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NOW APPROVED by the European Medicines Agency

In combination with low-dose cytarabine, for the treatment of newly diagnosed **de novo or secondary** AML in adult patients who are not candidates for standard induction chemotherapy

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021

Pfizer

Date of preparation May 2021: PP-GDG-GLB-0077

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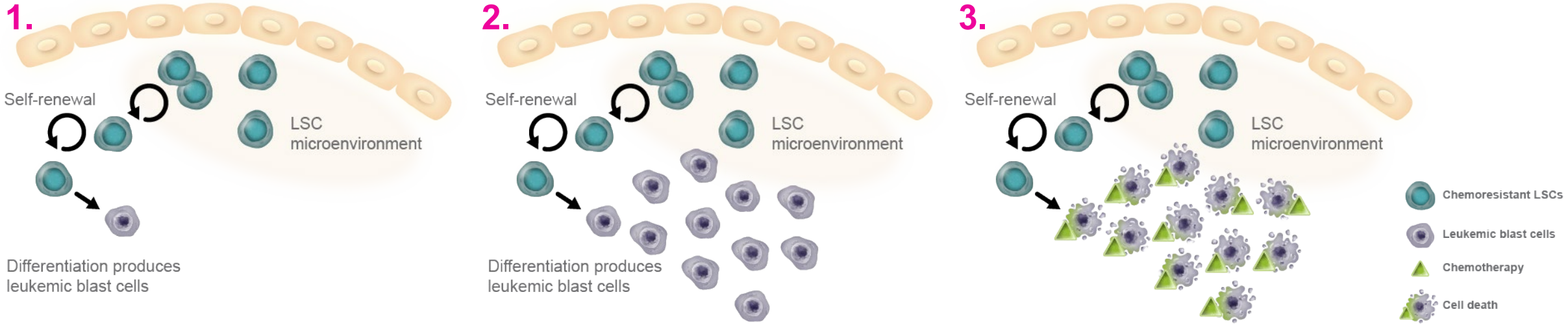
MECHANISM OF ACTION

Preclinical Evidence Suggests That Leukemic Stem Cells Can Be Resistant to Conventional Chemotherapies and Are a Potential Driver of Relapse



1. LSCs have the capacity to self-renew, differentiate and proliferate, and can reside in a dormant state for extended periods of time within the LSC microenvironment[1-5]
2. LSC differentiation produces leukemic blast cells which comprise the highly proliferative bulk AML population[5-6]
3. The dormancy and self-renewal properties of LSCs are thought to enable them to survive the effects of conventional chemotherapy, which primarily targets the proliferating leukemic blasts[1-6]

Chemoresistant LSCs can repopulate leukemic blast cells, and are a potential driver of relapse[1-7]

Increasing evidence suggests that targeting LSCs may improve outcomes for patients with AML[1-2, 5-7]

LSC=leukemic stem cell.

1. Wang X, et al. *Mol Cancer.* 2017;16(1):2. 2. Bahr C, et al. *EMBO J.* 2017;36(18):2667-2669. 3. Thomas D, et al. *Blood.* 2017;129(12):1577-1585. 4. Pollyea DA, et al. *Blood.* 2017;129(12):1627-1635. 5. Siveen KS, et al. *Mol Cancer.* 2017;16:13. 6. Pollyea DA, et al. *Hematologica.* 2014;99(8):1277-1284. 7. Shlush LI, *et al. Nature.* 2017;547(7661):104-108.

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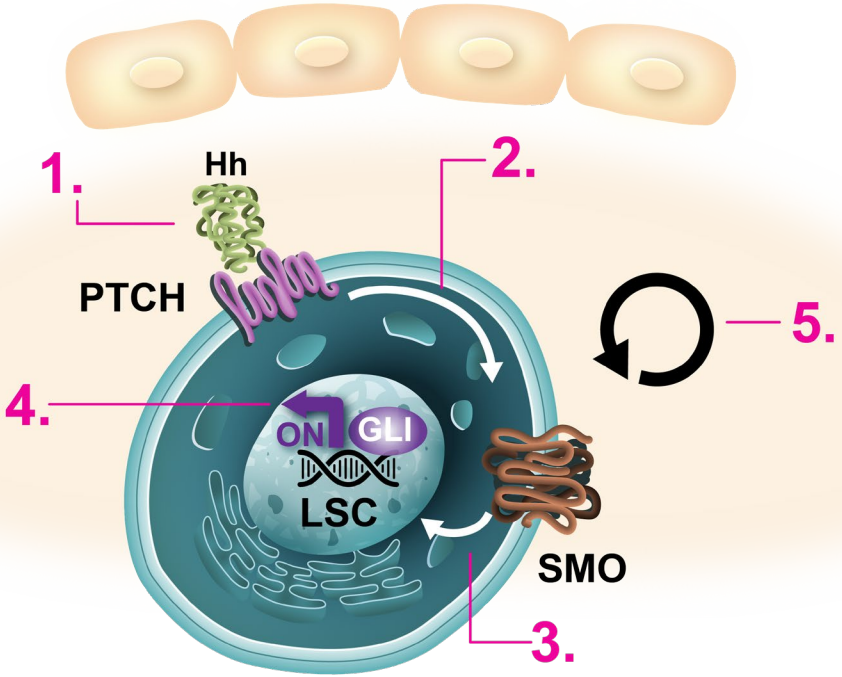
Preclinical Research Suggests That the Hedgehog Pathway Plays a Role in Regulating the Self-renewal and Dormancy of Leukemic Stem Cells in Some Hematologic Malignancies[1-3]

- The Hh signaling pathway is a major regulator of cell differentiation and proliferation.[1,4-5] This pathway plays a key role in embryogenesis but is largely inactive in adults[1,2]
- Preclinical research has suggested that inappropriate activation of the Hh pathway is associated with a variety of cancers, including hematologic malignancies[2,4,6]



The Hh pathway: Active state[1,3,4,6]

1. Extracellular Hh ligand binds to PTCH on the stem cell surface
2. PTCH releases suppression of SMO
3. SMO activation leads to accumulation of GLI transcription factors in the nucleus
4. GLI activates transcription of target genes involved in stem self renewal
5. This results in LSC self-renewal

GLI=glioma-associated oncoprotein; Hh=hedgehog; LSC=leukemic stem cell; PTCH=patched; SMO=smoothened.

1. Amakye D, et al. *Nat Med*. 2013;19(11):1410-1422. 2. Justilien V, et al. *Clin Cancer Res*. 2015;21(3):505-513. 3. Fukushima N, et al. *Cancer Sci*. 2016;107(10):1422-1429.
4. Rimkus TK, et al. *Cancers (Basel)*. 2016;8(2):e22. 5 Varjosalo M, et al. *Genes Dev*. 2008;22(18):2454-2472. 6. Cochrane CR, et al. *Cancers (Basel)*. 2015;7(3):1554-1585.

