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E
BENDAMUSTINE
IN VITRO

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152

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/2003 . 5/2008 .

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928/06.06.2012 .

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(e-mail: desdim_bg@abv.bg)

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				7
		Bendamustine	-	
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		Bendamustine	-	
				9
		Bendamustine	-	
				10
		Bendamustine		11
		Bendamustine		12
		Sub-G1	24-	
Bendamustine				13
		Bendamustine	Fludarabine	
				13
			Bendamustine	Fludarabine
				17
<i>In vitro</i>			IC ₃₅	
		Bendamustine	Cyclophosphamide	18
		Bendamustine	Cyclophosphamide	
				19
				20
				22
		Bendamustine		23
		Bendamustine		24
			Bendamustine	
				24
			Bendamustine	Fludarabine
				26
				27
				28
-				28
-				28
-				29
,				30
				30
				30
				31
,				31

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–
–
–

ATCC – American Type Culture Collection (/)

CR – Clinical Remission (/)

DSMZ – Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (/)

ErPC3 – Erufosine

Hb – Haemoglobin

IC₃₅ – Inhibition Concentration (35)

IC₅₀ – Inhibition Concentration ()

INN – International Nonproprietary Names ()

LDH – Lactate dehydrogenase- ()

Ly – Lymphocytes

– [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide],

NC – Noncompliance- (/)

NCI – National Cancer Institute- ()

p – ()

PR – Partial Remission ()

RPMI-1640 – Roswell Park Memorial Institute medium (*in vitro*)

SD –

Sg – eosinophils

Tr – thrombocytes

(). 2010 . 14,990
 4,390 (Howlader N, 2011).
 25 %
 5 73 %
 B-
 /
 12.
 11 13

Bendamustine (. 1) Ozegovski, 1963
 Cytostasan® (Schnabel R, 1967, Hesse P, 1972). O 1993 . Bendamustine
 Ribomustin®, 2008 Treanda® (Traynor K,
 2008)



4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid

1. Bendamustine

Bendamustine

(Ozegowski W, 1971).

- cross linking)
(cyclophosphamide, cisplatin, carmustine) (Strumberg D, 1996, Leong H, 2009).

Bendamustine

in vitro

1.

Bendamustine

2.

Mitomycin C Lomustine. Bendamustine

3.

4.

Bendamustine.

5.

Bendamustine Cyclophosphamide

6.

Bendamustine Fludarabine

7.

in vitro

1.

Bendamustine – Ribomustine® / Ribosepharm – 100 mg
Fludarabine – Fludara® / Schering Deutschland GmbH, 50 mg
Mitomycin C – Mitamycin-C Kyowa®, / Kyowa, 40 mg
Cyclophosphamide – Endoxan® / Hersteller: Baxter Oncology, 200 mg
Lomustine – CAS NO:13010-47-4 / Shangdong Panxin Biochem Co.Ltd.

2.

Voskoglou-Nomikos, 2003. (-), Mosmann 1983,

3.

Bendamustine

ATCC- A .

-80 °C

- 4. , de Vries JE , 1973.
- 5. ,
 . 1 /
 /. - 0 /
 /, I . / /, II . /
 , /, III . / / IV . /
 /.
- 6. /
 , Mitcheva M , 2006.
- 7. (-), Fau D, 1994.
- 8. (LDH), Bergmeyer HU, 1974.
- 9. , Nicoletti I, 1991.
- 10. - , Konstantinov, 1999.
- 11. , . Topashka-Ancheva, 1995, 1998.
- 12.

Microsoft

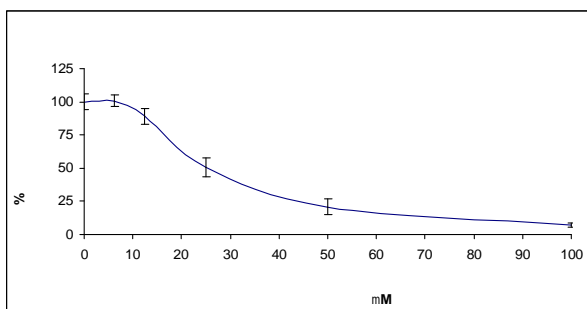
Office Microsoft Excel 2003.

- 13. — “ t- Student p 0.05, in vitro
 Origin Prizm. IC₅₀ IC₃₅ “ - ”.
 Drummond
 FM, 2001.

Bendamustine.

- 1640 , RPMI-
 96- . Bendamustine 24 h
 72 h. ” — ” IC₅₀ 48

Bendamustine

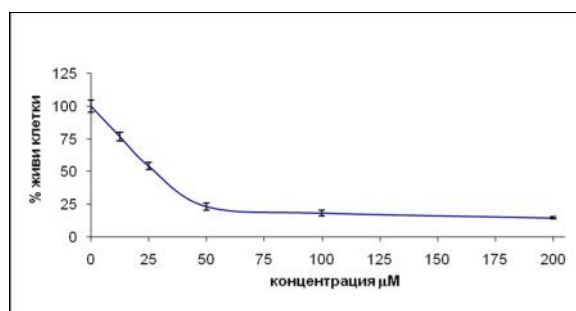


2.

Bendamustine
48 h

SKW-3

IC_{50} 25,42 μ M

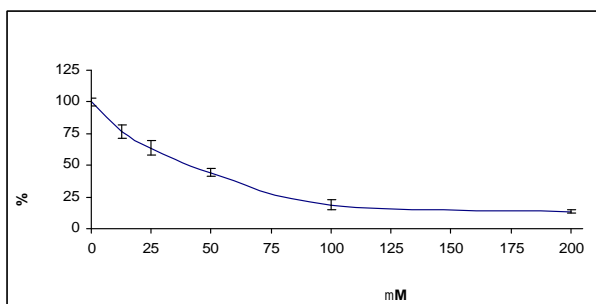


3.

