Aspacytarabine (BST-236) is Safe and Efficacious as a Single-Agent, First-Line Therapy for Patients with Acute Myeloid Leukemia Unfit for Standard Chemotherapy

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Shortcomings of Current Approaches for AML

- Intensive induction therapy with **cytarabine** + anthracycline (7+3) and intermediate or high dose cytarabine consolidation or CPX-351
    - Limited by toxicities; particularly in older and/or unfit patients
- **Hypomethylating agents (HMA)** have limited single-agent efficacy
- **Venetoclax + HMA** is a new standard for older and unfit patients; limited data in secondary AML
- **Targeted agents** in combination with 7+3 or HMA for small subgroups
- There is no standard approach for the majority of relapsed/refractory patients

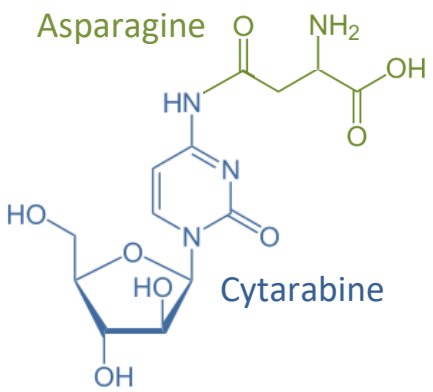
There is a need for more effective and less toxic chemotherapy approaches

SEER, NCCN, Cancer Research UK

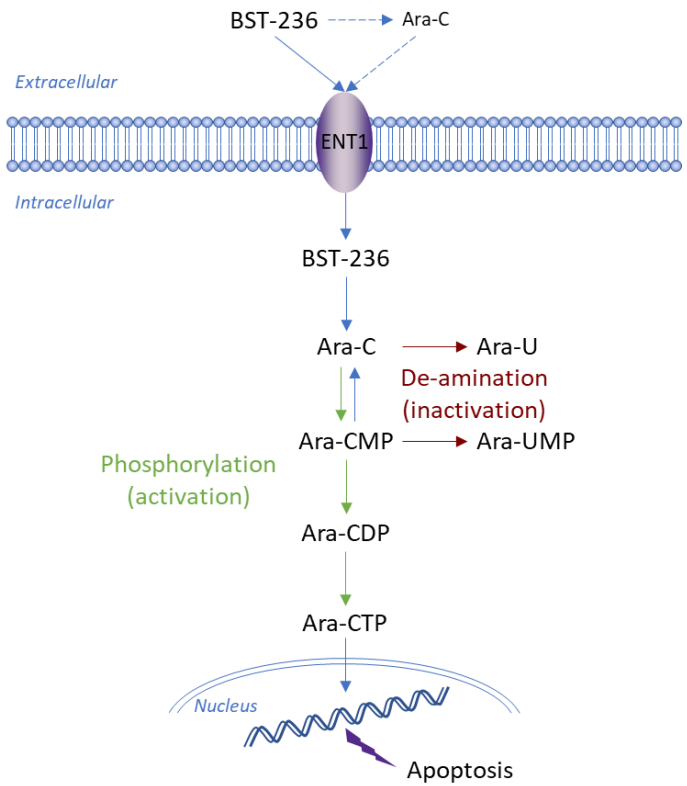
BST-236 – A Novel Anti-Metabolite For High-Dose Treatment with Reduced Toxicity

- BST-236 is a cytarabine pro-drug, composed of cytarabine covalently bound to asparagine
- Intact BST-236 is inactive, allowing high-dose administration
- BST-236 gradually releases cytarabine via non-enzymatic hydrolysis, avoiding peak toxic systemic exposure to cytarabine
- Until its release, cytarabine is protected from inactivation by deamination and activation by phosphorylation
- Released cytarabine is activated by phosphorylation, incorporated into the DNA and induces apoptosis, mainly in mitotic cells