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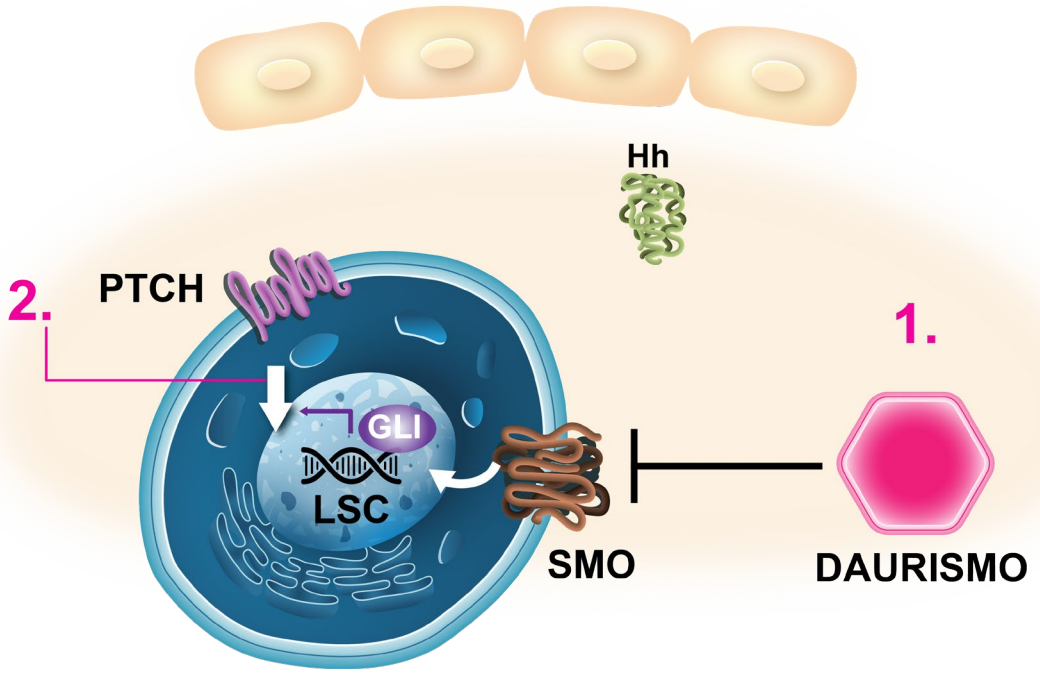
DAURISMO Inhibits the SMO Receptor, a Key Mediator of Hedgehog Pathway Signaling in Leukemic Stem Cells

In preclinical studies, DAURISMO has been shown to inhibit LSC dormancy and limit LSC self-renewal[1]

The mechanism of action of the combination is not fully understood



DAURISMO-mediated inhibition of the Hh pathway[1,2]

1. DAURISMO binds to and inhibits SMO[1,2]
2. Inhibition of SMO results in decreased GLI transcription factor activity and downstream pathway signalling[2]

Preclinical evidence suggests that DAURISMO-mediated inhibition of SMO results in LSC going from a less active state to active division, which may make them become more sensitive to chemotherapy[1]

Based on preclinical evidence, DAURISMO and LDAC are thought to work synergistically, with DAURISMO sensitizing LSCs to the chemotherapeutic effects of LDAC[1,2]

GLI=glioma-associated oncoprotein; Hh=hedgehog; LDAC=low-dose cytarabine; LSC=leukemic stem cell; PTCH=patched; SMO=smoothened.

1. Fukushima N, et al. *Cancer Sci*. 2016;107(10):1422-1429. 2. Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021.

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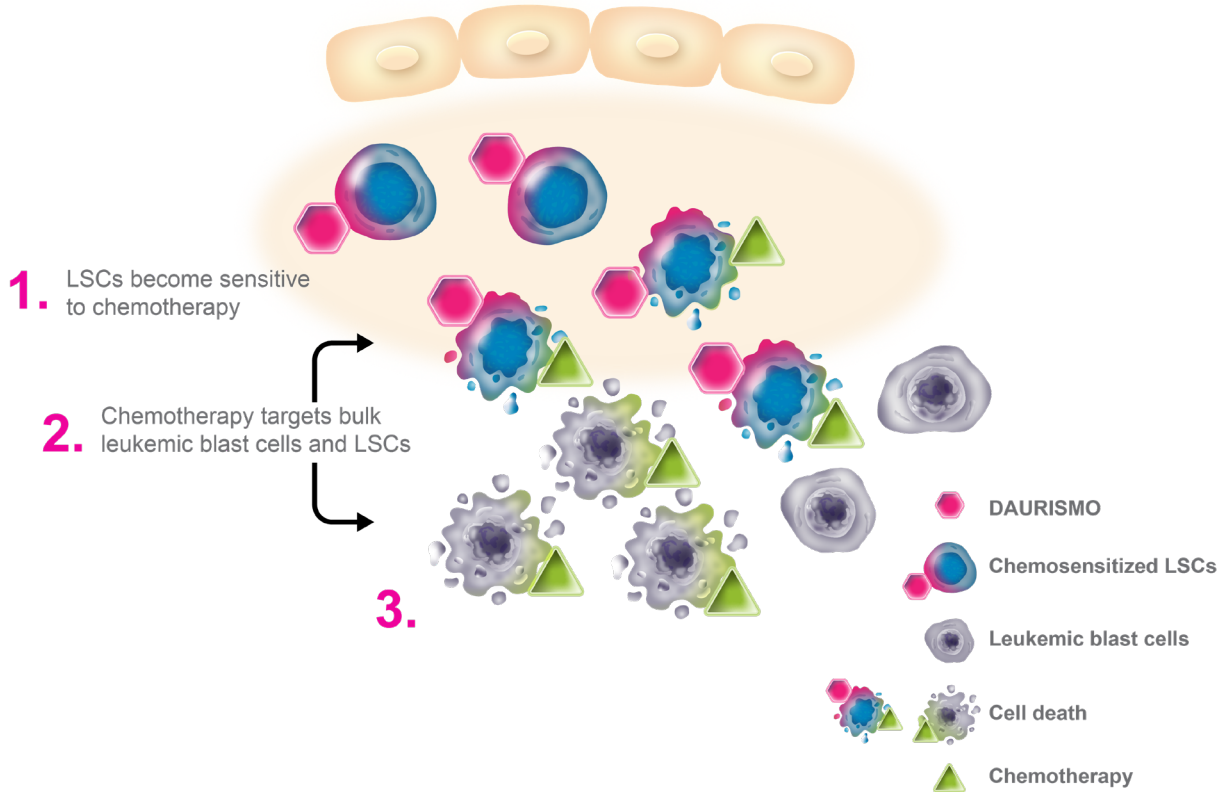

Based on preclinical evidence, DAURISMO and LDAC are thought to work synergistically:[1,2]

1. DAURISMO chemosensitizes LSCs and limits LSC self-renewal[1,2]
2. Chemotherapy targets both the bulk leukemic blast cells and the sensitized LSCs[1,3]
3. This results in cell death[1,3]

In a preclinical model of AML, DAURISMO in combination with LDAC inhibited tumor growth to a greater extent than DAURISMO or LDAC alone[2]

Hh=hedgehog; LDAC=low-dose cytarabine; LSC=leukemic stem cell; SMO=smoothened.

1. Fukushima N, et al. *Cancer Sci*. 2016;107(10):1422-1429. 2. Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021. 3. Siveen KS, et al. *Mol Cancer*. 2017;16:13.

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BRIGHT AML 1003: STUDY DESIGN

BRIGHT AML 1003: A Phase 2 Open-label, Randomized, Multicenter Study That Evaluated DAURISMO + LDAC in Patients Who Were Not Eligible for Intensive Chemotherapy

Study design[1,2]

Eligibility criteria

Adults aged ≥ 55 years[2] with previously untreated de novo or sAML* and one or more of the following criteria:

- ≥ 75 years of age
- Severe cardiac disease
- ECOG PS = 2
- Serum creatinine > 1.3 mg/dL

Randomization 2:1

DAURISMO + LDAC (n = 78)
DAURISMO 100 mg orally once daily on Days 1-28 + LDAC 20 mg twice daily subcutaneously on Days 1-10 of each 28-day cycle

LDAC alone (n = 38)
20 mg twice daily subcutaneously on Days 1-10 of each 28-day cycle

AML endpoint†: OS[2]

- Patients were stratified at randomization by cytogenetic risk (good/intermediate or poor)[1,2]
- Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent[2]

*sAML included AML evolving from MDS or other AHD and AML after previous cytotoxic therapy or radiation.[2]
†DAURISMO + LDAC was investigated in a total of 132 patients, which included 116 patients with previously untreated de novo or sAML who were not eligible to receive intensive chemotherapy.[1] The efficacy results presented here are from the AML population only.
AHD=antecedent hematologic disorder; ECOG PS=Eastern Cooperative Oncology Group performance status; LDAC=low-dose cytarabine; MDS=myelodysplastic syndrome; OS=overall survival; sAML=secondary AML.
1. Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021. 2. Cortes JE, et al. *Leukemia.* 2019;33(2):379-389.

