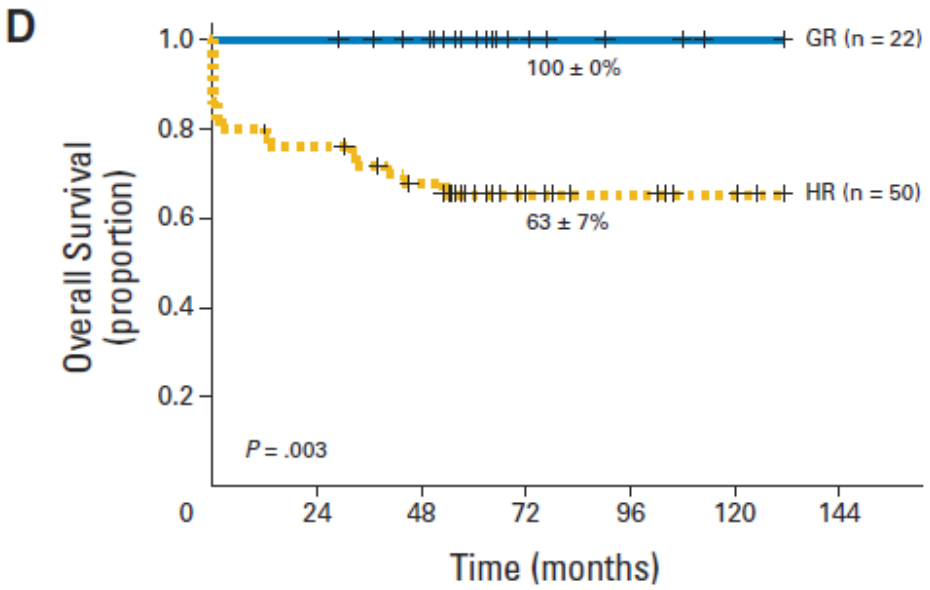
For adult and pediatric patients with a WBC count less than 5 × 10^9/L, no hydroxyurea was administered.

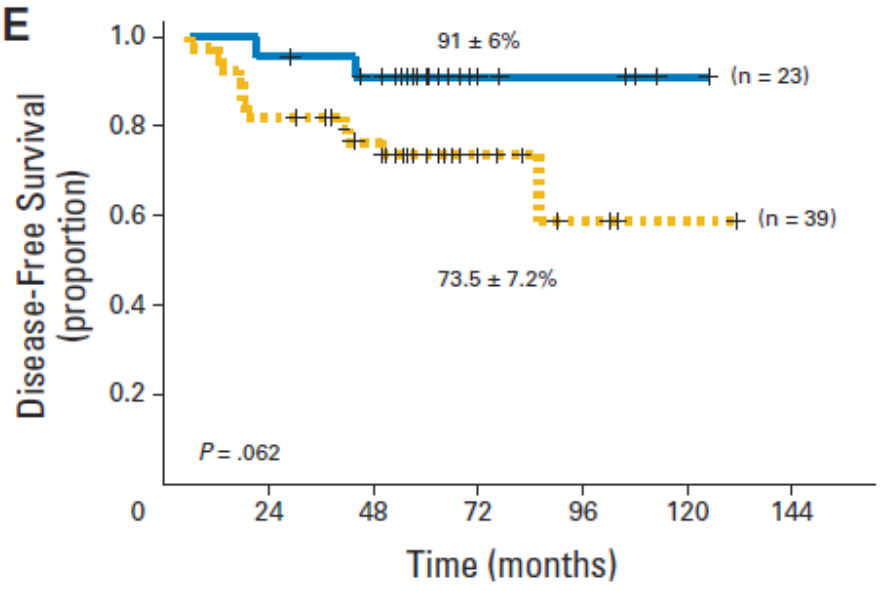
Anthracycline in INDUCTION only (one or two doses) if:
WBC > 50 x 10^9/Lt
Rapid leucocytosis
> 20 x 10^9/L week 1
> 50 x 10^9/L week 2
Differentiation syndrome not responding to therapy with steroids

BLOOD 2006 / JCO 2010

Single agent ATO based regimen:

Median follow up 58 months (5 yr KM estimate±1SE)





Long Term Follow up Data:

Multicenter study - IAPLSG04

7 center's India

RCT : 6 vs. 12 months maintenance

N = 159

5 yr OS	**75%**
5 yr EFS	**69%**

Good Risk Group Relapses = 2

(Only one received an anthracycline in induction)

High Risk Group Relapses = 11

5 year Kaplan-Meier estimate of OS:

LR = 100±0.0%

HR = 63±7.6%

JCO 2010

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 11, 2013 VOL. 369 NO. 2

Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia

F. Lo-Coco, G. Avvisati, M. Vignetti, C. Thiede, S.M. Orlando, S. Iacobelli, F. Ferrara, P. Fazi, L. Cicconi, E. Di Bona, G. Specchia, S. Sica, M. Divona, A. Levis, W. Fiedler, E. Cerqui, M. Breccia, G. Fioritoni, H.R. Salih, M. Cazzola, L. Melillo, A.M. Carella, C.H. Brandts, E. Morra, M. von Lilienfeld-Toal, B. Hertenstein, M. Wattad, M. Lübbert, M. Hänel, N. Schmitz, H. Link, M.G. Kropp, A. Rambaldi, G. La Nasa, M. Luppi, F. Ciceri, O. Finizio, A. Venditti, F. Fabbiano, K. Döhner, M. Sauer, A. Ganser, S. Amadori, F. Mandelli, H. Döhner, G. Ehninger, R.F. Schlenk, and U. Platzbecker for Gruppo Italiano Malattie Ematologiche dell'Adulto, the German–Austrian Acute Myeloid Leukemia Study Group, and Study Alliance Leukemia

Phase III prospective trial
Non-inferiority design
Low and Intermediate Risk APL

- **Phase II study: Iland et al.**
  Lancet Hematology 2015
- **UK MRC AML17 Phase III RCT.**
  Burnett AK et al.
  Lancet Oncology 2015

Introduction:

- Significant advances have been made in the management of acute promyelocytic leukemia (APL)
- Steady transition over the years to a non-myelotoxic therapy[1]
- Facilitated by increased understanding of the molecular mechanisms of disease and resistance
- Challenges remain in the real world[2,3,4], in patients with high risk disease at presentation and in those who relapse

1. Mathews V. Lancet Hematology 2015
2. Lehmann et al. Leukemia 2011
3. Park JH et al. Blood 2011
4. Jean-Baptiste Micol et al. ASH Abstract 2010

Management of Relapsed APL

- Available data - mostly in the context of relapse following conventional ATRA + chemotherapy regimens
- **Limited data on management of relapse when ATO has been used upfront**
- Available data would suggest that intensification with an autologous SCT is required post relapse

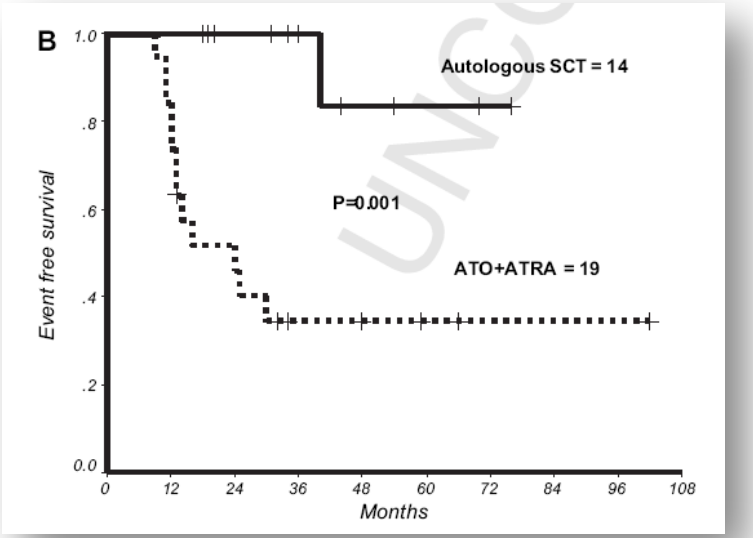
Management of Relapsed APL

ASBMT
American Society for Blood and Marrow Transplantation

Comparison of Clinical Outcomes of Patients with Relapsed Acute Promyelocytic Leukemia Induced with Arsenic Trioxide and Consolidated with Either an Autologous Stem Cell Transplant or an Arsenic Trioxide–Based Regimen

