

INO-VATE
ALL

Post hoc rationale

CR/CRi & MRD

HSCT

Survival

EMD/LBL

Safety

Conclusions

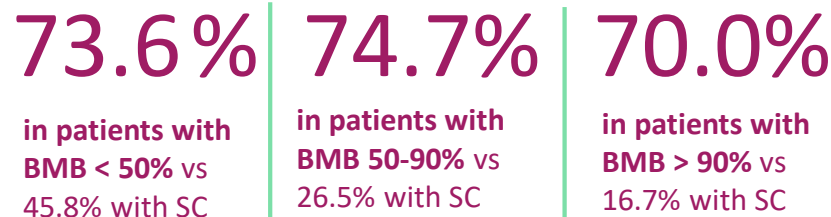
References



BESPONSA FOR R/R B-CELL ALL: OUTCOMES BY DISEASE BURDEN

For the full post hoc analysis, see:
DeAngelo DJ, et al. *Blood Cancer J.* 2020

Rates of CR/CRi in BESPONSA-treated patients were higher than with SC, irrespective of bone marrow blast count:¹



[Click here for the BESPONSA SmPC](#)

ALL=acute lymphoblastic leukemia; BMB=bone marrow blasts; CR=complete response; CRi=complete response with incomplete hematological recovery; EMD=extramedullary disease; HSCT=hematopoietic stem cell transplantation; LBL=lymphoblastic lymphoma; MRD=minimal residual disease; R/R=relapsed/refractory; SC=standard chemotherapy; SmPC=summary of product characteristics.

This material has been downloaded from the European Hematology Association Virtual Congress 2021. It has been approved for use in compliance with pharmaceutical industry codes of practice (CGR) in The Netherlands.

PP-INO-GLB-0138 May 2021.

▼ This medicinal product is subject to additional monitoring.

Indication: BESPONSA is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome-positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI).²

The INO-VATE ALL Study

INO-VATE ALL, the pivotal phase 3 registration study for BESPONSA, was an open-label, randomized study in adults (N = 326) with R/R B-cell ALL. CR/CRI and OS were the two primary endpoints³

Primary analysis (data cutoff: Oct 2, 2014)³

	BESPONSA	SC
CR/CRI ^{3,*}	80.7% (n = 88/109) (95% CI, 72.1-87.7)	29.4% (n = 32/109) (95% CI, 21.0-38.8)
2-sided P < 0.001		
OS: Not met mOS ³	7.7 months (n = 164) (95% CI, 6.0-9.2)	6.7 months (n = 162) (95% CI, 4.9-8.3)
HR 0.77 (97.5% CI, 0.58-1.03); 1-sided P = 0.04		

Long-term analysis (data cutoff: Jan 4, 2017)⁴

	BESPONSA	SC
CR/CRI ^{4,†}	73.8% (n = 121/164)	30.9% (n = 50/162)
1-sided P < 0.0001		
OS: Not met mOS ^{2,4†}	7.7 months (n = 164) (95% CI, 6.0-9.2)	6.2 months (n = 162) (95% CI, 4.7-8.3)
HR 0.75 (97.5% CI, 0.57-0.99); 1-sided P = 0.0105; HR = 0.751 (95% CI, 0.588-0.959); 2-sided P = 0.0210		
2-year survival ⁴	22.8% (95% CI, 16.7-29.6)	10.0% (95% CI, 5.7-15.5)
3-year survival ⁴	20.3% (95% CI, 14.4-27.0)	6.5% (95% CI, 2.9-12.3)

*Analyzed in the remission analysis population, which included the first 218 patients who underwent randomization in the ITT population.³

†Results are from the long-term follow-up of the phase 3 INO-VATE ALL study and include 326 patients who underwent randomization in the ITT population (data cutoff: Jan 4, 2017).⁴

ALL=acute lymphoblastic leukemia; CI=confidence interval; CR=complete remission; CRI=complete remission with incomplete hematologic recovery of peripheral blood cells; HR=hazard ratio; ITT=intention-to-treat; mOS=median overall survival; OS=overall survival; R/R=relapsed/refractory; SC=standard chemotherapy.