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Most Patients in the BRIGHT AML 1003 Study Were Aged ≥ 75 Years and Had Comorbidities That Made Them Difficult to Treat

Baseline demographic and disease characteristics		DAURISMO + LDAC (n = 78)	LDAC alone (n = 38)
Age[1] (years)	Median (range)	77 (64-92)	76 (58-83)
	≥ 75 years, n (%)	48 (62)	23 (61)
Sex[1], n (%)	Male	59 (76)	23 (61)
	Female	19 (24)	15 (39)
Disease history[1], n (%)	De novo AML	38 (49)	18 (47)
	sAML	40 (51)	20 (53)
	Prior HMA use (DEC or AZA)	11 (14)	6 (16)
ECOG PS[1†], n (%)	0-1	36 (46)	20 (53)
	2	41 (53)	18 (47)
ELN risk stratification for AML[2], n (%)	Favorable	5 (6)	3 (8)
	Intermediate-I	27 (35)	11 (29)
	Intermediate-II	21 (27)	8 (21)
	Adverse	25 (32)	16 (42)
Cytogenetic risk status[1], n (%)	Good/intermediate	49 (63)	21 (55)
	Poor	29 (37)	17 (45)
Medical history[1], n (%)	Baseline severe cardiac disease	52 (67)	20 (53)
	Baseline serum creatinine > 1.3 mg/dL	15 (19)	5 (13)

Patient characteristics were generally well balanced across the treatment arms[1,2]*

- **52%** of patients had sAML[1]
- **15%** of patients had received prior AZA or DEC therapy[1]
- The majority of patients (**51%**) had an ECOG PS of 2[1]
- **35%** of patients had adverse-risk disease[2]

*Except for sex and severe cardiac disease, using a cut-off criterion of > 10% difference between treatment arms. †Baseline ECOG PS was not reported for one patient in the DAURISMO + LDAC arm.
AZA=azacitidine; DEC=decitabine; ECOG PS=Eastern Cooperative Oncology Group performance status; ELN=European LeukeimaNet; HMA=hypomethylating agent; LDAC=low-dose cytarabine; sAML=secondary AML.

1. Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021. 2. Cortes JE, et al. *Leukemia.* 2019;33(2):379-389.

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At Baseline, Two Thirds of Patients Met ≥ 2 Criteria for Nonintensive Treatment

Objective criteria were used to define patients who were eligible for nonintensive treatment. To be eligible for study treatment, patients had to meet ≥ 1 of these criteria[1]

Baseline demographic and disease characteristics	DAURISMO + LDAC (n = 78)	LDAC alone (n = 38)
Criteria for non-intensive treatment[2], n (%)		
Aged ≥ 75 years	48 (62)	23 (61)
ECOG PS = 2	41 (53)	18 (47)
Serum creatinine > 1.3 mg/dL	15 (19)	5 (13)
Severe cardiac disease	52 (67)	20 (53)

All patients included in BRIGHT AML 1003 were not eligible for intensive chemotherapy based on ≥ 1 of these criteria[2,3]

- **61%** of patients were aged ≥ 75 years
- More than half (**51%**) of patients had ECOG PS 2
- Baseline serum creatinine was > 1.3 mg/dL in **17%** of patients
- Most patients (**62%**) had severe cardiac disease

Patients enrolled in the BRIGHT AML 1003 study had a very poor prognosis[1,4]

ECOG PS=Eastern Cooperative Oncology Group performance status; LDAC=low-dose cytarabine.

1. Cortes JE, et al. *Leukemia.* 2019;33(2):379-389. 2. Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021.
3. Wolska-Washer A, et al. *Future Oncol.* 2019;15(28):3219-3232. 4. Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194.

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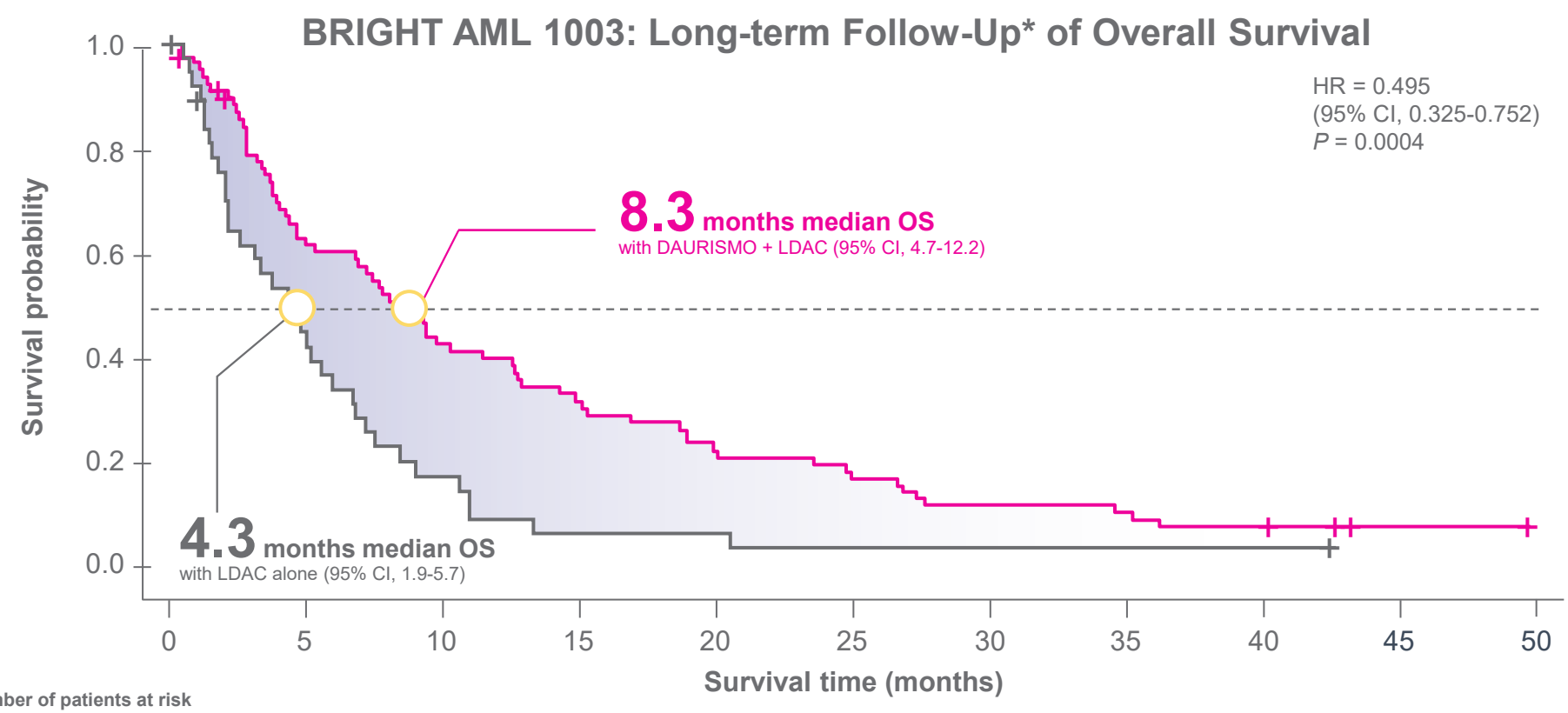
BRIGHT AML 1003: EFFICACY