Rajasekar Thirugnanam, Biju George, Ezhil Chendamarai, Kavitha M. Lakshmi, Poonkuzhali Balasubramanian, Auro Viswabandya, Alok Srivastava, Mammen Chandy, Vikram Mathews

BBMT 2009



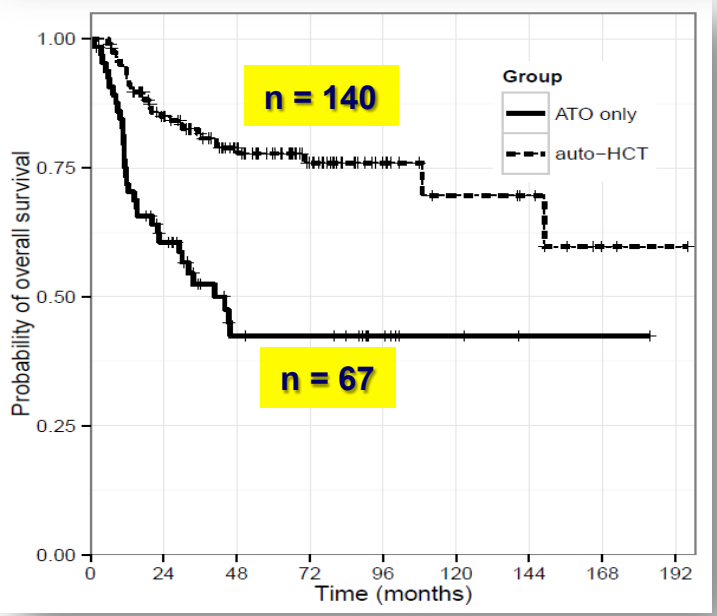
Bone Marrow Transplantation (2016), 1–4

www.nature.com/bmt

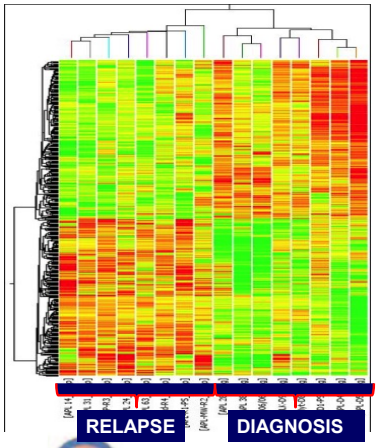
ORIGINAL ARTICLE

Autologous transplant remains the preferred therapy for relapsed APL in CR2

C Ganzel[1], V Mathews[2], K Alimoghaddam[3], A Ghavamzadeh[3], D Kuk[4], S Devlin[4], H Wang[5], M-J Zhang[5], D Weisdorf[6], D Douer[7], JM Rowe[1,8], E Polge[9,10], J Esteve[11], A Nagler[10,12], M Mohty[9,10] and MS Tallman[7]



RELAPSED PATIENTS ARE DIFFERENT



PLOS | ONE

RESEARCH ARTICLE

Comparison of Newly Diagnosed and Relapsed Patients with Acute Promyelocytic Leukemia Treated with Arsenic Trioxide: Insight into Mechanisms of Resistance

Ezhilarasi Chendamarai[1], Saravanan Ganesan[1], Ansu Abu Alex[1], Vandana Kamath[2], Sukesh C. Nair[2], Arun Jose Nellickal[3], Nancy Beryl Janet[1], Vivi Srivastava[4], Kavitha M. Lakshmi[1], Auro Viswabandya[1], Aby Abraham[1], Mohammed Aiyaz[5], Nandita Mullapudi[5], Raja Mugasimangalam[5], Rose Ann Padua[6], Christine Chomienne[6], Mammen Chandy[1], Alok Srivastava[1], Biju George[1], Poonkuzhali Balasubramanian[1], Vikram Mathews[1]*

Ezhilarasi

Leukemia (2016) 30, 1672–1681

www.nature.com/leu

OPEN

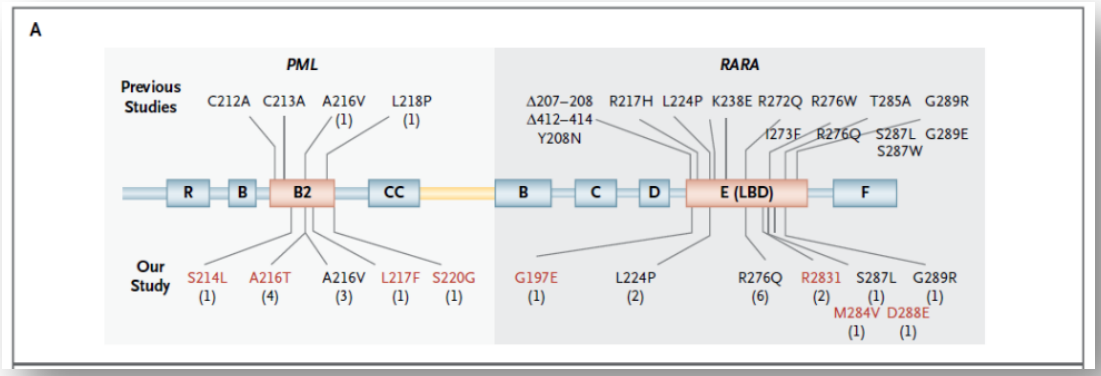
ORIGINAL ARTICLE

Comprehensive mutational analysis of primary and relapse acute promyelocytic leukemia

V Madan[1], P Shyamsunder[1,23], L Han[1,2,23], A Mayakonda[1,23], Y Nagata[3], J Sundaresan[1], D Kanojia[1], K Yoshida[3], S Ganesan[4], N Hattori[1], N Fulton[5], K-T Tan[1], T Alpermann[6], M-C Kuo[7], S Rostami[8], J Matthews[9], M Sanada[3], L-Z Liu[1], Y Shiraishi[10], S Miyano[10], E Chendamarai[4], H-A Hou[11], G Malnassy[5], T Ma[12], M Garg[1], L-W Ding[1], Q-Y Sun[1], W Chien[1], T Ikezoe[13], M Lill[14], A Biondi[15], RA Larson[16], BL Powell[17], M Lübbert[12], WJ Chng[1,2,18], H-F Tien[11], M Heuser[19], A Ganser[19], M Koren-Michowitz[20,21], SM Kornblau[9], HM Kantarjian[9], D Nowak[22], W-K Hofmann[22], H Yang[1], W Stock[5], A Ghavamzadeh[8], K Alimoghaddam[8], T Haferlach[6], S Ogawa[3], L-Y Shih[7], V Mathews[4,24] and HP Koeffler[1,14,18,24]

Comparison of newly diagnosed and relapsed patients with APL

- PML mutations in 16% at relapse[2]
- Neither mutations or a potential LSC could explain relapses in our patients
- Evidence of micro-environment mediated drug resistance (EM-DR) to ATO[1]



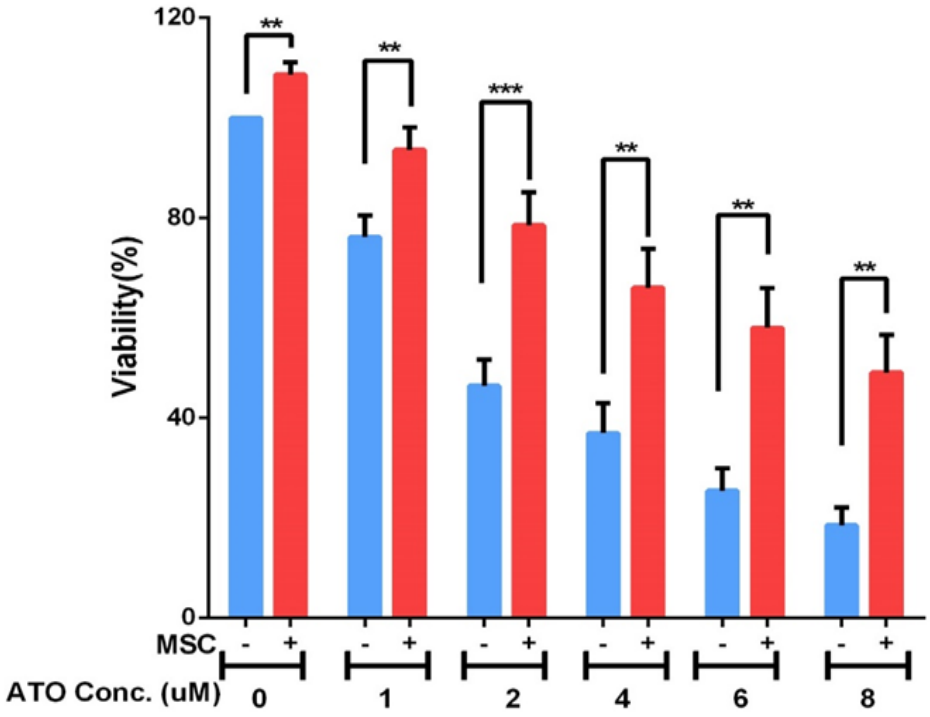
N = 35
25% PML mutations
<30% survival in those with mutations