BST-236 Structure

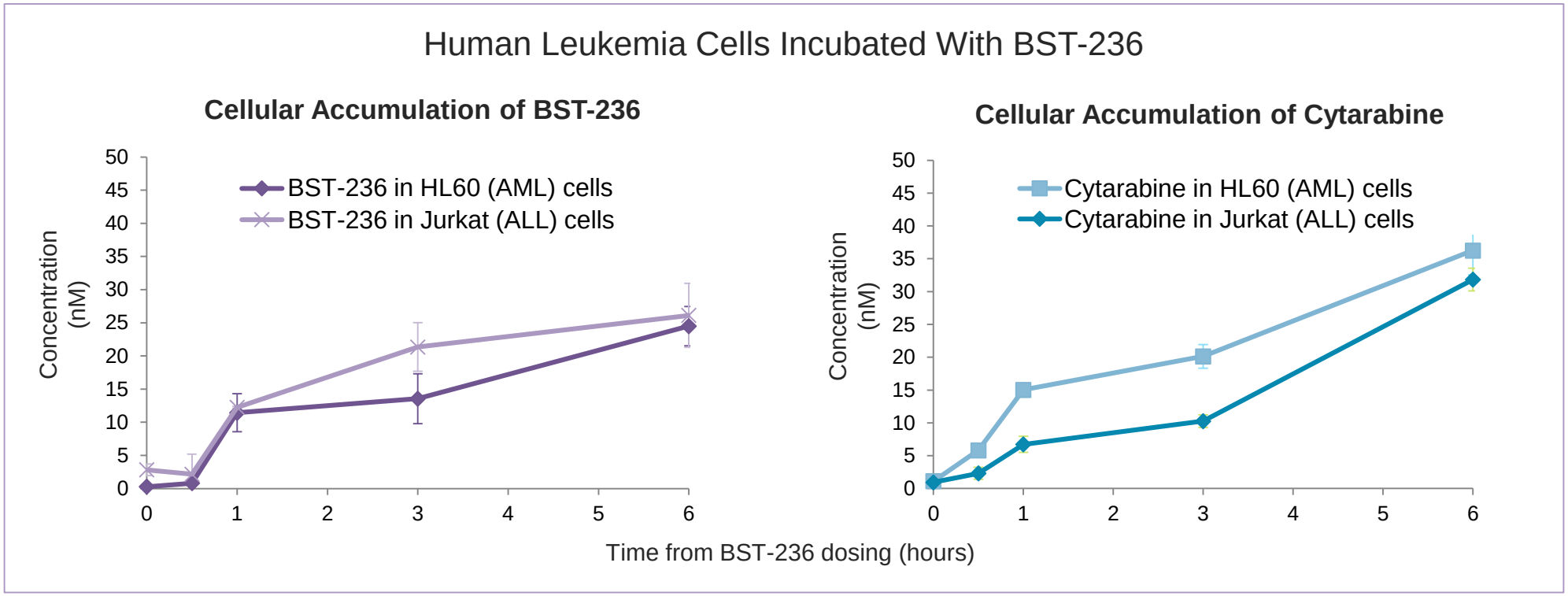


BST-236 Mechanism of Action



Cellular Accumulation of BST-236 and its Metabolite Cytarabine

BST-236 accumulates in human leukemia cells, accompanied by cellular accumulation of cytarabine



BST-236 Clinical Studies

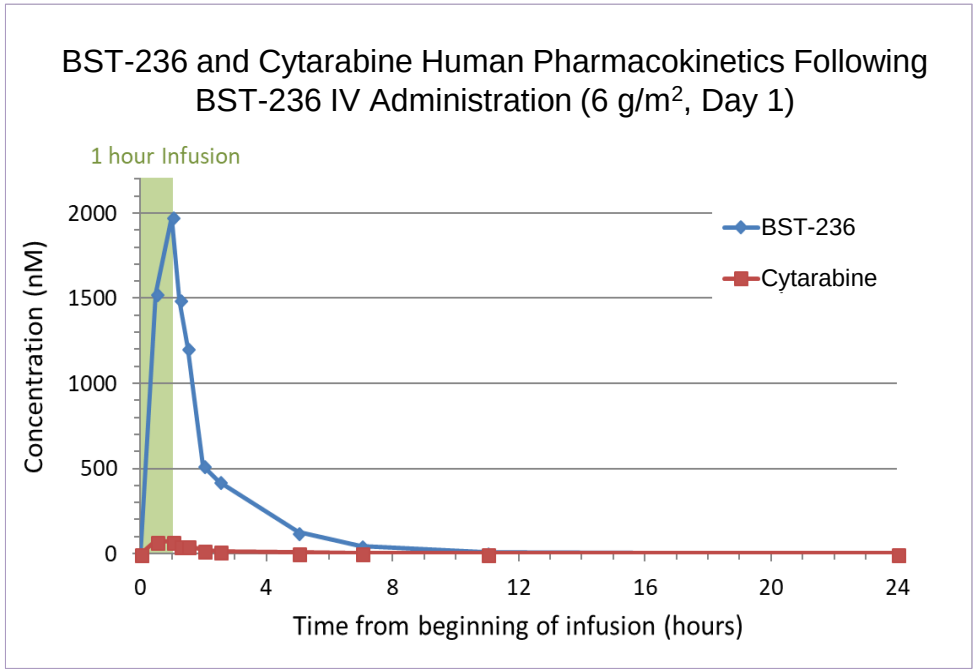
Study	**A Phase 1/2a Open-Label Study to Evaluate the Safety and Efficacy of BST-236 as a Single Agent in Adults with AML or ALL**	**A Phase 2b, Open Label, Single Arm, Multi-Center Study To Assess The Efficacy and Safety of BST-236 as Single Agent in Adults With Newly Diagnosed AML, Not Eligible for Standard Induction Therapy**
Status	Completed 2017	Enrolling
Study Design	Open label, dose escalation	Open label, single arm
Study Population	26 patients: • Newly-diagnosed AML (*de novo* or secondary), not eligible for chemotherapy (n=11) • Newly-diagnosed ALL, not eligible for standard chemotherapy • Relapsed/refractory AML or ALL	65 patients (12 enrolled to date): Newly-diagnosed AML (*de novo* or secondary), not eligible for standard chemotherapy
Primary Endpoint	MTD	CR
BST-236 Dose & Administration	0.3 - 6 g/m^2/d IV, 6-day cycles 1-2 inductions	4.5 g/m^2/d IV, 6-day cycles 1-2 inductions + 1-2 consolidations
Follow Up	3 months	1 year (+1 year post-study OS follow up)