Adding DAURISMO to LDAC Significantly Improved Median OS vs LDAC Alone



Median OS was nearly doubled in patients who received DAURISMO + LDAC vs LDAC alone

8.3 months (95% CI, 4.7-12.2) vs
4.3 months (95% CI, 1.9-5.7)
HR 0.495; ***P* = 0.0004**

1-year OS rate was > 4-fold higher with DAURISMO + LDAC vs LDAC alone

39.4% (95% CI, 28.3-50.3)
versus
8.4% (95% CI, 2.2-20.1)

- Efficacy was established by an improvement in OS in the DAURISMO + LDAC arm

++ censored. Data cut-off October 11, 2018.
*Approximately 20 additional months of follow-up from the primary completion date.
CI=confidence interval; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival.
Heuser M, et al. *Ann Hematol*. 2021;100(5):1181-1194.

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DAURISMO + LDAC Offers a Longer Median OS for Patients With Secondary AML Compared With LDAC Alone

Analyses of OS in the subgroup of patients with sAML were exploratory without adequate power to detect the difference between arms, and should be interpreted with caution

OS[1]	DAURISMO + LDAC (n = 78)	LDAC alone (n = 38)
sAML		
n	40	20
Median survival, months (95% CI)	9.1 (4.4-16.5)	4.1 (1.5-6.4)
HR (95% CI)*	0.287 (0.151-0.548)	
P-value†	**< 0.0001**	

- Outcomes for patients with sAML are poor. sAML is biologically distinct from de novo AML, associated with inferior OS, and is frequently resistant to conventional chemotherapy[2]

Median OS in patients with sAML who received DAURISMO + LDAC was more than doubled compared with patients who received LDAC alone[1]

9.1 months (95% CI, 4.4-16.5) vs
4.1 months (95% CI, 1.5-6.4)
HR 0.287; ***P* < 0.0001**

*Hazard ratio based on the cox proportional hazards model stratified by prognosis stratum; †1-sided *P*-value from stratified log-rank test based on cytogenetic risk.
CI=confidence interval; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival; sAML=secondary AML.
1. Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021. 2. Kuykendall MD, et al. *ASCO Educational Book.* 2018;38:555-573.

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DAURISMO + LDAC Improved Survival in Patients With De Novo AML Compared With LDAC Alone

Analyses of OS in the subgroup of patients with de novo AML were exploratory without adequate power to detect the difference between arms, and should be interpreted with caution

OS	DAURISMO + LDAC (n = 78)	LDAC alone (n = 38)
De novo AML		
n	38	18
Median survival, months (95% CI)	6.6 (3.7-12.4)	4.3 (1.3-10.7)
HR (95% CI)*	0.670 (0.362-1.239)	
P-value†	**0.0991**	

Median OS was numerically improved in patients with de novo AML who received DAURISMO + LDAC vs LDAC alone

6.6 months (95% CI, 3.7-12.4) vs
4.3 months (95% CI, 1.3-10.7)
HR 0.670; *P* = 0.0991

*Hazard ratio based on the cox proportional hazards model stratified by prognosis stratum; †1-sided *P*-value from stratified log-rank test based on cytogenetic risk.
CI=confidence interval; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival.
Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021

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Adding DAURISMO to LDAC Improved OS in Patients With Good/Intermediate Cytogenetic Risk vs LDAC Alone

OS	DAURISMO + LDAC (n = 78)	LDAC alone (n = 38)
Good/intermediate cytogenetic risk group		
n	49	21
Median survival, months (95% CI)	11.1 (7.1-14.9)	4.4 (1.8-8.7)
HR (95% CI)*	0.417 (0.233-0.744)	
P-value†	0.0011	
Poor cytogenetic risk group		
n	29	17
Median survival, months (95% CI)	4.4 (3.4-9.1)	3.1 (1.1-6.4)
HR (95% CI)*	0.528 (0.273-1.022)	
P-value†	0.0269	

DAURISMO + LDAC demonstrated longer OS for patients with good/intermediate cytogenetic risk compared with LDAC alone

Median OS in patients with good/intermediate cytogenetic risk who received DAURISMO + LDAC was > 2-fold greater than in patients who received LDAC alone
11.1 months (95% CI, 7.1-14.9) vs
4.4 months (95% CI, 1.8-8.7); HR 0.417; ***P* = 0.0011**

There is a slight imbalance toward good/intermediate-risk cytogenetics in the DAURISMO + LDAC arm versus the LDAC alone arm. Analyses of OS in the subgroup of patients with good/intermediate or poor cytogenetics were exploratory without adequate power to detect the difference between arms. The HRs associated with these analyses are unreliable due to the small sample size

*Hazard ratio based on the cox proportional hazards model stratified by prognosis stratum; †1-sided *P*-value from stratified log-rank test based on cytogenetic risk.
CI, confidence interval; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival.
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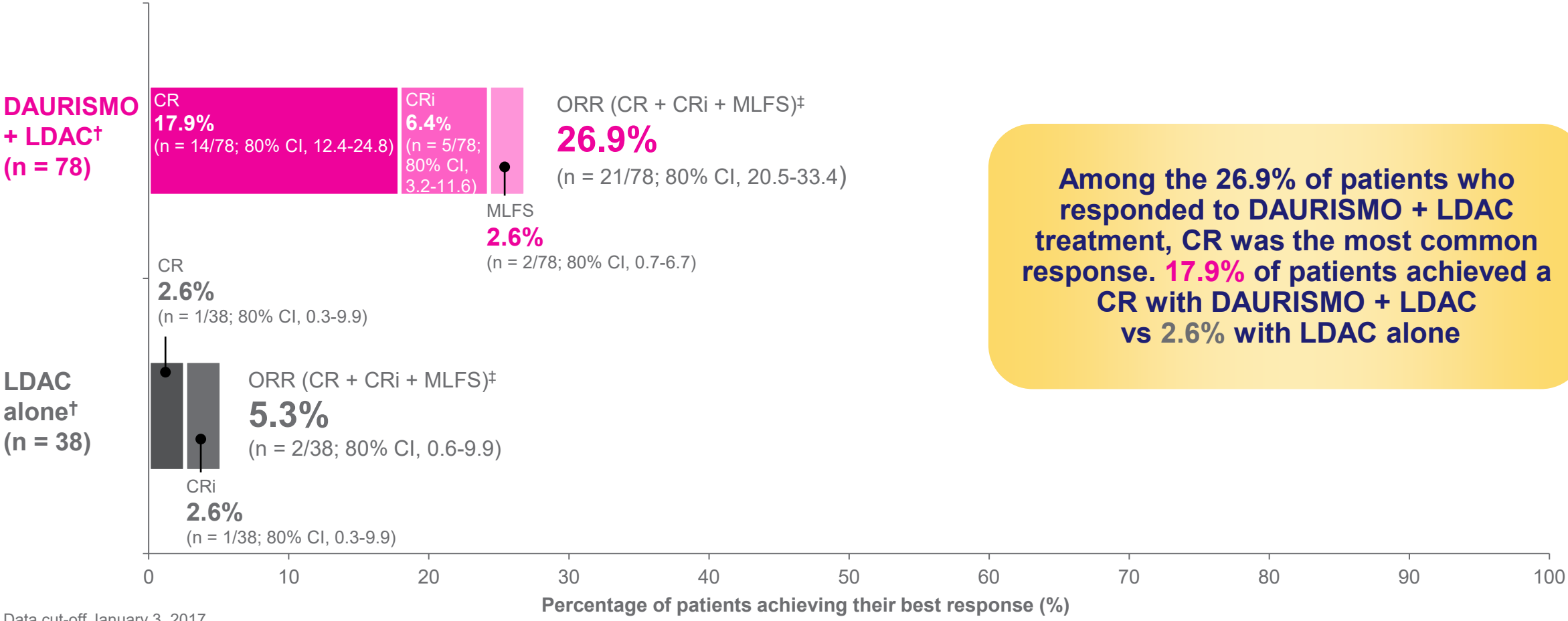
DAURISMO + LDAC Achieved Higher Overall Response Rates vs LDAC Alone*



