

Which Patients in Your Clinical Practice Would Benefit From Treatment With DAURISMO + LDAC?

The addition of DAURISMO to LDAC significantly extends overall survival and improves the quality of life of patients with AML who are not suitable for intensive chemotherapy¹⁻⁴

DAURISMO is indicated, 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 chemotherapy¹

! DAURISMO can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. DAURISMO present in semen may cause harm or death to an unborn child. Male patients prescribed DAURISMO must be provided with a patient alert card by HCPs¹

▼ 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 via the national reporting system.¹

Hypothetical patient profiles.

In the Benchmark Research Investigating Glasdegib in Hematologic Tumors (BRIGHT) AML 1003 study, 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.^{1,3} The efficacy results presented throughout this material are from the AML population only.

AML=acute myeloid leukemia; HCP=healthcare professional; LDAC=low-dose cytarabine; sAML=secondary acute myeloid leukemia.

1. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.

2. Solem C, et al. *Cancer*. 2020;126(19):4315-4321. 3. Cortes JE, et al. *J Hematol Oncol*. 2020;13(1):92.

4. Heuser M, et al. *Ann Hematol*. 2021;100(5):1181-1194.



Albert, aged 81 years

Grandfather of six, still leads an active life

De novo AML, not suitable for intensive chemotherapy

Cardiac disease, history of renal insufficiency

Review
case



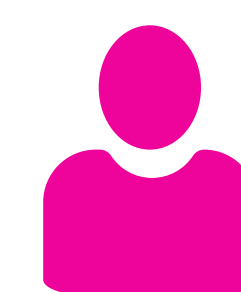
Elsie, aged 79 years

Mother of two, who would like to be treated in an outpatient setting

sAML, not suitable for intensive chemotherapy

History of cardiovascular disease, pancytopenic

Review
case



Francesco, aged 87 years

Lives far from the treatment center and has difficulty traveling

De novo AML, not suitable for intensive chemotherapy

Hepatic dysfunction, history of cardiovascular disease, pancytopenic

Review
case



Albert: Diagnosis

Patient evaluation

- 81-year-old male with six grandchildren
- Lives with his wife and has an active social life



Clinical presentation

- ECOG PS = 2
- Fatigued
- Recently experienced weight loss



Medical history

- Heart failure with reduced ejection fraction (< 40%)
- Myocardial infarction 3 years ago
- Coronary artery disease
- History of renal insufficiency
- Arthritis



Examination and laboratory findings

Cytogenetic and molecular profile

- Intermediate cytogenetic risk status
- Molecular risk profile: *NPM1*wt, *FLT3-ITD*wt

Blood tests

- BM aspirate/biopsy: blast count = 77%
- WBC count = 22,000/ μ L
- Hemoglobin = 9 g/dL
- Platelet count = 25,000/ μ L
- ANC = 900/ μ L
- Serum creatinine = 1.7 mg/dL



Diagnosis

De novo AML, not suitable for intensive induction chemotherapy

Which **clinical characteristics** would impact your first-line treatment decision for Albert?

AML=acute myeloid leukemia; ANC=absolute neutrophil count; BM=bone marrow; ECOG PS=Eastern Cooperative Oncology Group performance status; WBC=white blood count.



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Which Clinical Characteristics Would Impact Your First-Line Treatment Decision for Albert?



Most patients in the BRIGHT AML 1003 study were aged ≥ 75 years and had multiple comorbidities that made them difficult to treat^{1,2}

Albert	BRIGHT AML 1003 DAURISMO + LDAC arm (n = 78) ¹
Aged 81 years	62% of patients were aged ≥ 75 years
Newly diagnosed <u>de novo</u> AML	49%
Good/intermediate cytogenetic risk	63%
ECOG PS = 2	53%
Baseline severe cardiac disease	67%
Baseline serum creatinine > 1.3 mg/dL	19%

- Patients were **not eligible for intensive chemotherapy**, as defined by meeting ≥ 1 of the following criteria³
 - Aged ≥ 75 years
 - ECOG PS = 2
 - Serum creatinine > 1.3 mg/dL
 - Severe cardiac disease
- At baseline, **two-thirds of patients met ≥ 2 criteria for nonintensive treatment²**

AML=acute myeloid leukemia; ECOG PS= Eastern Cooperative Oncology Group performance status; LDAC=low-dose cytarabine.
1. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021. 2. Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194.
3. Cortes JE, et al. *Leukemia.* 2019;33(2):379-389.



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Albert

Initial Treatment Choice: DAURISMO + LDAC



Albert's Examination and Laboratory Findings After Three Cycles of DAURISMO + LDAC Treatment



Response

- CR after Cycle 3
- BM blasts aspirate/biopsy: blast count = 2%
- WBC count = 11,000/ μ L



Adverse reactions

- Anemia (Grade 1)
- Dysgeusia (Grade 1)
- Decreased appetite (Grade 1)



Bone marrow recovery

- Hemoglobin = 11 g/dL
- Platelet count = 105,000/ μ L
- ANC = 1500/ μ L



Quality of life

- No hospital admissions or episodes of febrile neutropenia
- Transfusion independent during first 3 months of treatment
- Good quality of life and social functioning

How does Albert compare with patients in the BRIGHT AML 1003 study?



AML=acute myeloid leukemia; ANC=absolute neutrophil count; BM=bone marrow; CR=complete remission; LDAC=low-dose cytarabine; WBC=white blood count.



