FSBRI «N.N. Blokhin Russian Cancer Research Center»

Possibilities of overcoming drug resistance of blast cells in children with relapsed of acute lymphoblastic leukemia

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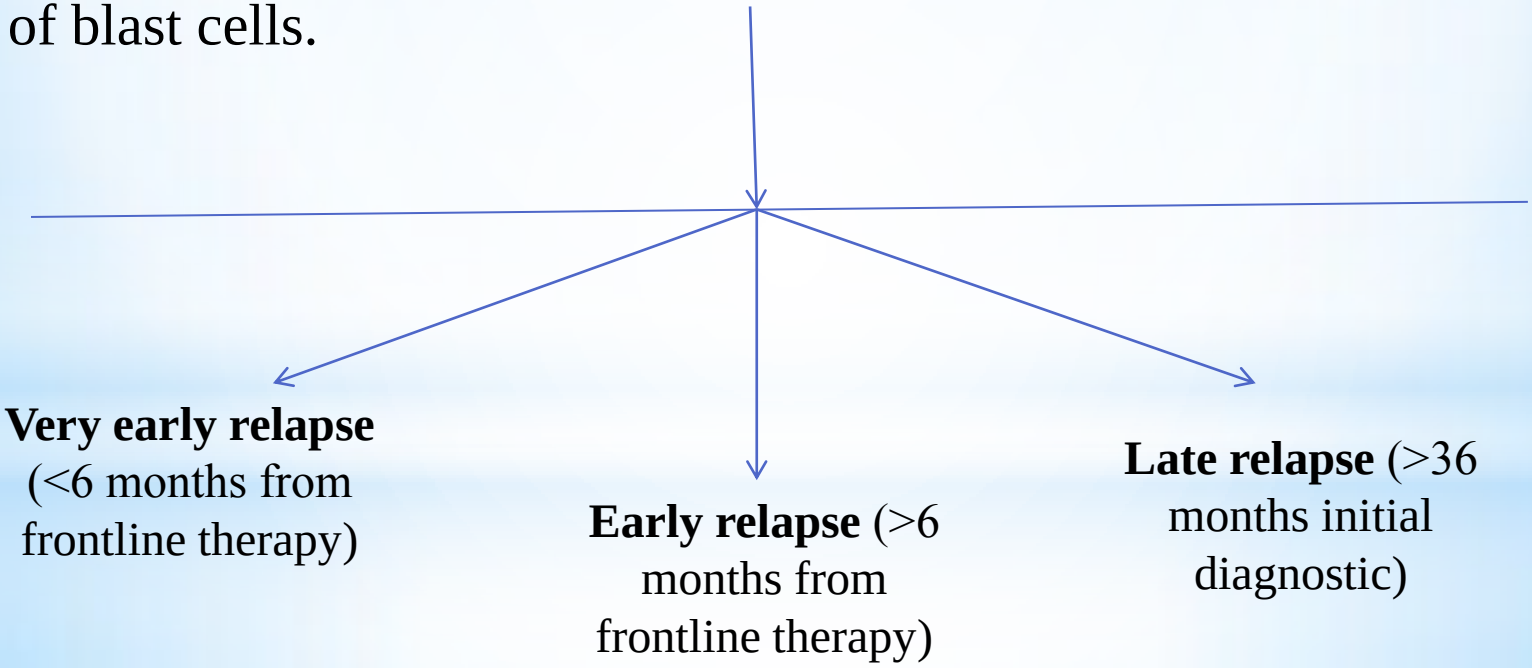
Definition of relapse

1. Isolated BM relapse: M3 marrow blasts (>25%), and no evidence of blasts in other sites;

2. Combined relapse: - extramedullary disease and ≥5% blasts in BM;

3. Isolated extramedullary relapse: extramedullary site and <5% of blast cells.



Possible mechanism of relapse

1. “**Sanctuary sites**” (e.g. testes, CNS)

Inadequate exposure to chemotherapy? – late extramedullary, combined relapse.

