Supplementary Information

Supplementary Figure Legends

Supplementary Figure 1 PML is highly expressed in the HSC compartment. **a**, Fractionated *Pml*$^{+/+}$ and *Pml*$^{-/-}$ haematopoietic cells were directly flow-sorted onto slides. Cells were stained with anti-mouse Pml (green, middle panels) and DAPI (blue, left panels) and analyzed by confocal microscopy. Representative data are shown (right panels). The number of PML-NBs in 150 randomly selected cells in each lineage was counted (n = 3). Data are mean numbers ± s.d. in each fraction (right). **b**, Cells of different lineages from healthy volunteers were directly flow-sorted into protein sample buffer and immunoblotted with anti-PML antibody. Representative blots are shown in the left pannel. Relative PML protein level normalized to β-actin are shown in the right panel. Asterisks indicate PML isoforms. **c**, CD34^{+} immature bone marrow cells express high levels of PML. Bone marrow samples of healthy volunteers (n= 5) were stained with anti-PML antibody (brown) and anti-CD34 (red). Representative PML-staining in CD34^{+} immature bone marrow cells and committed neutrophils is demonstrated in insets. **d**, Expression of PML in fractionated human haematopoietic cells from patients with CML. Cells were stained with anti-human PML (green, middle panels) and DAPI (blue, left panels) and analyzed by confocal microscopy. Representative data are shown (left panels). The number of PML-NBs in 50 randomly selected cells in each lineage was counted (right panel).

Supplementary Figure 2 Low PML expression predicts better overall survival in chronic phase CML. Patients receiving imatinib are divided into two groups; low PML group (PML Score 0 or 1) and high PML group (PML Score 2). Overall survival of these patients is shown. P–value was generated by a log-rank test.

Supplementary Figure 3 Progenitors numbers and function are normal in 8-week-old *Pml*$^{-/-}$ mice. **a**, Number of CMPs (common myeloid progenitors) (left), CLPs (common lymphoid progenitors) (middle), and lineage^{-} (right) in WT and *Pml*$^{-/-}$ mice . Results are mean relative numbers ± s.d. of cells in each fraction. **b, c**, Normal colony forming capacity of *Pml*$^{-/-}$ progenitors. *Pml*$^{+/+}$ and *Pml*$^{-/-}$ KSL cells were cultured on semi-solid medium and colonies were counted as colony forming units in culture (CFU-C) 7 days later (**b**). The high proliferative potential (HPP)-CFC of *Pml*$^{+/+}$ and *Pml*$^{-/-}$ KSL cells was evaluated using semi-solid culture. HPP-CFCs were identified as either very dense colonies over 0.5 mm diameter or moderately dense colonies over 1 mm diameter (**c**). Data shown are mean numbers ± s.d. of colonies (n = 3). **d**, Spleen colony formation by *Pml*$^{-/-}$ progenitor cells. Irradiated mice were transplanted with 2.5×10^2 KSL cells from *Pml*$^{+/+}$ or *Pml*$^{-/-}$ mice, and spleen colonies were counted on day 12 post-transplant (CFU-S12). Data shown are the mean numbers ± s.d. of colonies (n = 5).

Supplementary Figure 4 Defective repopulation capacity of *Pml*$^{-/-}$ HSCs. **a**, *Pml* deficiency affects all haematopoietic lineages in recipient mice after BMT. Data are mean ratios ± s.d. of the number of bone marrow cells in myeloid (left), B (middle) and T (right) cells in wild-type and *Pml*$^{-/-}$ mice compared to wild-type mice (n = 3). **b**, Minimal contribution by *Pml*$^{-/-}$ HSCs in more committed cells is found in recipient mice 6 months after BMT. Recipient mice were transplanted with $1.5\text{x}10^3$ KSL cells from *Pml*$^{+/+}$ or *Pml*$^{-/-}$ mice plus $4\text{x}10^5$ competitor cells in competition assays. Data shown are the mean relative percentage ± s.d. of donor-derived cells in fractionated haematopoietic cells in the bone marrow of recipient mice 4 months (black) and 6 months (gray) after transplantation (n = 3).

c, At the second transplant cycle, recipients of 500 KSL (left) or 50 $CD34^{neg}$KSL (right) $Pml^{-/-}$ donor-derived cells showed a significant reduction in survival relative to $Pml^{+/+}$ KSL recipients. *P*–value was generated by a log-rank test. **d**, Defective function of $Pml^{-/-}$ progenitors after BMT. 4 months after the 1st round of BMT, donor-derived KSL cells were cultured on semi-solid medium and colonies were counted as colony forming units in culture (CFU-C) 7 days later (n = 3). **e**, Decreased colony-forming capacity of 18-month-old $Pml^{-/-}$ progenitors. The number of colony-forming progenitor cells derived from 18-month-old $Pml^{+/+}$ and $Pml^{-/-}$ mice was determined. Data shown are mean numbers ± s.d. (n = 3). **f**, Short-term repopulating capacity of $Pml^{-/-}$ BM cells from 18 months mice. Recipients were transplanted with $4x10^5$ BM MNCs from 18-month-old $Pml^{+/+}$ and $Pml^{-/-}$ mice in a competition assay. Data shown are mean percentages ± s.d. of donor-derived cells 1 month (left) and 4 months (right) after transplantation (n = 3).

Supplementary Figure 5 PML plays a crucial role in LICs. **a**-**c**, Survival of recipient mice receiving transduced bone marrow cells from $Pml^{+/+}$ or $Pml^{-/-}$ mice at the 1st (**a**) and the 2nd round of BMT (**c**). WBC counts at the indicated time in the 1st round of BMT are shown (**b**). **d**, Splenomegaly in recipients transplanted with $p210^{bcr\text{-}abl}$ overexpressing $Pml^{+/+}$ bone marrow cells in the 3rd round of BMT. Ratio of spleen weight to that of recipient transplanted with MSCV-ires-GFP overexpressing WT KSL cells are shown (n = 3). **e**, Survival of recipient mice receiving WT BM cells infected with $p210^{bcr\text{-}abl}$ or empty vector in the 4th round of BMT. *P*–value was generated by a log-rank test.

Supplementary Figure 6 As_2O_3 reversibly decreased levels of PML expression *in vivo*. Mice were treated with As_2O_3 from 8- to 12-week-old (4W) and then observed from 12 to

16 weeks without treatment (8W; After Break). Pml expression in $CD34^{neg}$ KSL cells was analyzed by immunofluorescence. Representative Pml staining is shown (left). The number of PML NBs in 150 randomly selected cells was counted (n = 3). The staining of Pml and the number of NBs in $Pml^{-/-}$ $CD34^{neg}$KSL cells are also demonstrated as negative control.

Supplementary Figure 7 Rapamycin (RAPA) rescues defects of *Pml*-deficient HSCs and LICs. **a**, $CD34^{neg}$ KSL cells from 8-week-old $Pml^{+/+}$ and $Pml^{-/-}$ mouse were directly flow-sorted into protein sample buffer and immunoblotted with anti-P-S6, S6, Pml and actin antibody. Representative blots are shown in the left panel. Graph represents P-S6 levels normalized for total protein levels and β-actin. Asterisks indicate Pml isoforms. **b**, Treatment with rapamycin (RAPA) *in vitro* restores colony forming capacity of $Pml^{-/-}$ KSL cells. $Pml^{+/+}$ and $Pml^{-/-}$ KSL cells were cultured with stromal cells and rapamycin for the indicated number of weeks (W) and tested for colony formation. Data shown are the mean numbers ± s.d. of colonies formed (n = 3). **c**, Rapamycin treatment rescues defects in maintenance of quiescence in $Pml^{-/-}$ HSCs. Flow cytometric analysis of bone marrow cells from wild-type or $Pml^{-/-}$ mice treated with rapamycin from 4- to 8-week-old. Cell cycle status of HSCs was analyzed by flow cytometry. Data are mean percentages ± s.d. of Pyronin Y negative cells in KSL cells at 8 weeks of age (n = 3). **d**, $Pml^{+/+}$ or $Pml^{-/-}$ mice were treated with RAPA from 4- to 8-week-old and number of $CD34^{neg}$KSL cells was measured. Results are mean absolute numbers ± s.d. of $CD34^{neg}$KSL cells. **e**, Rapamycin restores the long-term reconstitution potential of $Pml^{-/-}$ HSCs. Recipient mice were transplanted with $1.5x10^3$ KSL cells from $Pml^{+/+}$ or $Pml^{-/-}$ mice plus $4x10^5$ competitor cells in a competition assay. Some recipient mice were treated with rapamycin for 16 weeks.

Results are mean percentages ± s.d. of donor-derived cells at the indicated number of weeks after BMT (n = 3). **f**, Restored haematopoietic reconstitution *in vivo* after long-term treatment with RAPA. KSL cells were isolated from 8-week-old $Pml^{+/+}$ and $Pml^{-/-}$ mice and transplanted to irradiated recipient mice. Some recipient mice were treated with rapamycin for 4 months after transplantation. Results are mean percentages ± s.d. of donor-derived cells 4 months after BMT (n = 3). **g**, Administration of rapamycin rescues maintenance defect of *Pml*-deficient LICs. Transduced KSL cells cultured on stromal cells and treated with rapamycin for the indicated number of weeks (W) were analyzed for colony formation (n = 3). **h**, Mice transplanted with transduced bone marrow cells from $Pml^{+/+}$ or $Pml^{-/-}$ mice were treated with rapamycin for 2 weeks. Survival of recipient mice at the 1st round of BMT is shown. **i**, Treatment with rapamycin restores the potential to develop CML-like disease of $Pml^{-/-}$ LICs. Transduced $Pml^{+/+}$ and $Pml^{-/-}$ bone marrow cells were transplanted to recipient mice. Some recipient mice were treated with rapamycin for 2 weeks during the 1st and 2nd round of BMT. In the third round of BMT, rapamycin treatment was discontinued. Survival of recipient mice in the third round of BMT is demonstrated. **j**, WBC counts at the indicated time in the 3rd round of BMT are demonstrated.

