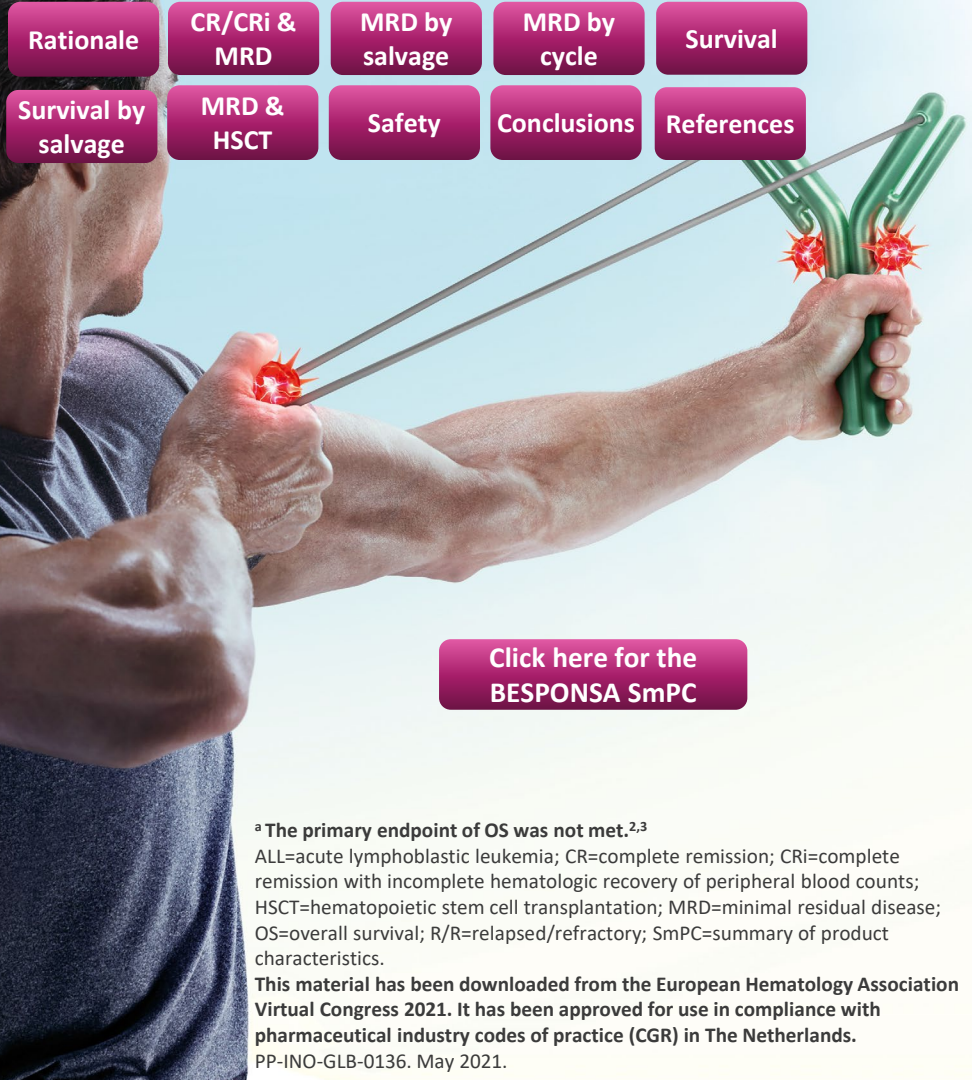

Click here for the BESPONSA SmPC

BESPONSA™ inotuzumab ozogamicin INJECTION FOR IV INFUSION

IMPACT OF MINIMAL RESIDUAL DISEASE STATUS IN PATIENTS WITH R/R B-CELL ALL TREATED WITH BESPONSA

For the full post hoc analysis, see:
Jabbour E, Gökbuget N, et al. *Leuk Res.* 2020

BESPONSA achieved:

14.1-month
Median OS in MRD-negative patients and 7.2 months in MRD-positive patients[1,a]

15.6-month
Median OS in MRD-negative patients when used in first salvage and 6.9 months in MRD-positive patients[1,a]

19.2-month
Median OS in MRD-negative patients who proceeded to HSCT and 6.3 months in MRD-positive patients who did not proceed to HSCT[1,a]

[a] **The primary endpoint of OS was not met.**[2,3]

ALL=acute lymphoblastic leukemia; CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; HSCT=hematopoietic stem cell transplantation; MRD=minimal residual disease; OS=overall survival; R/R=relapsed/refractory; SmPC=summary of product characteristics.