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How Does Albert Compare With Patients in the BRIGHT AML 1003 Study?



Overall survival

Response rates

Adverse reactions

Bone marrow
recovery

Quality of life



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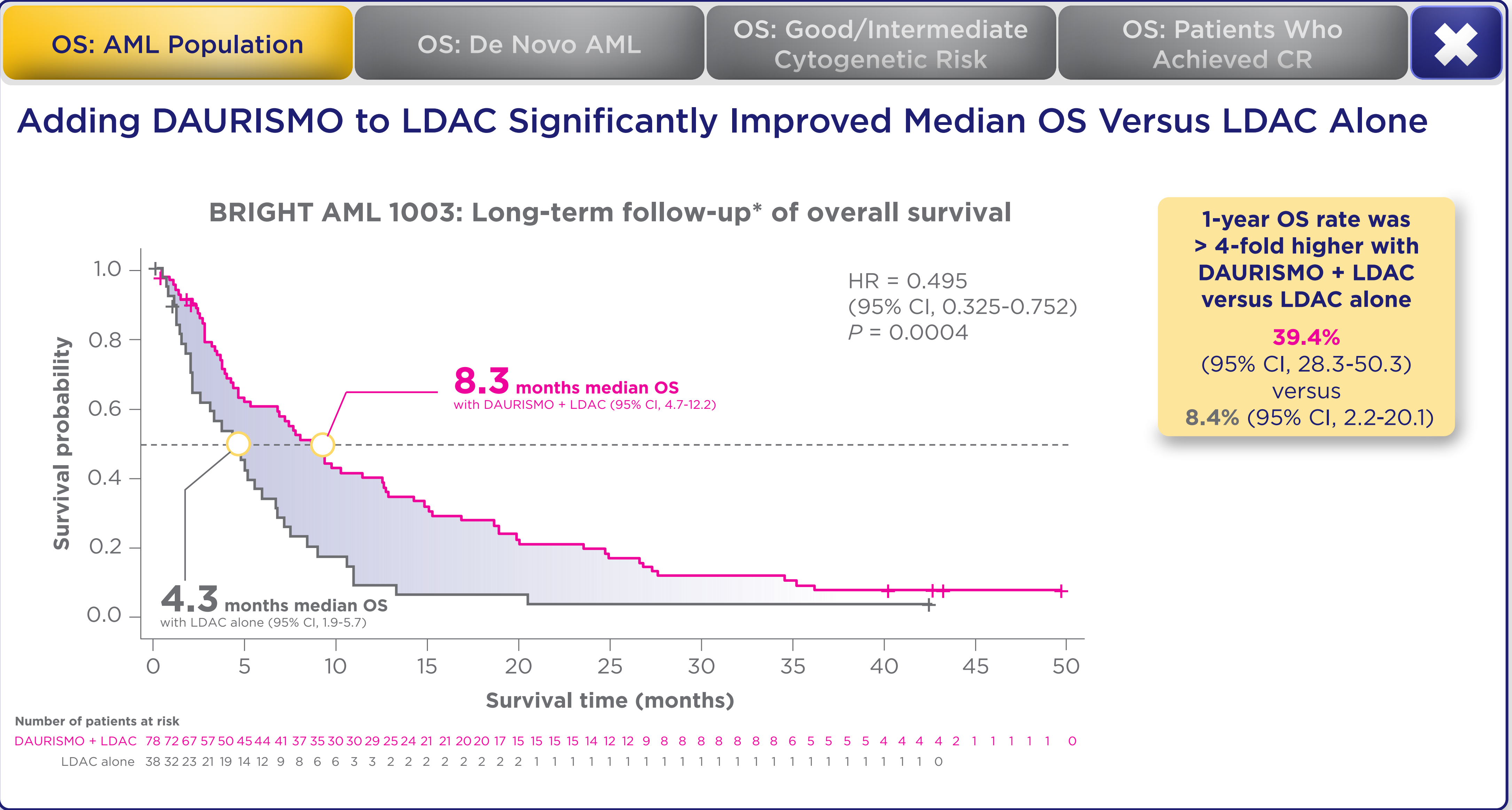
How Does Albert's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Diagnosis

Initial Treatment

Follow-up



++ censored.
*Approximately 20 additional months of follow-up from the primary completion date.
AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival.
Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194.