Bendamustine
72 h

SKW-3

IC_{50} 22,77 μ M

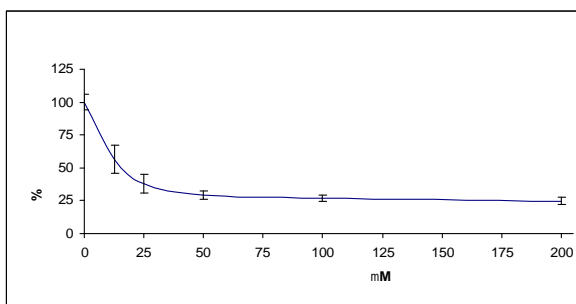


4.

Bendamustine
48 h

DOHH-2

IC_{50} e 42,30 μ M

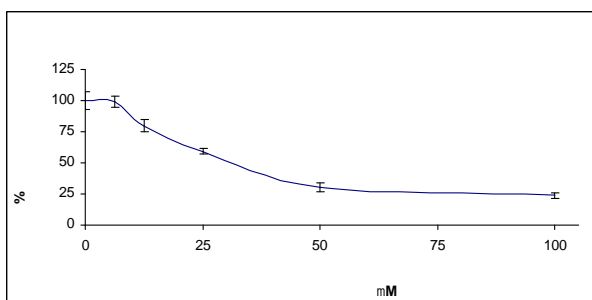


5.

Bendamustine
72 h

DOHH-2

IC_{50} e 11,48 μ M



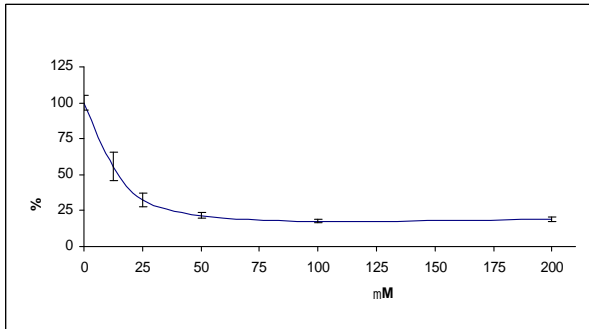
6.

Bendamustine
48 h

REH

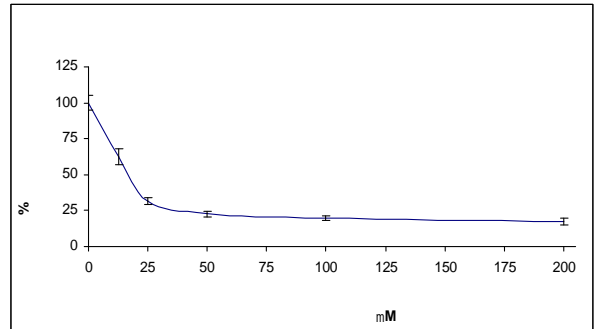
IC_{50} e 31,48 μ M

Bendamustine



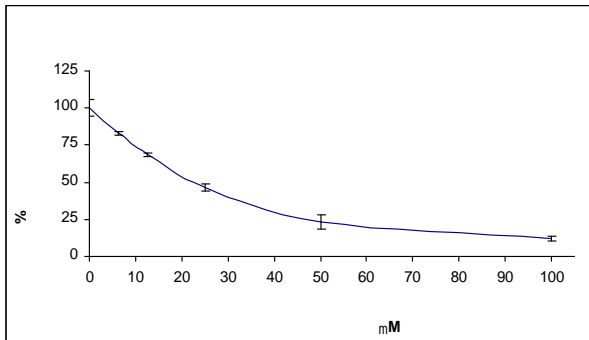
7.

Bendamustine CML-T1
48 h
IC₅₀ e 15 μ M



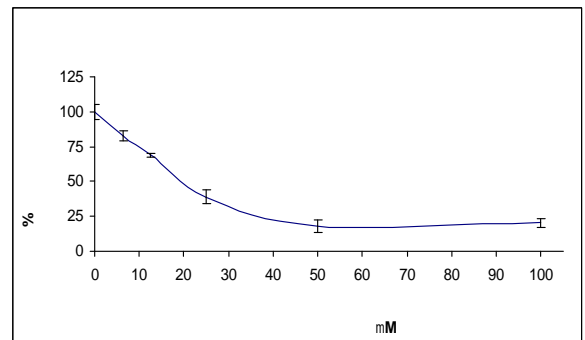
8.

Bendamustine CML-T1
72 h
IC₅₀ e 17,59 μ M



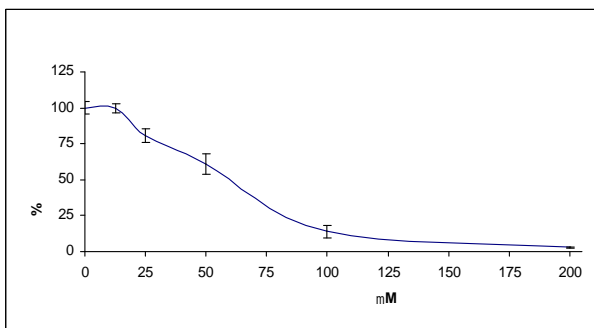
9.

Bendamustine BV-173
48 h
IC₅₀ e 22,97 μ M



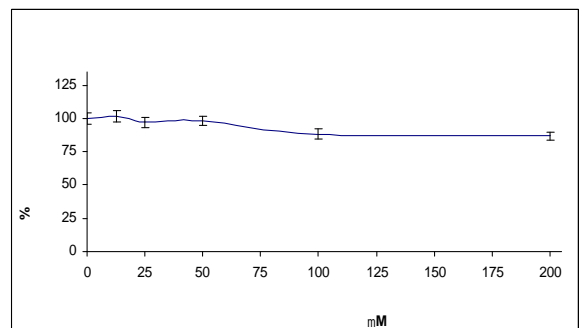
10.