Supplementary Figure 8 As_2O_3 treatment does not induce apoptosis in either LICs or HSCs. Bone marrow cells infected with $p210^{bcr/abl}$ or empty vector (MSCV-ires-GFP) were co-cultured with stromal cells for 2 weeks. Apoptosis in KSL cells was analyzed by flow cytometry (n = 3). As a positive control, cells were treated with 10μM etoposide for two days and lineage positive cells were stained with Annexin V.

Supplementary Figure 9 Co-treatment with As_2O_3 and Ara-C induces apoptosis in LICs. **a,** Transduced *Pml*$^{+/+}$ KSL cells were cultured on stromal cells with As_2O_3 for 9 days. Then cells were co-treated with As_2O_3 and Ara-C for 5 days. KSL cells were stained with Annexin V and analyzed by flow cytometry. Results are percentages ± s.d. of Annexin V positive cells (n = 3). **b**, Combined therapy with As_2O_3 and Ara-C induces remarkable survival advantage and complete cure in more than half of the recipient mice. Transduced BM cells ($1.5x10^4$ cells) co-cultured with stromal cells were treated with As_2O_3 for two weeks and with Ara-C for 5 days. CD45 positive cells were sorted and transplanted into recipient mice with competitor cells ($4x10^5$ MNCs). Survival of recipient mice in the 2nd round of BMT is shown. P–value was generated by a log-rank test.

Supplementary Figure 10 LICs cycle more than normal HSCs. **a**, Bone marrow cells infected with empty vector (MSCV-ires-GFP) or p210$^{bcr\text{-}abl}$ were co-cultured with stromal cells for two weeks. KSL cells were stained with Pyronin Y and analyzed by flow cytometry. Mean percentages ± s.d. of Pyronin Y negative cells in KSL cells (n = 3) are shown. **b**, *Pml*$^{+/+}$ bone marrow cells infected with p210$^{bcr\text{-}abl}$ or empty vector were transplanted into irradiated recipient mice. Donor-derived KSL cells were stained with Pyronin Y and analyzed by flow cytometry 14 days after BMT. Mean percentages ± s.d. of Pyronin Y negative cells in donor-derived KSL cells is shown (n = 3). **c**, LICs are more sensitive to cell cycle entry by As_2O_3. KSL cells overexpressing p210$^{bcr\text{-}abl}$ or empty vector were co-cultured with stromal cells with As_2O_3 for two weeks. KSL cells were stained with Pyronin Y and analyzed by flow cytometry. Results are mean relative Pyronin Y negative cells in KSL cells treated with As_2O_3 compared with p210$^{bcr\text{-}abl}$ or empty vector overexpressing cells without treatment respectively (n = 3). **d**, *Pml*$^{+/+}$ and *Pml*$^{-/-}$ BM cells

overexpressing $p210^{bcr\text{-}abl}$ or empty vector were transplanted into irradiated recipient mice. Cell cycle status of donor-derived KSL cells was analyzed by Pyronin Y staining 14 days after BMT. Relative percentages of Pyronin Y negative cells in $Pml^{-/-}$ cells compared with $Pml^{+/+}$ cells infected with each vector is demonstrated (n = 3). **e**, Co-treatment with Ara-C and As_2O_3 affects LICs more than HSCs. KSL cells overexpressing $p210^{bcr\text{-}abl}$ or empty vector were co-cultured with stromal cells with As_2O_3 for two weeks and Ara-C for 5 days. KSL cells were stained with Annexin V and analyzed flow cytometry. Results are percentages ± s.d. of Annexin V positive cells in KSL cells (n = 3).

Supplementary Figure 11 **a**, **b**, Mice transplanted with transduced BM cells are treated with As_2O_3 for 9 days from the next day of BMT. Then mice were co-treated with As_2O_3 and Ara-C for 5 days. $1.5x10^6$ BMMNCs were collected from recipient mice 2 weeks after the first BMT and were transplanted into other recipient mice (second BMT). Third transplantation was also performed in the same manner. Survival of recipient mice in the first (**a**) and the third round (**b**) of BMT is shown. Log rank statistical analysis was performed to obtain p.

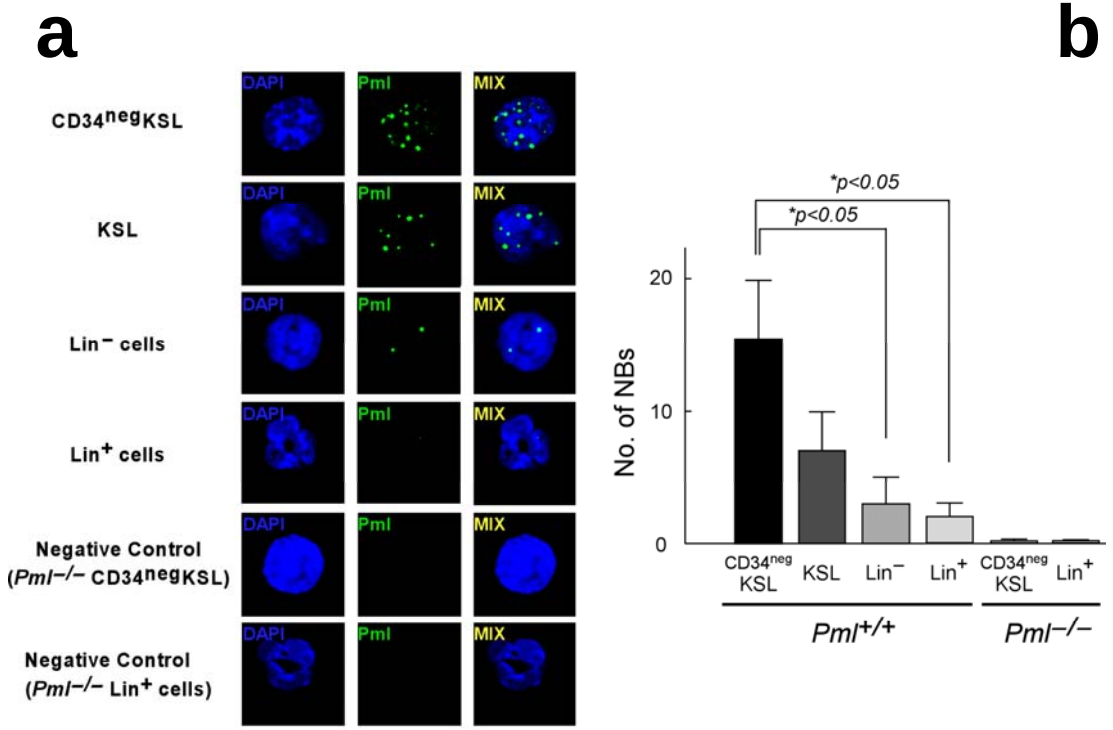
Supplementary Figure 12 As_2O_3 treatment induces more cycling in human primary LICs than normal HSCs. **a**, $Lin^-CD34^+CD38^{low/neg}$ cells from CML-CP patients at diagnosis were sorted and cultured with As_2O_3 for 3 days. PML expression was analyzed by immunofluorescence. Representative data are shown (left panels). The number of PML NBs in 50 randomly selected cells in each lineage was counted (right panel). **b**, $Lin^-CD34^+CD38^{low/neg}$ cells from healthy volunteers and CML patients were stained with CFSE and cultured with SCF+TPO+Flt-3L. After three days in culture, fluorescence intensity of

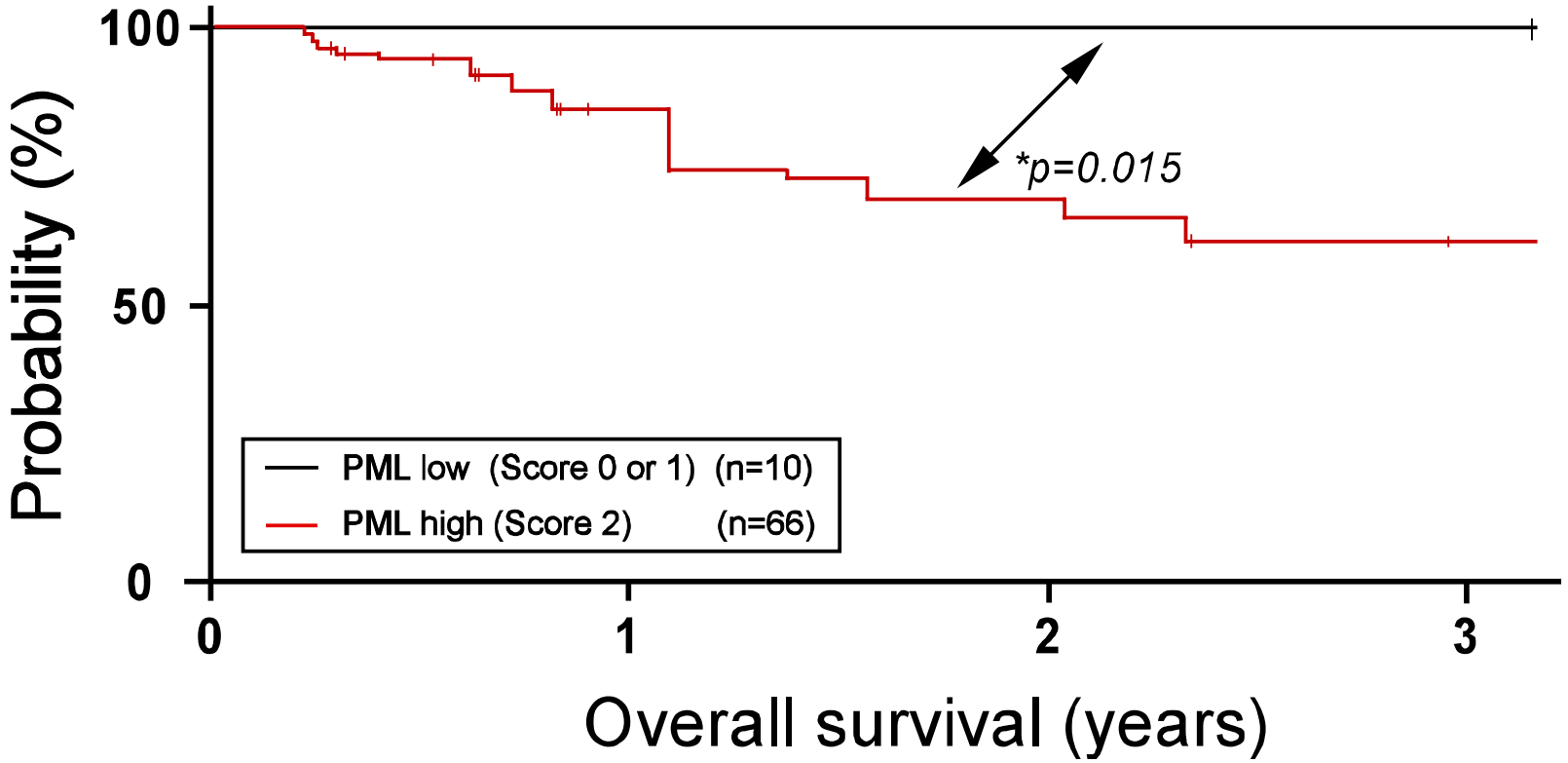
CFSE was analyzed by flow cytometry. Representative CFSE profile is shown. **c**, Single cell sorting of $Lin^{-}CD34^{+}CD38^{low/neg}c\text{-}Kit^{+}$ cells was performed and cells were cultured with SCF+TPO+Flt-3L. Cell division of these cells was monitored daily.