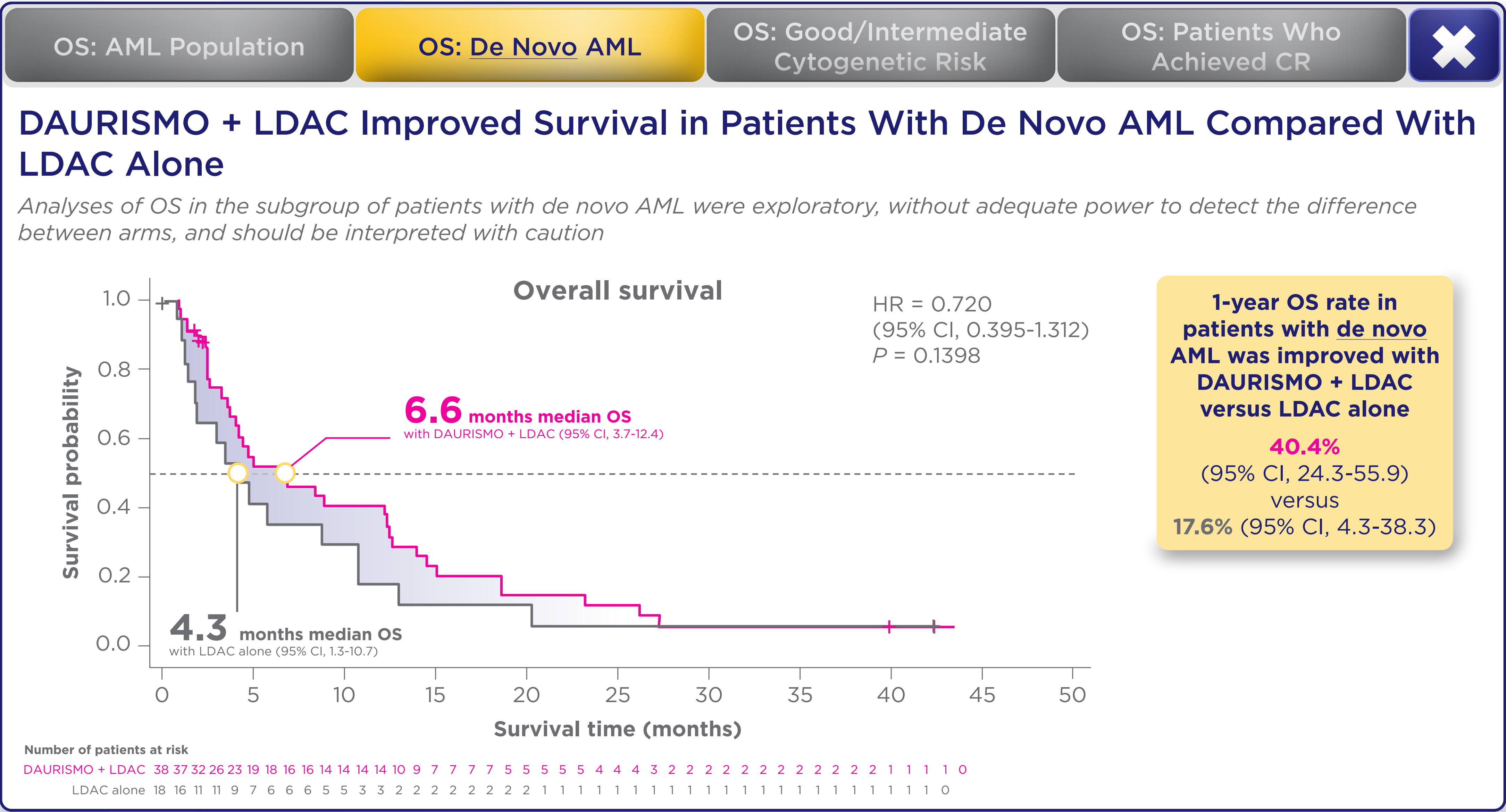
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Diagnosis

Initial Treatment

Follow-up



++ censored.
Data cut-off: October 11, 2018.
AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival.
Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194.

How Does Albert's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



OS: AML Population

OS: De Novo AML

OS: Good/Intermediate
Cytogenetic Risk

OS: Patients Who
Achieved CR



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

There is a slight imbalance towards 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

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	

Median OS in patients with good/intermediate cytogenetic risk who received DAURISMO + LDAC was > 2-fold greater than in patients who received LDAC alone

*HR based on the Cox proportional hazards model stratified by prognosis stratum. [†]One-sided P-value from stratified log-rank test based on cytogenetic risk. AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.



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How Does Albert's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



OS: AML Population

OS: De Novo AML

OS: Good/Intermediate Cytogenetic Risk

OS: Patients Who Achieved CR

X

Adding DAURISMO to LDAC Improved OS in Patients Who Achieved CR Versus 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

OS	DAURISMO + LDAC (n = 78)	LDAC alone (n = 38)
Patients who achieved CR		
n	15	1
Median OS, months (95% CI)	26.1 (12.3-34.6)	12.9 (NE-NE)

The 1-year OS rate in patients who achieved CR in the DAURISMO + LDAC arm was **86.7%** (95% CI, 56.4-96.5)