Bendamustine BV-173
72 h
IC₅₀ e 19,5 μ M



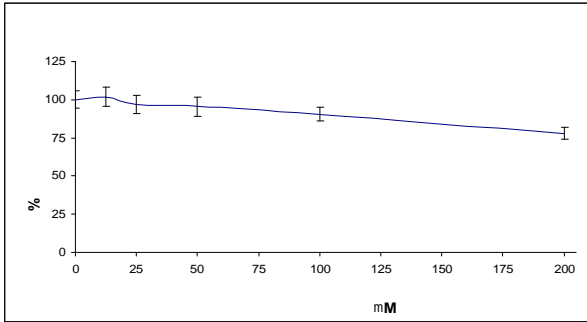
11.

Bendamustine HL-60
48 h
IC₅₀ e 60,18 μ M

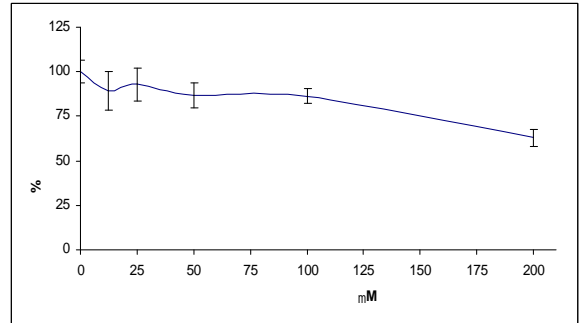


12.

Bendamustine THP-1
48 h

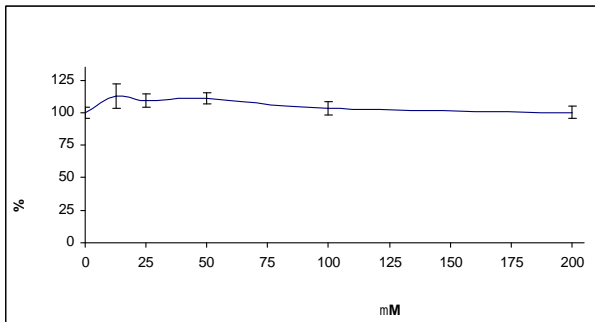


13.
Bendamustine K-562
48 h

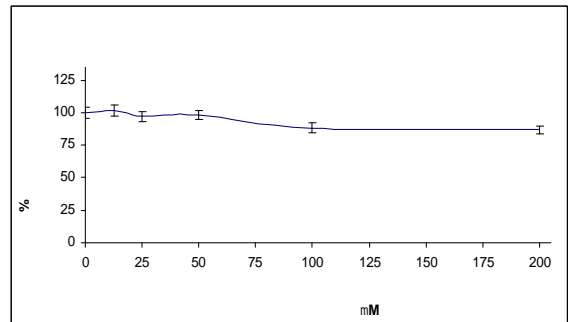


14.
Bendamustine LAMA-84
48 h

Bendamustine



15.
Bendamustine MCF-7
48 h



16.
Bendamustine MDA-MB-231
48 h

Клетъчна линия	Морфология	Експозиция часове	IC ₅₀ μM
SKW-3	Лимфоцитна	48	25,41
		72	27,77
REN	Лимфобластна	48	31,48
DONN-2	Лимфобластна	48	42,30
		72	11,48
CML-T1	Миелоидна	48	15
		72	17,59
BV-173	Миелоидна	48	22,97
		72	19,5
HL-60	Миелоидна	48	60,18
THP-1	Моноцитна	48	>200
K-562	Миелоидна	48	>200
LAMA-84	Миелоидна	48	>200
MCF-7	Епителна	48	>200
MDA-MB-231	Епителна	48	>200

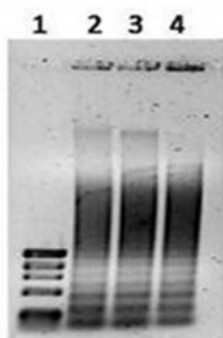
1. IC₅₀

50 % (IC₅₀).
1.
Bendamustine IC₅₀>200 μM. 3 6
Bendamustine (IC₅₀ 15-60 μM). IC₅₀ -
-SKW-3, REH DOHH-2.

Bendamustine

(.17) Bendamustine
() SKW-3
17). HL-60 (.17) 37.5, 75 100 μM ()
160 μM, Erufosin (ErPC3)

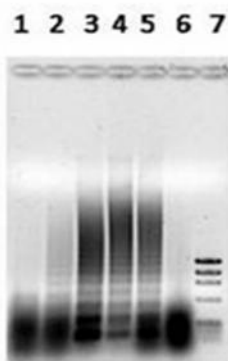
SKW-3 лимфоидни клетки



1 – Маркер
2 – 37,5 μM
3 – 75 μM
4 – 100 μM

а)
17.

HL-60 миелоидни клетки



1 – 40 μM
2 – 80 μM
3 – 160 μM
4 – ErPC3 40 μM
5 – ErPC3 20 μM
6 – нетретиранни контролни клетки
7 – Маркер

б)

