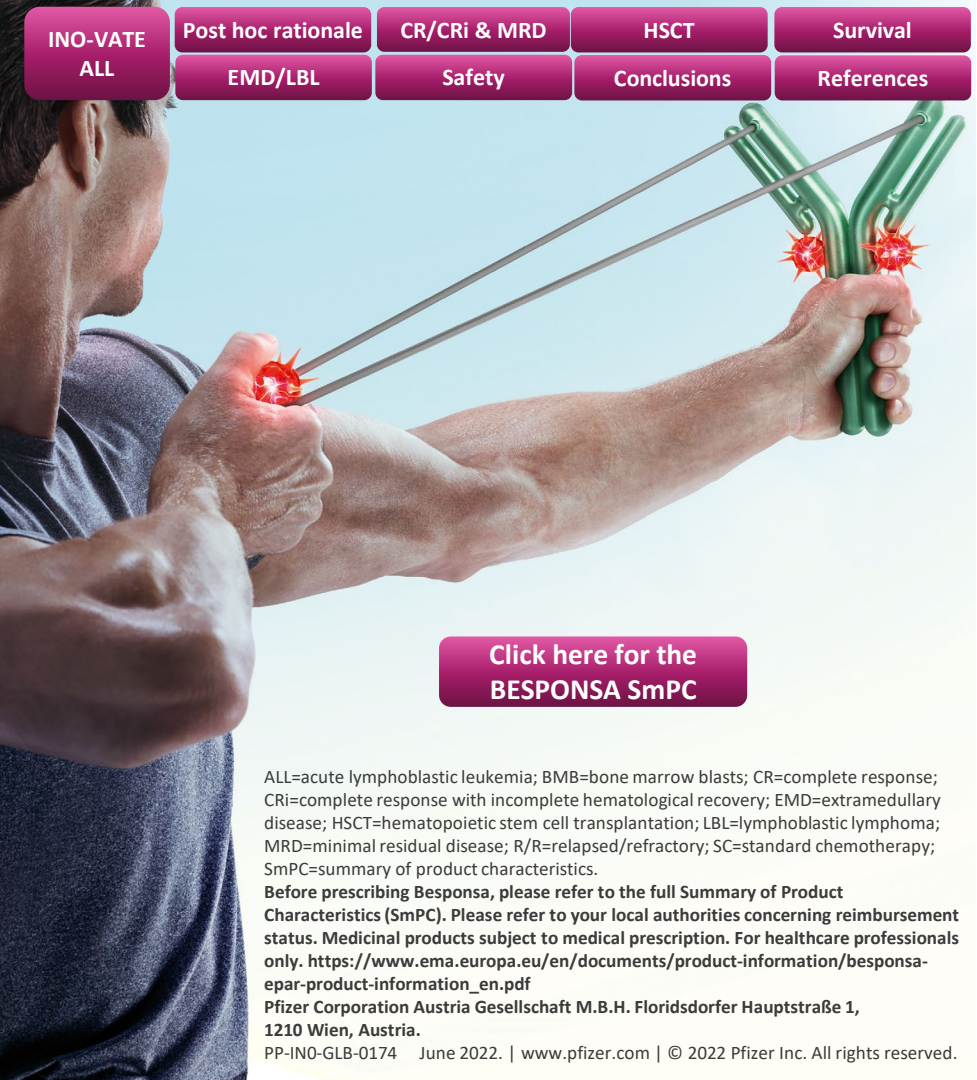

BESPONSA™ inotuzumab ozogamicin INJECTION FOR IV INFUSION

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

Click here for the BESPONSA SmPC

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]

73.6% in patients with **BMB < 50%** vs 45.8% with SC

74.7% in patients with **BMB 50-90%** vs 26.5% with SC

70.0% in patients with **BMB > 90%** vs 16.7% with SC

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.

Before prescribing Besponsa, please refer to the full Summary of Product Characteristics (SmPC). Please refer to your local authorities concerning reimbursement status. Medicinal products subject to medical prescription. For healthcare professionals only. https://www.ema.europa.eu/en/documents/product-information/besponsa-epar-product-information_en.pdf

Pfizer Corporation Austria Gesellschaft M.B.H. Floridsdorfer Hauptstraße 1, 1210 Wien, Austria.

PP-IN0-GLB-0174 June 2022.

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 endpoints[3]

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); 2-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.