2**. Primary resistance**

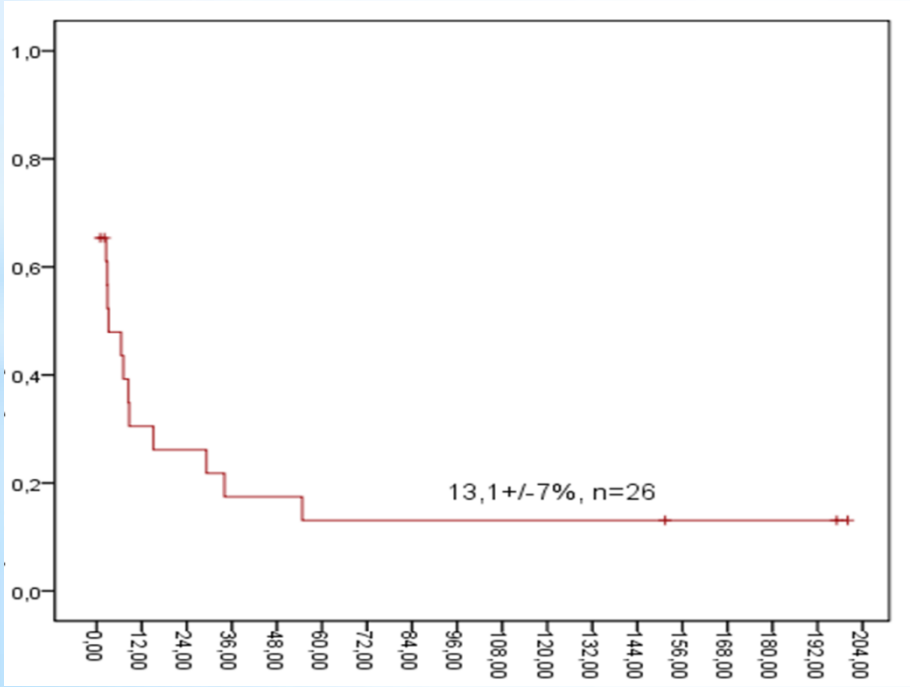
intrinsic property of the cells present at the diagnosis: very early, early BM relapse.

3. Secondary resistance

After exposure of the frontline treatment – late BM relapse.

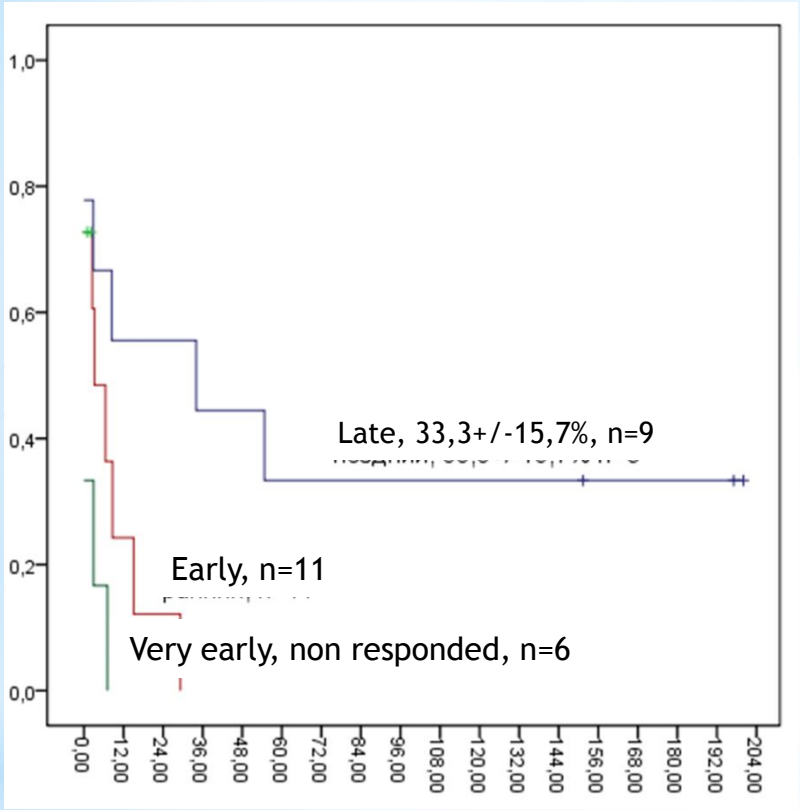
ALL REZ BFM 1996 protocol
1995 - 2011 period, 26 patients