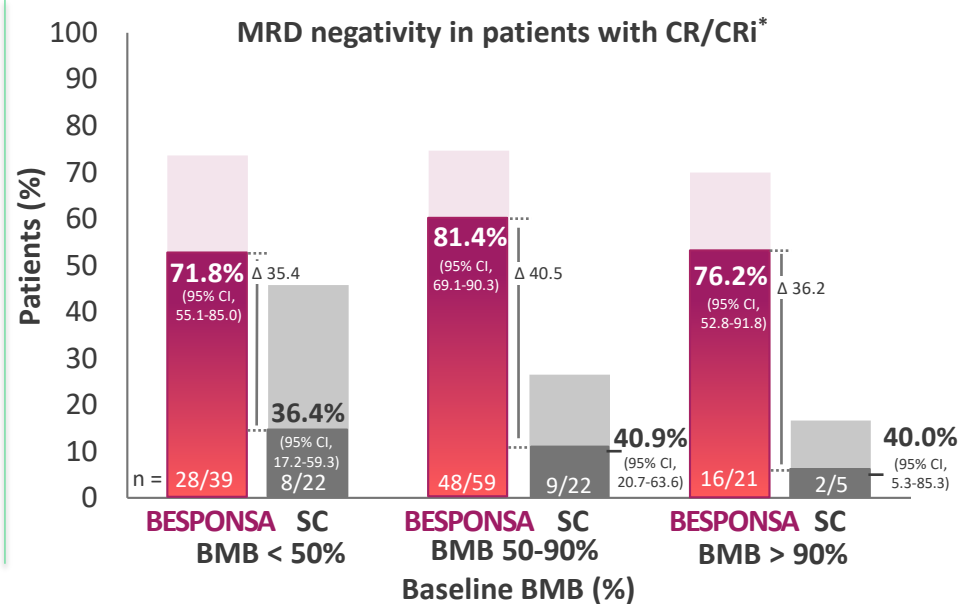
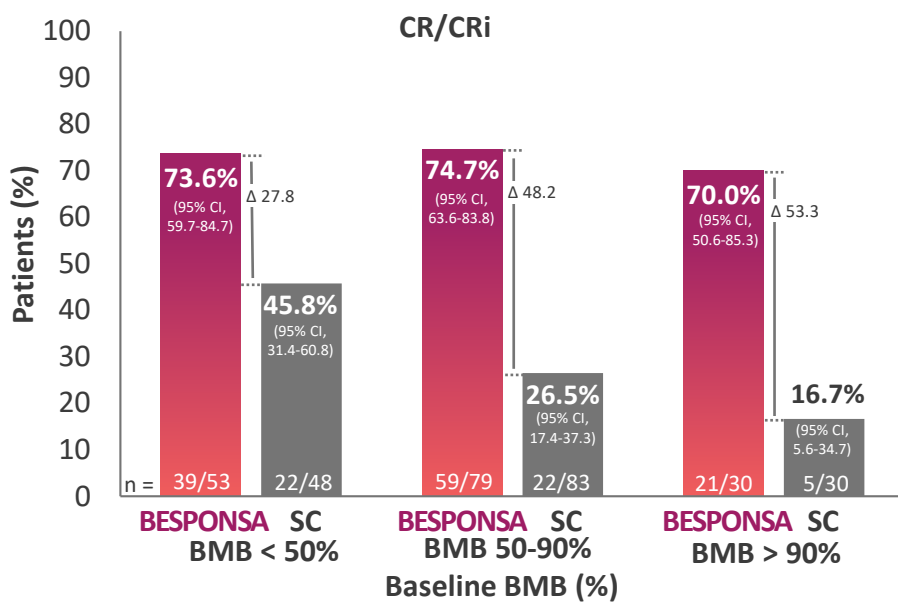
INO-VATE ALL: Post Hoc Analysis of Outcomes by Disease Burden

Aims

- In the phase 3 INO-VATE ALL trial, the majority of patients with R/R B-cell ALL had high bone marrow blast counts (BMB $\geq 50\%$) at baseline in the BESPONSA and SC arms³
 - BMB $< 50\%$: 28% vs 27%, respectively
 - BMB $\geq 50\%$: 71% vs 72%, respectively
- This post hoc analysis of INO-VATE ALL aimed to compare BESPONSA vs SC in terms of:
 - Efficacy and safety for patients with low (BMB $< 50\%$), moderate (BMB 50-90%), or high (BMB $> 90\%$) bone marrow blast counts¹
 - **In the primary analysis, CR/ CRi rates were improved with BESPONSA compared with SC irrespective of bone marrow blast count^{1,3}**
 - BMB $< 50\%$: 86.7% vs 41.4%, respectively
 - BMB $\geq 50\%$: 77.9% vs 24.4%, respectively
 - However, it is not known whether outcomes differ for patients with a higher bone marrow blast count (BMB $> 90\%$)¹
 - Whether outcomes differ for patients with EMD or LBL¹

ALL=acute lymphoblastic leukemia; BMB=bone marrow blasts; CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; EMD=extramedullary disease; LBL=lymphoblastic lymphoma; R/R=relapsed/refractory; SC=standard chemotherapy.