BV-173 миелоидни клетки

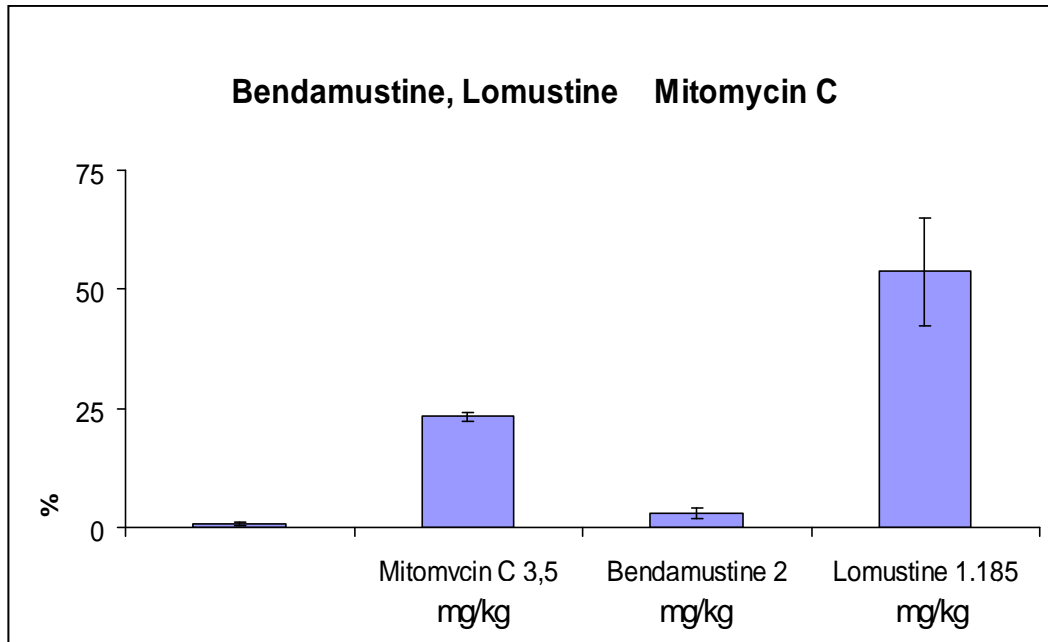


M – Маркер
1 – 50 μM
2 – 100 μM
3 – нетретиранни контролни клетки

в)

BV-173 (.17) 80 % 50
100 μM Bendamustine, -
Bendamustine,
, () ,

Bendamustine



18.

Bendamustine, Lomustine Mitomycin C

(.18)

Bendamustine

5%

Mitomycin C

8

Lomustine

50%

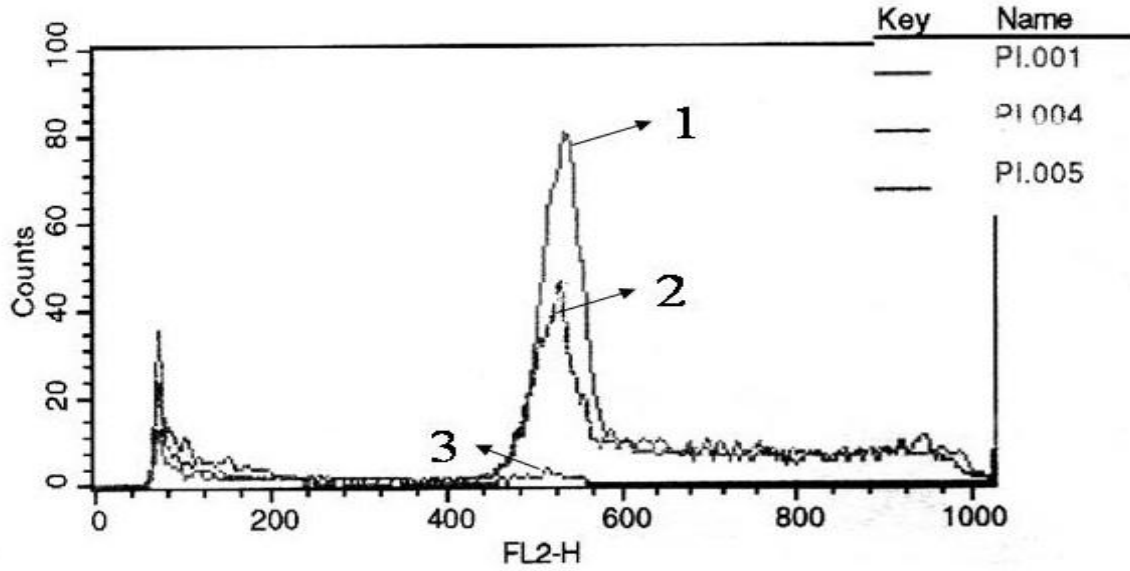
Bendamustine

Bendamustine

Mitomycin C.

Bendamustine

Поточна цитометрия на SKW-3 клетки след третиране с Bendamustine (оцветяване на ядрена ДНК с пропидиев йодид)



1 – нетретирана контрола
 2 – 65 μM Bendamustine
 3 – 130 μM Bendamustine

19. SKW-3 , 65 130 μM Bendamustine.
 19. , 130 μM (3)
 Bendamustine -
 50% (2)
 (1). Bendamustine. G1 S

Bendamustine Fludarabine

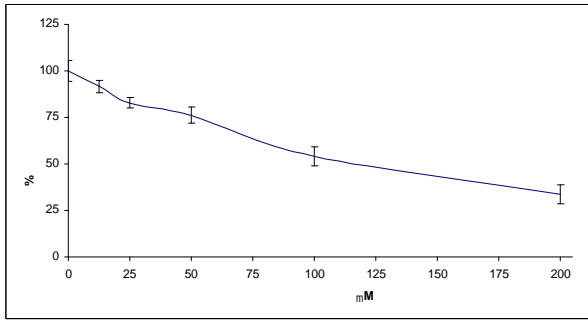
10

5 ml.