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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 ≥ 50%) at baseline in the BESPONSA and SC arms[3]
  - BMB < 50%: 28% vs 27%, respectively
  - BMB ≥ 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 counts[1]
    - **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 ≥ 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 LBL[1]

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.

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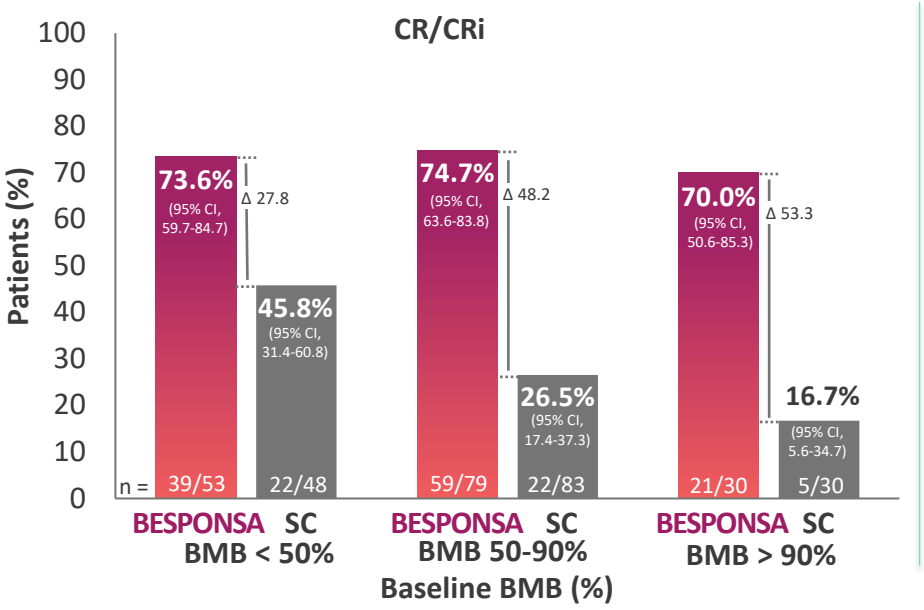
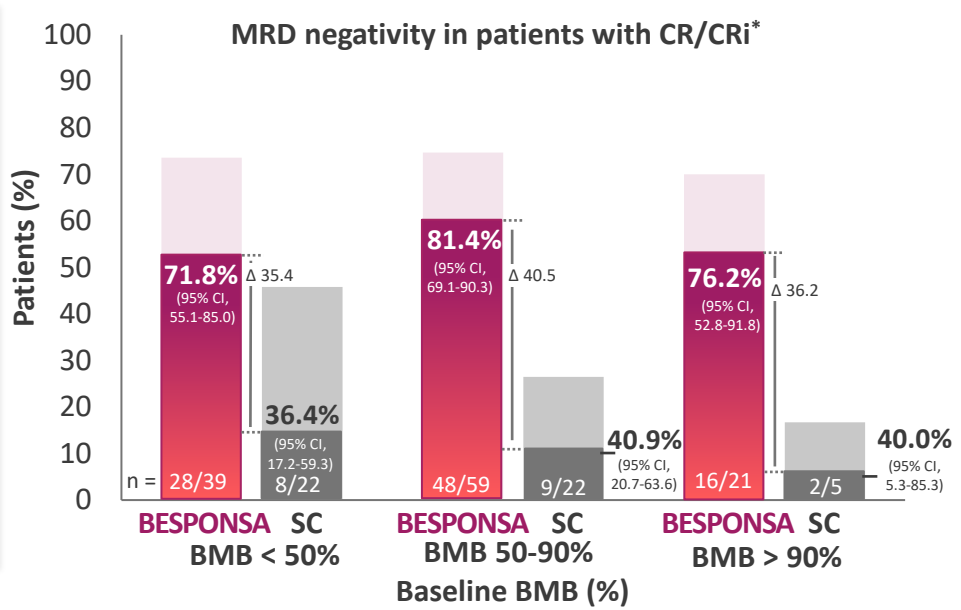
Rates of CR/CRi and MRD negativity in BESPONSA-treated Patients Were Higher Than With SC, Irrespective of Bone Marrow Blast Count[1]





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 bar 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.

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A Greater Proportion of Patients Proceed to HSCT With BESPONSA Compared with SC, Irrespective of Bone Marrow Blast Count[1]

	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.