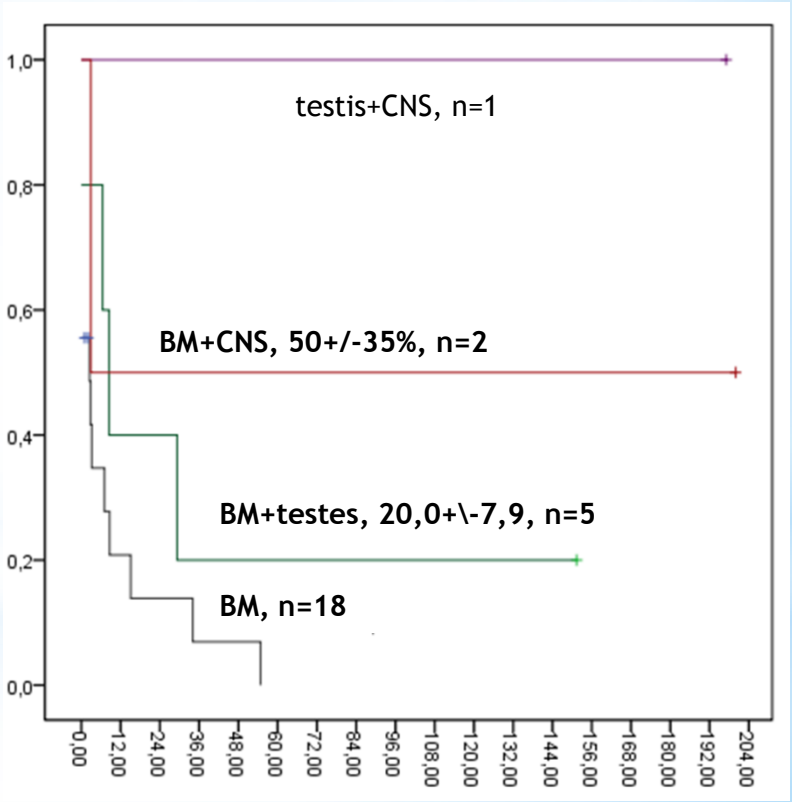
	Very early relapse	Early relapse	Late relapse
BM	5	8	5
BM+testis	0	3	2
BM+CNS	1	0	1
Testes+CNS	0	0	1



- Disease-free survival 13,1+/-7%, 26 patients
- Median follow-up >204 months

ALL REZ BFM 1995, DFS





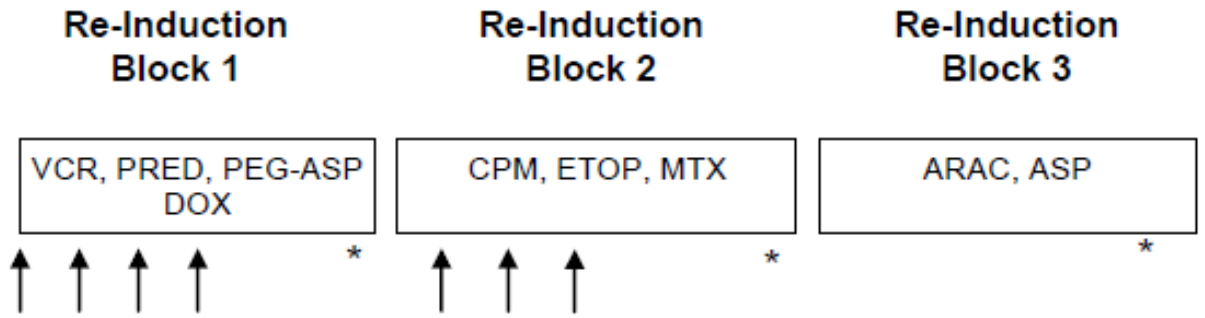
Complete remission - 15 pts (57,6%)

- Bortezomib (Velcade), a dipeptidyl boronic acid, is a selective inhibitor of the ubiquitin proteasome pathway, which is essential for the degradation of most short-lived and many longlived intracellular proteins in eukaryotic cells. Bortezomib specifically inhibits the 26S proteasome, an ATP-dependent multi-subunit protein that degrades proteins involved in multiple cellular processes, including cell cycle regulation, transcription factor activation, apoptosis, and cell trafficking. Proteasome inhibition stabilizes many cell cycle-regulatory proteins that are overexpressed in leukemia cells. Proteasome inhibition may sensitize malignant hematologic cells to apoptosis induced by both radiation and chemotherapy.

In nonclinical studies, bortezomib:

1. Stabilized cell-cycle regulatory proteins;
2. Inhibited NF-ƙB activation;
3. Limited angiogenesis;
4. Induced apoptosis.