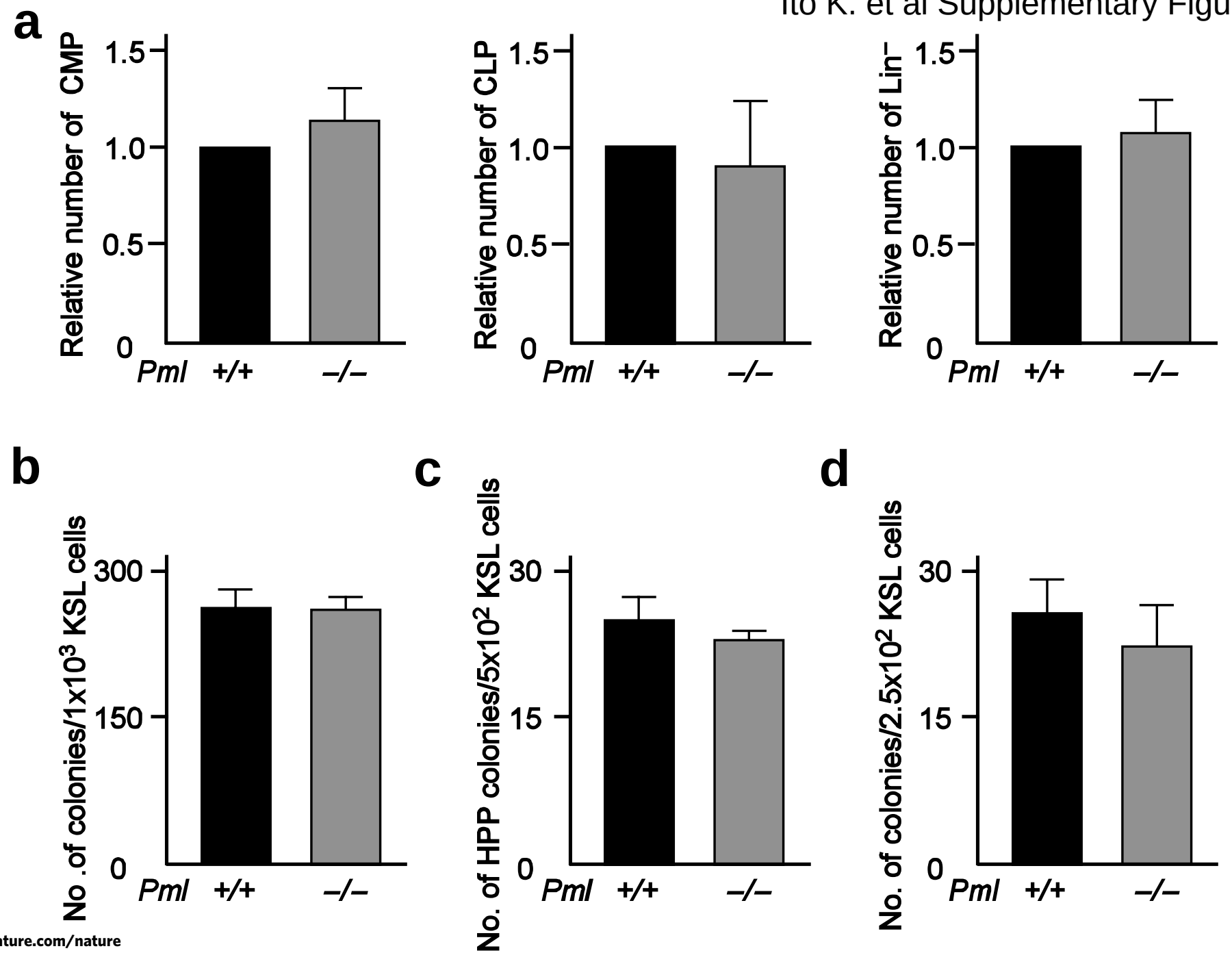
Supplementary Table 1 Co-treatment with Ara-C and As_2O_3 *ex vivo* has the potential of completely eradicating LICs. Transduced BM cells ($1.5x10^4$ cells) co-cultured with stromal cells were treated with As_2O_3 for two weeks and with Ara-C for 5 days. CD45 positive cells were sorted and transplanted into recipient mice with competitor cells ($4x10^5$ MNCs). Percentage of MRD-detection is shown at the indicated time after the 2nd BMT (upper) and at 2 weeks after the 1st round BMT (lower).

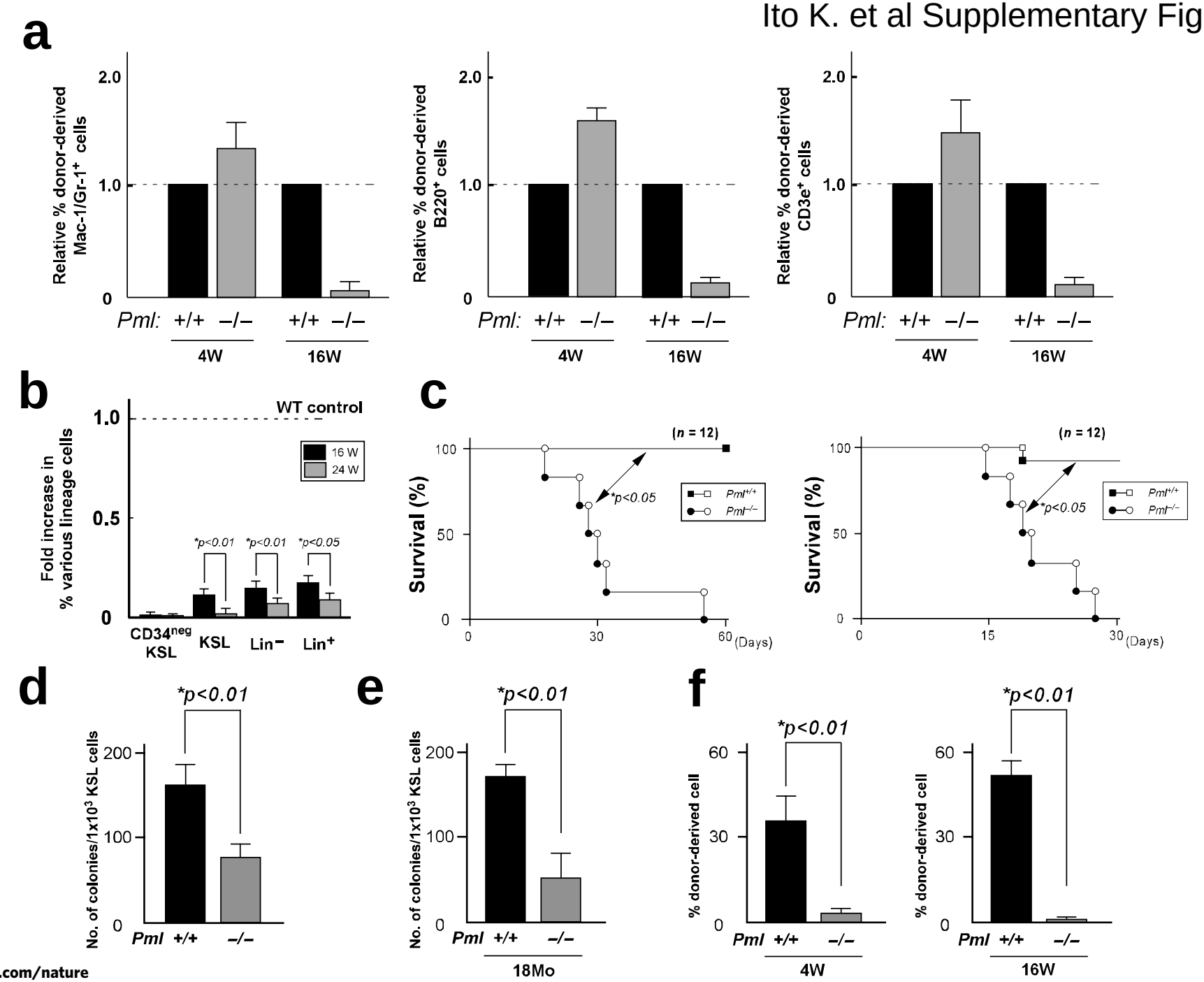
Supplementary Table 2 *In vivo* combined Ara-C and As_2O_3 therapy completely eradicates LICs. Percentage of MRD-detection is shown at 2 weeks after the 3rd BMT (upper) and 2nd round BMT (lower).