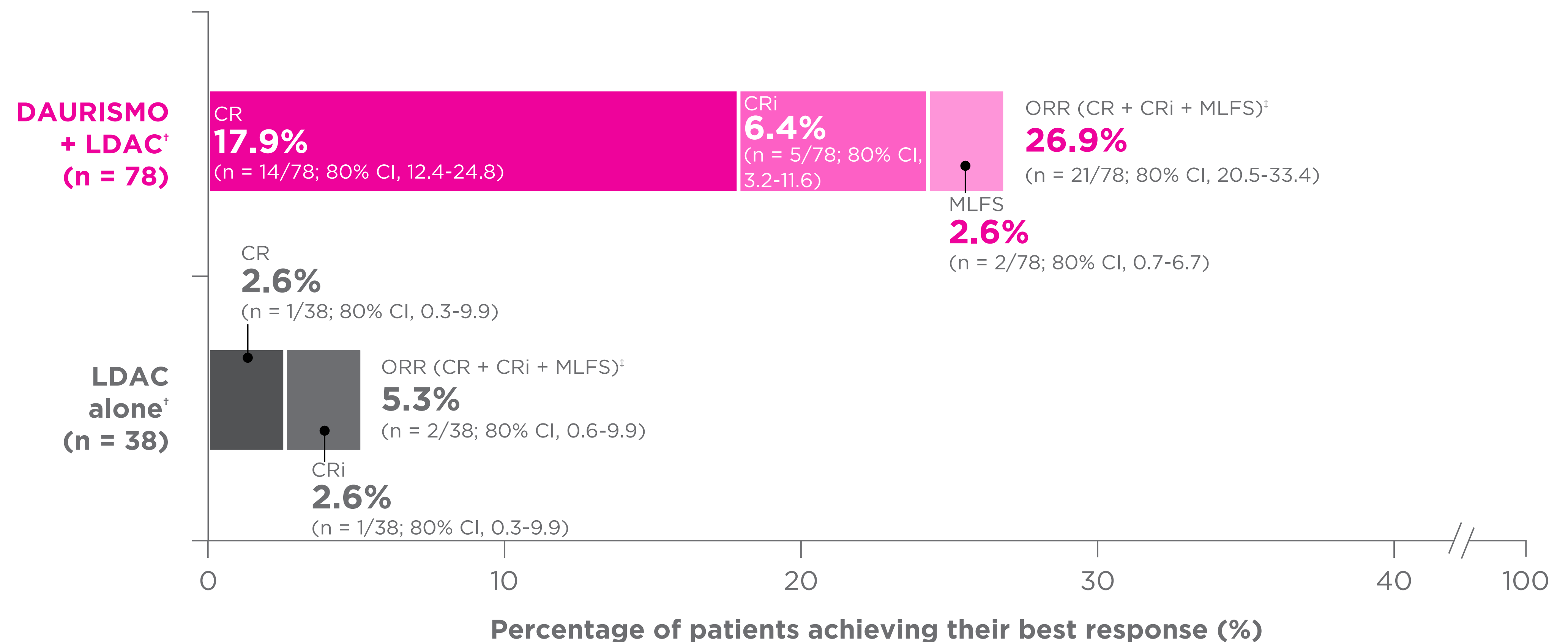
Adapted from Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. Data cut-off: October 2018. AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; LDAC=low-dose cytarabine; NE=not evaluable; OS=overall survival. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92.

How Does Albert's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Response Rates

DAURISMO + LDAC Achieved Higher Overall Response Rates Versus LDAC Alone^{1,2,*}



Data cut-off: January 3, 2017.

*Using exact method based on binomial distribution and CIs expressed in percentages.² [†]In the DAURISMO + LDAC and LDAC alone arms, 24 and 16 patients, 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.² [‡]Using normal approximation for further endpoints of interest and CIs expressed in percentages.²

AE=adverse event; AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; LDAC=low-dose cytarabine; MLFS=morphologic leukemia-free state; ORR=overall response rate.

1. Cortes JE, et al. *Leukemia*. 2019;33(2):379-389. 2. Cortes JE, et al. *Leukemia*. 2019;33(2):379-389 (supplementary appendix).



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How Does Albert's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Adverse Reactions

DAURISMO + LDAC Has a Tolerable and Manageable Safety Profile^{1,2}

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

TEAEs* occurring during the first 90 days of treatment in patients who achieved CR²

MedDRA term n (%)	DAURISMO + LDAC (n = 15)	LDAC alone (n = 1)	MedDRA term n (%)	DAURISMO + LDAC (n = 15)	LDAC alone (n = 1)
Anemia	8 (53.3)	0	Constipation	3 (20.0)	1 (100)
Nausea	5 (33.3)	0	Edema peripheral	5 (33.3)	0
Febrile neutropenia	6 (40.0)	0	Dysgeusia	7 (46.7)	0
Decreased appetite	3 (20.0)	0	Vomiting	4 (26.7)	0
Thrombocytopenia	6 (40.0)	0	Cough	2 (13.3)	0
Diarrhea	6 (40.0)	0	Dizziness	4 (26.7)	0
Fatigue	5 (33.3)	0	Dyspnea	1 (6.7)	0
Pneumonia	2 (13.3)	0	Muscle spasm	6 (40.0)	0
Pyrexia	3 (20.0)	0	Weight decreased	4 (26.7)	0

The safety profile of Daurismo + LDAC is consistent with the toxicities reported for elderly patients receiving chemotherapy and the toxicities reported for other marketed smoothened inhibitors¹

Adapted from Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92 (supplementary appendix). Data cut-off: October 2018.

*Any-Grade all-causality TEAEs occurring in ≥ 20% of patients with AML (receiving Daurismo + LDAC or LDAC alone in the BRIGHT AML 1003 study. Daurismo + LDAC, n = 75; LDAC alone, n = 36).

AE=adverse event; AML=acute myeloid leukemia; CR=complete remission; LDAC=low-dose cytarabine; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

1. Cortes JE, et al. *Leukemia.* 2019;33(2):379-389. 2. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92 (supplementary appendix).