1. Chendamarai et al. Plos One 2015
2. Madan V et al. Leukemia 2015
3. Huang et al. NEJM 2014

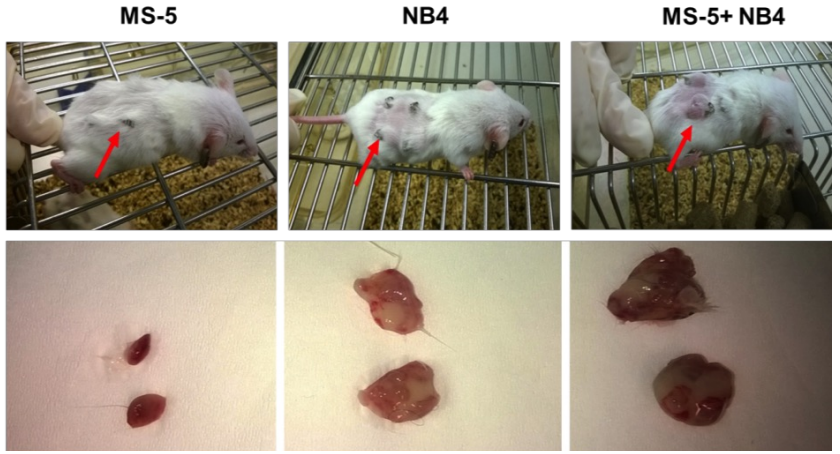
EM-DR in acute promyelocytic leukemia

- Protective effect seen in non-contact dependent system (Transwell)
- ICATO levels between NB4 and NB4 in co-culture remained the same
- Protective effect is not seen on NB4 cells when co-cultured with
  - HUVEC
  - COS-7
  - PBMNCs

HS-5 co-culture



** - P=0.005, ***-P=0.001



Stromal cells provide survival advantage to malignant promyelocytes (NB4) against arsenic trioxide.

Rationale for combining ATO with proteasome inhibitors

Saravanan

Leukemia (2016), 1–10
www.nature.com/leu

ORIGINAL ARTICLE

Rationale and efficacy of proteasome inhibitor combined with arsenic trioxide in the treatment of acute promyelocytic leukemia

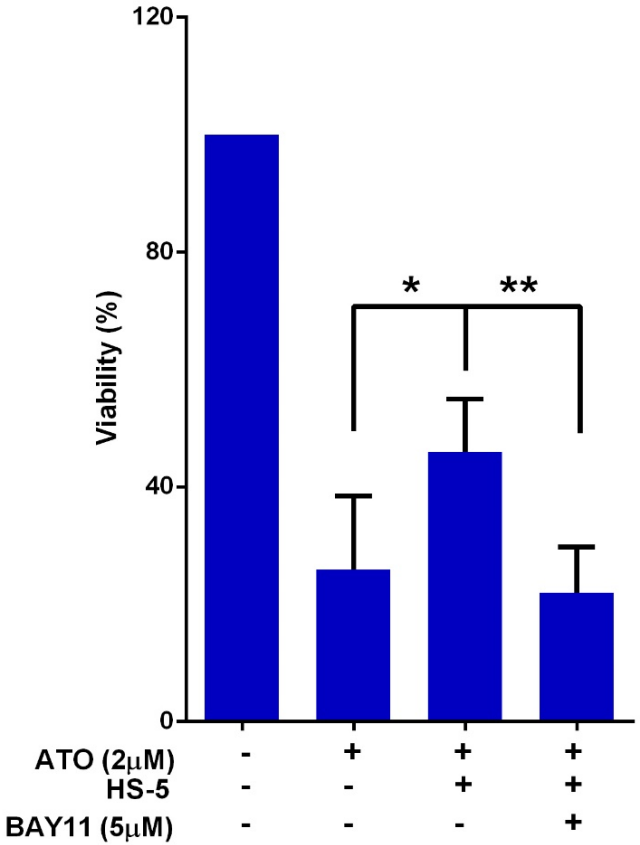
S Ganesan[1], AA Alex[1], E Chendamarai[1], N Balasundaram[1], HK Palani[1], S David[1], U Kulkarni[1], M Aiyaz[2], R Mugasimangalam[2], A Korula[1], A Abraham[1], A Srivastava[1], RA Padua[3,4], C Chomienne[3,4], B George[1], P Balasubramanian[1] and V Mathews[1]

- Prominent upregulation of the NF-Kβ pathway and genes[1]
- Similar upregulation in relapsed patients even without stromal co-culture
- Direct or indirect inhibition of this pathway could overcome EM-DR
- Proteasome inhibitors combined with ATO

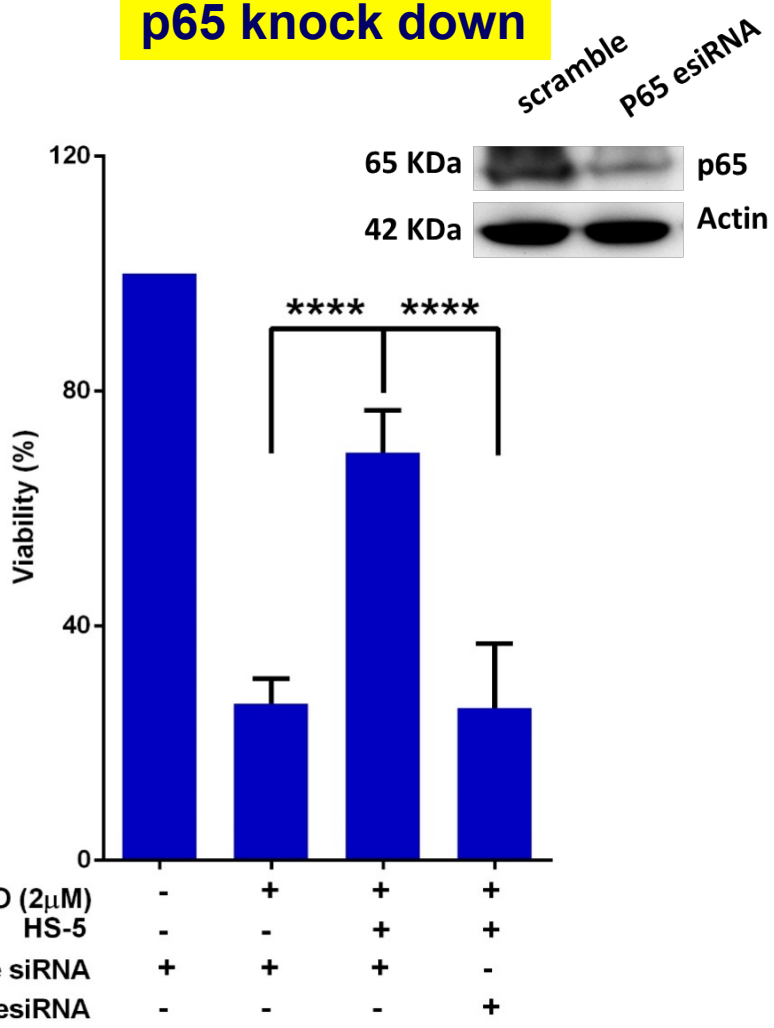
1. Jacamo et al. Blood 2014

Inhibiting NF- κB pathway by chemical inhibitor or knockdown of p65 overcomes EM-DR to ATO