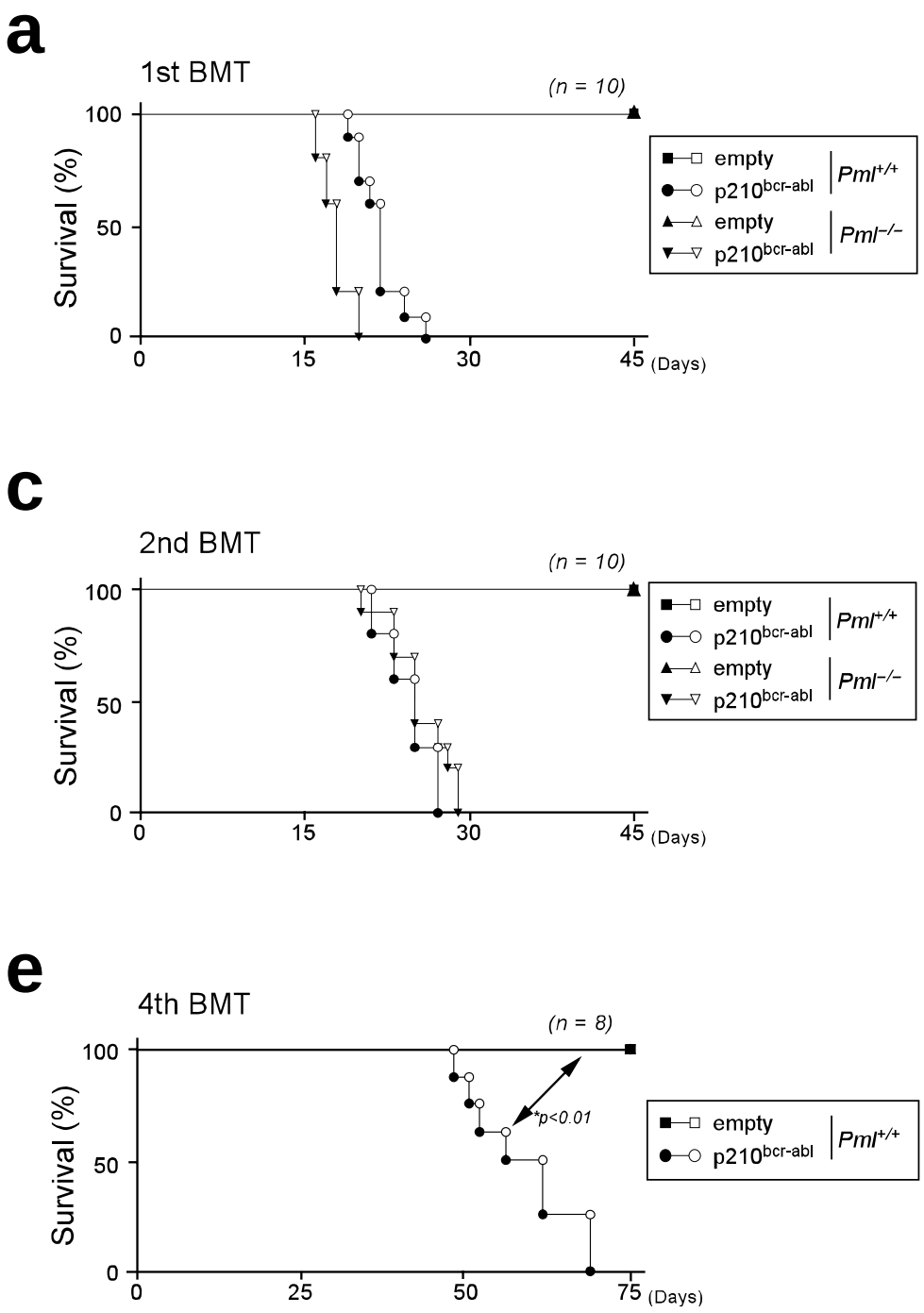
Supplementary Table 3, 4 Clinical and immunohistochemical characteristics of CML patients.

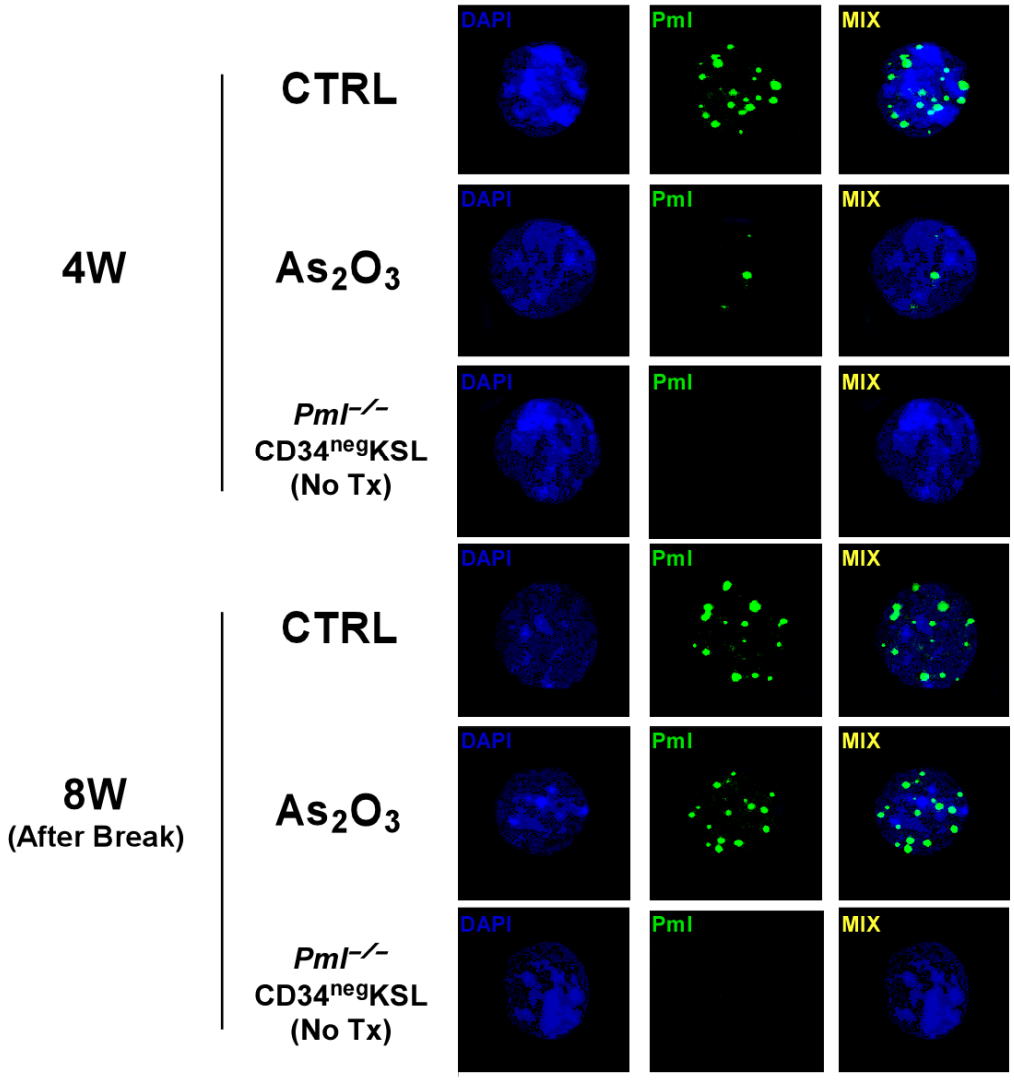

a
DAPI
Pml
MIX
CD34negKSL
KSL
Lin− cells
Lin+ cells
Negative Control
(Pml−/− CD34negKSL)
Negative Control
(Pml−/− Lin+ cells)
*p<0.05
*p<0.05
No. of NBs
20
10
0
CD34neg KSL
KSL
Lin−
Lin+
CD34neg KSL
Lin+
Pml+/+
Pml−/−
b
CD34+Lin−
Lin−
Lin+
PML
β-actin
Relative PML expression
(v.s. CD34+Lin− cells)
1.0
0.5
0
c
Committed
neutrophil
Committed
neutrophil
CD34+
immature cells
Committed
neutrophil
d
CD34+Lin− cells
Lin− cells
Lin+ cells
DAPI
PML
MIX
*p<0.05
No. of NBs
20
10
0
CD34+Lin−
Lin−
Lin+

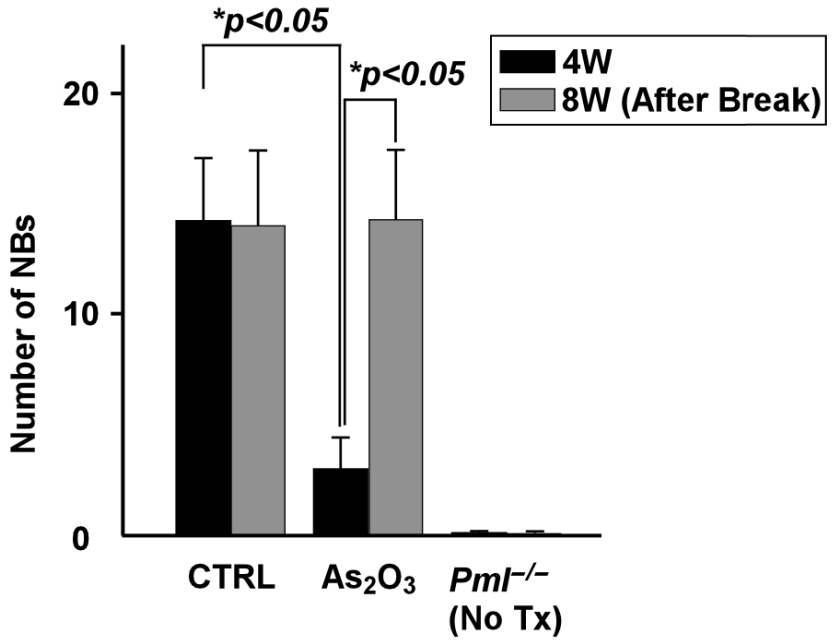

100
50
0
Probability (%)
*p=0.015
PML low (Score 0 or 1) (n=10)
PML high (Score 2) (n=66)
0
1
2
3
Overall survival (years)