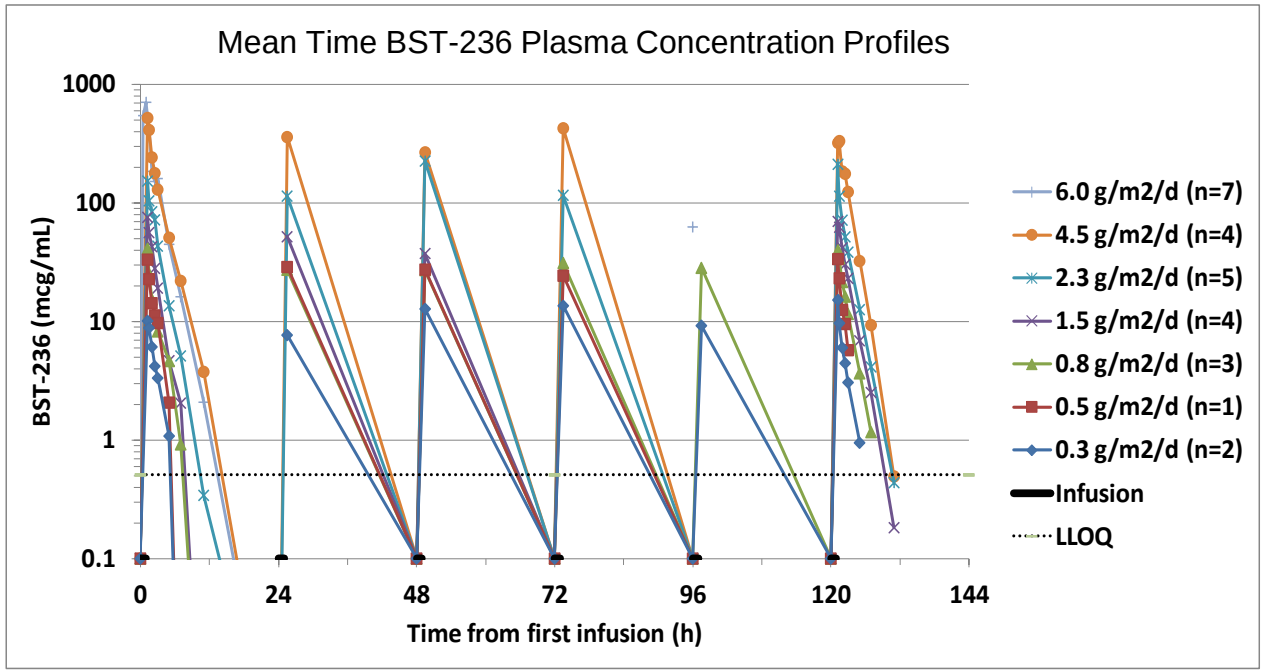
Baseline Characteristics – Newly-Diagnosed AML