Among the 26.9% of patients who responded to DAURISMO + LDAC treatment, CR was the most common response. 17.9% of patients achieved a CR with DAURISMO + LDAC vs 2.6% with LDAC alone

Data cut-off January 3, 2017.

*Using exact method based on binomial distribution and CIs expressed in percentages. †24 and 16 patients in the DAURISMO + LDAC and LDAC alone arms, respectively, were not evaluable for response. In addition to seven patients who were randomized but not treated, the majority of patients in both arms who were not evaluable for disease response had an AE or died prior to on-study bone marrow evaluation. ‡Using normal approximation for further endpoints of interest and CIs expressed in percentages.

AE=adverse event; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete blood count recovery; LDAC=low-dose cytarabine; MLFS=morphologic leukemia-free state; ORR=overall response rate.

Cortes JE, et al. *Leukemia.* 2019;33(2):379-389 (and supplement).

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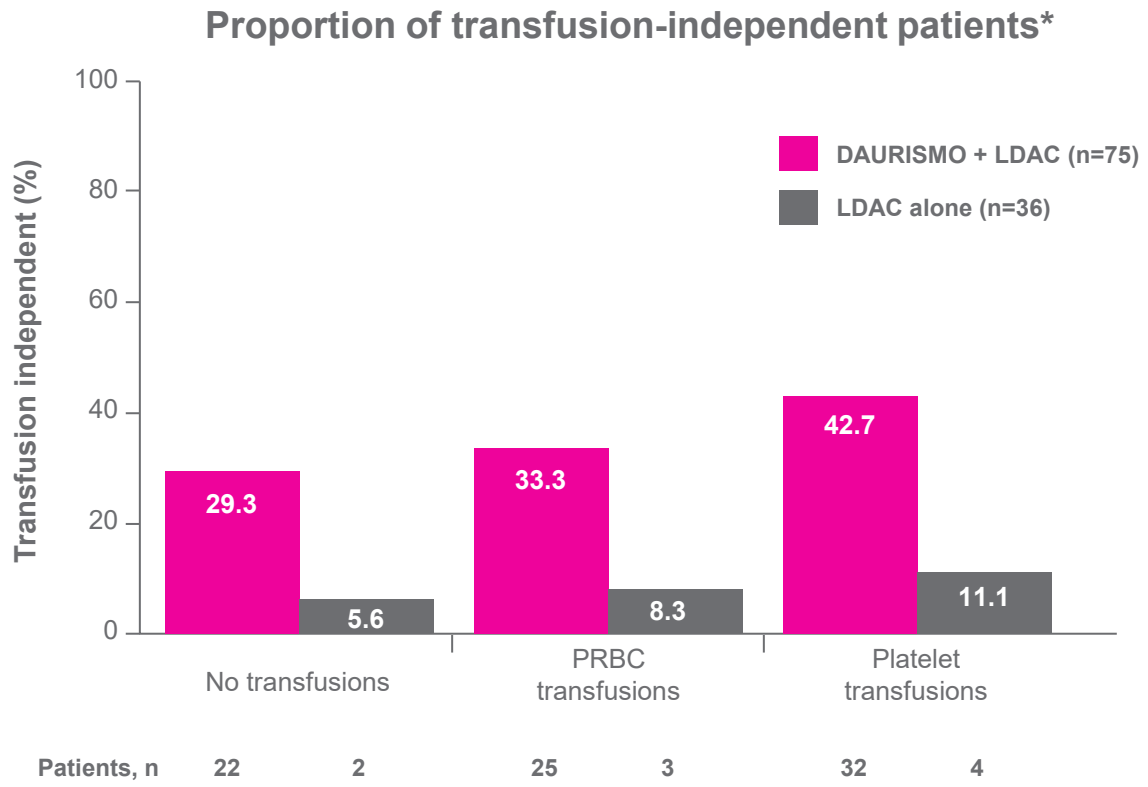
BRIGHT AML 1003: QUALITY OF LIFE

Higher Rates of Transfusion-Independence Were Reported With DAURISMO + LDAC vs LDAC Alone

Analyses were post hoc and not powered to detect statistical significance. Small patient numbers and lack of multiplicity adjustments can be a limitation of these analyses



DAURISMO reduced transfusion requirements in patients with AML who were not suitable for intensive chemotherapy

Transfusion independence was achieved by 29.3% of patients receiving DAURISMO + LDAC and 5.6% of patients receiving LDAC alone

Data cut-off October 11, 2018.
*Required no PRBC or platelet transfusions for ≥ 8 weeks.
AML=acute myeloid leukaemia; LDAC=low-dose cytarabine; PRBC=packed red blood cell.
Heuser M *et al*. *Ann Hematol* 2021;100(5):1181-1194.

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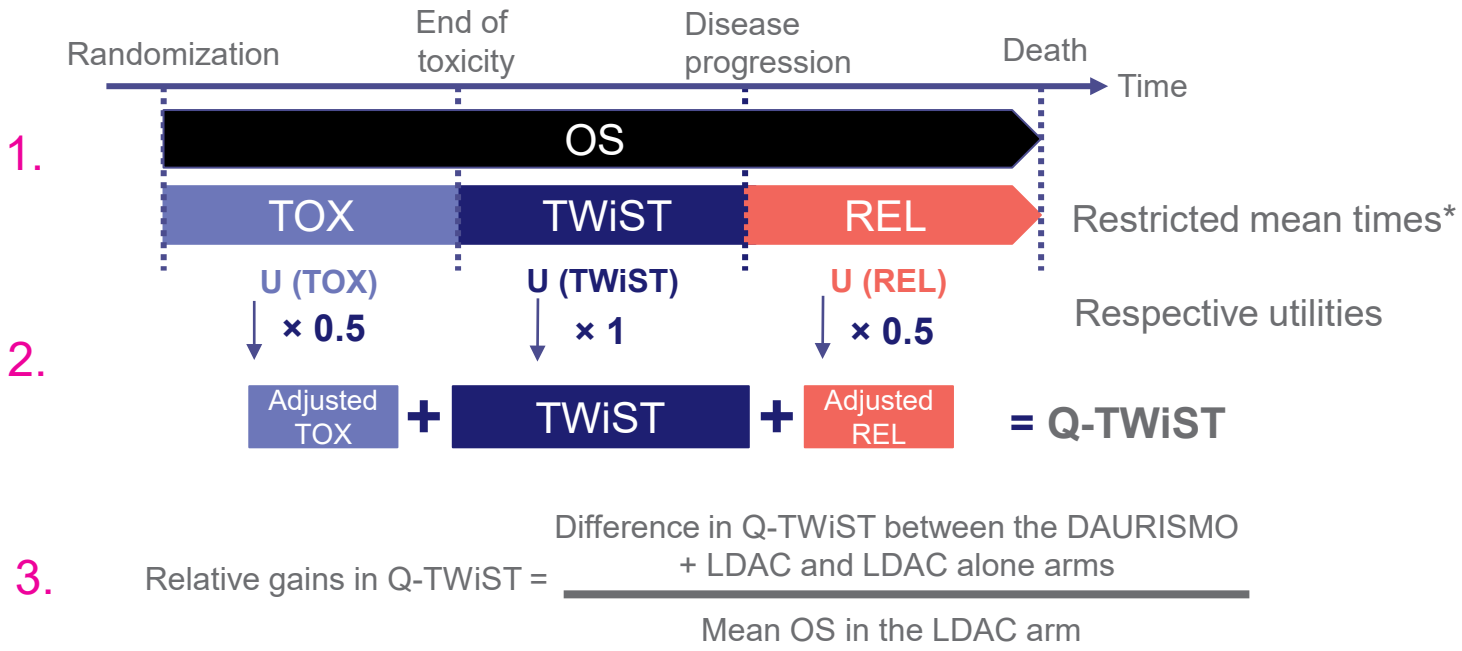
Q-TWiST Analysis Was Used to Estimate the Quality-Adjusted Survival of DAURISMO + LDAC in BRIGHT AML 1003