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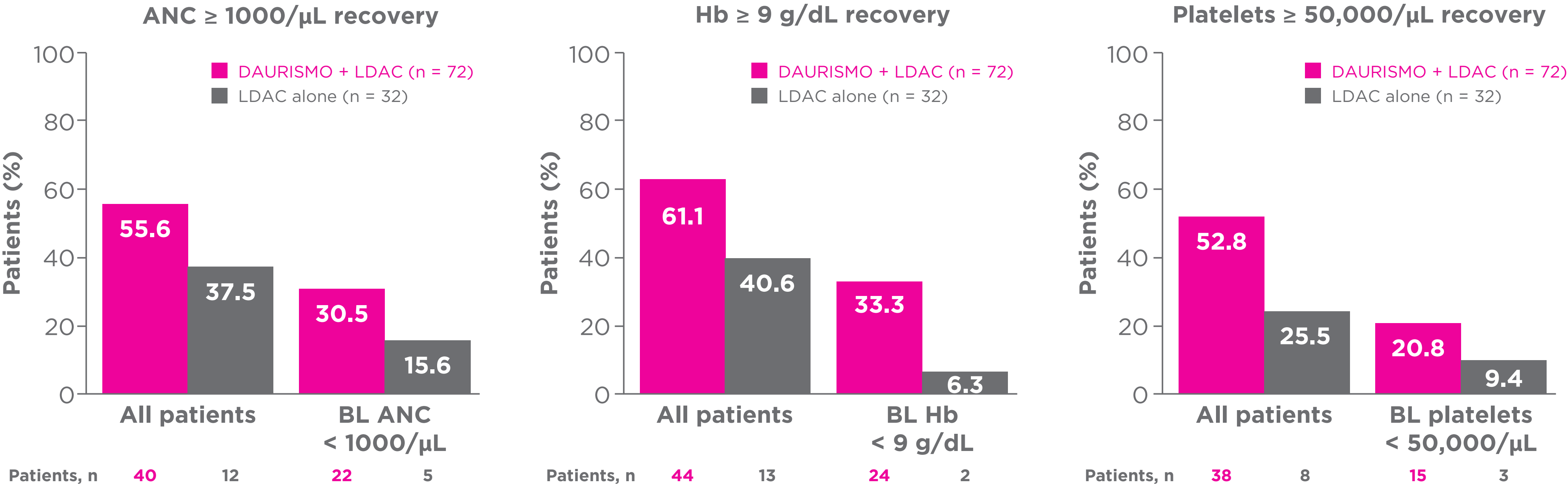


Bone Marrow Recovery

In the Overall Population, Rates of Bone Marrow Recovery Were Consistently Higher With DAURISMO + LDAC Versus LDAC Alone Across All Three Cell Lineages

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

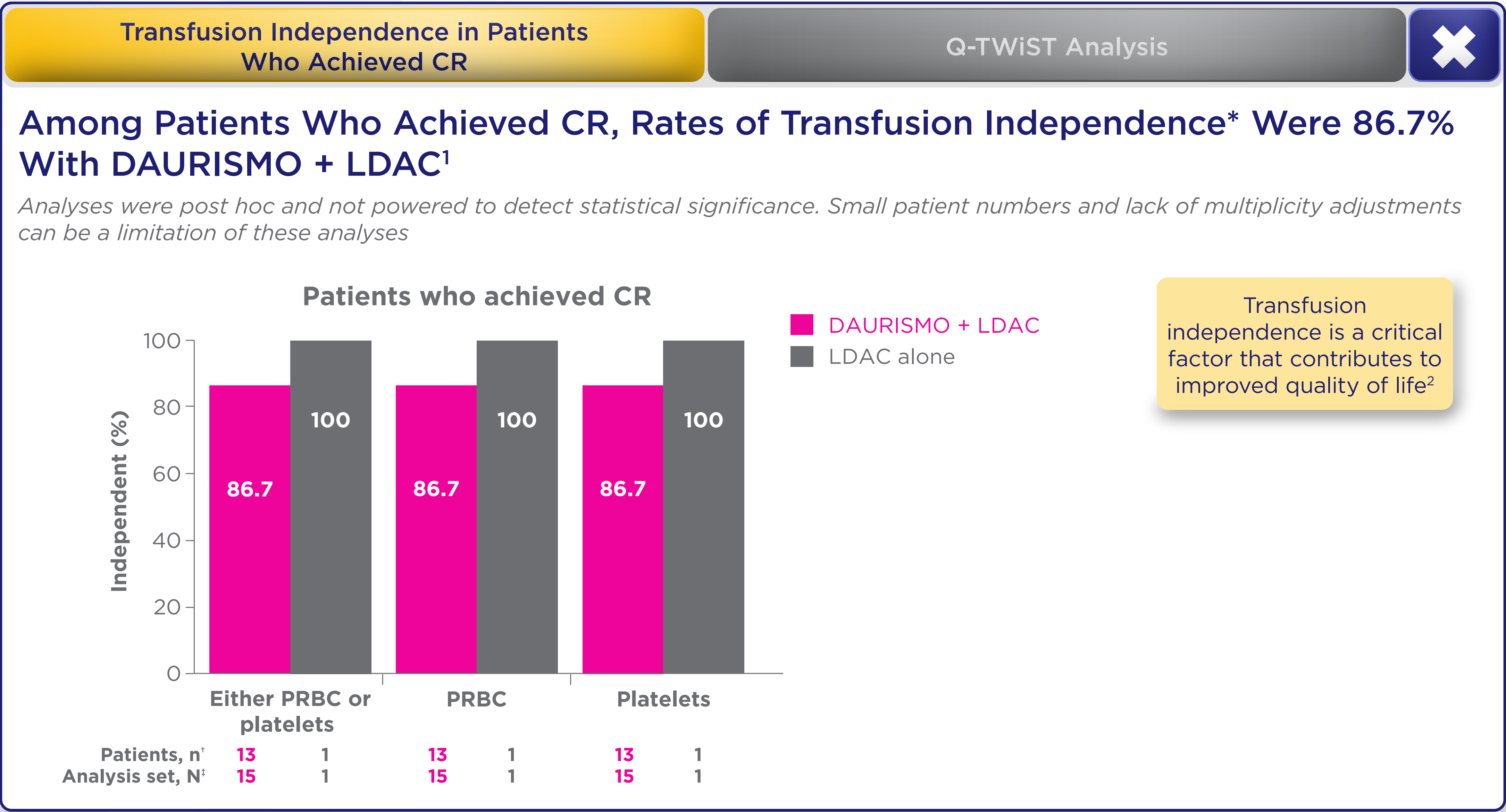
Prolonged* ANC, Hb, and platelet recovery at any time during study