▼ **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).

INO-VATE ALL: Rationale for the Post Hoc Analyses

INO-VATE ALL, the pivotal phase 3 registration study for BESPONSA, was an open-label, randomized trial in adults (N = 326) with R/R B-cell ALL[2,4]

- **CR/CRi and OS were the two primary endpoints[2]**
  - **Patients treated with BESPONSA had significantly higher rates of remission** compared with those treated with SC (CR/CRi: 80.7% vs 29.4%, $P < 0.001$)[2,a]
  - The primary endpoint of OS was not met[2,3]
- **MRD negativity in patients who achieved CR/CRi was a secondary endpoint[2]**
  - **Among patients achieving CR/CRi, BESPONSA achieved higher rates of MRD negativity** (78.4% [95% CI, 68.4-86.5]) compared with SC (28.1% [95% CI, 13.7-46.7])[2,a]
- **Few studies have investigated the significance of MRD in relapsed disease.**
  Post hoc analyses of INO-VATE ALL have been conducted to explore the impact of MRD status on outcomes in patients with R/R B-cell ALL who were treated with BESPONSA[1]

For the full post hoc analysis, see:
Jabbour E, Gökbuget N, et al. *Leuk Res.* 2020

[a] Results are from the phase 3 INO-VATE ALL study remission-analysis population, which included the first 218 patients who underwent randomization in the intention-to-treat population.[2]
ALL=acute lymphoblastic leukemia; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; MRD=minimal residual disease; OS=overall survival; R/R=relapsed/refractory; SC=standard chemotherapy.

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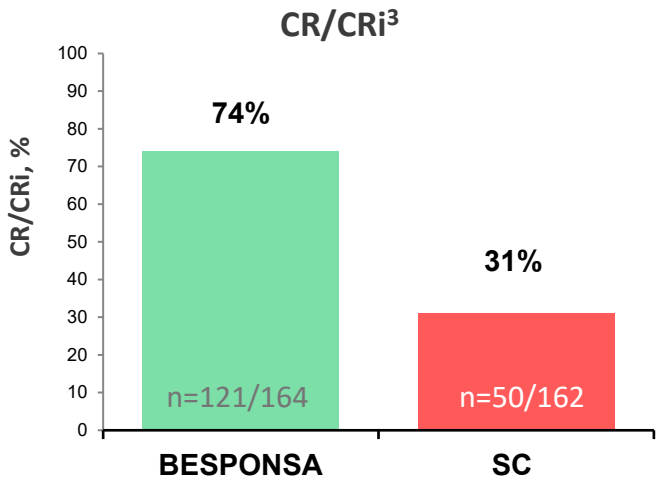
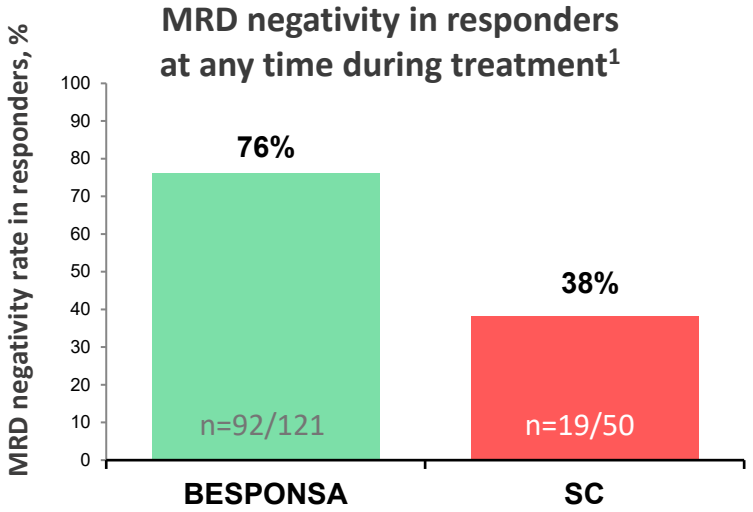
BESPONSA Achieved Higher Rates of CR/CRi and MRD-negativity Among Responders vs Standard Chemotherapy