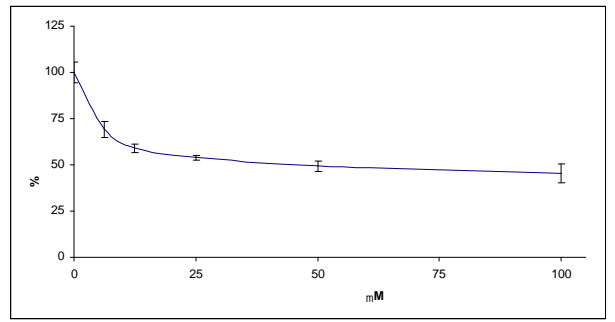
/B-

Fc-

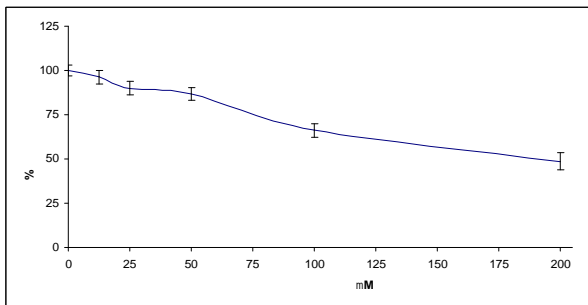
./



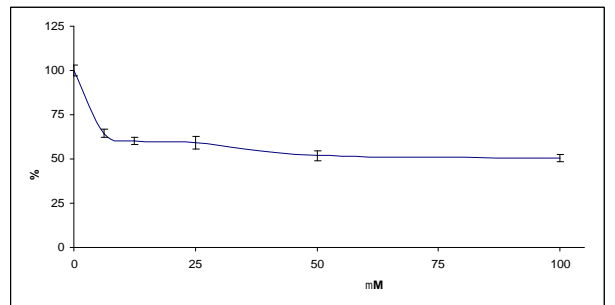
20.
 Bendamustine LDM-CLL 72
 h . (1)



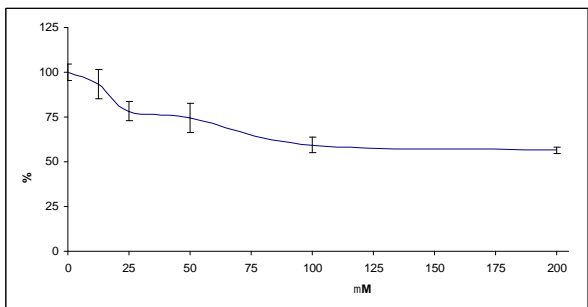
21.
 Fludarabine LDM-CLL 72 h
 . (1)



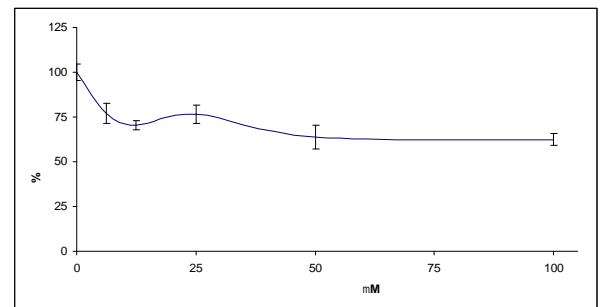
22.
 Bendamustine AKI-CLL 72
 h . (2)



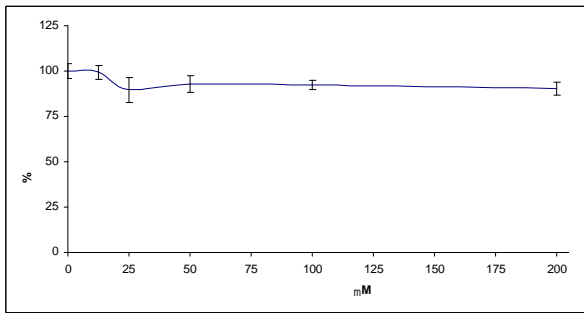
23.
 Fludarabine AKI-CLL 72 h
 . (2)



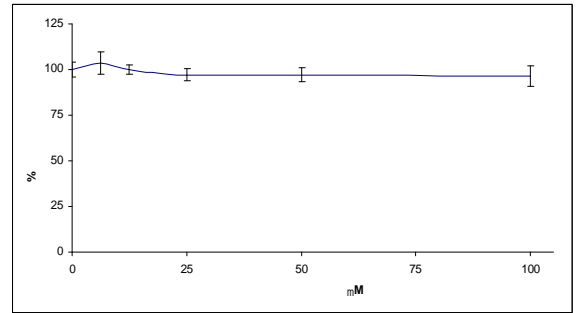
24.
 Bendamustine MPP-CLL 72 h
 . (3)



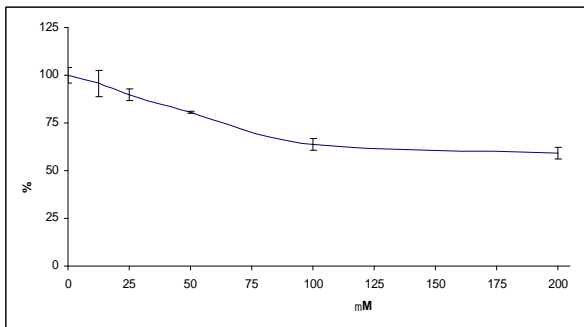
25.
 Fludarabine MPP-CLL 72
 h . (3)



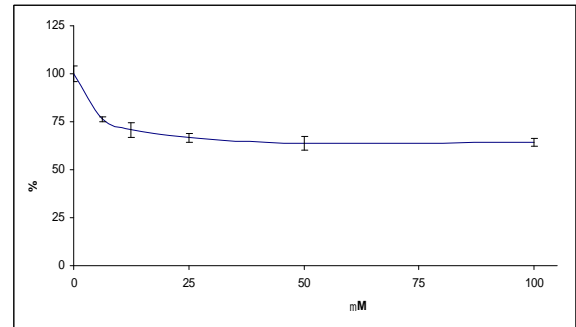
26.
Bendamustine VTK-CLL
72 h . (4)



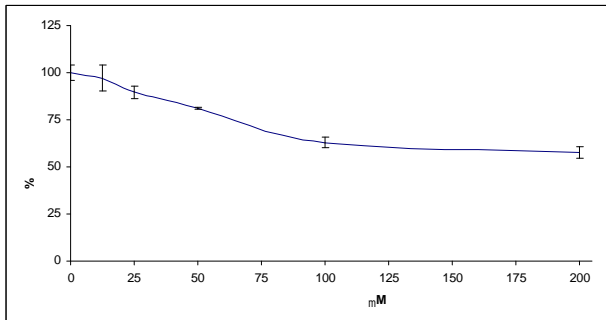
27.
Fludarabine VTK-CLL 72 h
. (4)