Rates of CR/CRI and MRD negativity in BESPONSA-treated Patients Were Higher Than With SC, Irrespective of Bone Marrow Blast Count¹



Note: Due to the small sample size, results should be interpreted with caution. BMB data was not available for three of the 326 patients in INO-VATE ALL.

*Lighter-colored grey and pink segments represent patients who achieved CR/CRI but did not achieve MRD negativity.

BMB=bone marrow blasts; CI=confidence interval; CR=complete remission; CRI=complete remission with incomplete hematologic recovery;

MRD=minimal residual disease; SC=standard chemotherapy.

A Greater Proportion of Patients Proceed to HSCT With BESPONSA Compared with SC, Irrespective of Bone Marrow Blast Count¹

	BESPONSA % (n/N)	SC % (n/N)
Proportion of patients proceeding to post-treatment HSCT		
BMB < 50%	50.9 (27/53)	27.1 (13/48)
BMB 50-90%	48.1 (38/79)	26.5 (22/83)
BMB > 90%	46.7 (14/30)	3.3 (1/30)

Note: Due to the small sample size, results should be interpreted with caution.

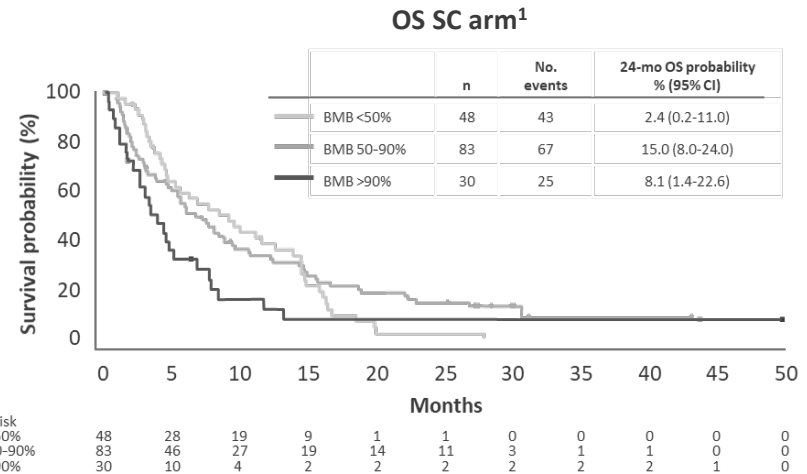
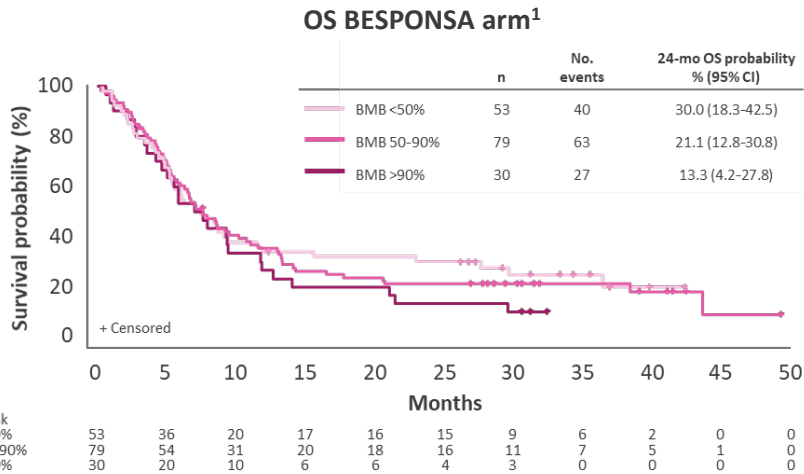
VOD/SOS with BESPONSA versus SC, according to bone marrow blast count

- **Grade ≥ 3 VOD/SOS, BESPONSA vs SC:**
 - BMB < 50%: 13.2% (n = 7/53) vs 2.3% (n = 1/43)
 - BMB 50-90%: 12.7% (n = 10/79) vs 2.8% (n = 2/71)
 - BMB > 90%: 6.7% (n = 2/30) vs 0% (n = 0/28)
- **Post-HSCT VOD/SOS, BESPONSA vs SC:**
 - BMB < 50%: 25.9% (n = 7/27) vs 7.7% (n = 1/13)
 - BMB 50-90%: 23.7% (n = 9/38) vs 9.5% (n = 2/21)
 - BMB > 90%: 14.3% (n = 2/14) vs 0% (n = 0/1)

BMB=bone marrow blasts; HSCT=hematopoietic stem cell transplant; SC=standard chemotherapy; SOS=sinusoidal obstruction syndrome; VOD=veno-occlusive disease.