- 326 patients underwent randomization in INO-VATE ALL with **164 patients receiving BESPONSA** and 162 patients receiving SC[1]





- In responders treated with BESPONSA, median age was 43 (range 20–78) years; 87 (72%) patients were treated as S1; 66 (55%) patients had first CR duration <12 months; and 20 patients (17%) had undergone prior SCT

ALL=acute lymphoblastic leukemia; CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; MRD=minimal residual disease; S1=salvage 1; SC=standard chemotherapy; SCT=stem cell transplantation.

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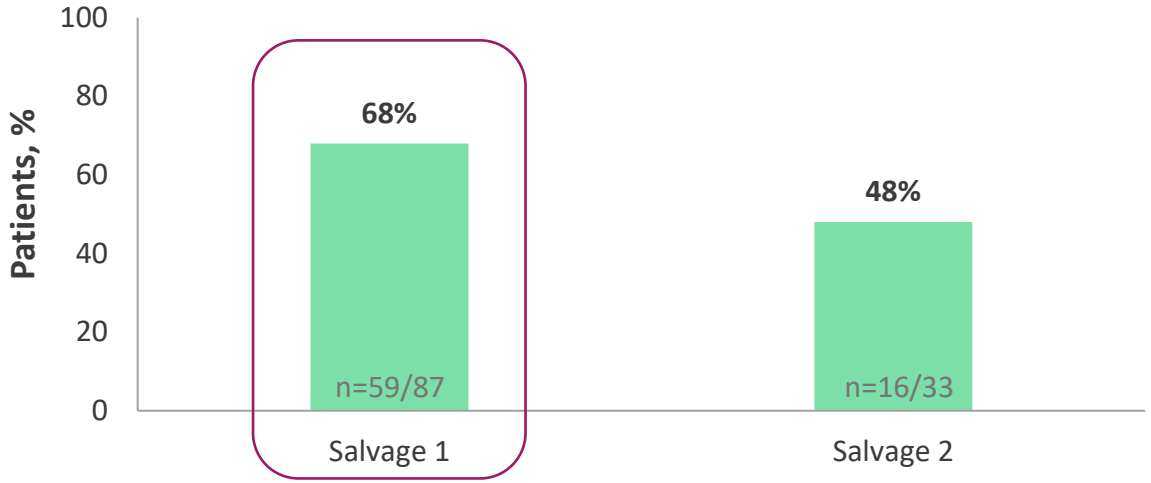
BESPONSA Was Associated With Higher MRD Negativity Rates When Used in First Salvage[1]

MRD status in responders at the end of treatment by salvage status[1,a]



- Among the 164 patients treated with BESPONSA who achieved CR/CRi (n = 121), **63% (n=76) remained MRD negative at the end of treatment**[1]
- **16 patients** who had achieved MRD-negative best response were no longer MRD negative at the end of treatment[1]

[a] One patient was listed as 'Other', defined as Salvage ≥ 3 or missing.
CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; MRD=minimal residual disease.