Baseline Characteristics		Phase 1/2a	Phase 2b	All
N		11	12	**23**
Age, median, y (range)		78 (70-88)	75 (67-80)	**76 (67-88)**
≥75 years, n (%)		8 (73)	6 (50)	**14 (61)**
ECOG, n (%)	0-1	9 (82)	8 (67)	**17 (74)**
	2	2 (18)	4 (33)	**6 (23)**
Secondary AML, n (%)		8 (73)	8 (67)	**16 (70)**
Prior HMA for MDS, n (%)		5 (45)	4 (33)	**9 (39)**
Bone marrow blasts, n (%)	<30	1 (9)	5 (42)	**6 (26)**
	30-50	3 (27)	2 (17)	**5 (22)**
	>50	7 (64)	5 (42)	**12 (52)**
ELN risk score, n (%)	Favorable	1 (9)	2 (17)	**3 (13)**
	Intermediate	4 (36)	5 (42)	**9 (39)**
	Adverse	6 (55)	5 (42)	**11 (48)**

BST-236 Pharmacokinetics

- BST-236 t ½ ≈ 80 minutes
- Low level of free cytarabine in plasma, hence avoiding peak toxic cytarabine levels
- Dose-dependent exposure with no day-to-day accumulation





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Adverse Events

Treatment-Emergent Adverse Events (TEAEs)

TEAEs, Grade ≥3 (≥10% of Patients), n (%)	
Febrile neutropenia	7 (30)
Neutropenia	5 (22)
Pneumonia	5 (22)
Thrombocytopenia	5 (22)
Pancytopenia	4 (17)
Anemia	3 (13)
Atrial fibrillation/flutter	3 (13)
Hypertension	3 (13)
Hypoxia	3 (13)

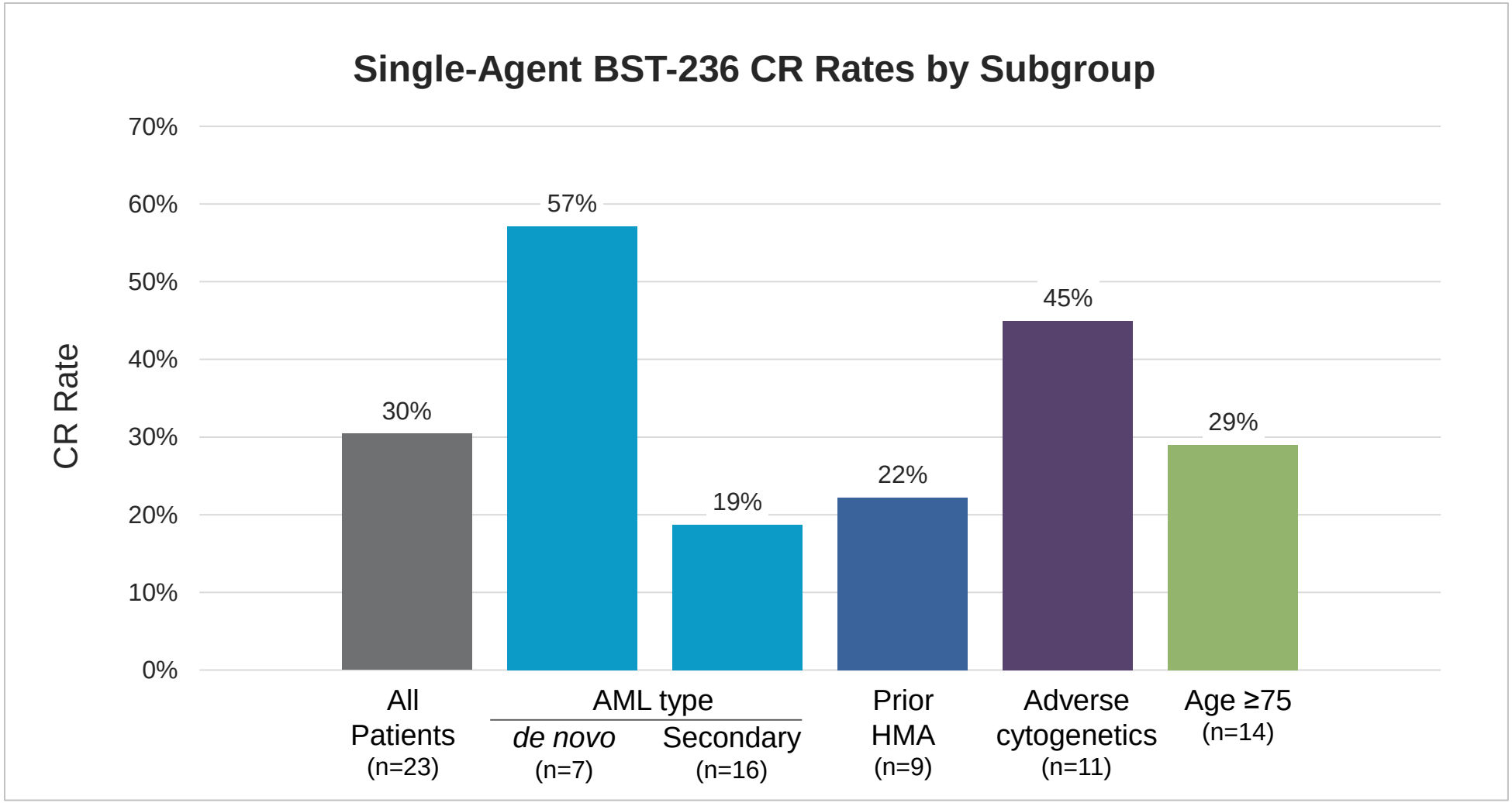
Related TEAEs, Any Grade (≥10% of Patients), n (%)	
Febrile neutropenia	8 (35)
Vomiting	5 (22)
Diarrhea	4 (17)
Pancytopenia	4 (17)
Chills	3 (13)
Nausea	3 (13)
Pneumonia	3 (13)
Thrombocytopenia	3 (13)