BESPONSA Improves Survival, Irrespective of Bone Marrow Blast Count

- There was a trend towards improved OS with BESPONSA compared with SC¹
- Irrespective of bone marrow blast count, the 2-year OS probability with BESPONSA was higher compared with SC (30.0% vs 2.4% [low], 21.1% vs 15.0% [moderate], and 13.3% vs 8.1% [high])¹
- Irrespective of bone marrow blast count, PFS was also improved with BESPONSA compared with SC¹

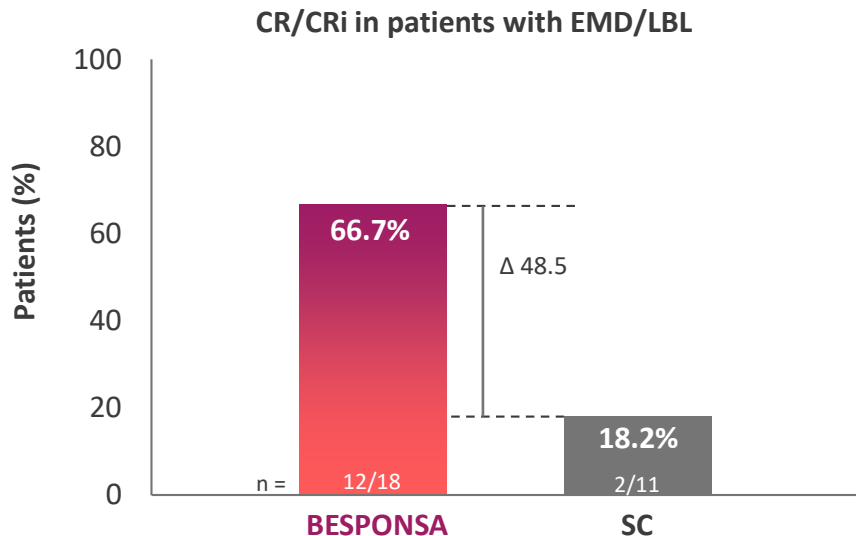


The primary endpoint of OS was not met³

BMB=bone marrow blasts; CI=confidence interval; mPFS=median progression-free survival; mo=months; OS=overall survival; PFS= progression-free survival; SC=standard chemotherapy.



For Patients With EMD/LBL, Outcomes Appeared Improved With BESPONSA vs SC, However, Sample Sizes Were Very Small¹



Patients with EMD/LBL	BESPONSA	SC	HR BESPONSA vs SC
MRD negativity in patients with CR/CRI	58.3% n = 7/12	50.0% n = 1/2	-
mPFS, mo	4.4 (95% CI, 1.9-7.1)	1.6 (95% CI, 0.8-3.7)	0.50 (97.5% CI, 0.20-1.24)

Note: Due to the small sample size, results should be interpreted with caution. This study was not powered to look at these subsets.

CI=confidence interval; CR=complete response; CRI=complete response with incomplete hematologic recovery; EMD=extramedullary disease; HR=hazard ratio; LBL=lymphoblastic lymphoma; mo=months; mPFS=median progression-free survival; MRD=minimal residual disease; SC=standard chemotherapy.

The Safety Profile for BESPONSA Was Similar for All Bone Marrow Blast Count Subgroups¹

With both BESPONSA and SC, the most frequent TEAEs were hematologic, irrespective of bone marrow blast count

- **In patients treated with BESPONSA, febrile neutropenia appeared to increase with increasing bone marrow blast count (range: 17-53%); febrile neutropenia was high in all bone marrow blast count subgroups in patients treated with SC (range: 56-46% [low to high bone marrow blast count])**
- Grade ≥ 3 hematologic laboratory abnormalities appeared to increase with increasing bone marrow blast count in the BESPONSA arm

Dose reductions and temporary or permanent discontinuations due to TEAEs were either equally common or more common with BESPONSA versus SC, irrespective of bone marrow blast count

SC=standard chemotherapy; TEAE=treatment-emergent adverse event.