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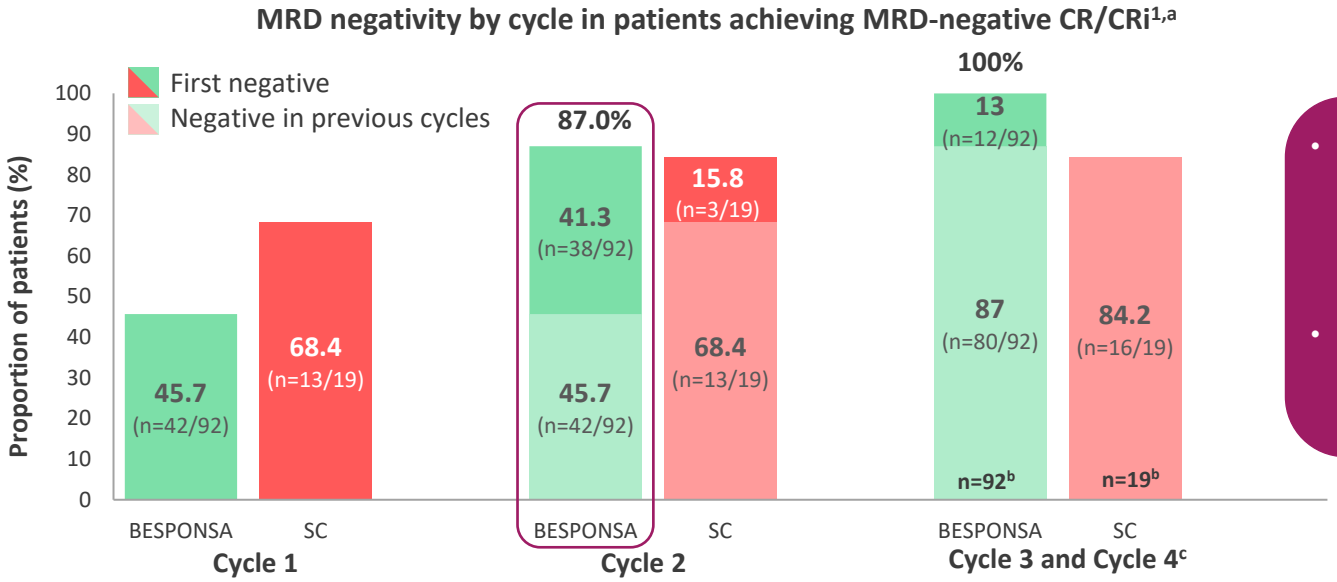
MRD Negativity Was Achieved in the Majority of Responders Within Two Cycles of BESPONSA[1]



- The majority of patients achieved first MRD-negative CR/CRi status after **one (45.7%; n=42/92)** or **two (41.3%; n=38/92) cycles with BESPONSA[1]**
- 80 of 92 **(87.0%)** patients achieving MRD-negative CR/CRi with BESPONSA did so in **≤ 2 cycles[1]**

- Another exploratory post hoc analysis is supportive of these data**, demonstrating a survival benefit (along with lower rates of post-HSCT NRM and VOD) with BESPONSA** in responders proceeding to HSCT **who received ≤ 2 cycles versus those who received > 2 cycles[5]**
- **These data reinforce the value of a second cycle of BESPONSA for patients proceeding to transplant[1,5]**

[a] MRD negativity is defined as minimum MRD < 0.01%.
[b] Total number of patients achieving MRD negativity.
[c] 3 patients (15.8%) in the SC arm achieved MRD negativity during follow-up.
CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; HSCT=hematopoietic stem cell transplantation; MRD=minimal residual disease; NRM=non-relapse mortality; SC=standard chemotherapy; VOD=veno-occlusive disease.