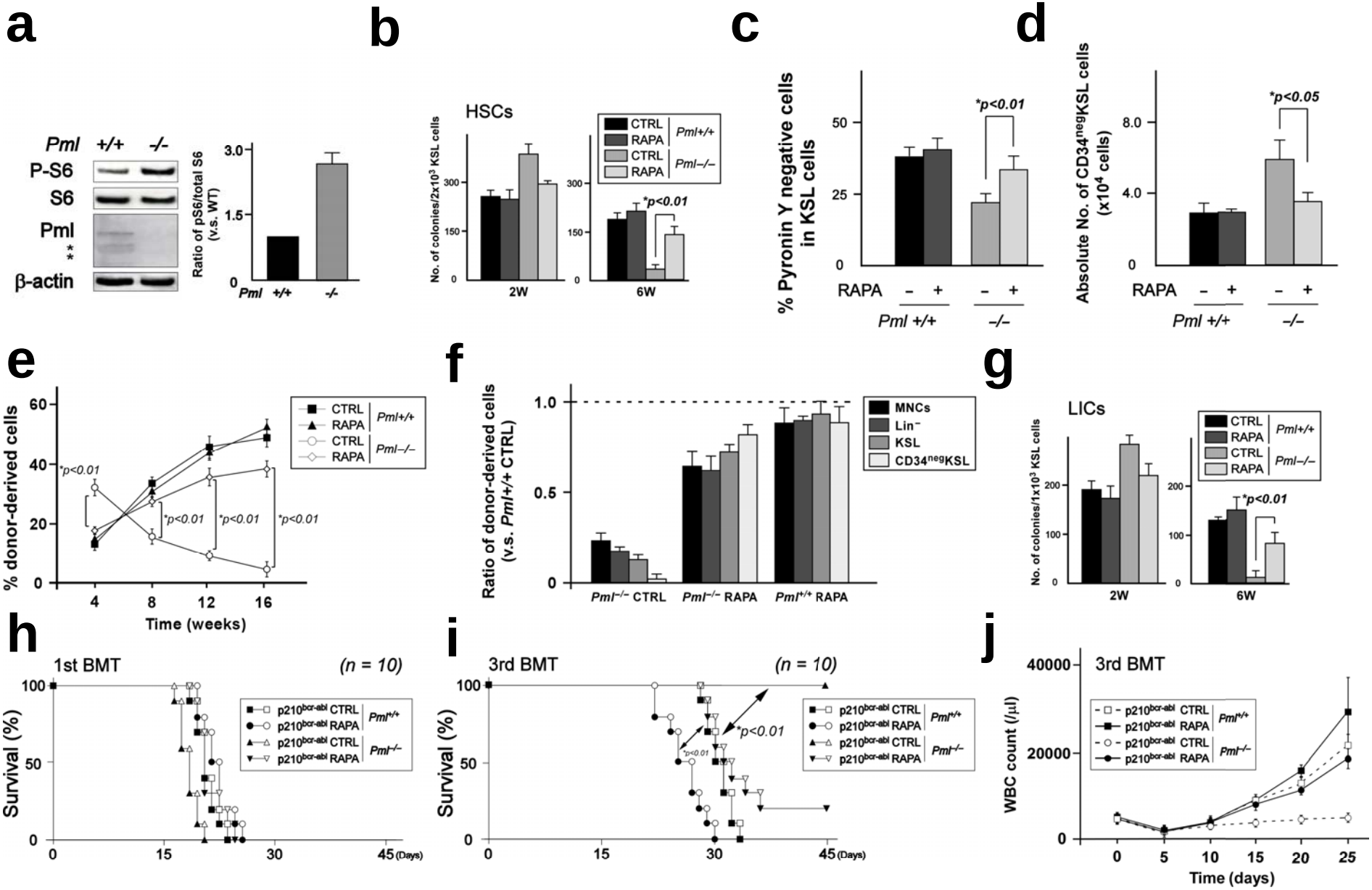

a
Relative number of CMP
1.5
1.0
0.5
0
Pml +/+ –/–
Relative number of CLP
1.5
1.0
0.5
0
Pml +/+ –/–
Relative number of Lin⁻
1.5
1.0
0.5
0
Pml +/+ –/–
b
No .of colonies/1x10³ KSL cells
300
150
0
Pml +/+ –/–
c
No. of HPP colonies/5x10² KSL cells
30
15
0
Pml +/+ –/–
d
No. of colonies/2.5x10² KSL cells
30
15
0
Pml +/+ –/–

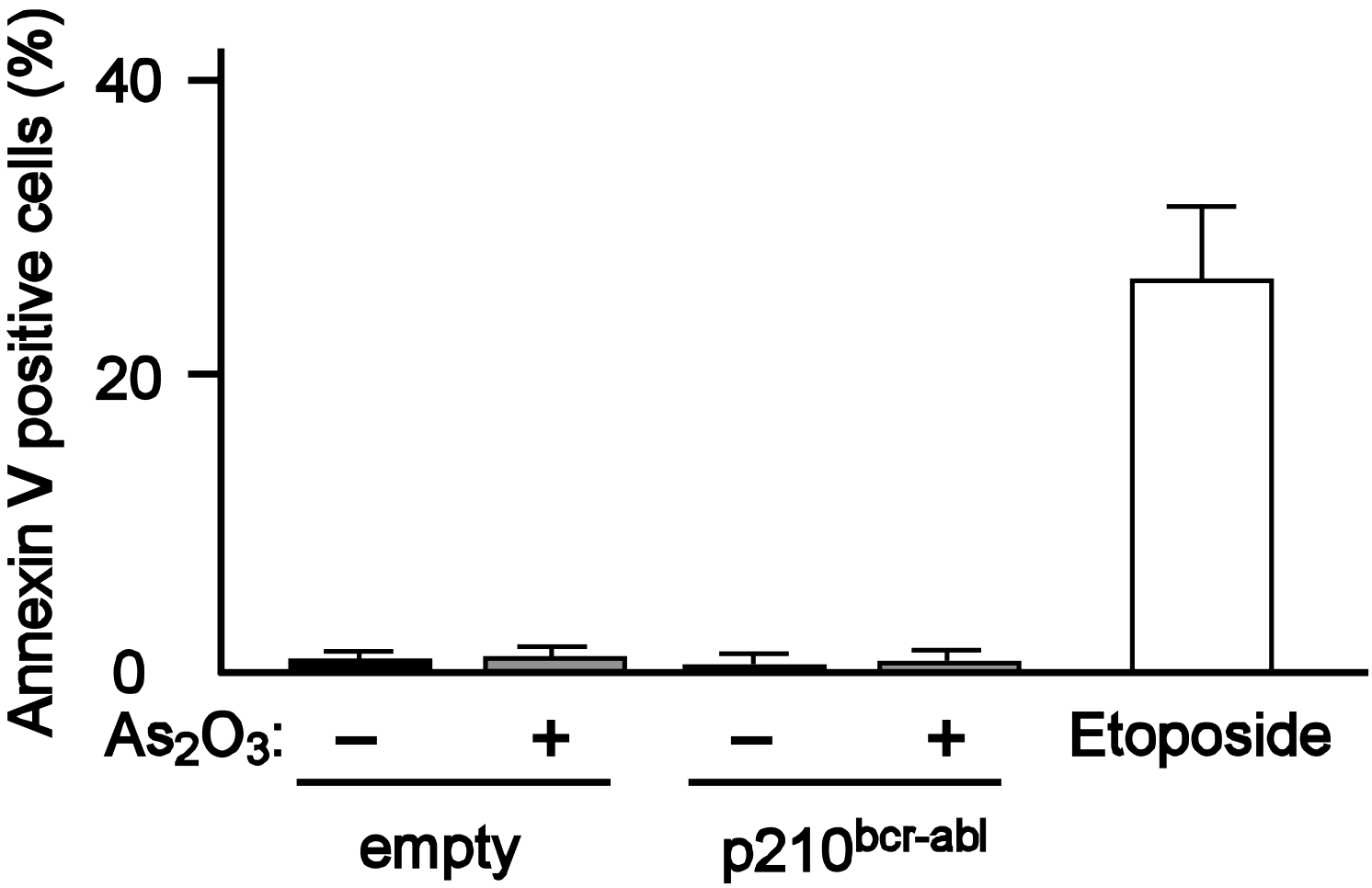

a
Relative % donor-derived Mac-1/Gr-1+ cells
Relative % donor-derived B220+ cells
Relative % donor-derived CD3e+ cells
2.0
1.0
0
Pml: +/+ –/– +/+ –/–
4W
16W
b
Fold increase in % various lineage cells
WT control
16 W
24 W
*p<0.01
*p<0.01
*p<0.05
CD34neg KSL
KSL
Lin–
Lin+
c
Survival (%)
(n = 12)
*p<0.05
Pml+/+
Pml–/–
100
50
0
30
60
15
(Days)
d
*p<0.01
No. of colonies/1x10³ KSL cells
200
100
Pml +/+ –/–
e
*p<0.01
18Mo
f
*p<0.01
% donor-derived cell
60
30
4W
16W