Serious Adverse Events (SAEs)

SAE, >1 patient, n (%)	
Pneumonia	4 (17)
Febrile neutropenia	3 (13)

Related SAEs (n): pneumonia (2) , periorbital cellulitis (1), platelet count decreased (1), thrombocytopenia (1)

Complete Remission (CR) Rates by Subgroups



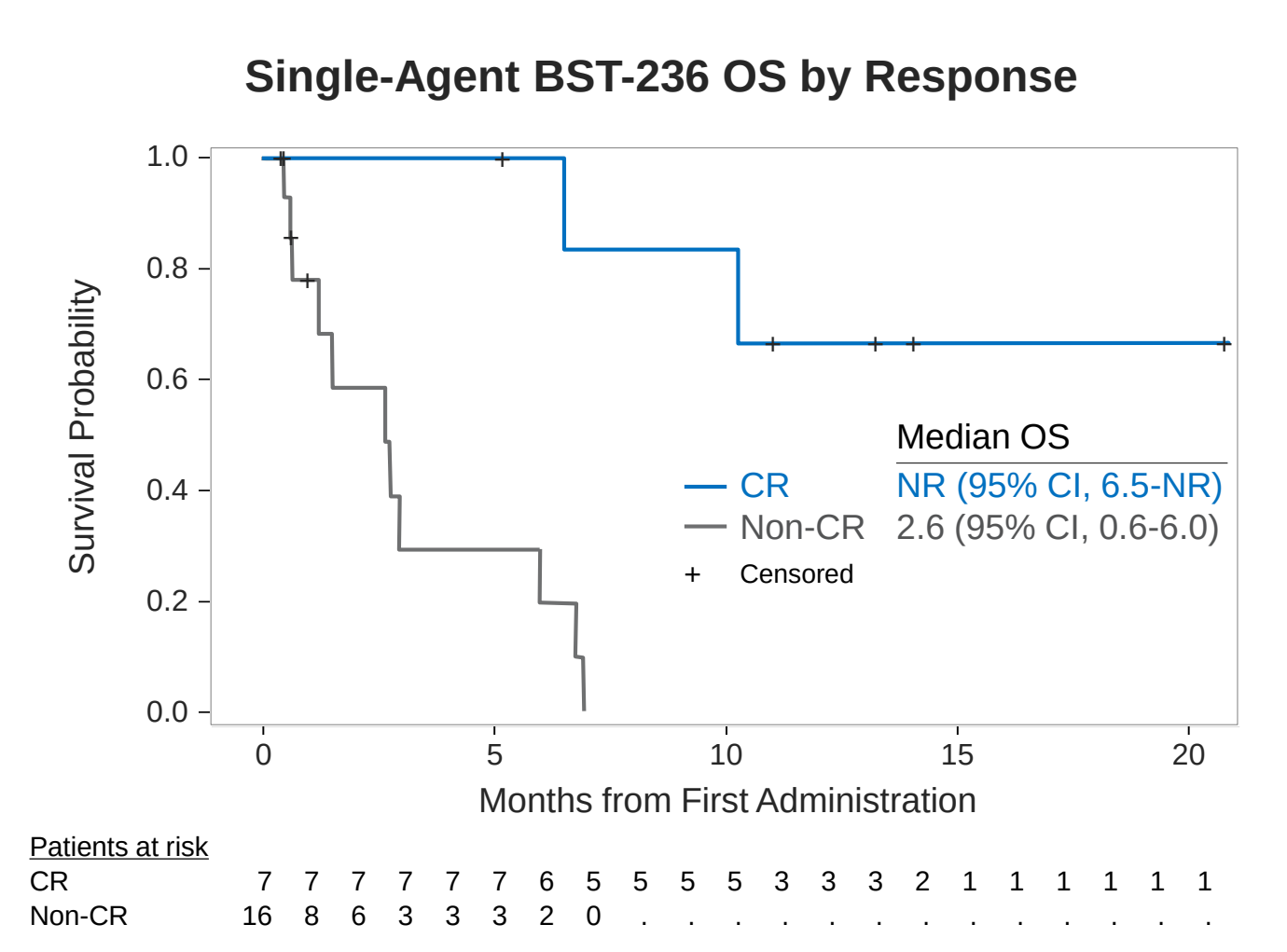
Including 1 CR case defined as CRp due to impaired timing of BM and blood tests