Data cut-off: October 11, 2018.
*At any time during the study, required threshold measurement at ≥ 2 consecutive visits.
AML=acute myeloid leukemia; ANC=absolute neutrophil count; BL=baseline; CR=complete remission; Hb=hemoglobin; LDAC=low-dose cytarabine.
Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194.



How Does Albert's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Adapted from Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. Data cut-off: October 2018.

*Transfusion-independent patients were defined as those who had ≥ 8 weeks (56 days) without any type of transfusion at any point of the study. All other patients are considered transfusion dependent.[†]Number of patients meeting recovery criteria in the cycle. [‡]Number of patients with results in the cycle.

AML=acute myeloid leukemia; CR=complete remission; LDAC=low-dose cytarabine; PRBC=packed red blood cells; Q-TWiST=quality-adjusted time without symptoms of disease progression or toxicity.

1. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. 2. Wang ES, et al. EHA 2019. Poster presentation (Abstract PF272).

How Does Albert's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



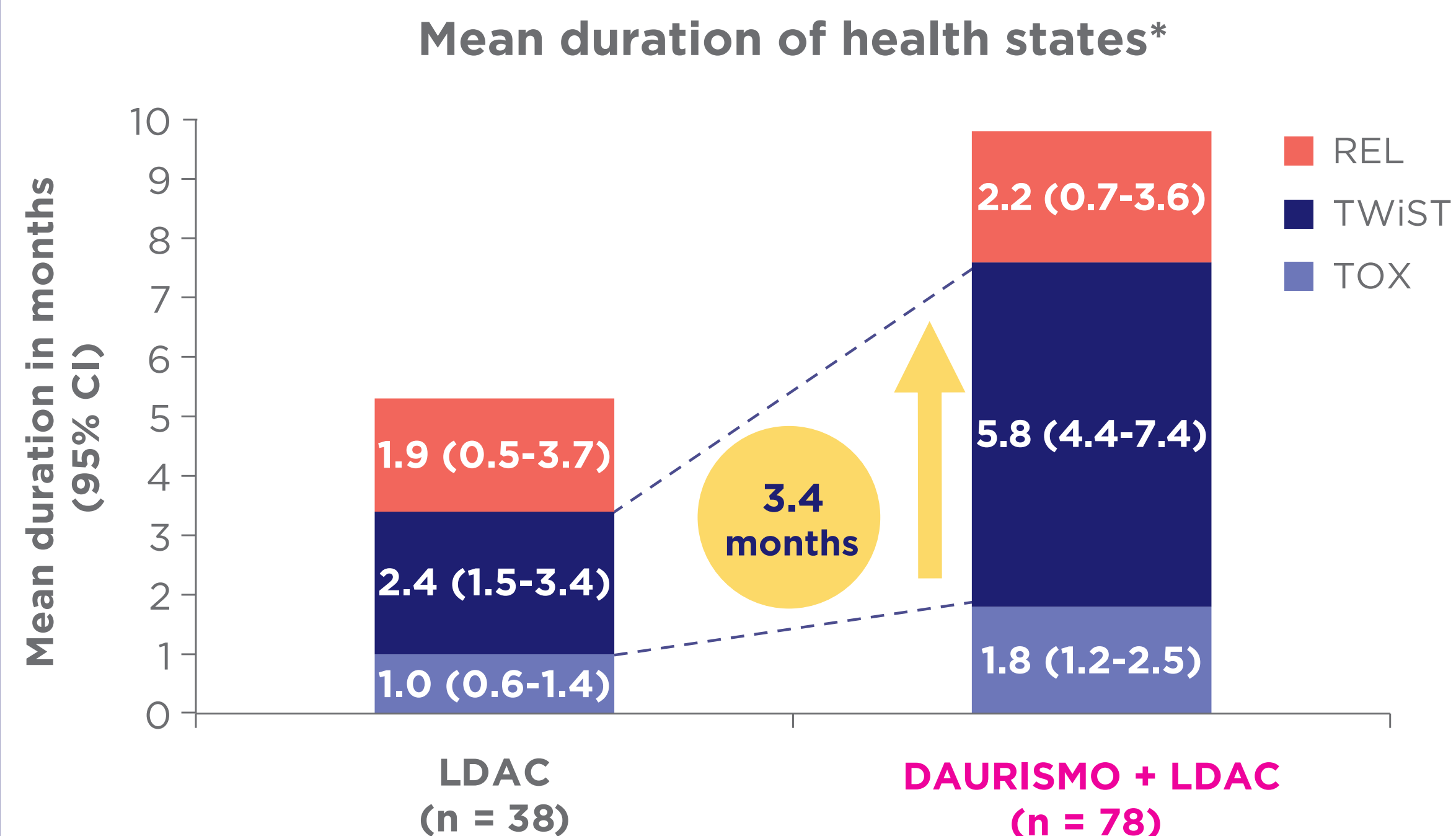
Transfusion Independence in Patients Who Achieved CR