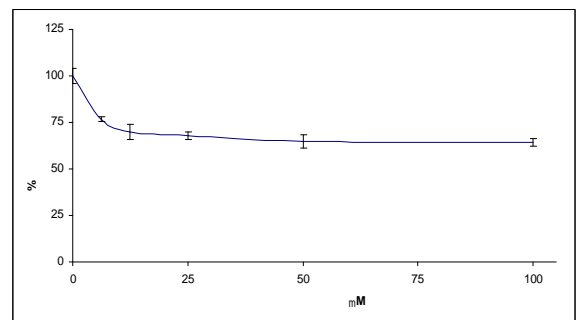
28.
Bendamustine GVD-CLL
72 h . (5)



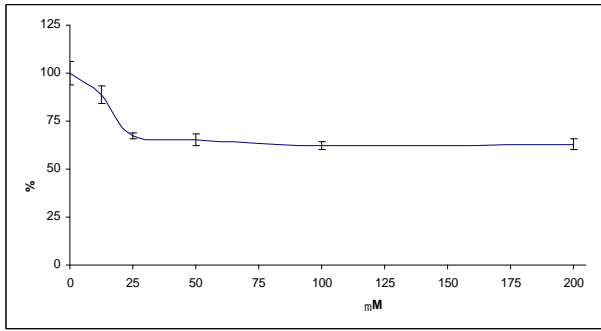
29.
Fludarabine GVD-CLL 72 h
. (5)



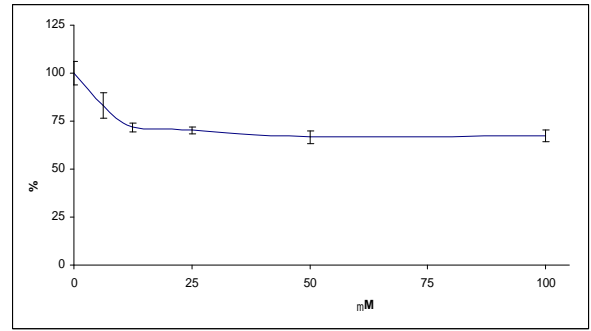
30.
Bendamustine GLD-CLL
72 h . (6)



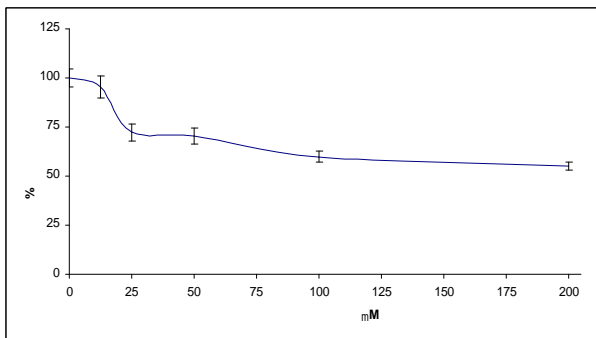
31.
Fludarabine GLD-CLL 72 h
. (6)



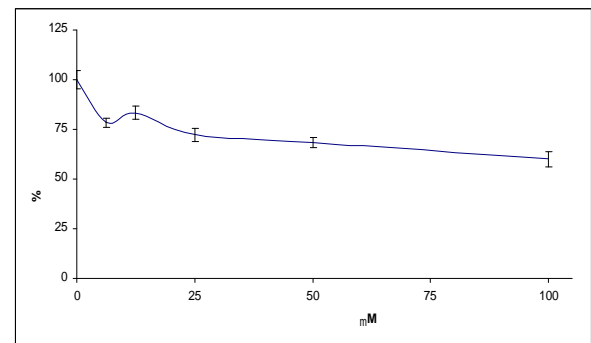
32.
Bendamustine VPK-CLL
72 h . (7)



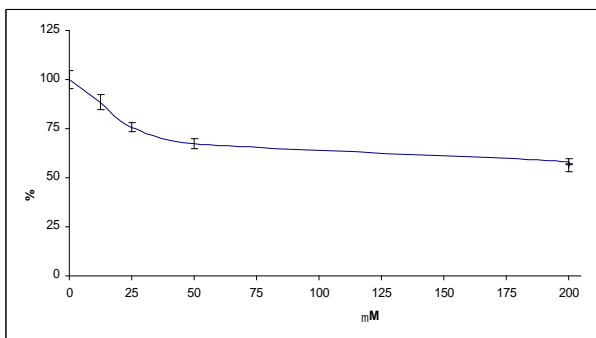
33.
Fludarabine VPK-CLL
72 h . (7)



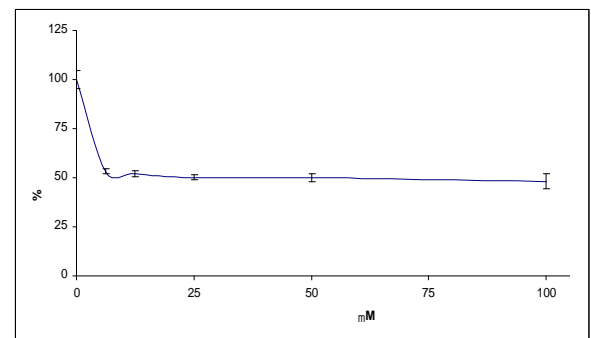
34.
Bendamustine RSG-CLL
72 h . (8)