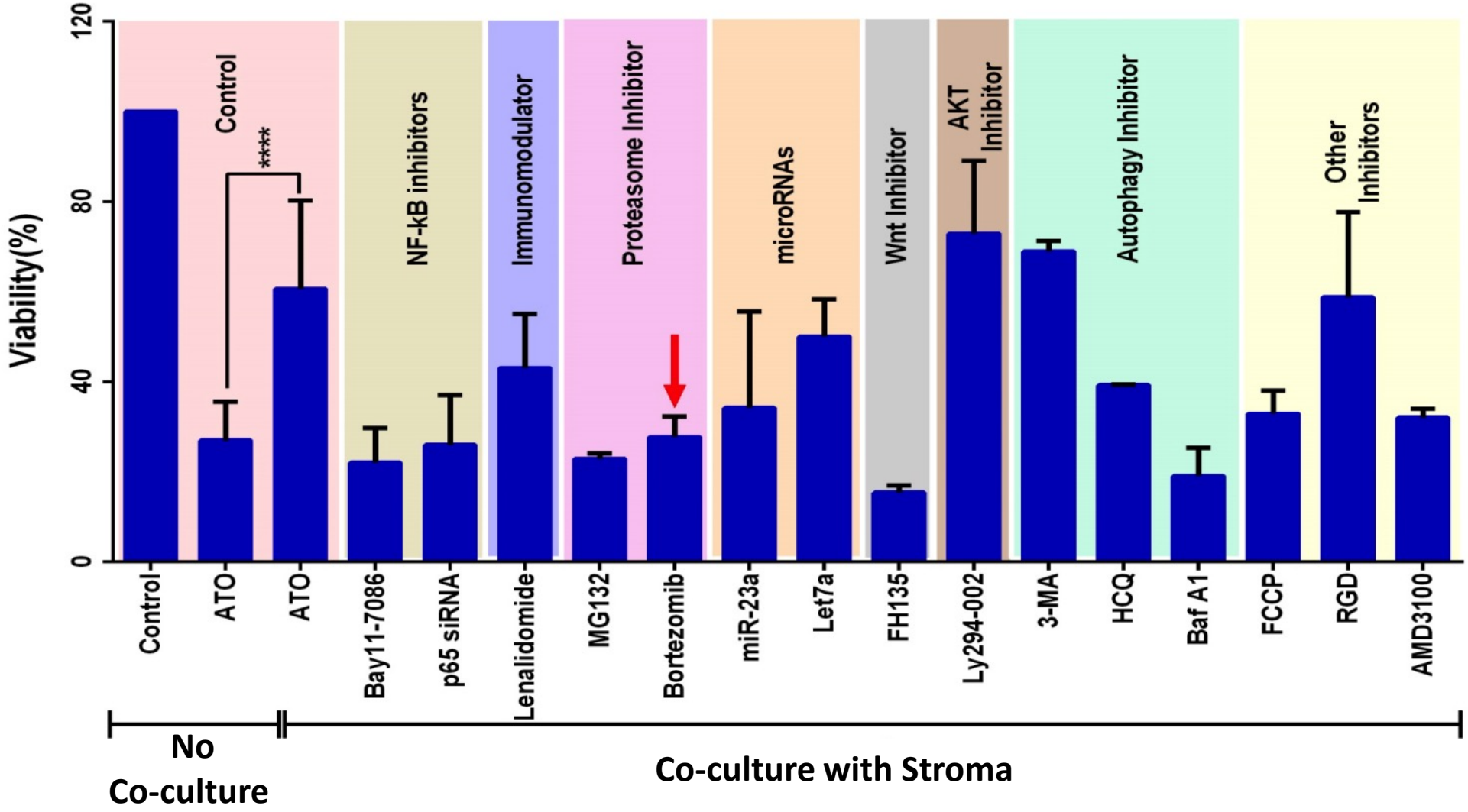
Bay11-7082



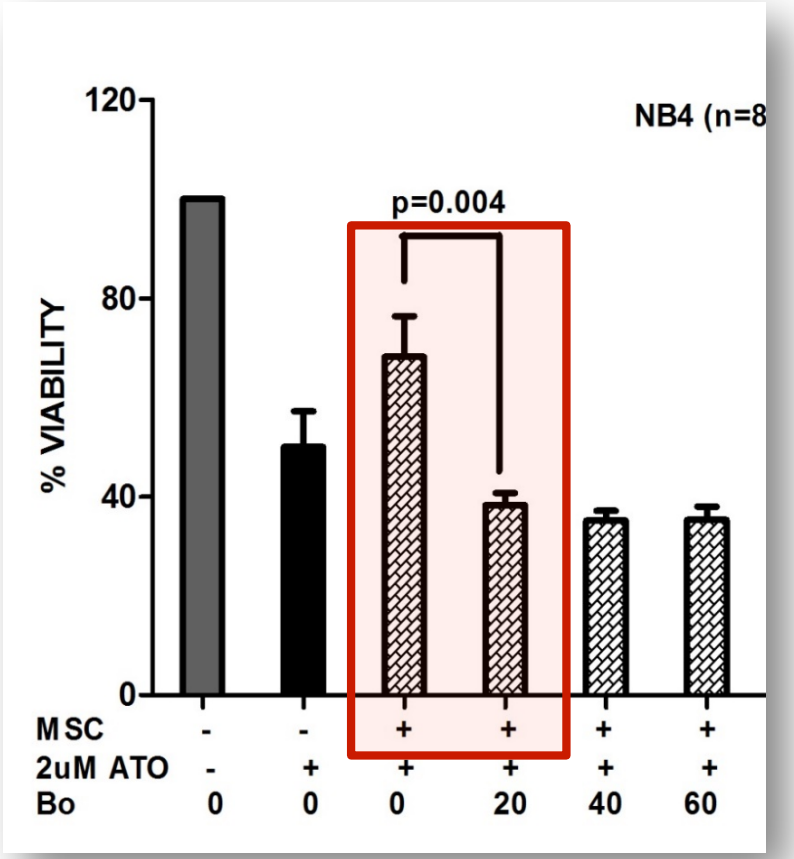
p65 knock down

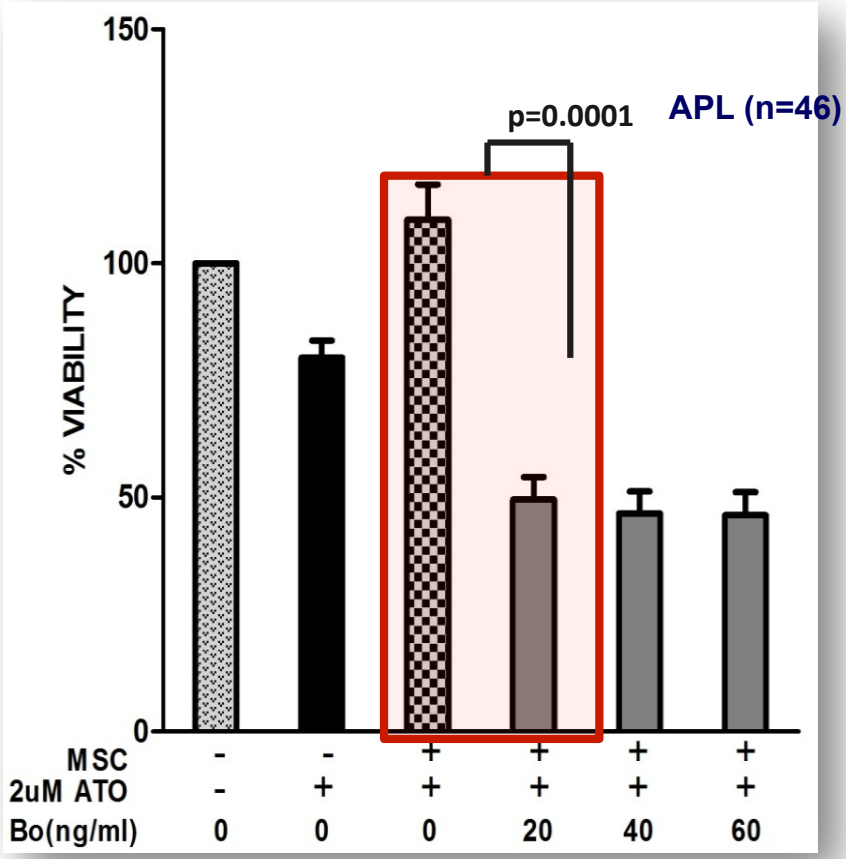


Screening of Inhibitors



Bortezomib (proteasome inhibitor) overcomes EM-DR to ATO

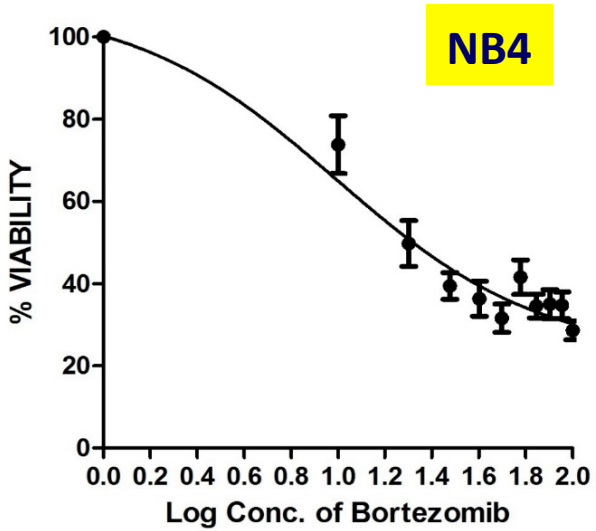


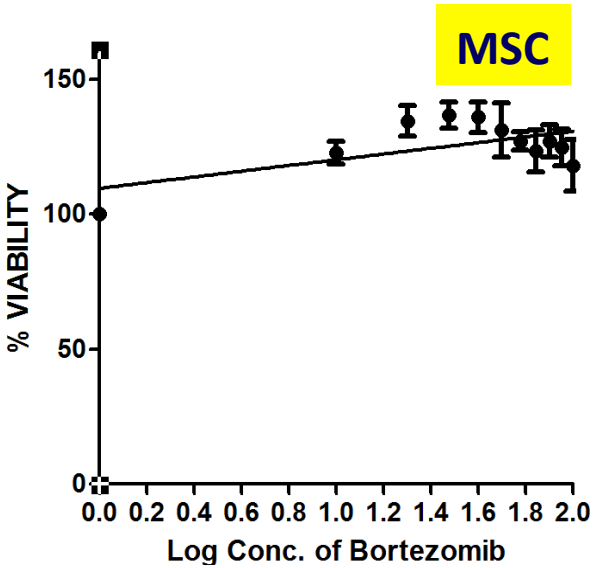


Bortezomib at pharmacologically relevant concentrations, restores the sensitivity of malignant promyelocytes to arsenic trioxide

Ganesan S et al. Leukemia 2016

Bortezomib has direct cytotoxicity on promyelocytic leukemia cells





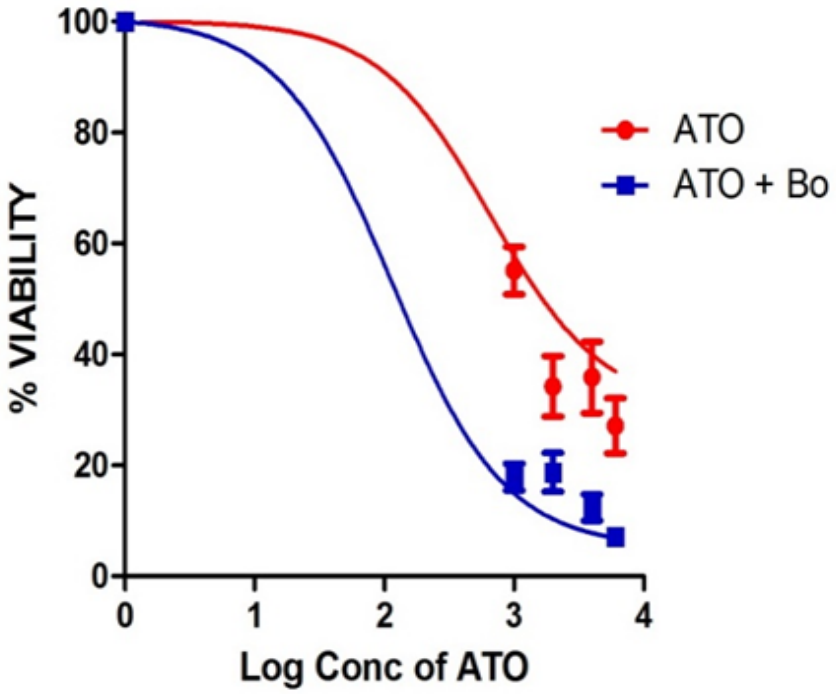