Overall Survival (OS)

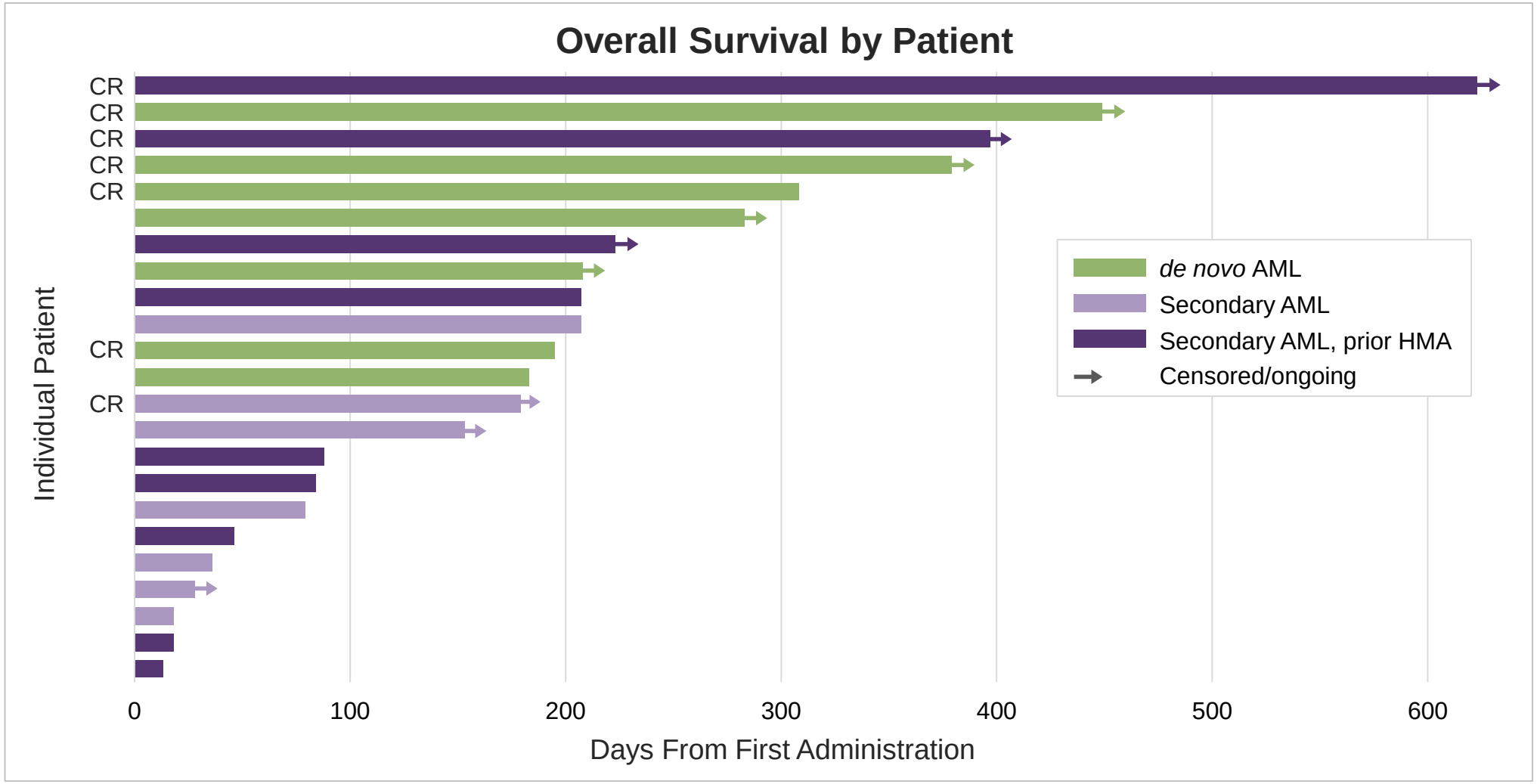
	CR	Non-CR
N	7	16
Age, median, y (range)	77 (70-81)	76 (67-88)
# induction courses, average (range)	1.4 (1-2)	1.1 (1-2)
# consolidation courses, average (range)	0.9 (0-2)	-
Median OS, months	NR	2.6
1-year survival, %	67	0