Protocol design



↑ Bortezomib on
Days 1, 4, 8 & 11 of Block 1
Days 1, 4, & 8 of Block 2

* MRD at the completion of each block

VCR = Vincristine
PRED = Prednisone
PEG-ASP = PEG-asparaginase
DOX = Doxorubicin
CPM = Cyclophosphamide
ETOP = Etoposide
MTX = Methotrexate
ARAC = Cytarabine
ASP = L-Asparaginase

COG AALL07P1 protocol

2011- 2015 period

24 patients, median age 8,5 years.

- boys – 18 (75,0%);
- girls – 6 (25,0%)

B-cell ALL – 17 patients (70,9%)

T-cell ALL – 7 patients 29,1%

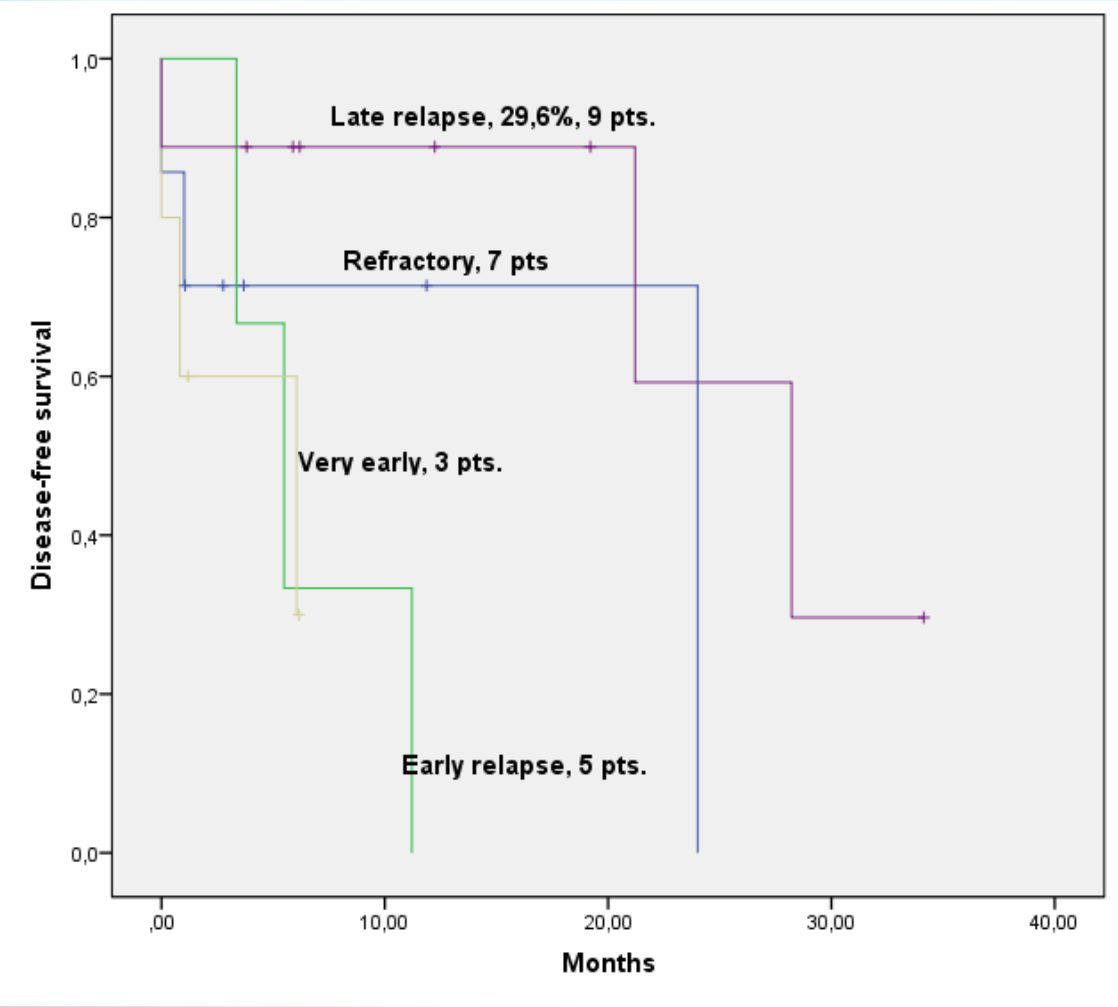
	Refractory	Very early	Early	Late
BM	7	2	1	6
BM+testes	0	0	1	3
BM+CNS	0	1	3	0

Response rate

	Refractory	Very early	Early	Late
CR after 1st course	4	3	3	7
CR after 2nd course	1	0	0	2
No response	2	0	0	0
No data	0	0	2	0