TEAEs and Hematologic Laboratory Abnormalities¹

Event, n (%)	Low (BMB < 50%)		Moderate (BMB 50-90%)		High (BMB > 90%)	
	BESPONSA	SC	BESPONSA	SC	BESPONSA	SC
	(n = 53)	(n = 43)	(n = 79)	(n = 71)	(n = 30)	(n = 28)
TEAEs (grade ≥ 3)^a						
Any	47 (88.7)	42 (97.7)	71 (89.9)	69 (97.2)	29 (96.7)	26 (92.9)
Blood and lymphatic system disorders	41 (77.4)	38 (88.4)	62 (78.5)	63 (88.7)	26 (86.7)	22 (78.6)
Febrile neutropenia	9 (17.0)	24 (55.8)	17 (21.5)	39 (54.9)	16 (53.3)	13 (46.4)
Hepatobiliary disorders	11 (20.8)	3 (7.0)	13 (16.5)	6 (8.5)	4 (13.3)	3 (10.7)
VOD/SOS ^b	7 (13.2)	1 (2.3)	10 (12.7)	2 (2.8)	2 (6.7)	0
Infections and infestations	18 (34.0)	25 (58.1)	18 (22.8)	38 (53.5)	12 (40.0)	15 (53.6)
Investigations	18 (34.0)	10 (23.3)	23 (29.1)	14 (19.7)	8 (26.7)	9 (32.1)
Metabolism and nutrition disorders	9 (17.0)	8 (18.6)	12 (15.2)	16 (22.5)	6 (20.0)	7 (25.0)
Hematologic laboratory abnormalities (grade ≥ 3)						
Hemoglobin decreased	17 (32.1)	27 (62.8)	27 (34.2)	54 (76.1)	23 (76.7)	20 (71.4)
Leukocytes decreased	36 (67.9)	42 (97.7)	66 (83.5)	70 (98.6)	29 (96.7)	27 (96.4)
Lymphopenia	32 (60.4)	38 (88.4)	56 (70.9)	58 (81.7)	26 (86.7)	21 (75.0)
Neutrophil count decreased	38 (71.7)	36 (83.7)	71 (89.9)	56 (78.9)	29 (96.7)	22 (78.6)
Platelet count decreased	34 (64.2)	42 (97.7)	60 (75.9)	71 (100.0)	29 (96.7)	27 (96.4)

Data represent the safety population. TEAEs and hematologic laboratory abnormalities were graded according to the NCI CTCAE, version 3.0.

^aAll-causality TEAEs grade ≥ 3 with ≥ 10% incidence occurring in either arm (any treatment cycle, any BMB subgroup).

^bIn July 2017 (after the clinical database was locked), a fourth case of VOD/SOS was confirmed to have occurred in an SC arm patient.

This case of VOD/SOS occurred in March 2013, was not entered on the clinical report form, and is therefore not included.

BMB=bone marrow blasts; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; SC=standard chemotherapy; SOS=sinusoidal obstruction syndrome; TEAE=treatment-emergent adverse event; VOD=veno-occlusive disease.



Conclusions

- BESPONSA remains efficacious for patients with R/R B-cell ALL in challenging subpopulations, including patients with high bone marrow blast counts¹
- In this post hoc analysis of outcomes by disease burden, patients treated with BESPONSA had improved CR/CRi rates, MRD negativity rates, HSCT rates, and PFS, with a trend towards improved OS, compared with SC, irrespective of bone marrow blast counts¹
- For patients with EMD or LBL, remission rates appeared to improve with BESPONSA versus SC; however, the sample sizes were very small and were not powered to look at these subsets¹
- The safety profile of BESPONSA was similar for all bone marrow blast count subgroups, suggesting that high bone marrow blast count does not negatively impact the safety profile of BESPONSA¹

**BESPONSA provides consistently high remission rates versus SC,
irrespective of bone marrow blast counts¹**

ALL=acute lymphoblastic leukemia; CR=complete response; CRi=complete response with incomplete hematologic recovery; EMD=extramedullary disease; HSCT=hematopoietic stem cell transplantation; LBL=lymphoblastic lymphoma; MRD=minimal residual disease; OS=overall survival; PFS=progression-free survival; R/R=relapsed/refractory; SC=standard chemotherapy.

References

1. DeAngelo DJ, Advani AS, Marks DI, et al. Inotuzumab ozogamicin for relapsed/refractory acute lymphoblastic leukemia: outcomes by disease burden. *Blood Cancer J.* 2020;10(8):81.
2. Pfizer Limited. BESPONSA™ (inotuzumab ozogamicin) summary of product characteristics. 2020.
3. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard care for acute lymphoblastic leukemia. *N Engl J Med.* 2016;375(8):740-753.
4. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. *Cancer.* 2019;125(14):2474-2487.