Including 1 CR case defined as CRp due to impaired timing of BM and blood tests

NR = not reached



Overall Survival



Summary – BST-236 (Aspacytarabine), a Novel Anti-Metabolite

- Safe and well-tolerated (4.5 g/m^2/d), enabling delivery of high cytarabine doses to older and unfit patients
- Mainly “on-target” events; no cerebellar toxicity, no mucositis, no alopecia, no renal failure
- Promising single-agent activity:
  - Including in patients with poor-risk features
  - Neutrophil and platelet recovery within 36 days
  - Durable CRs; median OS of responders not reached at >1 year
- A potential novel first-line therapy for older adults not fit for intensive chemotherapy
- First-line single-agent phase 2b AML trial is ongoing
  - MRD assessment (phase 2b)
- Additional trials in AML and MDS under development, addressing wide unmet need

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- We wish to thank the study staff at participating centers:
  - Northwestern University, Chicago IL, USA
  - Rambam Health Care Campus, Technion, Haifa, Israel
  - Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA
  - University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA
  - Georgia Cancer Center, Augusta University, Augusta, GA, USA
  - Baylor Scott & White Research Institute, Dallas TX, USA
  - Soroka University Medical Center, Beer Sheva, Israel
  - Rabin Medical Center, Petach Tikva, Israel
  - Sourasky Medical Center, Tel-Aviv, Israel
  - Shaare Zedek Medical Center, Jerusalem, Israel
- We wish to thank the sponsor, Biosight Ltd.

THANK YOU

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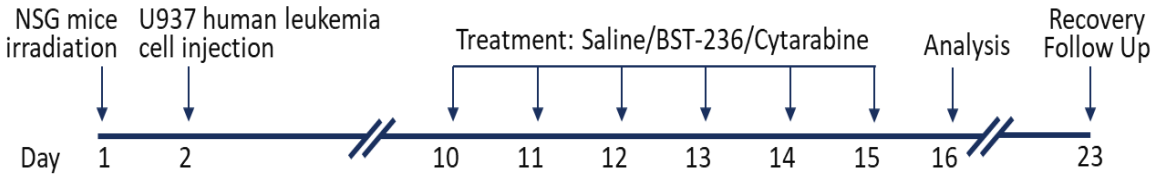
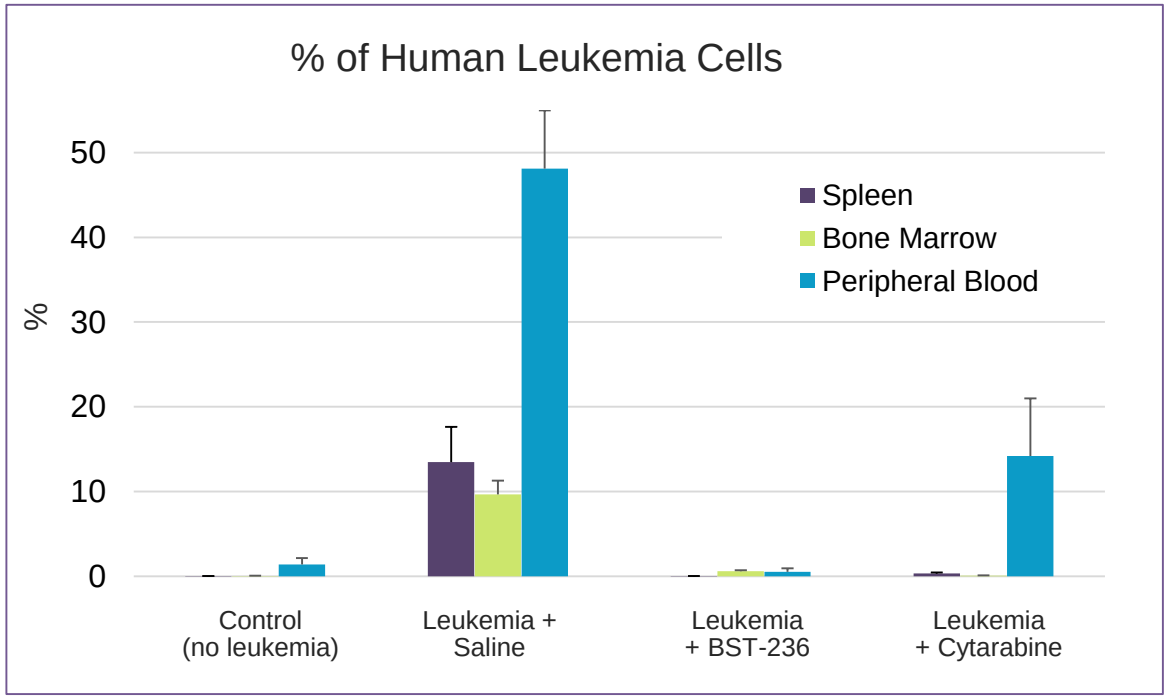
BST-236 Has Superior Efficacy/Safety Profile Compared to Cytarabine