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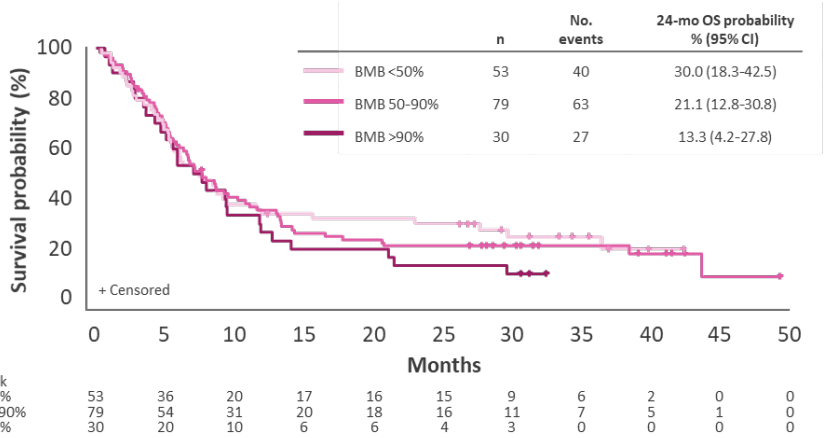
BESPONSA Improves Survival, Irrespective of Bone Marrow Blast Count

- **There was a trend towards improved OS with BESPONSA** compared with SC[1]
- **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 SC[1]

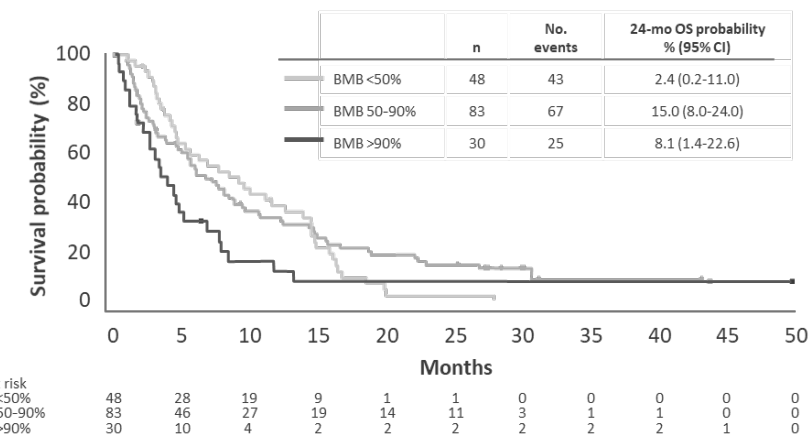
OS BESPONSA arm[1]



	n	No. events	24-mo OS probability % (95% CI)
BMB <50%	53	40	30.0 (18.3-42.5)
BMB 50-90%	79	63	21.1 (12.8-30.8)
BMB >90%	30	27	13.3 (4.2-27.8)

No. at risk											
BMB <50%	53	36	20	17	16	15	9	6	2	0	0
BMB 50-90%	79	54	31	20	18	16	11	7	5	1	0
BMB >90%	30	20	10	6	6	4	3	0	0	0	0

OS SC arm[1]



	n	No. events	24-mo OS probability % (95% CI)
BMB <50%	48	43	2.4 (0.2-11.0)
BMB 50-90%	83	67	15.0 (8.0-24.0)
BMB >90%	30	25	8.1 (1.4-22.6)

No. at risk											
BMB <50%	48	28	19	9	1	1	0	0	0	0	0
BMB 50-90%	83	46	27	19	14	11	3	1	1	0	0
BMB >90%	30	10	4	2	2	2	2	2	2	1	0

The primary endpoint of OS was not met[3]

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

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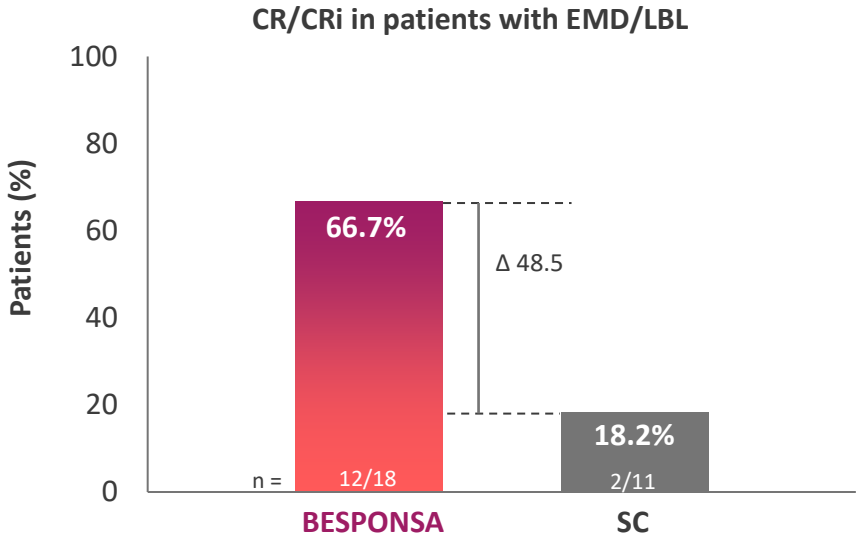
For Patients With EMD/LBL, Outcomes Appeared Improved With BESPONSA vs SC, However, Sample Sizes Were Very Small[1]