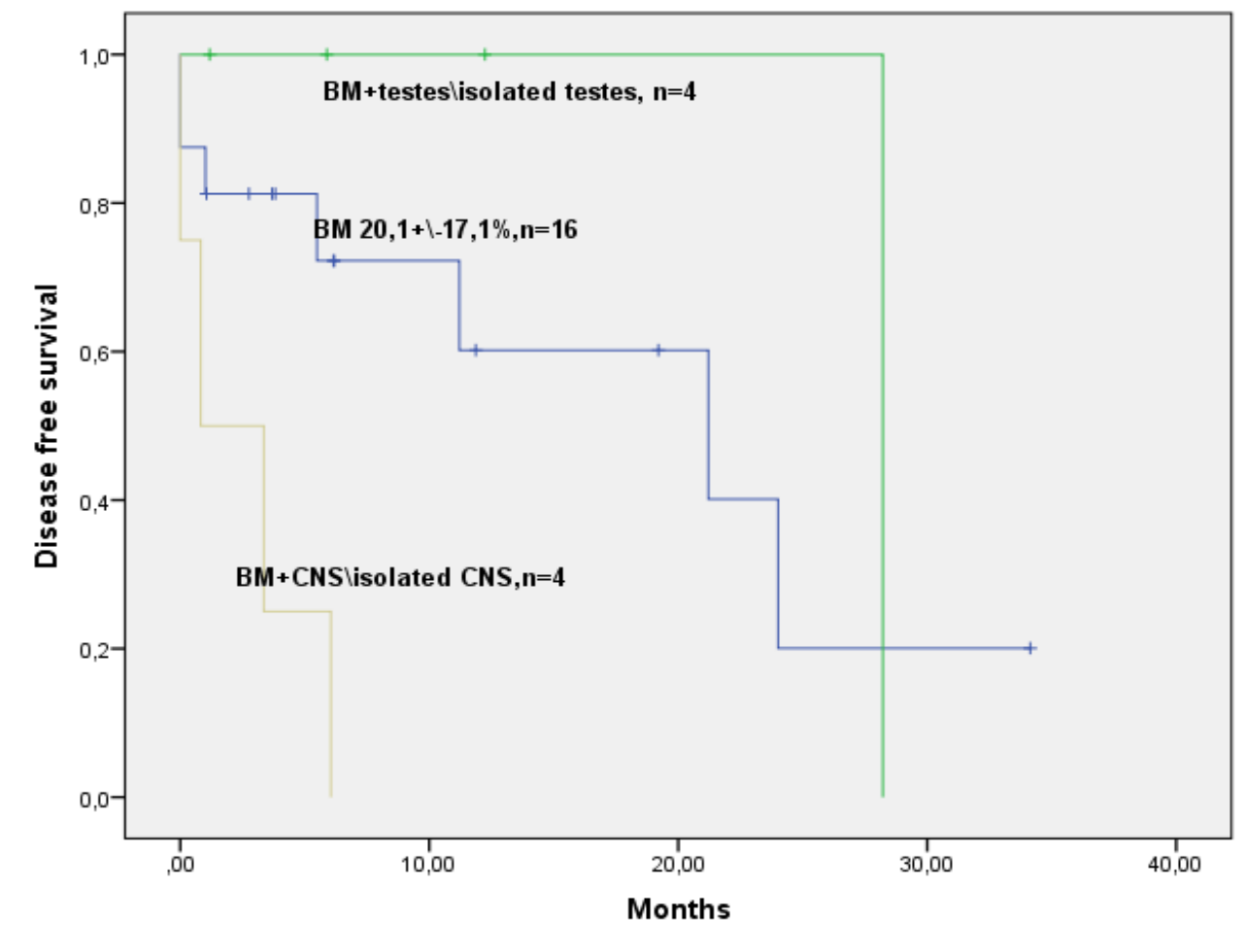
- **Complete remission** - 20 cases (83,3%);
- **Evaluation of MRD** – 14 pts (58,3%), 11 (45,8%) – negative MRD.