Q-TWiST Analysis



DAURISMO + LDAC Achieves Significantly Increased Quality-Adjusted Overall Survival

- Q-TWiST analysis was used to estimate the quality-adjusted survival of DAURISMO + LDAC in BRIGHT AML 1003¹

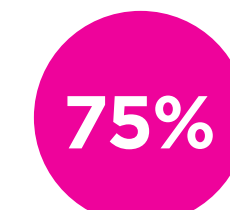


Patients who received DAURISMO + LDAC had a significantly longer mean duration of 3.4 months (95% CI, 1.8-5.2 months) without symptoms of disease or toxicity versus LDAC alone¹



months

Q-TWiST was **4 months** longer (95% CI, 2.1-5.8 months) for DAURISMO + LDAC versus LDAC alone¹



Gain in quality-adjusted survival

The increase in Q-TWiST translates into a **75% relative gain in quality-adjusted survival**, relative to LDAC alone, and **exceeds the clearly clinically important threshold, which is 15%, 5-fold^{1,2}**

Figure adapted from Solem C, et al. *Cancer*. 2020;126(19):4315-4321.

*OS restricted to a follow-up of 20 months.

AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; 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 treatment-emergent adverse event; 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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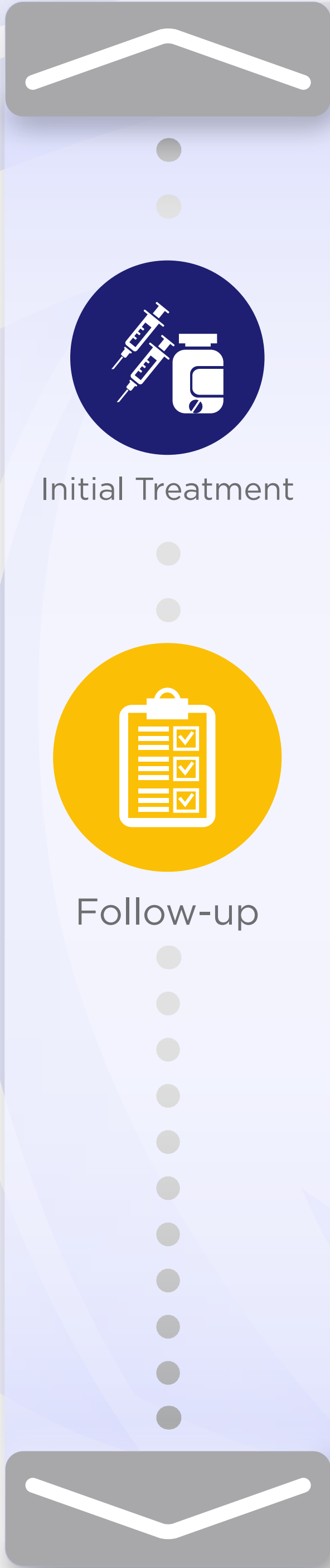
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Albert's Examination and Laboratory Findings After 20 Cycles of DAURISMO + LDAC Treatment



Response

- Relapsed
- BM aspirate/biopsy: blast count = 9%
- WBC = 3500/ μ L

Adverse reactions

- Weight loss (Grade 1)
- Dysgeusia (Grade 1)
- Anemia (Grade 3)

Bone marrow recovery

- Hemoglobin = 7.7 g/dL
- Platelet count = 100,000/ μ L
- ANC = 1000/ μ L

Quality of life

- Hemoglobin levels decreased slowly, requiring more frequent RBC transfusions
- Hospitalized for last week of life
- Was able to stay at home for 18 months of treatment and had a good quality of life

How does Albert compare with patients in the BRIGHT AML 1003 study?

- De novo AML
- Intermediate-risk cytogenetics
- CR after Cycle 3

	Albert	BRIGHT AML 1003 DAURISMO + LDAC arm
Duration of treatment	20 cycles	Median duration of treatment: 17 cycles (range: 1-44) in patients who achieved CR (n = 15) ¹
OS following initiation of treatment	21 months	Median OS for patients with de novo AML: 6.6 months (95% CI, 3.7-12.4) (n = 38) ^{2,*}
		Median OS for patients who achieved CR: 26.1 months (95% CI, 12.3-34.6) (n = 15) ^{1,*}
		Median OS for patients with good/intermediate cytogenetic risk: 11.1 months (95% CI, 7.1-14.9) (n = 49) ^{3,*}

Data cut-off: October 2018.
*Analyses were exploratory, without adequate power to detect the difference between arms, and should be interpreted with caution.
AML=acute myeloid leukemia; ANC=absolute neutrophil count; BM=bone marrow; CI=confidence interval; CR=complete remission; LDAC=low-dose cytarabine; OS=overall survival; RBC=red blood cell; WBC=white blood count.
1. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. 2. Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194. 3. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.