S.No	Cell line	IC50 (ng/ml)
1	NB4	5.5
2	NB4 EV-AsR1(A216V)	6.6
6	HS-5	NA
8	MNC	NA
10	MSC (Primary)	NA

NA- Not applicable since bortezomib did not kill these cells at the concentrations used in the experiments.

1. Ganesan S et al. Leukemia 2016
2. Canestraro M et al. Cancer Genet Cytogenet 2010
3. Takenokuchi M et al. Anticancer Res 2015

Arsenic trioxide and bortezomib are synergistic to each other

Combination index : 0.7 (Calcusyn software)

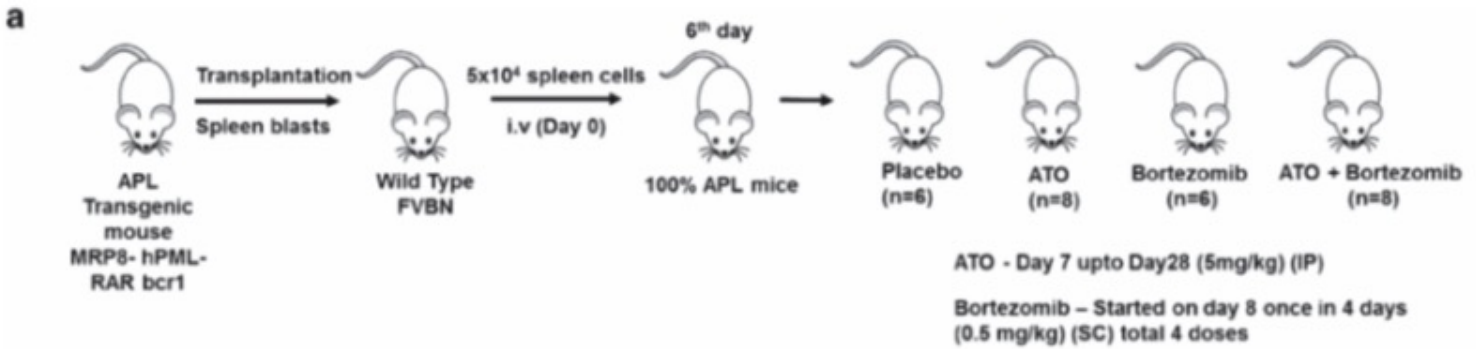


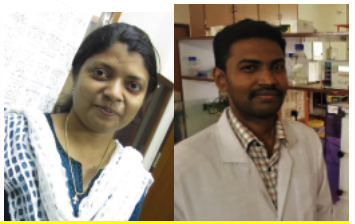
ATO IC50 – 0.9 uM
ATO + Bo IC50 – 0.2 uM

Mechanism of synergy:

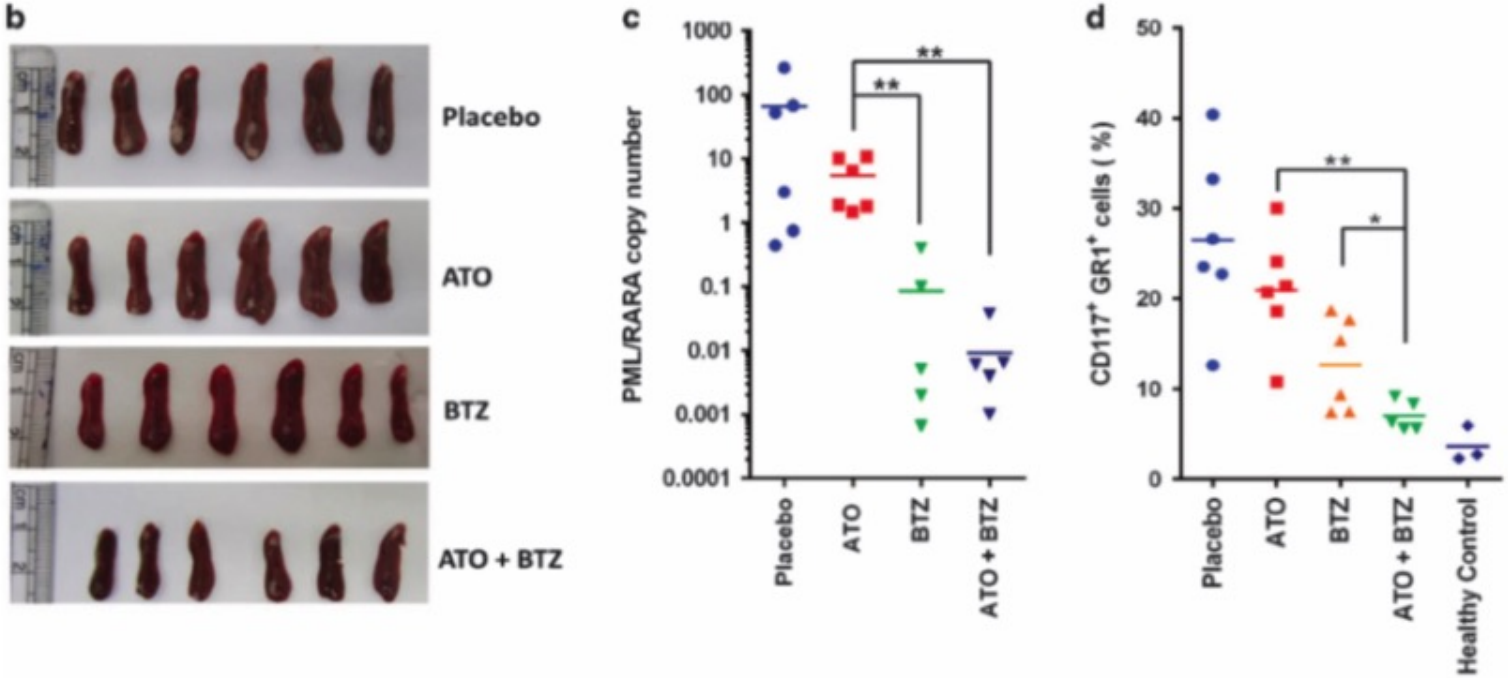
- UPR pathway
- Increase ROS and decreased MMP
- Activation of caspases

Ganesan S et al. Leukemia 2016



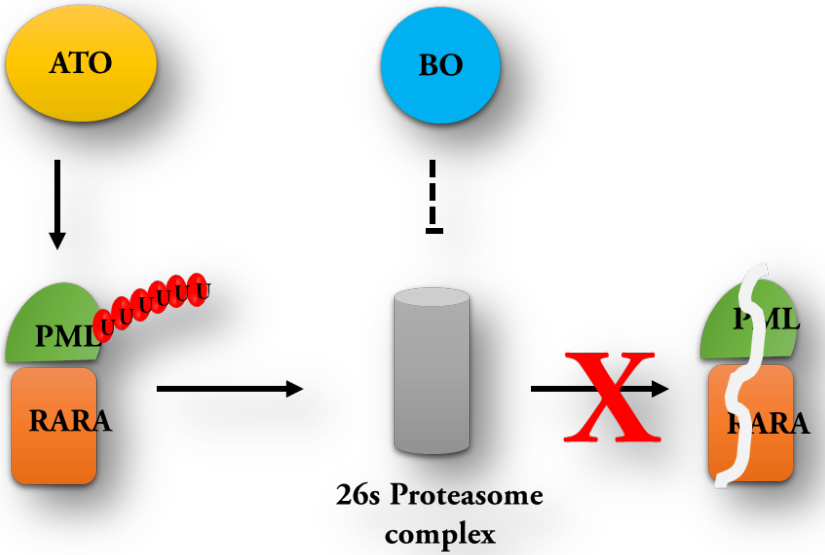


Ansu Sachin



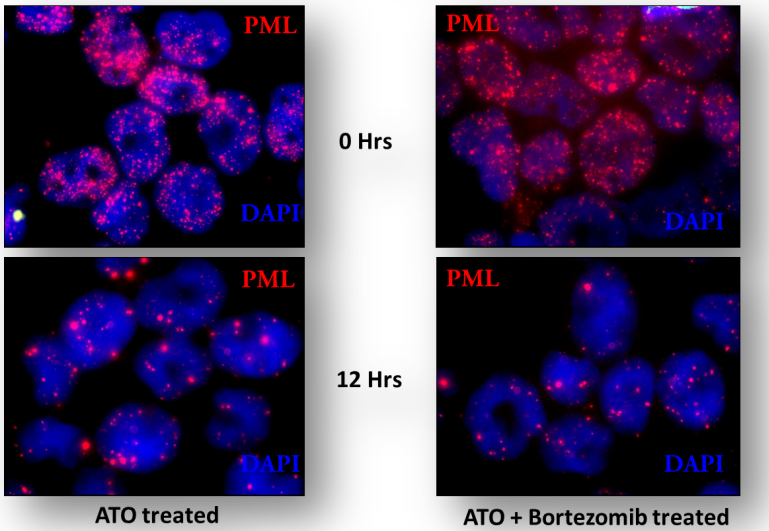
Mouse APL blasts - a kind gift from Dr. Christine Chomienne Inserm UMR-S1131. Hôpital Saint-Louis
With the permission from Dr. Scott Kogan, Dr.Michael Bishop (University of California–San Francisco)

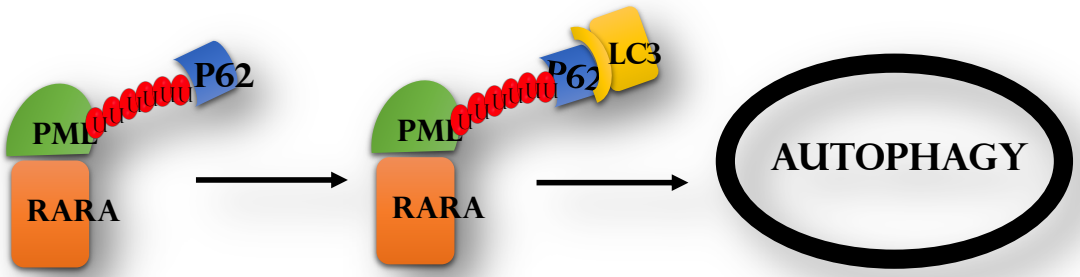
Fate of PML-RARA with this combination?



Alternative pathway of PML-RARA degradation:

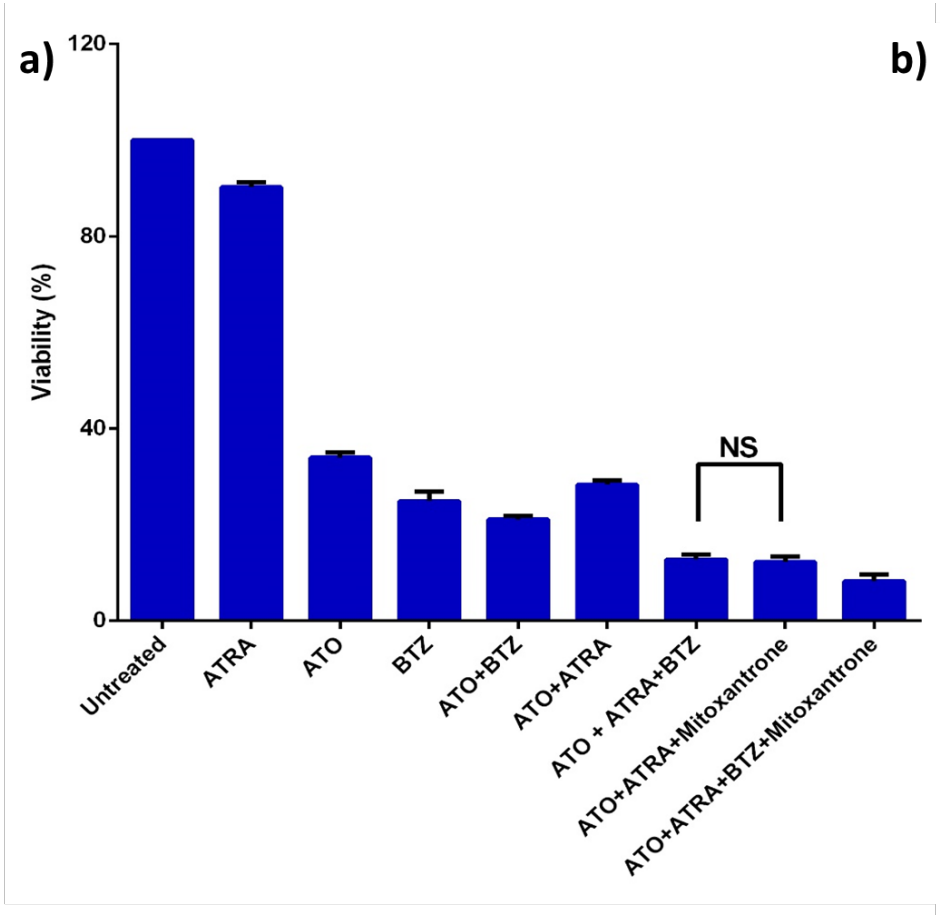
- Induction of autophagy
- Additive effect on combining ATO with Bo
- p62 dependent