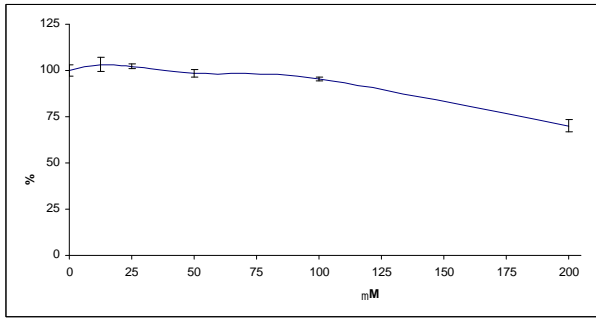
35.
Fludarabine RSG-CLL
72 h . (8)



36.
Bendamustine VM-CLL
72 h . (9)

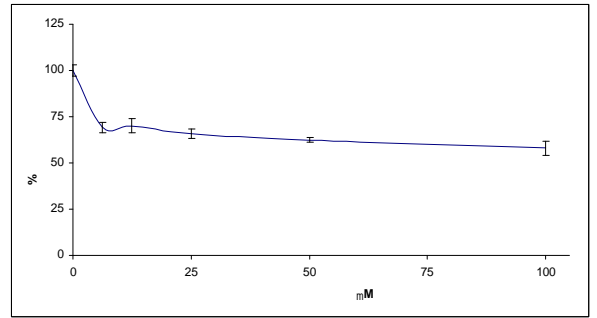


37.
Fludarabine VM-CLL
72 h . (9)



38.

Bendamustine VPG-CLL
72 h . (10)



39.

Fludarabine VPG-CLL
72 h . (10)

Bendamustine

Fludarabine

IC₃₅

	/			IC ₃₅	M
				Fludarabine	Bendamustine
1	LDM60	-II .	PR	4,1	50
2	AKI	-	exitus letalis 28-	4,8	82
3	MPP	-II .	PR	6,4	39
4	VTK	-IV .	NC	>100	>100
5	GVD	-IV .	PR	6,4	64
6	GLD	-III .	NC	43	62
7	VPK	-III .	PR	30	62
8	RSG	-II .	NC	4,6	>100
9	VM	-IV .	PR	4,6	>100
10	VPG	-IV .	NC	4,6	>100

2 IC₃₅

Bendamustine Fludarabine,

CR = ; Ly < 4 x 10⁹, Sg > 1,5 x 10⁹, Tr > 100 x 10⁹ / l, Hb >110 g/L,
< 30 % Ly;

PR = 50 % / , , /, Sg > 1,5 x
10⁹, Tr > 100 x 10⁹, Hb > 100 g/L 50 %;

PR = - Binet.

NC = -

IC₃₅ “ (. 2) ”,

in vitro
AKI (2) CLL-

(4, 6, 8 10)

(NC) Bendamustine.

Bendamustine
IC₃₅. (4, VTK)
Fludarabine. Bendamustine (PR)

(1, 3, 5, 7 9).
4/5 (IC₃₅ 39 62) 9, IC₅₀
100 μM, (GVD)

Bendamustine (IC₃₅=64 μM).
Fludarabine (IC₃₅=6,4 μM). (VM)

(PR) *in vitro*
(IC₃₅>100 μM) 9. Bendamustine (190 / 2)

) PR
VPK, MPP LDM *in vitro*
Bendamustine (IC₃₅ 62, 39 50 μM).
in vitro
Bendamustine *in vitro*

“ ”,

In vitro

Bendamustine

Cyclophosphamide

Bendamustine (20-130 μ),
μ . 3. (6%) 20 μ - 50 % 130
, Cyclophosphamide 20 μ , 27 %
, - 130 μ - 73 % -
130 μ , Bendamustine 38 % -
Cyclophosphamide. Bendamustine

Bendamustine - Cyclophosphamide.
 Bendamustine Cyclophosphamide.

	(%)	(%)
	100 ± 5,3	
20 μM Bendamustine	94 ± 5,1 ###	6
45 μM Bendamustine	90 ± 3,4***###	10
60 μM Bendamustine	64 ± 1,4***###	36
80 μM Bendamustine	52 ± 1,7***##	48
130 μM Bendamustine	50 ± 1,3***###	50
20 μM Cyclophosphamide	73 ± 2,2***	27
45 μM Cyclophosphamide	71 ± 2,8***	29
60 μM Cyclophosphamide	55 ± 0,5***	45
80 μM Cyclophosphamide	45 ± 2,4***	55
130 μM Cyclophosphamide	36 ± 2,7***	64

3. Bendamustine Cyclophosphamide ** p<0.01;
 *** p<0.001 , ## p<0.01; ### p<0.001 Cyclophosphamide.

Bendamustine Cyclophosphamide

	LDH (%)	(%)
	100 ± 0,02	
20 μM Bendamustine	151 ± 0,02***	51
45 μM Bendamustine	182 ± 0,01***###	82
60 μM Bendamustine	198 ± 0,001***###	98
80 μM Bendamustine	321 ± 0,01***###	221
130 μM Bendamustine	365 ± 0,02***###	256
20 μM Cyclophosphamide	156 ± 0,02***	56
45 μM Cyclophosphamide	266 ± 0,004***	166
60 μM Cyclophosphamide	354 ± 0,001***	254
80 μM Cyclophosphamide	373 ± 0,02***	273
130 μM Cyclophosphamide	407 ± 0,002***	307

4. Bendamustine Cyclophosphamide LDH
 ** p<0.01; *** p<0.001 , ## p<0.01; ### p<0.001
 Cyclophosphamide

4. , Bendamustine -
 LDH, -
 . Bendamustine
 Cyclophosphamide.

20 μ M, LDH 51
 %
 - 256% 130 μ M
 Cyclophosphamide
 Bendamustine. Cyclophosphamide, 20 μ M LDH 56 %, 130
 μ M, LDH 307 %

Bendamustine Fludarabine,

IC₃₅.

(5).