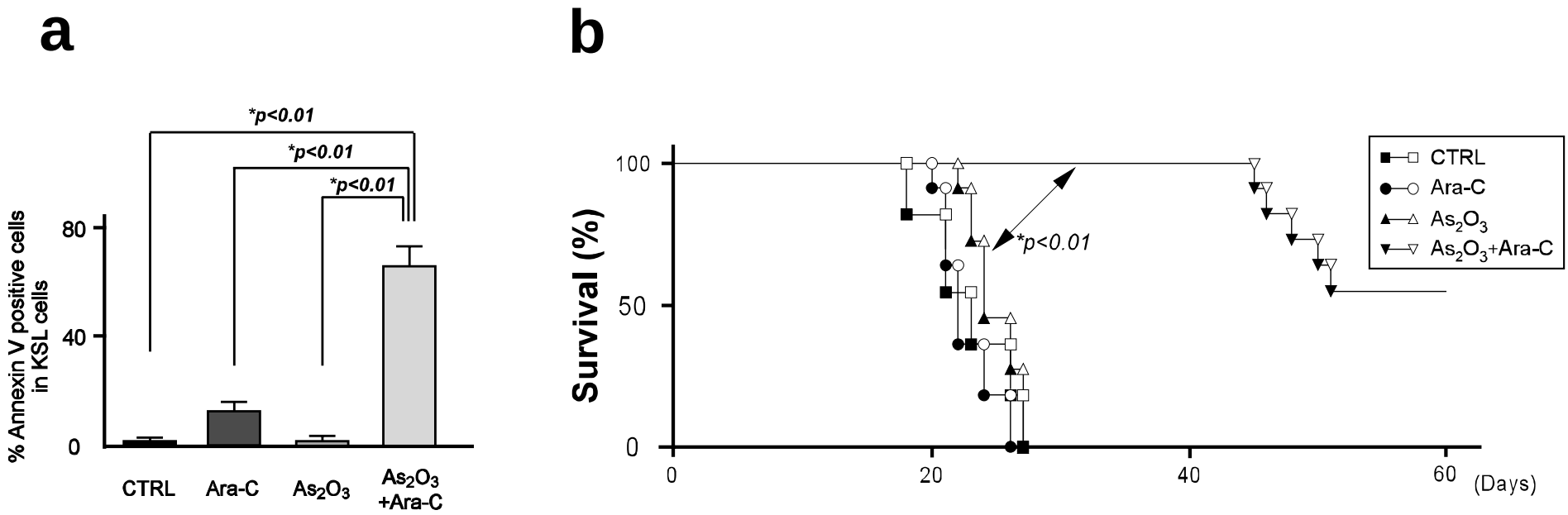

a
1st BMT
(n = 10)
Survival (%)
100
50
0
0
15
30
45 (Days)
empty
p210bcr-abl
Pml+/+
empty
p210bcr-abl
Pml−/−
b
WBC count (/μl)
60000
40000
20000
0
0
5
10
15
20
Time (days)
empty
p210bcr-abl
Pml+/+
empty
p210bcr-abl
Pml−/−
c
2nd BMT
(n = 10)
Survival (%)
100
50
0
0
15
30
45 (Days)
empty
p210bcr-abl
Pml+/+
empty
p210bcr-abl
Pml−/−
d
Relative weight of spleen
3.0
2.0
1.0
0
empty
p210bcr-abl
Pml+/+
Pml−/−
e
4th BMT
(n = 8)
Survival (%)
100
50
0
0
25
50
75 (Days)
*p<0.01
empty
p210bcr-abl
Pml+/+

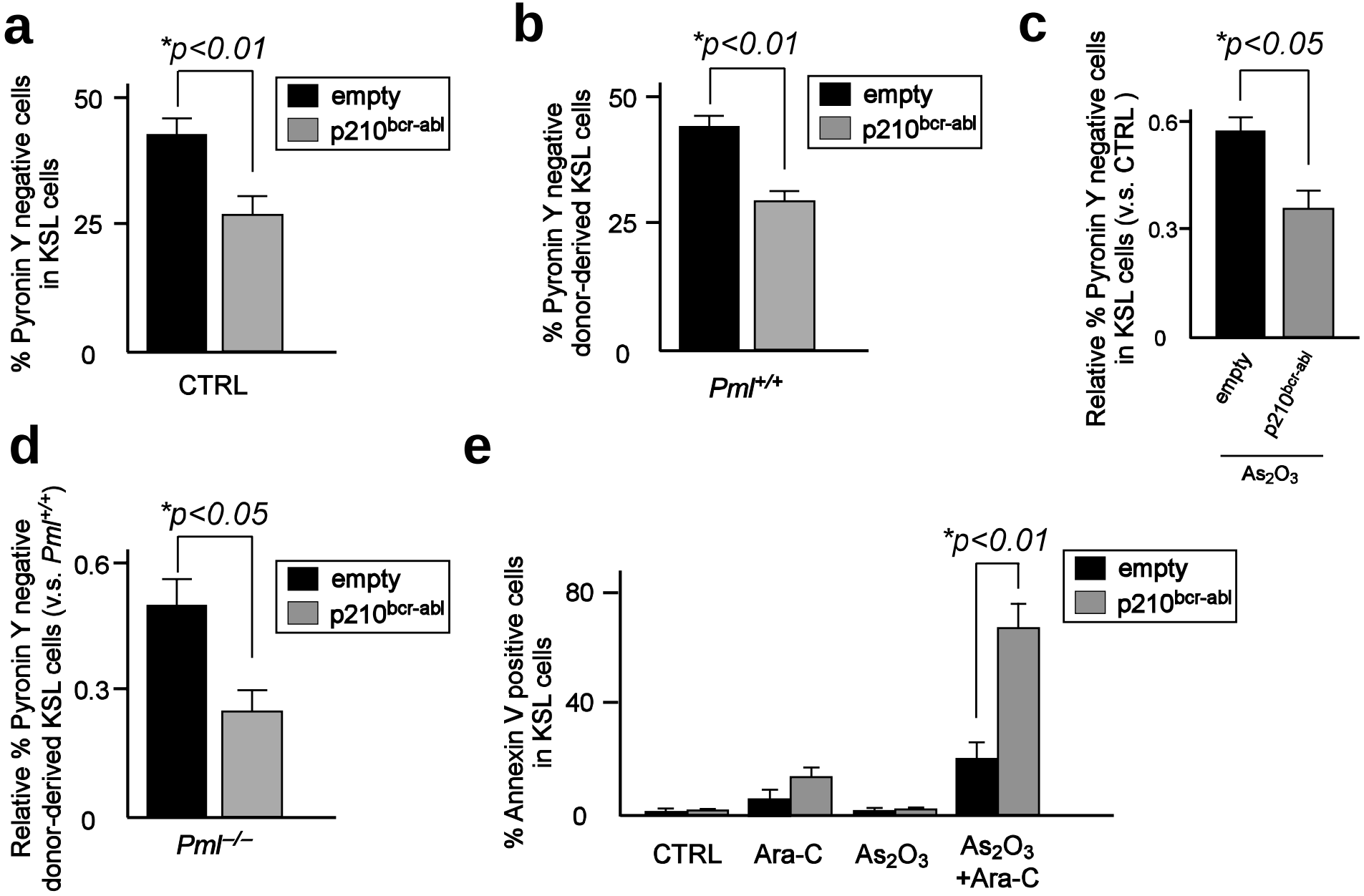

4W
CTRL
As2O3
Pml−/− CD34negKSL (No Tx)
8W (After Break)
CTRL
As2O3
Pml−/− CD34negKSL (No Tx)
DAPI
Pml
MIX

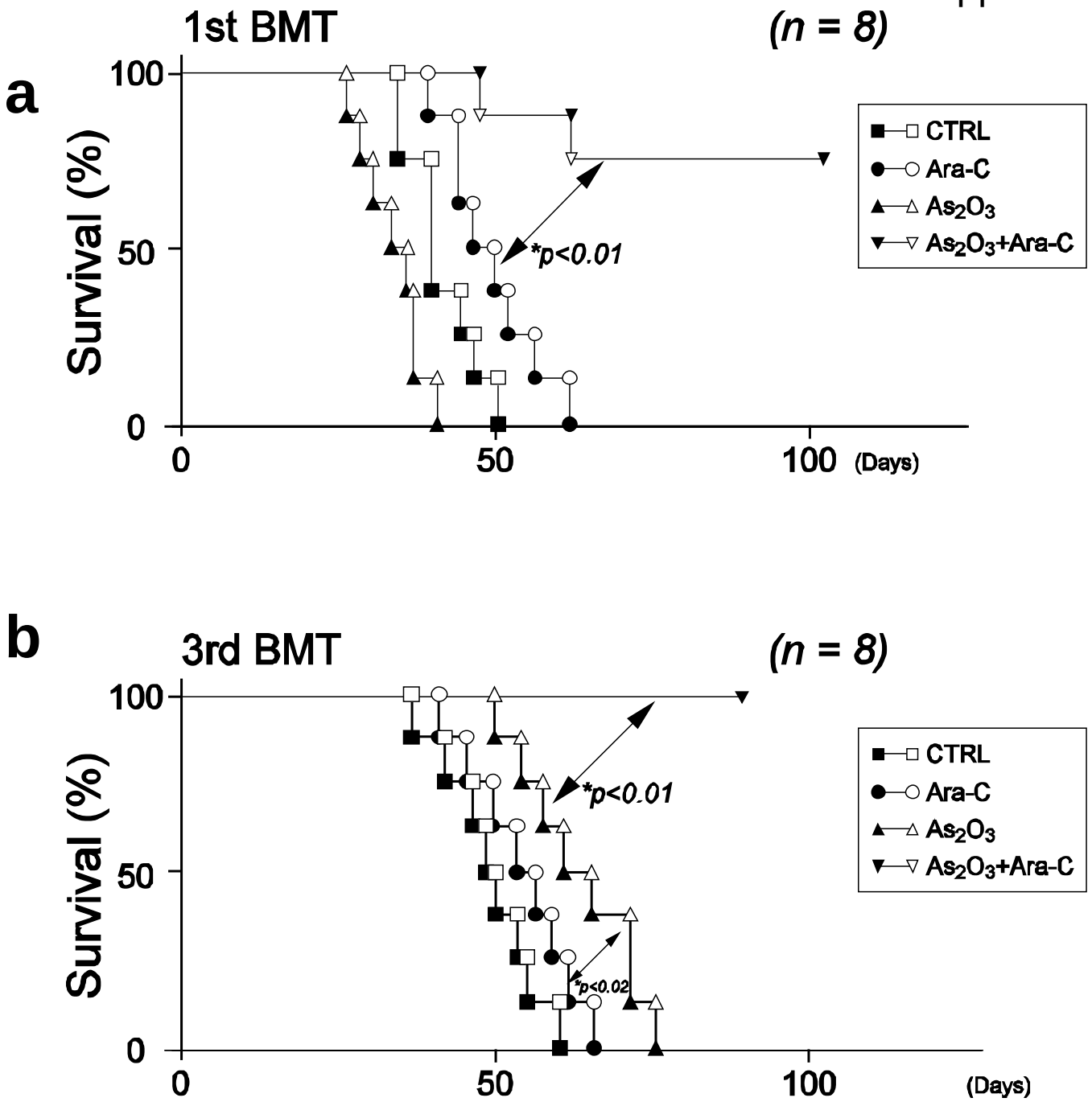

*p<0.05
*p<0.05
4W
8W (After Break)
Number of NBs
20
10
0
CTRL
As2O3
Pml−/− (No Tx)