- The Q-TWiST method provides an integrated measurement of both quality and quantity of survival that is used to evaluate the trade-offs between toxicity and survival.[1-3] It is widely used to estimate the overall benefit of oncology treatments for patients with cancer,[1,3] such as AML,[4] CLL,[5,6] and other hematologic malignancies[7-9]

Q-TWiST method overview[1,10]



1. OS data from each treatment arm* of the BRIGHT AML 1003 study were partitioned into three different health states[1]

   TOX: Time with any Grade ≥ 3 TEAE†
   TWiST: Time without symptoms of disease progression or toxicity
   REL: Time after treatment discontinuation due to insufficient clinical response, relapse, or death‡

2. Q-TWiST was calculated by multiplying the restricted mean time in each state by respective utilities and then summing the adjusted time[1,2,10]

3. Relative gains in Q-TWiST were calculated by dividing the difference in Q-TWiST between the DAURISMO + LDAC and LDAC alone arms by the mean OS in the LDAC alone arm[1]

*OS was restricted to a follow-up of 20 months. †For TOX, the duration of an AE was calculated as the difference between the AE start and end dates. If the end date occurred on the same date as or after REL, the end date for the AE was imputed as the REL date and was counted as an event, in order to not double count time after REL. A patient in this circumstance would have no TWiST, by definition. AEs with overlapping duration were also truncated; only unique AE days were counted towards TOX to avoid redundancy or double counting. ‡Patients who discontinued treatment for other reasons (including AEs) were censored at the date of discontinuation unless death occurred ≤ 28 days of discontinuation.
AE=adverse event; CLL=chronic lymphocytic leukemia; LDAC=low-dose cytarabine; OS=overall survival; Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity; REL=time after treatment discontinuation due to insufficient clinical response, relapse, or death; TEAE=treatment-emergent adverse event; TOX=time with any Grade ≥ 3 TEAE; TWiST=time without symptoms of disease progression or toxicity; U=utility.

1. Solem C, et al. *Cancer* 2020;126(19):4315-4321. 2. Husson O and Jones R. *Cancer.* 2017;123(12):2200-2202. 3. Patil S, et al. *Br J Cancer.* 2012;106(10):1587-1590. 4. Parsons S, et al. *J Clin Oncol.* 1999;17(7):2144-2152. 5. Levy V, et al. *J Clin Epidemiol.* 2001;54(7):747-754. 6. Tedeschi A, et al. *Blood.* 2017;130(supplement 1):1746. 7. Marcus R, et al. *Br J Cancer.* 2010;102(1):19-22. 8. Porcher R, et al. *Qual Life Res.* 2002;11(2):91-99. 9. Mounier N, et al. *Blood.* 2000;95(12):3687-3692. 10. Tabernero J, et al. *ESMO Open.* 2017;2(5):e000284.

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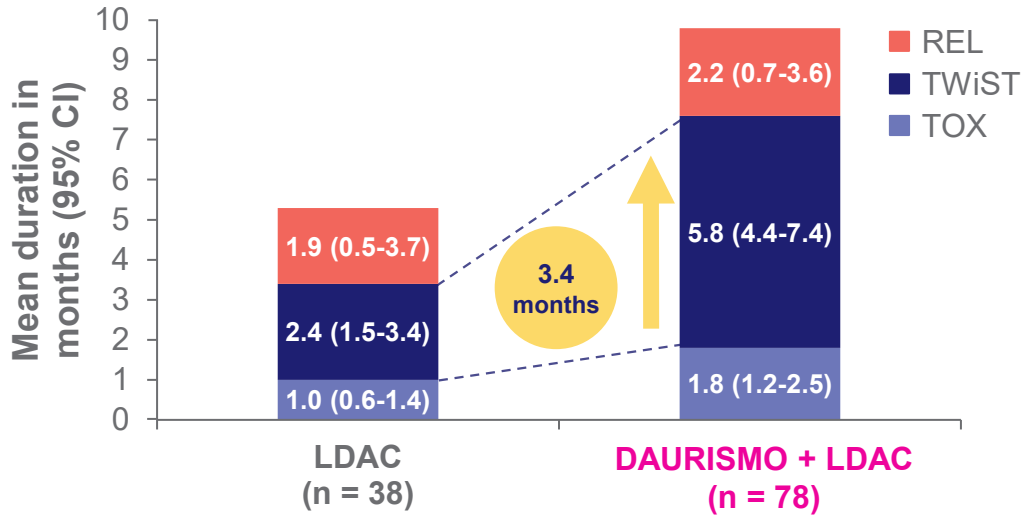
DAURISMO + LDAC Achieves Significantly Increased Quality Adjusted Overall Survival

BRIGHT AML 1003 Q-TWiST analysis

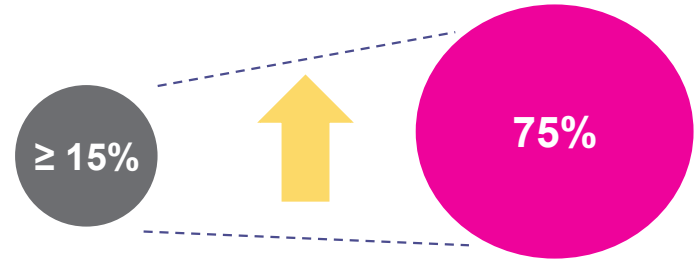
Compared to patients who received LDAC alone, patients who received DAURISMO + LDAC had a significantly longer mean time without symptoms of disease or toxicity (TWiST) of 3.4 months (95% CI, 1.8-5.2 months)[1]

Mean duration of health states*



Q-TWiST was 4 months (95% CI, 2.1-5.8 months) longer for DAURISMO + LDAC vs LDAC alone, which translated into a 75% relative improvement in quality-adjusted survival, relative to LDAC alone. This exceeded the clinically meaningful threshold of ≥ 15%, suggesting that the benefits of DAURISMO + LDAC vs LDAC alone outweigh the risks[1]

Relative gains in quality-adjusted survival



Adapted from Solem C, et al. *Cancer.* 2020;17(5):356-365. *OS restricted to a follow-up of 20 months.
CI=confidence interval; LDAC=low-dose cytarabine; OS=overall survival; Q-TWiST=quality-adjusted time without symptoms of disease progression or toxicity; REL=time after treatment discontinuation due to insufficient clinical response, relapse or death; TOX=time with any Grade ≥ 3 TEAE; TWiST=time without symptoms of disease progression or toxicity.
1. Solem C, et al. *Cancer* 2020;126(19):4315-4321. 2. Revicki DA, et al. *Qual Life Res.* 2006;15(3):411-423.