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.

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The Safety Profile for BESPONSA Was Similar for All Bone Marrow Blast Count Subgroups[1]

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.

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TEAEs and Hematologic Laboratory Abnormalities[1]

Event, n (%)	Low (BMB < 50%)		Moderate (BMB 50-90%)		High (BMB > 90%)	
	BESPONSA (n = 53)	SC (n = 43)	BESPONSA (n = 79)	SC (n = 71)	BESPONSA (n = 30)	SC (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.
[a]All-causality TEAEs grade ≥ 3 with ≥ 10% incidence occurring in either arm (any treatment cycle, any BMB subgroup).
[b]In 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.

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Conclusions

- BESPONSA remains efficacious for patients with R/R B-cell ALL in challenging subpopulations, including patients with high bone marrow blast counts[1]
- 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 counts[1]
  - Improvements in MRD negativity rates and OS were not statistically significant for all BMB% subgroups[1]
- 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 subsets[1]
- 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 BESPONSA[1]

BESPONSA provides consistently high remission rates versus SC, irrespective of bone marrow blast counts[1]

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.

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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. Besponsa summary of product characteristics, February 2022.
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.

Before prescribing Besponsa, please refer to the full Summary of Product Characteristics (SmPC).

Please refer to your local authorities concerning reimbursement status. Medicinal product subject to medical prescription.

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Fachkurzinformation

BESPONSA 1 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung

Qualitative und quantitative Zusammensetzung: Jede Durchstechflasche enthält 1mg Inotuzumab Ozogamicin. Nach der Rekonstitution enthält 1 ml Lösung 0,25 mg Inotuzumab Ozogamicin.

Liste der sonstigen Bestandteile: Sucrose, Polysorbat 80, Natriumchlorid, Tromethamin.

Anwendungsgebiete: BESPONSA ist indiziert als Monotherapie für die Behandlung von Erwachsenen mit rezidivierter oder refraktärer CD22-positiver B-Vorläufer-ALL (akuter lymphatischer Leukämie). Erwachsene Patienten mit Philadelphia-Chromosom-positiver (Ph+) rezidivierter oder refraktärer B-Vorläufer-ALL sollten eine vorhergehende erfolglose Behandlung mit mindestens 1 Tyrosinkinase-Inhibitor (TKI) aufweisen.

Gegenanzeigen: Überempfindlichkeit gegen den Wirkstoff oder einen der in Abschnitt 6.1 der Fachinformation genannten sonstigen Bestandteile. Patienten mit vorhergehender bestätigter schwerer oder bestehender venookklusiver Lebererkrankung/ sinusoidalem Obstruktionssyndrom (VOD/ SOS). Patienten mit schwerer bestehender Lebererkrankung (z. B. Leberzirrhose, nodulär regenerative Hyperplasie der Leber, aktive Hepatitis).

Pharmakotherapeutische Gruppe: Antineoplastische Mittel, andere antineoplastische Mittel, monoklonale Antikörper. ATC-Code: L01XC26.

Inhaber der Zulassung: Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Brüssel, Belgien.

Stand der Information: Februar 2022.

Rezeptpflicht/Apothekenpflicht: Rezept- und apothekenpflichtig, wiederholte Abgabe verboten. **Angaben zu besonderen Warnhinweisen und Vorsichtsmaßnahmen für die Anwendung, Wechselwirkungen mit anderen Arzneimitteln und sonstigen Wechselwirkungen, Fertilität, Schwangerschaft und Stillzeit und Nebenwirkungen entnehmen Sie bitte der veröffentlichten Fachinformation.**

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