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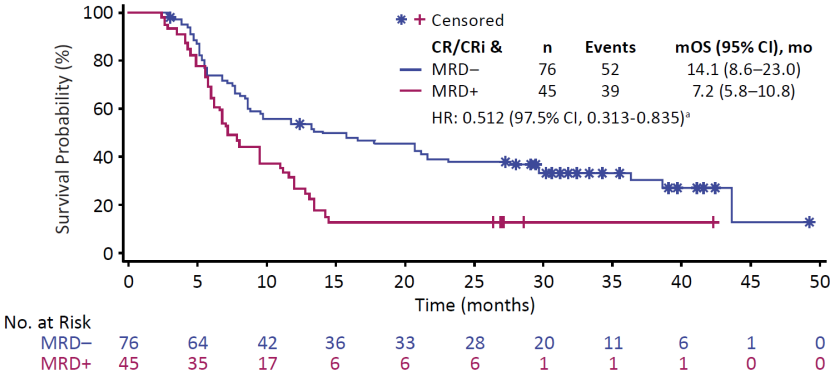
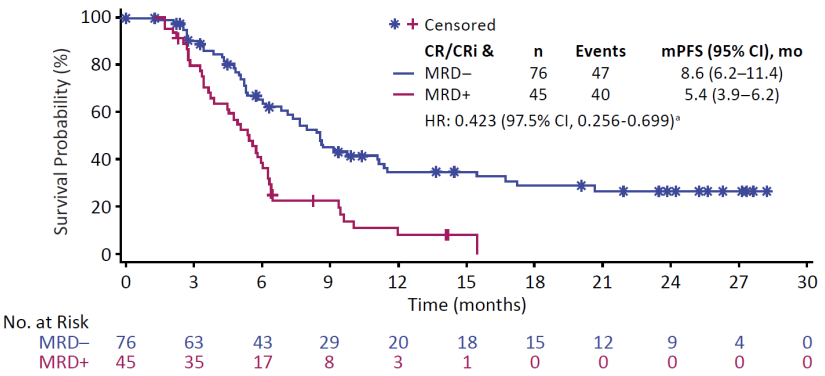
MRD Negativity Was Associated With an OS Benefit in Patients Treated With BESPONSA[1]

OS in patients treated with BESPONSA who were MRD-negative vs MRD-positive



PFS in patients treated with BESPONSA who were MRD-negative vs MRD-positive



Median OS was **14.1 months in MRD-negative patients** compared with **7.2 months** in patients who were MRD-positive[1]

Median PFS was **8.6 months in MRD-negative patients** compared with **5.4 months in** patients who were MRD-positive[1]

The primary endpoint of OS was not met.[2,3]

[a] Unstratified; reference group, CR/CRi and MRD-positive.

CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; HR=hazard ratio; mo=months; mOS=median overall survival; mPFS=median progression-free survival; MRD=minimal residual disease; MRD–/MRD+=minimal residual disease negative/positive; OS=overall survival; PFS=progression-free survival.

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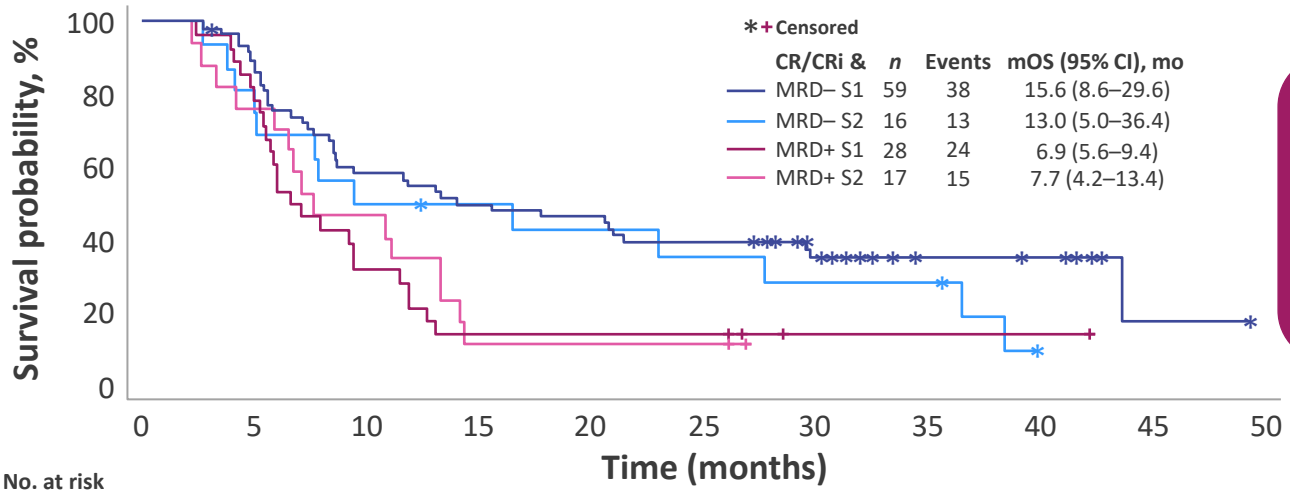
Survival Was Improved in MRD-negative Patients Treated With BESPONSA, And Was Even Greater in First Salvage[1]