		(min)
1.		2
2.	Ficolle Paque	1
3.		20
4.		2
5.		5
6.		1
7.		4
8.		7
9.		2
10.		2
11.	96	10
12.	96	1
13.		3
14.		72
15.		60

5.

72 h.

60 min,

	(.)		(.)
	6.64	1-96	6.64
	0.035	60 min	2.08
	0.049	10 min	0.49
			9.21

6.

- 9.21 6.64 . . 2.08
. 0.49
(6.).

	-		
Bendamustine	9.21	6	1.535
Fludarabine	9.21	9	1.02

7.

Fludarabine -

INN ()	+			() ⁶
Bendamustine	324.81	70-100 mg/m ² (2)	324.81 x 2=649.62	649.62 x 6= 3897.72
Fludarabine	304.536	25 mg/m ²	304.54 x 5=1522.68	1522.68 x 6 =9136.08

8.

10 Bendamustine , 38
977.20 .
Fludarabine, 91 360.80 .

	Bendamustine	Fludarabine	
10	38 977.20	91 360.80	52 383.60
	15 590.88	9 136.08	-6 454.80
/	54 568.08	100 496.88	45 928.80

9.

10

Fludarabine, Bendamustine, 4 10 Bendamustine, 1 10
 Fludarabine, Bendamustine, 54 568.08 100 496.88 Fludarabine (9). /
 Fludarabine, Bendamustine, 45 928.80
 IC35,
 35%
 (IC35)
 - Bendamustine Fludarabine.
 10
 IC35

Bendamustine

1987, Herold M, 2006). (Herold M,

Cyclophosphamide,
 Agner G, 1975.

Bendamustine,

Bendamustine

Bendamustine

Bendamustine

in vitro

Bendamustine

(Rowley JD, 1975),
t(9;22) (q34;q11). CML-T1 K-562, e BCR-ABL,
b3 2 b2a2. :
2 *bcr* 2 *abl*, — 3 BCR 2 ABL (Histerkamp
N, 1985). 210 000
Da. CML-T1 Bendamustine BCR-
ABL SKW-3, HL-60 THP-1 Bendamustine
MTT- Bendamustine
Bendamustine Bendamustine
(Kath R, 2001).
Bendamustine HL-60, THP-1 K-562.
MCF-7 MDA-MB-231
Bendamustine.
Bendamustine
Bendamustine
Bendamustine SKW-3 HL-60 BV-173
Bendamustine e
200 2000
Nicoletti I (1991),
Bendamustine
Bendamustine.
G1 S ,
Sub G1
B ndamustine
()
Bendamustine
Lomustine. , *Bendamustine*
Bendamustine

Leoni (2008).

Bendamustine

in vitro

(Guillouzo A, 1986).

Bendamustine,
LDH.

Bendamustine

Bendamustine

Cyclophosphamide.

Bendamustine

LDH,

Bendamustine Cyclophosphamide

Bendamustine. Cyclophosphamide

450-

(Pass GJ, 2005).

Boddy AV&Yule SM (2000)

Cyclophosphamide

CYP2B

(Boddy AV&Yule SM, 2000).

Bendamustine

450-

CYP1A2

N-

(Teichert J, 2005).

Bendamustine

Chlorambucil (Alkeran®)

Cyclophosphamide.

Cyclophosphamide/

Vincristine/ Prednizolone (

CVP)

).

(Fludarabine, Balakrishnan K, 2010),

(ra C, de Vries JF, 2006)

(

, Di Raimondo F, 1997)

(Tsimberidou AM, 2008).

(),

Fludarabine
 Bendamustine,

Fludarabine
 Bendamustine *in vitro*

(

S-

S-

Plunkett W (1980),

Bendamustine

Fludarabine
 M. Keating, 1989; O'Brien, 1993).

2/3
 60%

Bendamustine

Bendamustine

G1

S-

Bendamustine

Bendamustine

G1

S- (), -
Bendamustine in vitro

Bendamustine - (Konstantinov SM, Kostovski A, 2002).

, *in vitro*
 Fludarabine / 75-90 %
 Bendamustine.
 / *in vitro – in vivo*
in vitro in vivo

– *in vitro*

, *Bendamustine*
 (),
 (NHL), *Bendamustine*
Hodgkin -Hodgkin-

Fludarabine. Bendamustine

-
 Fludarabine, -
in vivo Fludarabine,
 ,
 Fludarabine 45 928,80 ,
 - 10 (91 360,80 .)
 ,
in vitro ,

1. Bendamustine 11
e (MCF-7 MDA-
MB-231) (SKW-
3, REH, DOHH-2)
2. Bendamustine: THP-1, -562 LAMA-84 HL-60
CML-T1 BV-173.
3. (SKW-3, HL-60 BV-173) , Bendamustine
4. Bendamustine
75-85 % (SKW-3, REH DOHH-2) 92 % Sub-G1
CML-T1 BV-173 50 %
5. Bendamustine Mitomycin C
Lomustine. 3,28 % Mitomycin C
23 % , Lomustine 56 %
6. Bendamustine -
Cyclophosphamide.
Cyclophosphamide.
7. Bendamustine Fludarabine
in vitro
8. Fludarabine 50 %
3 10 (1, 2, 9)
40-45 % 6 10 (3, 5, 6, 7, 8 10)
, Bendamustine 100 μ M 40 % 1 10, 4.
4 10

(3, 6, 7 8)

(4 10).

Fludarabine,

10

Bendamustine

9. 90 %

Bendamustine

>100 μM).

in vitro 90 %

(IC₅₀

10.

Fludarabine

45 928, 80

I.

1.

Bendamustine

Bendamustine

Bendamustine

().

II.

1.

()

C57Bl

Bendamustine

Mitomycin C 17, 9

Lomustine.

2.

Bendamustine

3.

Bendamustine,

III.

in vitro

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Bendamustine

Fludarabine -2003" " , "

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" , , : . - . , .

LDH

, 2, 1000.

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