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SAFETY PROFILE

Summary of DAURISMO Safety Profile

ARs reported in clinical studies[1,*]

System organ class	Preferred term	All Grade	
		All Grades (%)	Grade ≥ 3 (%)
Infections and infestations	Pneumonia	28.5	23.8
	Sepsis	5.9	5.9
	Urinary tract infection	5.9	1.1
Blood and lymphatic system disorders	Anemia	45.2	41.6
	Febrile neutropenia	35.7	35.7
	Thrombocytopenia	30.9	30.9
	Neutropenia	15.4	11.9
Metabolism and nutrition disorders	Decreased appetite	33.3	3.5
Nervous system disorders	Dysgeusia	26.1	0.0
Cardiac disorders	Electrocardiogram QT prolonged	8.3	3.5
	Atrial fibrillation	7.1	2.3
Vascular disorders	Hemorrhages	45.2	11.9
Respiratory, thoracic, and mediastinal disorders	Dyspnea	25.0	7.1

System organ class	Preferred term	All Grade	
		All Grades (%)	Grade ≥ 3 (%)
Gastrointestinal disorders	Nausea	35.7	2.3
	Diarrhea	28.5	4.7
	Constipation	25.0	1.1
	Abdominal pain	25.0	0.0
	Vomiting	21.4	2.3
	Stomatitis	4.7	0.0
Skin and subcutaneous tissue disorders	Rash	25.0	2.3
	Alopecia	10.7	0.0
Musculoskeletal and connective tissue disorders	Muscle spasms	30.9	5.9
	Arthralgia	11.9	0.0
General disorders and administration site conditions	Fatigue	30.9	14.2
	Weight decreased	20.2	2.3
	Pyrexia	29.7	2.3
	Edema peripheral	26.1	0.0
Investigations	Platelet count decreased	16.6	16.6
	White blood cell count decreased	15.4	13.0
	Neutrophil count decreased	13.0	13.0

The most frequently reported ARs (≥ 30%) in patients receiving DAURISMO were anemia (45.2%), hemorrhages (45.2%), febrile neutropenia (35.7%), nausea (35.7%), decreased appetite (33.3%), fatigue (30.9%), muscle spasms (30.9%), and thrombocytopenia (30.9%)[1]

Distinct on-target Hh inhibitor-associated ARs[2] (≥ 10%) reported in patients who received DAURISMO were muscle spasms (30.9%), dysgeusia (26.1%), and alopecia (10.7%)[1]

*The overall safety profile of DAURISMO is based on data from clinical studies, including BRIGHT AML 1003.
AR=adverse reaction; Hh=hedgehog.
1. Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021. 2. Lacouture ME, et al. *Oncologist.* 2016;21(10):1218-1229.

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Treatment Duration, Modification, and Discontinuations

ARs reported in clinical studies[1,*]

- The median exposure to DAURISMO across the dataset was 75.5 days

Event	DAURISMO
Most frequently reported ARs leading to dose reduction, %	
Muscle spasms	4.7
Fatigue	3.5
Febrile neutropenia	3.5
Anemia	2.3
Thrombocytopenia	2.3
Electrocardiogram QT prolonged	2.3

The most frequently reported ARs leading to permanent discontinuation in patients receiving DAURISMO were pneumonia (5.9%), febrile neutropenia (3.5%), and nausea (2.3%)[1]

The safety profile of DAURISMO + LDAC is consistent with toxicities reported for elderly patients receiving chemotherapy and toxicities reported for other marketed smoothened inhibitors[2]

*The overall safety profile of DAURISMO is based on data from clinical studies, including BRIGHT AML 1003.
AR=adverse reaction; MDS=myelodysplastic syndrome.
1. Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021. 2. Cortes JE, et al. *Leukemia.* 2019;33(2):379-389.

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DAURISMO Special Warnings and Precautions for Use (1/3)

Embryo-fetal toxicity

- Based on its mechanism of action and findings from animal embryo-fetal developmental toxicity studies, DAURISMO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the fetus
- DAURISMO should not be used during pregnancy and in women of childbearing potential not using contraception.
  The pregnancy status of female patients of childbearing potential should be verified prior to initiating treatment with DAURISMO.
  Women of childbearing potential should be advised to always use effective contraception during treatment with DAURISMO and for at least 30 days after the last dose

Males

- DAURISMO may be present in semen. Male patients with female partners should be advised of the potential risk of exposure through semen and to always use effective contraception, including a condom (with spermicide, if available), even after vasectomy, to avoid exposure of a pregnant partner or a female partner of childbearing potential during treatment with DAURISMO, and for at least 30 days after the last dose
- If a female patient or female partner of a male patient becomes pregnant, or suspects a pregnancy during treatment with DAURISMO, or during the 30 days after the last dose, they must inform their healthcare provider immediately
- Based on non-clinical safety findings, DAURISMO has the potential to impair reproductive function in males. Men should seek advice on effective fertility preservation prior to initiating treatment with DAURISMO

Males prescribed DAURISMO must be provided with a patient alert card by HCPs

HCP=healthcare provider.

Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021.

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DAURISMO Special Warnings and Precautions for Use (2/3)

QT interval prolongation

- In BRIGHT AML 1003, Grade 3/4 ECG QT prolonged was reported in 3.5% of patients treated with DAURISMO + LDAC compared with 2.4% of the patients treated with LDAC alone[1,2]
- Electrolytes should be assessed prior to initiation of DAURISMO, at least once weekly for the first month and then once monthly for the duration of therapy. Electrolyte abnormalities should be corrected[1]
- Concomitant medicinal products should be assessed. For medicinal products that have known QT interval prolongation effects and/or strong CYP3A4 inhibitor potential, alternatives should be considered[1]
- ECGs should be monitored prior to the initiation of DAURISMO, approximately 1 week after initiation, and then once monthly for the next 2 months to assess for QTc prolongation. In patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products with known QT prolonging effects, more frequent ECG monitoring is recommended. ECG should be repeated if abnormal. Abnormalities should be managed promptly, and dose modifications should be considered[1]

Muscle-related adverse events

- In BRIGHT AML 1003, muscle spasms were observed in 22.6% of patients treated with DAURISMO + LDAC compared with 4.8% of the patients treated with LDAC alone[1,2]
- All patients starting therapy with DAURISMO must be informed of the risk of muscle-related adverse events. They must be instructed to report promptly any unexplained muscle pain, tenderness, or weakness occurring during treatment with DAURISMO or if symptoms persist after discontinuing treatment[1]
- Serum CK levels should be obtained prior to initiating DAURISMO and as clinically indicated thereafter (e.g. if muscle signs and symptoms are reported). Management of high-grade CK elevation based on current standards of medical practice and following appropriate treatment guidelines is recommended. Dose modification or management recommendations should be followed[1]

CK=creatine kinase; CYP=cytochrome P450; ECG=electrocardiogram; LDAC=low-dose cytarabine; QTc=corrected QT interval.

1. Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021. 2. Wolska-Washer A, et al. *Future Oncol.* 2019;15(28):3219-3232.