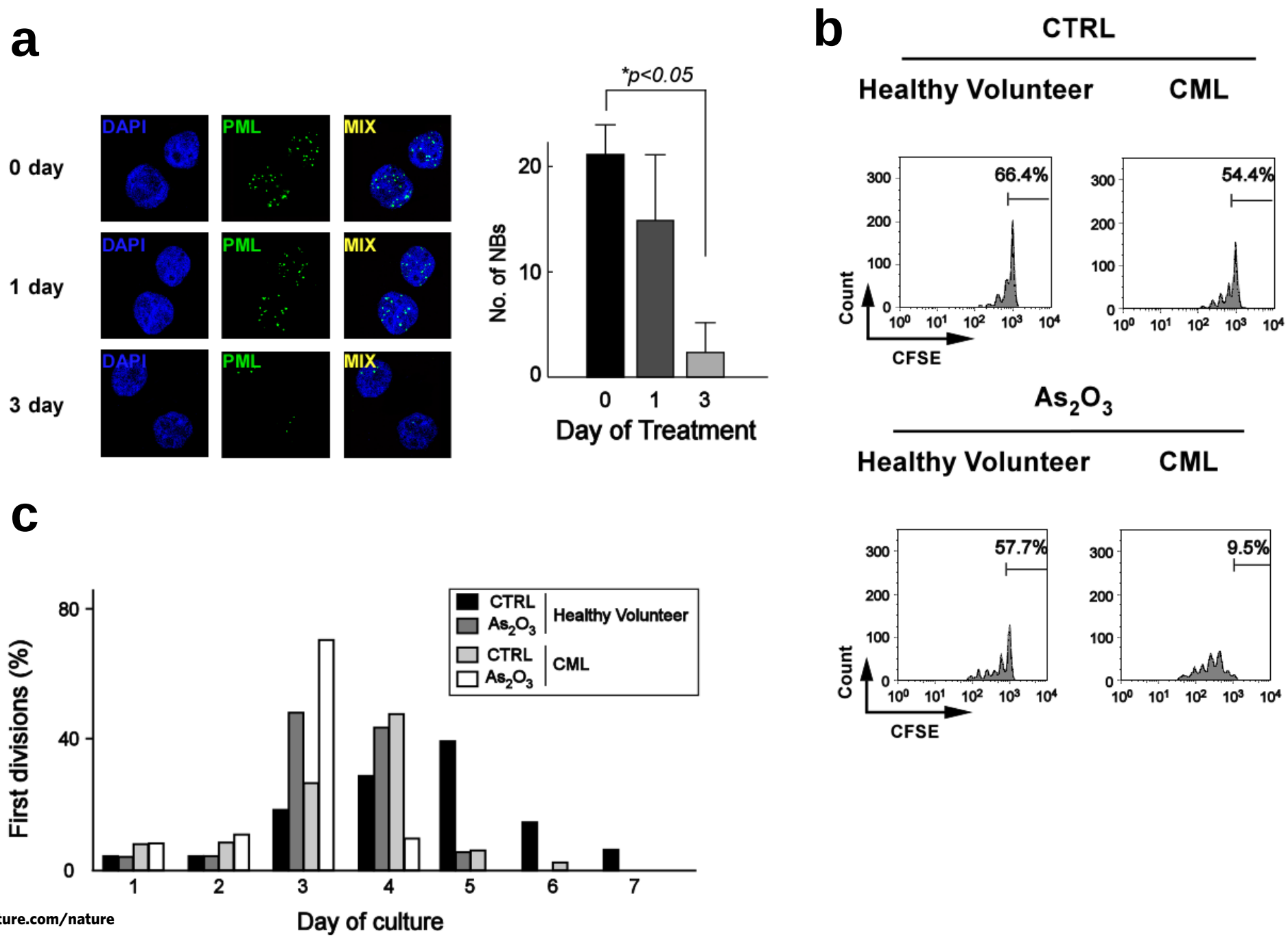

a
Pml +/+ -/-
P-S6
S6
Pml
β-actin
Ratio of pS6/total S6 (v.s. WT)
b
HSCs
No. of colonies/2x10³ KSL cells
CTRL
RAPA
Pml+/+
Pml−/−
*p<0.01
2W
6W
c
% Pyronin Y negative cells in KSL cells
*p<0.01
RAPA
Pml +/+
−/−
d
Absolute No. of CD34negKSL cells (x10⁴ cells)
*p<0.05
e
% donor-derived cells
*p<0.01
Time (weeks)
f
Ratio of donor-derived cells (v.s. Pml+/+ CTRL)
MNCs
Lin⁻
KSL
CD34negKSL
Pml−/− CTRL
Pml−/− RAPA
Pml+/+ RAPA
g
LICs
No. of colonies/1x10³ KSL cells
h
1st BMT
(n = 10)
Survival (%)
p210bcr-abl CTRL
p210bcr-abl RAPA
Pml+/+
Pml−/−
(Days)
i
3rd BMT
(n = 10)
j
3rd BMT
WBC count (/μl)
Time (days)


Annexin V positive cells (%)
40
20
0
As2O3: – + – +
Etoposide
empty
p210bcr-abl


a
*p<0.01
*p<0.01
*p<0.01
% Annexin V positive cells in KSL cells
80
40
0
CTRL
Ara-C
As2O3
As2O3 +Ara-C
b
Survival (%)
100
50
0
0
20
40
60
(Days)
*p<0.01
CTRL
Ara-C
As2O3
As2O3+Ara-C


a
*p<0.01
% Pyronin Y negative cells in KSL cells
50
25
0
empty
p210bcr-abl
CTRL
b
*p<0.01
% Pyronin Y negative donor-derived KSL cells
50
25
0
empty
p210bcr-abl
Pml+/+
c
*p<0.05
Relative % Pyronin Y negative cells in KSL cells (v.s. CTRL)
0.6
0.3
0
empty
p210bcr-abl
As2O3
d
*p<0.05
Relative % Pyronin Y negative donor-derived KSL cells (v.s. Pml+/+)
0.6
0.3
0
empty
p210bcr-abl
Pml−/−
e
*p<0.01
% Annexin V positive cells in KSL cells
80
40
0
empty
p210bcr-abl
CTRL
Ara-C
As2O3
As2O3 +Ara-C


a
1st BMT
(n = 8)
Survival (%)
100
50
0
0
50
100
(Days)
*p<0.01
CTRL
Ara-C
As2O3
As2O3+Ara-C
b
3rd BMT
(n = 8)
Survival (%)
100
50
0
0
50
100
(Days)
*p<0.01
*p<0.02
CTRL
Ara-C
As2O3
As2O3+Ara-C


a
0 day
1 day
3 day
DAPI
PML
MIX
*p<0.05
No. of NBs
Day of Treatment
b
CTRL
Healthy Volunteer
CML
66.4%
54.4%
Count
CFSE
As2O3
57.7%
9.5%
c
First divisions (%)
Day of culture
CTRL
As2O3
Healthy Volunteer
CML

Supplementary Table 1 Analysis of MRD by nested RT-PCR

2nd round of BMT	14 days				60 days
Ara-C	−	+	−	+	+
As_2O_3	–	–	+	+	+
MRD-detection by PCR	3/3 (100%)	3/3 (100%)	3/3 (100%)	0/3 (0%)	0/6 (0%)

1st round of BMT	14 days			
Ara-C	−	+	−	+
As_2O_3	–	–	+	+
MRD-detection by PCR	4/4 (100%)	4/4 (100%)	4/4 (100%)	0/4 (0%)

Supplementary Table 2 Analysis of MRD by nested RT-PCR

3rd round of BMT	14 days			
Ara-C	−	+	−	+
As_2O_3	−	−	+	+
MRD-detection by PCR	3/3 (100%)	3/3 (100%)	3/3 (100%)	0/3 (0%)

2nd round of BMT	14 days			
Ara-C	−	+	−	+
As_2O_3	−	−	+	+
MRD-detection by PCR	4/4 (100%)	4/4 (100%)	4/4 (100%)	0/4 (0%)

Supplementary Table 3 Clinical and immunohistochemical characteristics of CML patients