BST-236 dose = 5 mg/mouse; Cytarabine dose = 3.4 mg/mouse (equimolar cytarabine doses)



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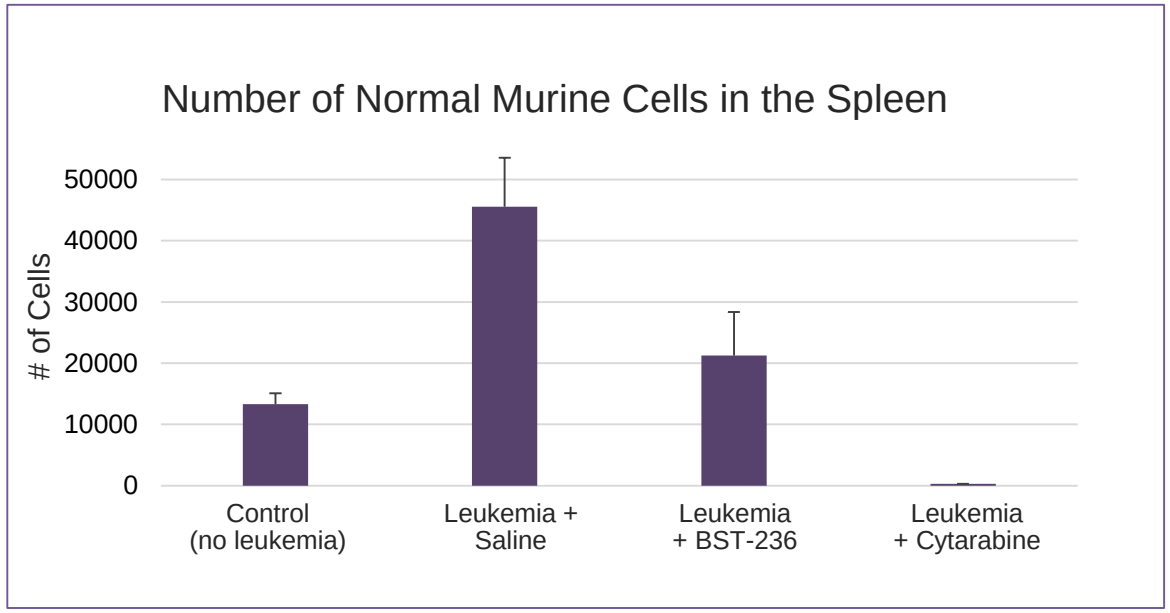
BST-236 and cytarabine show similar efficacy in eliminating leukemia cells in BM, spleen, and blood



After 1 week recovery follow up: all BST-236 mice showed no clinical signs, all cytarabine mice were dead

BST-236 is significantly safer: better normal cells recovery, less weight loss, better viability