OS in patients by MRD response stratified by salvage status



No. at risk											
MRD– S1	59	52	34	29	27	23	16	7	6	1	0
MRD– S2	16	12	8	7	6	5	4	4	0	0	0
MRD+ S1	28	22	9	4	4	4	1	1	1	0	0
MRD+ S2	17	13	8	2	2	2	0	0	0	0	0

Median OS was **15.6 months in MRD-negative patients in first salvage** compared with **6.9 months** in patients who were MRD-positive[1]

The primary endpoint of OS was not met.[2,3]

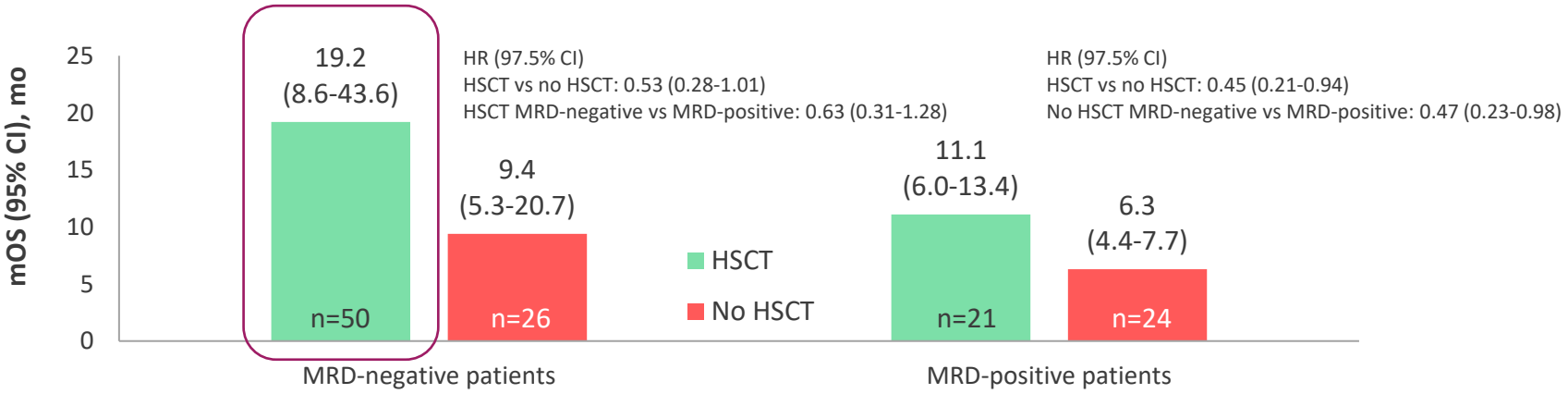
CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; mo=months; mOS=median overall; MRD=minimal residual disease; MRD–/MRD+=minimal residual disease negative/positive; OS=overall survival; S=salvage.

BESPONSA™ inotuzumab ozogamicin

Achieving MRD Negativity and Receiving HSCT Was Associated With Improved Survival[1]

- **Median OS** was **19.2 months** in MRD-negative patients **who underwent HSCT**, and was **6.3 months** in MRD-positive patients **who did not receive HSCT**[1]

OS by MRD and HSCT status[1]



The primary endpoint of OS was not met.[2,3]

- Although there was a higher frequency of early deaths post HSCT (at Day 100) in the BESPONSA arm, there was evidence of a late survival benefit for BESPONSA. If patients do proceed to HSCT, signs and symptoms of VOD/SOS should be monitored closely[4]

CI=confidence interval; HR=hazard ratio; HSCT=hematopoietic stem cell transplantation; mo=months; mOS=median overall survival; MRD=minimal residual disease; OS=overall survival; VOD=veno-occlusive disease.