Patient #	Phase	Age	Gender	% Blasts	PML Score	Cytogenesis at diagnosis	Therapy	Cytogenetic response status (Interval since diagnosis - months)	Molecular response status (Interval since diagnosis - months)
1	CP[a]	30	M	5	2	Ph1 Chr[b] 100% interphase cells karyotype	BMT	No	No
2	CP	64	F	2	2	Ph1-Chr present (100%)	Hydroxyurea, Gleevec	CCyR[c] (3 Mo)	No
3	CP	61	M	3	2	Ph1-Chr present (100%)	Gleevec	No	No
4	CP	54	M	6	1	Ph1 chromosme present (72%)	Hydroxyurea, Gleevec	CCyR (3 Mo)	CMR[d] (9Mo)
5	CP	64	F	3	2	Ph1-Chr present (100%)	IFN, Ara-c	CCyR (4 Mo)	No
6	CP	14	M	4	2	Ph1-Chr present (100%)	Gleevec	No	No
7	CP	39	F	1	2	Ph1-Chr present (99.8%)	Gleevec	CCyR (4 Mo)	No
8	CP	12	M	2	2	Ph1-Chr present (100%)	Hydroxyurea, IFN, BMT	No	No
9	CP	39	F	1	2	Ph1-Chr present (100%)	Geelvec	CCyR (8 Mo)	No
10	CP	48	M	2	2	Ph1 chromosme present (100%)	Hydroxyurea, IFN	CCyR (10 Mo)	No
11	CP	45	F	1	2	Ph1 chromosme present (41%)	Gleevec	CCyR (3 Mo)	No
12	CP	38	M	4	2	t(9;22)(q34;q11.2); trisomy 8, extra Ph1	Gleevec	No	No
13	CP	46	F	2	2	Ph1-Chr present (100%)	Gleevec	No	No
14	CP	33	F	2	2	t(9;22)(q34;q11.2) with variant translocation	Hydroxyurea, Gleevec	CCyR (3 Mo)	CMR (25Mo)
15	CP	41	M	2	2	Ph1-Chr present (100%)	Gleevec	CCyR (7Mo)	No
16	CP	32	F	2	2	Ph1-Chr present (100%)	Gleevec	No	No
17	CP	73	M	2	2	Ph1-Chr present (96%)	Gleevec	CCyR (7 Mo)	No
18	CP	47	F	3	2	Ph1-Chr present (96%)	Gleevec	No	No
19	CP	49	M	6	2	Ph1 Chr 98.4% interphase cells karyotype, extra copy Ph1-Chr 1.4%	Gleevec	CCyR (3 Mo)	No
20	CP	54	M	1	1	Ph1-Chr present (96%)	Gleevec	CCyR (3 Mo)	CMR (8Mo)
21	CP	33	F	6	2	Ph1-Chr present (96%)	Gleevec, PBSCT	CCyR (10 Mo)	No
22	CP	37	M	2	2	Ph1-Chr present (100%)	Gleevec	No	No
23	CP	73	M	1	2	Ph1 Chr 59% interphase cells karyotype, FISH 61% interphase cells	Gleevec	CCyR (10 Mo)	CMR (13 Mo)
24	CP	40	F	3	2	Ph1-Chr present (41.8%)	Gleevec	No	No
25	CP	60	M	1	2	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	No	No
26	CP	52	F	2	2	Ph1-Chr present (100%)	Gleevec	CCyR (6 Mo)	No
27	CP	46	F	1	2	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	CCyR (6 Mo)	No
28	CP	55	F	2	2	Ph1+ karyotype, FISH 24.3% interphase cells	Gleevec	CCyR (6 Mo)	No
29	CP	40	F	3	2	Ph1-Chr present (100%)	Gleevec	CCyR (5 Mo)	No
30	CP	65	M	2	2	Ph1 Chr 99.6% interphase cells karyotype, extra copy Ph1-Chr 0.4%	Gleevec	No	No
31	CP	67	M	3	2	Ph1+ karyotype, FISH 99% interphase cells	Gleevec	No	No
32	CP	19	F	2	1	Ph1+ karyotype, FISH 84.5% interphase cells	Gleevec	CCyR (4 Mo)	CMR (8Mo)
33	CP	54	F	4	2	Ph1+ karyotype, FISH 51.2% interphase cells	Gleevec	No	No
34	CP	47	M	2	2	Ph1-Chr present (100%)	Hydroxyurea, Gleevec	No	No
35	CP	32	F	1	2	Ph1+ karyotype, FISH 99.25% interphase cells	Gleevec	CCyR (3 Mo)	CMR (18 Mo)
36	CP	44	M	3	2	Ph1+ karyotype, FISH 99.2% interphase cells	Gleevec	CCyR (4 Mo)	No
37	CP	41	M	1	1	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	CCyR (11 Mo)	CMR (14 Mo)
38	CP	67	M	1	2	Ph1+ karyotype, FISH 76.2% interphase cells	Gleevec	CCyR (3 Mo)	No
39	CP	55	M	6	2	Ph1-Chr present (100%)	Hydroxyurea Gleevec	CCyR (5 Mo)	CMR (17Mo)
40	CP	71	M	1	2	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	CCyR (3 Mo)	No
41	CP	59	F	2	2	Ph1-Chr present (100%)	Gleevec	No	No

[a] CP : chronic phase
[b] Chr : chromosome
[c] CCyR: complete cytogenetic response
[d] CMR : complete molecular response

Supplementary Table 4 Clinical and immunohistochemical characteristics of CML patients

Patient #	Phase	Age	Gender	% Blasts	PML Score	Cytogenesis at diagnosis	Therapy	Cytogenetic response status (Interval since diagnosis - months)	Molecular response status (Interval since diagnosis - months)
42	CP	24	M	1	2	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	CCyR (6 Mo)	No
43	CP	38	M	3	2	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	CCyR (6 Mo)	No
44	CP	62	M	2	2	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	CCyR (4 Mo)	No
45	CP	40	M	2	1	Ph1 chromosme present (100%)	Gleevec	CCyR (6 Mo)	CMR (18 Mo)
46	CP	83	F	2	2	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	CCyR (6 Mo)	No
47	CP	46	F	1	2	Ph1+ karyotype, FISH 94% interphase cells	Gleevec	CCyR (6 Mo)	No
48	CP	55	F	1	2	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	CCyR (6 Mo)	No
49	CP	53	F	3	1	Ph1-Chr present (96%)	Gleevec	CCyR (8 Mo)	CMR (15 Mo)
50	CP	47	M	2	2	t(9;22)(q34;q11);add(19)(p11)	Gleevec	CCyR (6 Mo)	No
51	CP	53	M	1	2	Ph1 Chr 98% interphase cells karyotype	Gleevec	No	No
52	CP	56	F	1	2	Ph1 Chr 100% interphase cells karyotype	Gleevec	CCyR (5 Mo)	No
53	CP	46	F	1	2	Ph1 Chr 99.8% interphase cells karyotype, extra copy Ph1-Chr 0.2%	Gleevec	CCyR (10 Mo)	No
54	CP	35	M	1	2	Ph1-Chr present (100%)	Gleevec	CCyR (3 Mo)	No
55	CP	25	M	3	2	Ph1+ karyotype, FISH 32% interphase cells	Gleevec; BMT	CCyR (6 Mo)	No
56	CP	73	M	1	2	Ph1-Chr present (100%)	Gleevec	CCyR (10 Mo)	No
57	CP	48	M	1	2	Ph1 Chr 100% interphase cells karyotype, FISH 100% interphase cells	Gleevec	CCyR (3 Mo)	No
58	CP	61	F	3	2	Ph1 Chr 20% interphase cells karyotype, FISH 36.4% interphase cells	Gleevec	No	No
59	CP	32	M	2	2	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	CCyR (11 Mo)	CMR (19 Mo)
60	CP	69	M	1	2	Ph1 Chr 14% interphase cells karyotype, FISH 17% interphase cells	Gleevec	No	No
61	CP	33	F	2	2	Ph1 Chr 5% interphase cells karyotype, FISH 4% interphase cells	Gleevec	CCyR (6 Mo)	No
62	CP	22	F	1	2	Ph1 Chr 99.8% interphase cells karyotype	Gleevec	CCyR (8 Mo)	No
63	CP	69	F	3	2	Ph1 Chr 70% interphase cells karyotype, der(9)t(9;22)t(4;9), Trisomy Chr-8 (26%	Gleevec	CCyR (3 Mo)	No
64	CP	57	M	3	1	Ph1-Chr present (100%)	Gleevec	CCyR (3 Mo)	CMR (13 Mo)
65	CP	53	F	3	2	Ph1 Chr 99.4% interphase cells karyotype, extra copy Ph1-Chr 0.6%	Gleevec	No	No
66	CP	31	M	2	2	Ph1 Chr 100% interphase cells karyotype	Gleevec	CCyR (3 Mo)	CMR (14 Mo)
67	CP	32	M	2	2	Ph1 Chr 100% interphase cells karyotype	Gleevec	No	No
68	CP	53	F	1	2	Ph1+ karyotype, FISH 99% interphase cells	Gleevec	CCyR (6 Mo)	No
69	CP	47	M	1	2	Ph1+ karyotype, FISH 94% interphase cells	Gleevec	CCyR (4 Mo)	No
70	CP	30	F	1	2	Ph1+ karyotype , FISH 94.4% interphase cells	Gleevec	CCyR (7 Mo)	No
71	CP	64	M	1	2	Ph1 Chr 100% interphase cells karyotype	Hydroxyurea, Gleevec	CCyR (3 Mo)	No
72	CP	50	F	0	2	Ph1+ karyotype, Monosomy Chr-7 (20%), Trisomy c-8 (5.75%)	BMT; Gleevec	CCyR (6 Mo)	No
73	CP	37	M	1	2	Ph1+ karyotype, FISH 99% interphase cells	Gleevec	No	No
74	CP	40	F	2	2	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	CCyR (4 Mo)	No
75	CP	41	M	2	0	Ph1-Chr present (100%)	Gleevec	CCyR (3 Mo)	CMR (12 Mo)
76	CP	49	F	3	2	Ph1+ karyotype, FISH 100% interphase cells	Gleevec	CCyR (7 Mo)	No
77	CP	47	M	1	2	Ph1+ karyotype, FISH 98.5% interphase cells	Gleevec	CCyR (4 Mo)	No
78	CP	54	M	0	2	Ph1 Chr 100% interphase cells karyotype, FISH 100% interphase cells	BMT	CCyR (3 Mo)	No
79	CP	57	M	1	2	Ph1+ karyotype, FISH 85% interphase cells	Gleevec	CCyR (4 Mo)	No
80	CP	58	M	2	1	Ph1 chromosme present (100%)	Gleevec	CCyR (4 Mo)	CMR (9Mo)
81	CP	59	M	2	1	Ph1-Chr present (96%)	Gleevec	CCyR (6 Mo)	No