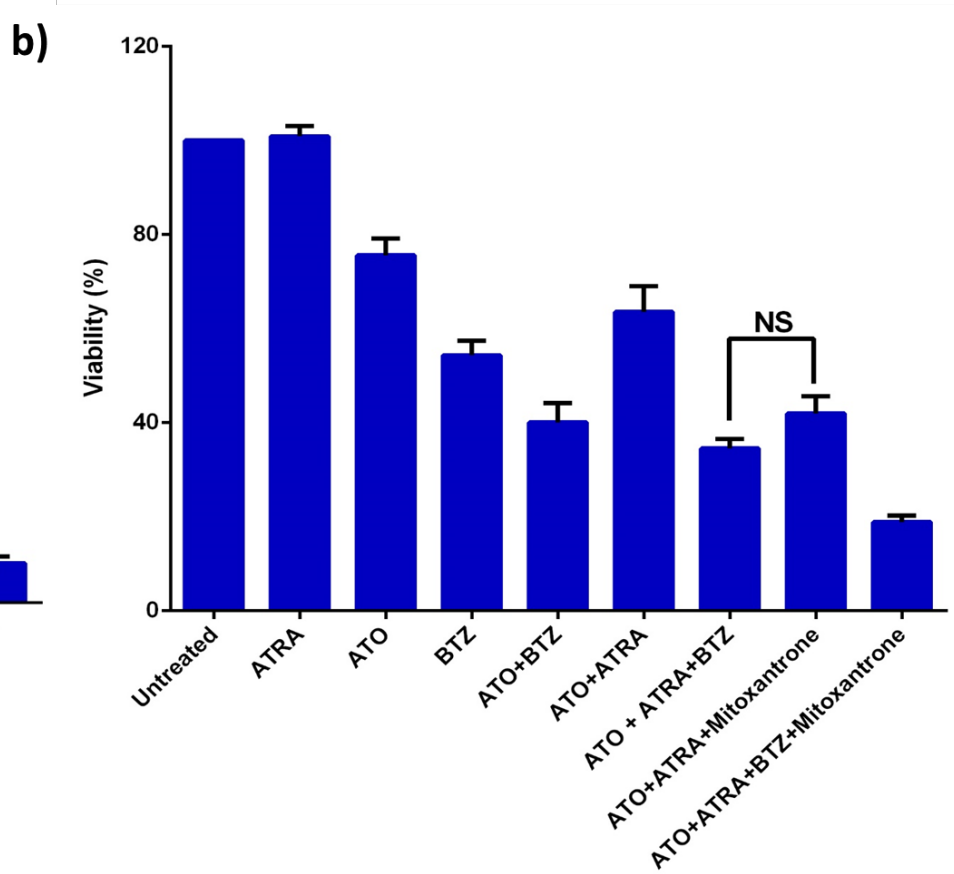




Ganesan S et al. Leukemia 2016
Ganesan S et al. ASH 2016. Poster 3281

Combination with ATRA and Mitoxantrone





ATO sensitive

ATO resistant

Ganesan S et al. Leukemia 2016

Preliminary clinical experience

Case	Age	Sex	Relapse number	Duration of last CR (months)	Prior autologous SCT	Post remission SCT	Duration of current CR (months)
RS	**25**	**M**	**2**	**19**	**Yes**	**No**	**61**
BJ	31	M	1	15	No	Yes (auto)	60
TK	35	M	2	24	Yes	Yes (MUD)	60
SS	34	F	3	19	No	No	5
AA	29	F	1	12	No	No	42

Phase II Clinical Trial

- IRB approved: IRB Min 8225, 27th Feb, 2013
- Study is registered in the public domain - Clinical Trials.gov: NCT01950611
- Proteasome inhibition in acute promyeloytic leukemia (PIAPL)
- Open-labeled, single arm, single center Phase II Study

Phase II Clinical Trial

Inclusion criteria:

- Diagnosis of relapsed PML-RARα positive APL confirmed by RT-PCR.
- Patient or guardian willing to give informed consent / assent. Must not have a psychiatric disorder(s) that would interfere with consent, study participation, or follow-up.
- Patients may have received hydroxyurea, 48 hours or less of ATRA, and 1 dose of an anthracycline and still be eligible for participation in this study.
- No age limit for entry into study.
- ECOG PS ≤ 2

Phase II Clinical Trial

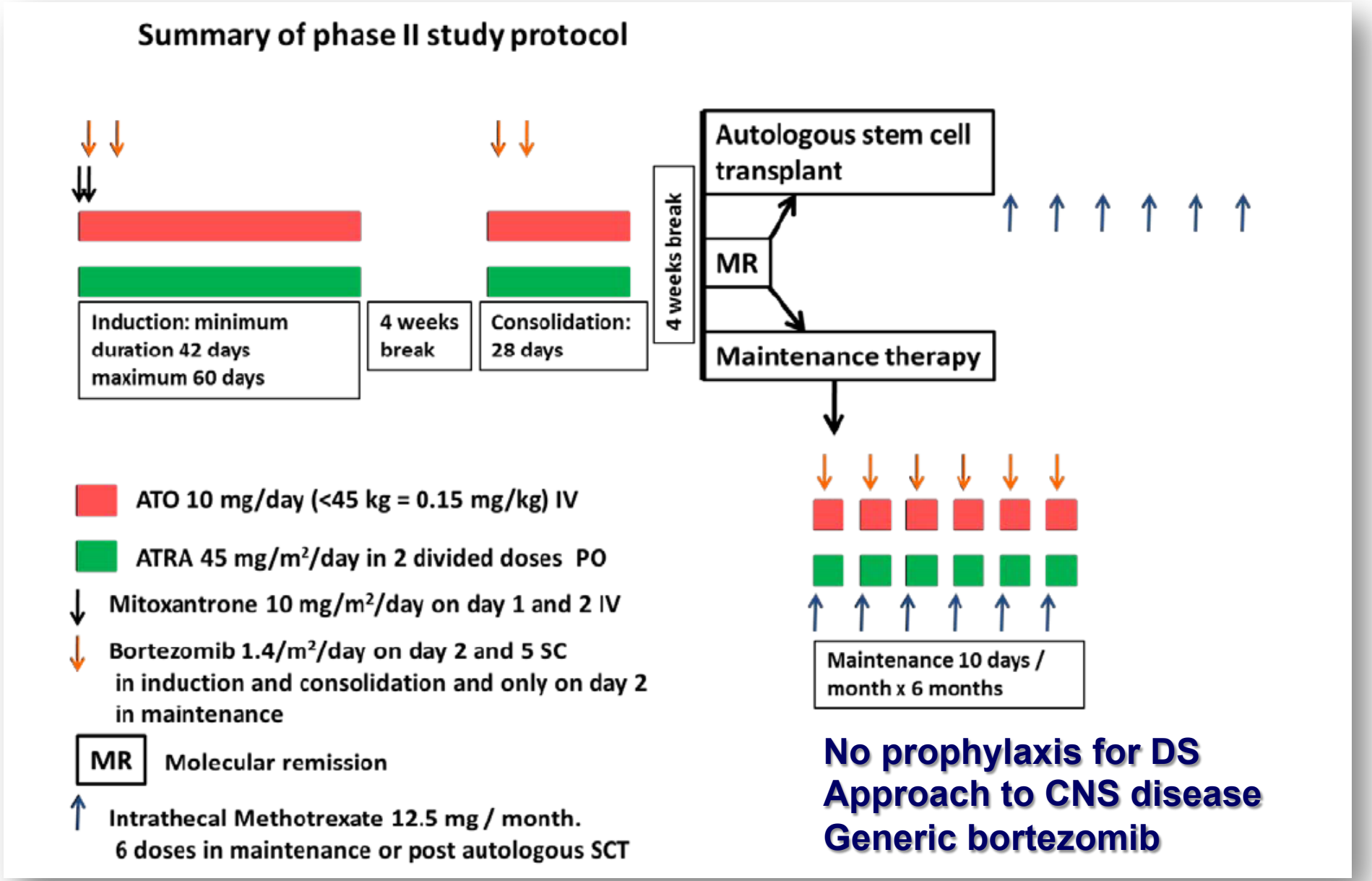
Exclusion criteria:

- Intracranial bleed at diagnosis
- History of or active IHD/MI or CCF
- Acute hepatitis (Bilirubin ≥ 5mg% or liver enzymes ≥ 4 times above laboratory normal value)
- Acute renal failure or serum creatinine ≥ 2 mg%
- Pregnancy or lactation.
- Patients with proven intolerance to the study drugs

Phase II Clinical Trial

- Single centre study
- Target of 30 patients over three years
- Primary objective to study the safety of the combination of ATO with bortezomib
- Secondary objective was to evaluate molecular response rates, relapse rates, event free and overall survival
- Comparison with historical control with interim analysis at 2 years post first patient recruitment
- Stop study rules based on Grade III/IV non-haematological toxicity were specified

Phase II Clinical Trial: schedule



Phase II Clinical Trial

- Between Sep 2013 – June 2016
- n = 18 enrolled (all received ATO upfront)
- Median age 24 years (range: 9 – 53)
- Males 9 (50%)
- Median time from diagnosis to first relapse was 21 months (range:8 – 128)
- All patients had medullary disease with evidence of hematological relapse at enrollment. 6 (33%) had additional CNS involvement
- The median WBC and platelet count at diagnosis was 2.9 (0.5-100.3) and 112 (15-192)x10^9/Lt

Phase II Clinical Trial: Remission Induction

- Median time to CHR – 45 days (42 – 63)
- 17 (94%) were RT-PCR negative post induction
- All patients achieved molecular remission
- None of the patients had any major bleeding or thrombotic events during induction
- One patient had a differentiation syndrome
- Median duration of admission for induction therapy was 22 days (range: 0 – 38)

Phase II Clinical Trial: Toxicity profile

- Grade IV neurotoxicity as peripheral neuropathy was seen in one patient. Discontinued Bo after 3 maintenance cycles
- Rest ≤ Grade II. Transient, did not require dose interruption
  - Headache 8
  - Peripheral neuropathy 2
  - Hepatotoxicity 3
  - diarrhea, mild rash, redness of eyes, oral ulcers, vertigo (1 each)
- Post induction no further in-patient admissions

Phase II Clinical Trial

- Post consolidation therapy and achieving molecular remission
  - 8 (44.4%) autologous SCT
  - 11 (60.6%) maintenance therapy
- All patients have completed intended therapy.
- Actuarial median follow up 24 months
  (range: 10 – 35)
- One patient who opted for maintenance therapy relapsed 6 months after completing treatment

Historical control n = 29: Group 1
20 (69%) received an autologous SCT

Comparison with historical control

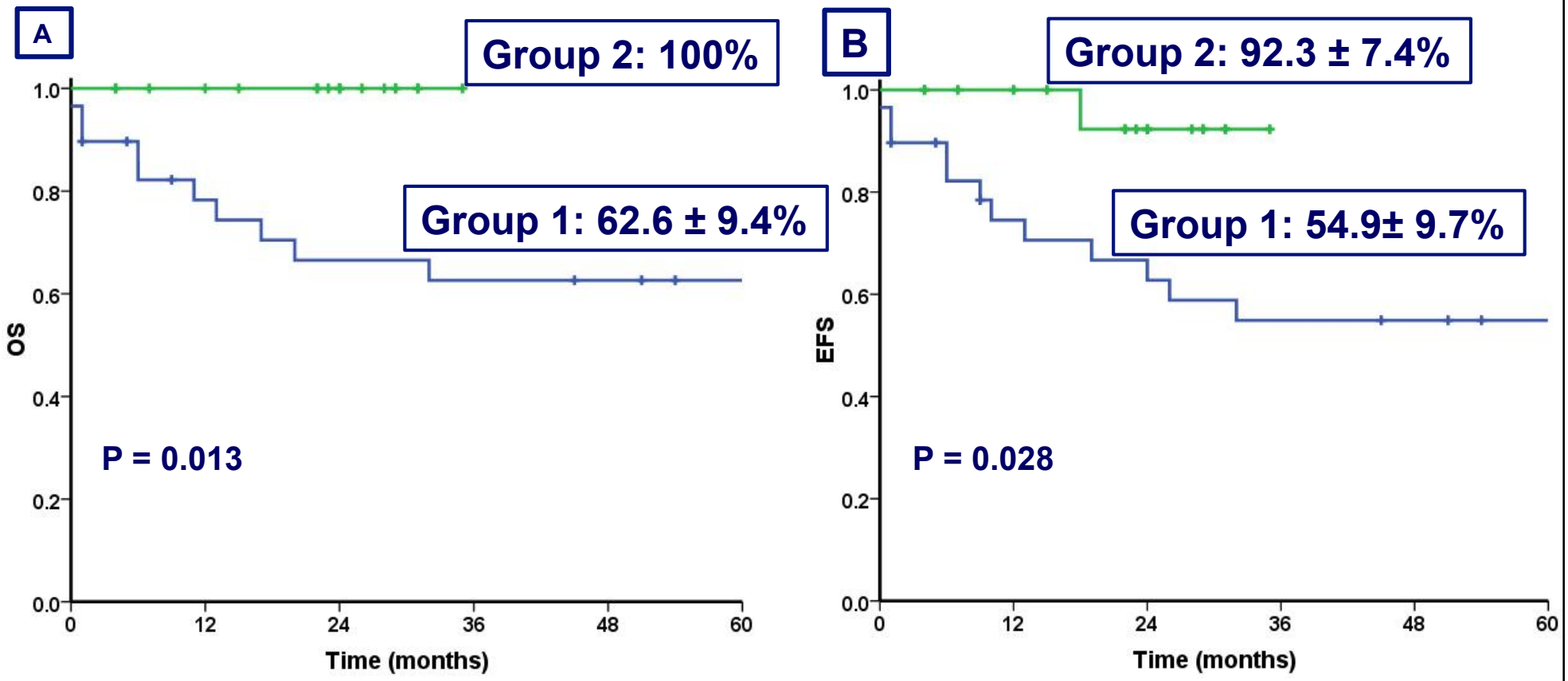
Variables	Group 1 (n = 29) Median (range)	Group 2 (n=18) Median (range)	p-value
FFP	4 (0-32)	0 (0-44)	0.045
Cryo	5.5 (0-42)	0 (0-35)	0.429
Platelet	11 (0-41)	10 (0-64)	0.538
PC	1.5(0-8)	1 (0-5)	0.710

	Historical controls	Phase II study
Median follow up	51 months	24 months
Relapses	8 (27.6%)	1 (5.6%)

Impact on coagulopathy:

- Reduction in coagulopathy
- Reduction in consumption of blood bank products.
- Early data suggests reduction in TF, Annexin II, and reduction in Etosis (provisional)
- Potential to reduce incidence of differentiation syndrome (hypothesis)

A. Overall survival B. Event free survival.
Comparison between historical Group 1 and Group II patients enrolled on Phase II Study with additional bortezomib



Resource Utilization Using MicroCosting Method and Cost Effectiveness Analysis of Treatment of Acute Promyelocytic Leukemia with Generic ArsenicTrioxide

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ATO based	Lifetime cost (US$)
Newly Diagnosed	8500
Relapsed	12200
Chemotherapy based	
ND	24300

ASH 2017

Conclusion:

- Combination of ATO and bortezomib is well tolerated. Optimal dose and schedule remain to be defined
- Larger study and longer follow up required
- More potent PI are available - ? Greater efficacy in combination
- If data holds out in non-autologous stem cell arm, one could consider omitting this procedure in relapsed APL.

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