BESPONSA™ inotuzumab ozogamicin

BESPONSA Safety Profile

Most common all-cause AEs (≥ 30% BESPONSA arm) with BESPONSA vs SC*[2]

AE, n (%)	BESPONSA (n = 139)	SC (n = 120)
Thrombocytopenia	62 (45)	73 (61)
Neutropenia	67 (48)	53 (44)
Anemia	42 (30)	64 (53)
Nausea	44 (32)	56 (47)

Tables adapted from Table S1, Kantarjian HM, et al. *N Engl J Med*. 2016;375(8):740-753 (suppl. appendix).

Most common grade ≥ 3 treatment-emergent AEs (≥ 10% BESPONSA arm) with BESPONSA vs SC*[2]

TEAE, n (%)	BESPONSA (n = 139)	SC (n = 120)
Thrombocytopenia	28 (20)	56 (47)
Neutropenia	47 (34)	43 (36)
Anemia	15 (11)	35 (29)
Febrile neutropenia	20 (14)	48 (40)
Leukopenia	21 (15)	31 (26)
Lymphopenia	15 (11)	22 (18)

BESPONSA significantly increased the risk of VOD/SOS above that of SC regimens in this patient population (reported in 23 [14%] patients in the BESPONSA arm of the pivotal clinical trial [n=164]). This risk was most marked in patients who underwent subsequent HSCT (18 [23%] out of 79 patients)[4]

Higher frequency of early death post HSCT: Although there was a higher frequency of early deaths post HSCT (at Day 100) in the BESPONSA arm, there was evidence of a late survival benefit for BESPONSA. If patients do proceed to HSCT, signs and symptoms of VOD/SOS should be monitored closely[4]

For more information on AEs, see the BESPONSA SmPC

*Data represent the safety population (data cut-off date of October 2, 2014); AEs were graded according to the NCI CTCAE Version 3.0.
AE=adverse event; ALL=acute lymphoblastic leukemia; HSCT=hematopoietic stem cell transplant; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; SC=standard chemotherapy; SOS=sinusoidal obstructive syndrome; TEAE=treatment-emergent adverse event; VOD=veno-occlusive disease.

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Conclusions

- BESPONSA was associated with **higher MRD negativity rates when used in first salvage** (68% vs. 48% in salvage 2)[1]
- MRD negative CR/CRi was **achieved in the majority (87.0%) of responders within 2 cycles** of BESPONSA[1]
- **MRD negativity was associated with an OS benefit** in patients treated with BESPONSA[1]
- **Survival was improved** in MRD-negative patients treated with BESPONSA, and was even greater in **first salvage**[1]
- **Achieving MRD negativity and receiving HSCT** was associated with **improved survival**[1]

BESPONSA achieved:

14.1-month
Median OS in MRD-negative patients and 7.2 months in MRD-positive patients[1,a]

15.6-month
Median OS in MRD-negative patients when used in first salvage and 6.9 months in MRD-positive patients when used in first salvage[1,a]

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[a] **The primary endpoint of OS was not met.**[2,3]
HSCT=hematopoietic stem cell transplantation; MRD=minimal residual disease; OS=overall survival; SC=standard chemotherapy.

BESPONSA™ inotuzumab ozogamicin

References

1. Jabbour E, Gökbuget N, Advani A, et al. Impact of minimal residual disease status in patients with relapsed/refractory acute lymphoblastic leukemia treated with inotuzumab ozogamicin in the phase III INO-VATE trial. *Leuk Res.* 2020;88:106283 and supplementary appendix.
2. 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 and supplementary appendix.
3. 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.
4. BESPONSA [summary of product characteristics]. Pfizer; 2020.
5. Cassaday RD, Marks DI, DeAngelo DJ, et al. Impact of number of cycles on outcomes of patients with relapsed or refractory acute lymphoblastic leukaemia treated with inotuzumab ozogamicin. *Br J Haematol*. 2020. doi: 10.1111/bjh.17029.

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.

BESPONSA™ inotuzumab ozogamicin