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DAURISMO Special Warnings and Precautions for Use (3/3)

Renal impairment

- Patients with pre-existing renal impairment or risk factors for renal dysfunction should be monitored closely. Renal function should be assessed prior to initiation of therapy, and at least once weekly for the first month of therapy with DAURISMO. Electrolytes and renal function should be monitored once monthly for the duration of therapy

Excipients

Lactose intolerance

- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product

Sodium content

- This medicinal product contains < 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’

For details on monitoring and dose modifications with DAURISMO please click here

Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021.

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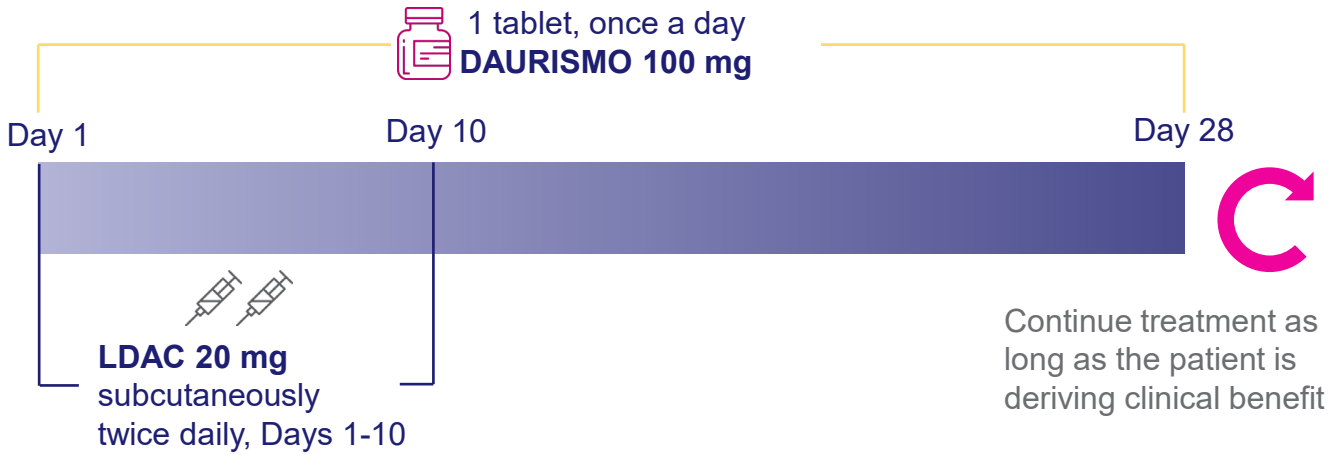
DOSING AND ADMINISTRATION

Once-daily, Oral DAURISMO + LDAC Provides a Treatment Regimen That Can Potentially Be Administered in the Outpatient Setting or Administered at Home*

DAURISMO + LDAC dosing schedule[1]

- The recommended dose of DAURISMO is **100 mg taken orally once daily on Days 1-28** in combination with 20 mg LDAC taken subcutaneously twice daily on Days 1-10 of each 28-day cycle
- DAURISMO should be continued for as long as the patient is deriving clinical benefit



Dosing and administration considerations

DAURISMO may be taken with or without food[1]

DAURISMO can be administered as an outpatient or as at-home treatment[1-3]

Dose modifications[1]

DAURISMO is available in 100 mg and 25 mg film-coated tablets, offering dose flexibility for treatment management

Dose modifications may be required based on individual safety and tolerability. If dose reduction is necessary then the dose of DAURISMO should be reduced to 50 mg taken orally once daily

*Per institutional guidelines.
LDAC=low-dose cytarabine.
1. Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021. 2. Burnett AK, et al. *Cancer.* 2007;109(6):1114-1124. 3. Heuser M, et al. *Ann Oncol.* 2020:31(6):697-712.

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DAURISMO Monitoring and Dose Modifications

- Dose modifications may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose of DAURISMO should be reduced to 50 mg taken orally once daily
- No starting dose adjustments are required on the basis of patient age, race, sex or body weight

Assessment	Prior to initiation of DAURISMO	During treatment
Complete blood count	✔	Monitor at least once weekly for the first month
Electrolytes	✔	Monitor at least once weekly for the first month and then once monthly for the duration of therapy
Renal function	✔	Monitor at least once weekly for the first month and then once monthly for the duration of therapy
Hepatic function	✔	Monitor at least once weekly for the first month
Serum CK	✔	Obtain as indicated clinically thereafter (e.g. if muscle signs and symptoms are reported)
ECGs	✔	Monitor approximately 1 week after initiation, and then once monthly for the next 2 months to assess for QTc prolongation; repeat if abnormal. Certain patients may require more frequent and ongoing ECG monitoring

Abnormalities should be managed promptly and dose modifications considered
Click here for full prescribing information in the DAURISMO SmPC

For details on specific patient populations who require more frequent ECG monitoring please click here to see special warnings and precautions for DAURISMO

CK=creatine kinase; ECG=electrocardiogram; SmPC=Summary of Product Characteristics; QTc=corrected QT interval.

Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021.

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SUMMARY

DAURISMO + LDAC Showed Superior OS With Improvements in Patient QoL, Higher ORR Rates, and a Manageable Safety Profile vs LDAC Alone

- For patients with AML who are candidates for nonintensive standard induction chemotherapy, adding DAURISMO to LDAC resulted in improved median OS compared with LDAC alone (**8.3 months** vs **4.3 months**; HR 0.495; ***P* = 0.0004**)[1,*]
- DAURISMO + LDAC improved 1-year OS by > 4× compared with LDAC alone (**39.4%** vs **8.4%)**[1,*]
- Exploratory subgroup analyses of OS indicate consistent benefit with DAURISMO + LDAC vs LDAC alone for patients with good/intermediate cytogenetic risk and for patients with sAML[2]
  - Good/intermediate cytogenetic risk groups: Median OS **11.1 months** vs **4.4 months;** HR 0.417; ***P* = 0.0011**, for DAURISMO + LDAC vs LDAC alone, respectively
  - Secondary AML: Median OS **9.1 months** vs **4.1 months**; HR 0.287; ***P* = < 0.0001**, for DAURISMO + LDAC vs LDAC alone, respectively
- The addition of DAURISMO to LDAC resulted in a higher ORR vs LDAC alone (**26.9%** vs **5.3%**)[3,†]
- DAURISMO + LDAC has a tolerable and manageable safety profile consistent with toxicities reported for elderly patients receiving chemotherapy and toxicities reported for other marketed Smoothened inhibitors[3]
- Higher rates of transfusion independence were reported with DAURISMO + LDAC vs LDAC alone (**29.3%** vs **5.6%**)[4,*]
- DAURISMO + LDAC demonstrated a **75% relative improvement in quality-adjusted survival benefit** vs LDAC alone, that greatly exceeded the clearly clinically important threshold of 15%[5]
- DAURISMO + LDAC offers the option of outpatient treatment or administration at home[2,6,7]

*Data cut-off October 11, 2018. †Data cut-off January 3, 2017.
CI=confidence interval; CR=complete remission; HR=hazard ratio; LDAC=low-dose cytarabine; ORR=overall response rate; OS=overall survival; sAML=secondary AML; QoL=quality of life.
1. Heuser M, et al. *Ann Hematol*. 2021;100(5):1181-1194. 2. Pfizer Ltd. DAURISMO® (glasdegib) summary of product characteristics. 2021. 3. Cortes JE, et al. *Leukemia*. 2019;33(2):379-389. 4. Heuser M *et al*. *Ann Hematol* 2021;100(5):1181-1194. 5. Solem C, et al. *Cancer* 2020;126(19):4315-4321. 6. Burnett AK, et al. *Cancer*. 2007;109(6):1114-1124. 7. Heuser M, et al. *Ann Oncol*. 2020:31(6):697-712.

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