Disease-free survival according to time of relapse



Median follow up – 16,4 months

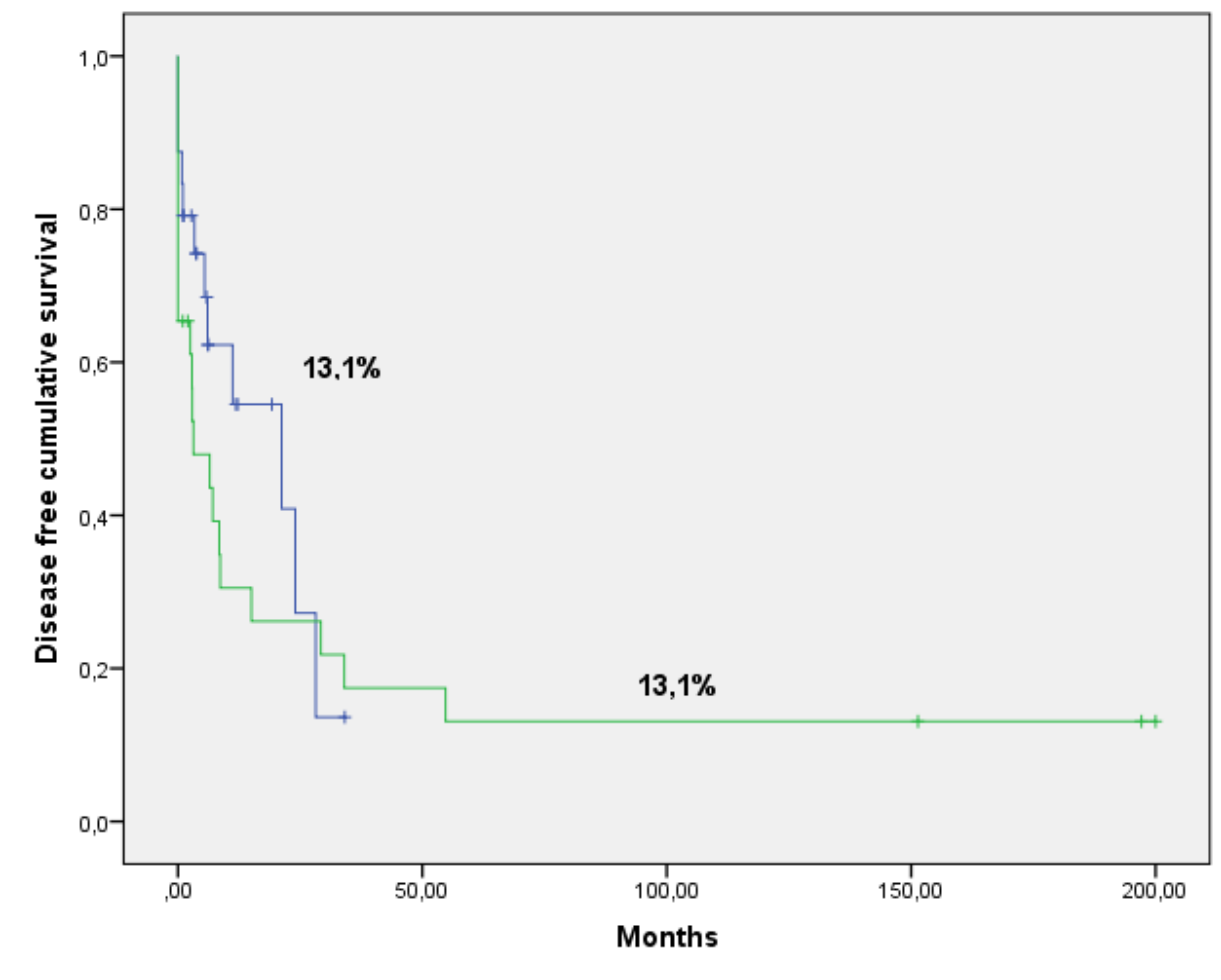
Disease-free survival according to localisation of relapse



At present 7 pts (29.2%) are alive in CR:

- 5 (20.9%) patients with late isolated BM relapse (B-cell ALL),
- two pts with late relapse of T-lymphoblastic lymphoma.
- Seven (29.2%) pts with BM relapse underwent a SCT, now 4 pts after transplantation are alive in complete remission.

Disease-free survival for ALL REZ BFM 96\COG AALL07P1



Conclusion:

The percentage of complete response after induction chemotherapy with bortezomib 83.3%, whereas complete response after induction chemotherapy ALL REZ BFM 96 was only 57.6%. Comparing the disease-free survival of patients with relapse and refractory ALL, received program chemotherapy ALL REZ BFM 96\COG AALL07P1, where are no significant difference: 13,1%.

Thank you for attention!