Elsie: Diagnosis

Patient evaluation

- 79-year-old retired dentist who lives with one of her daughters
- Would like to be treated in an outpatient setting to allow her to spend more time with her family



Clinical presentation

- ECOG PS = 2
- Flu-like symptoms (fever, fatigue, headache) and bruising
- Pancytopenic



Medical history

- History of CV disease
- Diagnosed with MDS 1 year ago, and has been treated with AZA
- Received six cycles of AZA with initial response, then six more cycles until disease progression



Examination and laboratory findings

Cytogenetic and molecular profile

- Intermediate cytogenetic risk (del[7q])
- Molecular risk profile: *NPM1*wt, *FLT3*wt, *IDH1/2*wt

Blood tests

- BM aspirate/biopsy: progression to sAML. Blast count = 60%
- WBC count = 2500/ μ L
- Hemoglobin: 9 g/dL
- Platelet count: 42,000/ μ L
- ANC: 800/ μ L



Diagnosis

sAML after failure of AZA

Which **clinical characteristics** would impact your 1L treatment decision for Elsie?

AML=acute myeloid leukemia; ANC=absolute neutrophil count; AZA=azacitidine; BM=bone marrow; CV=cardiovascular; ECOG PS=Eastern Cooperative Oncology Group performance status; MDS=myelodysplastic syndrome; sAML=secondary acute myeloid leukemia; WBC=white blood count; wt=wild-type.



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Which Clinical Characteristics Would Impact Your First-Line Treatment Decision for Elsie?

Most patients in the BRIGHT AML 1003 study were aged ≥ 75 years and had multiple comorbidities that made them difficult to treat^{1,2}

Elsie	BRIGHT AML 1003 DAURISMO + LDAC arm (n = 78) ¹
Aged 79 years	62% of patients were aged ≥ 75 years
Secondary AML	51%
Good/intermediate cytogenetic risk	63%
ECOG PS = 2	53%
Prior HMA therapy	14%

- Patients were **not eligible for intensive chemotherapy**, as defined by meeting ≥ 1 of the following criteria³
 - Aged ≥ 75 years
 - ECOG PS = 2
 - Serum creatinine > 1.3 mg/dL
 - Severe cardiac disease
- At baseline, **two-thirds of patients met ≥ 2 criteria for nonintensive treatment²**





Diagnosis



Initial Treatment



AML=acute myeloid leukemia; ECOG PS= Eastern Cooperative Oncology Group performance status; HMA=hypomethylating agent; LDAC=low-dose cytarabine; sAML=secondary acute myeloid leukemia.
 1. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021. 2. Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194.
 3. Cortes JE, et al. *Leukemia.* 2019;33(2):379-389.

Elsie

Initial Treatment Choice: DAURISMO + LDAC



Elsie's Examination and Laboratory Findings After Four Cycles of DAURISMO + LDAC Treatment

 Response	 Adverse reactions	 Bone marrow recovery	 Quality of life
• CRi after Cycle 4 • BM aspirate/biopsy: blast count = 3% • WBC count = 3500/μL	• Muscle spasms, CK = 3.5 $\times$ ULN (Grade 2) • Anemia (Grade 1) • Febrile neutropenia during Cycle 1 (Grade 3)	• Hemoglobin = 10 g/dL • Platelet count = 80,000/μL • ANC = 1000/mL (Cycle 1)	• Two-day hospital admission for febrile neutropenia during Cycle 1 • RBC and platelet transfusions received once per month

How does Elsie compare with patients in the BRIGHT AML 1003 study?

AML=acute myeloid leukemia; ANC=absolute neutrophil count; BM=bone marrow; CK=creatinine kinase; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; LDAC=low-dose cytarabine; RBC=red blood cell; ULN=upper limit of normal; WBC=white blood count.



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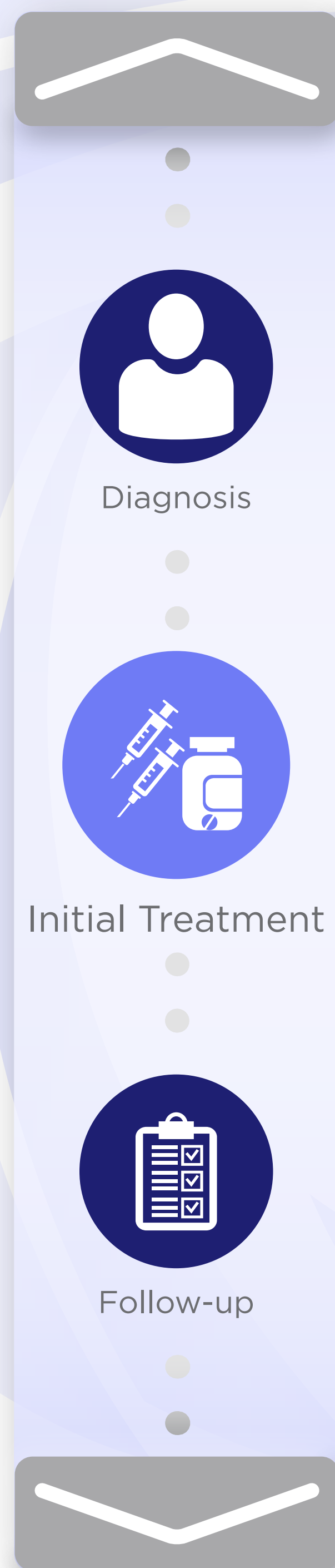
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How Does Elsie's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Overall survival

Response rates

Adverse reactions

Bone marrow
recovery

Quality of life



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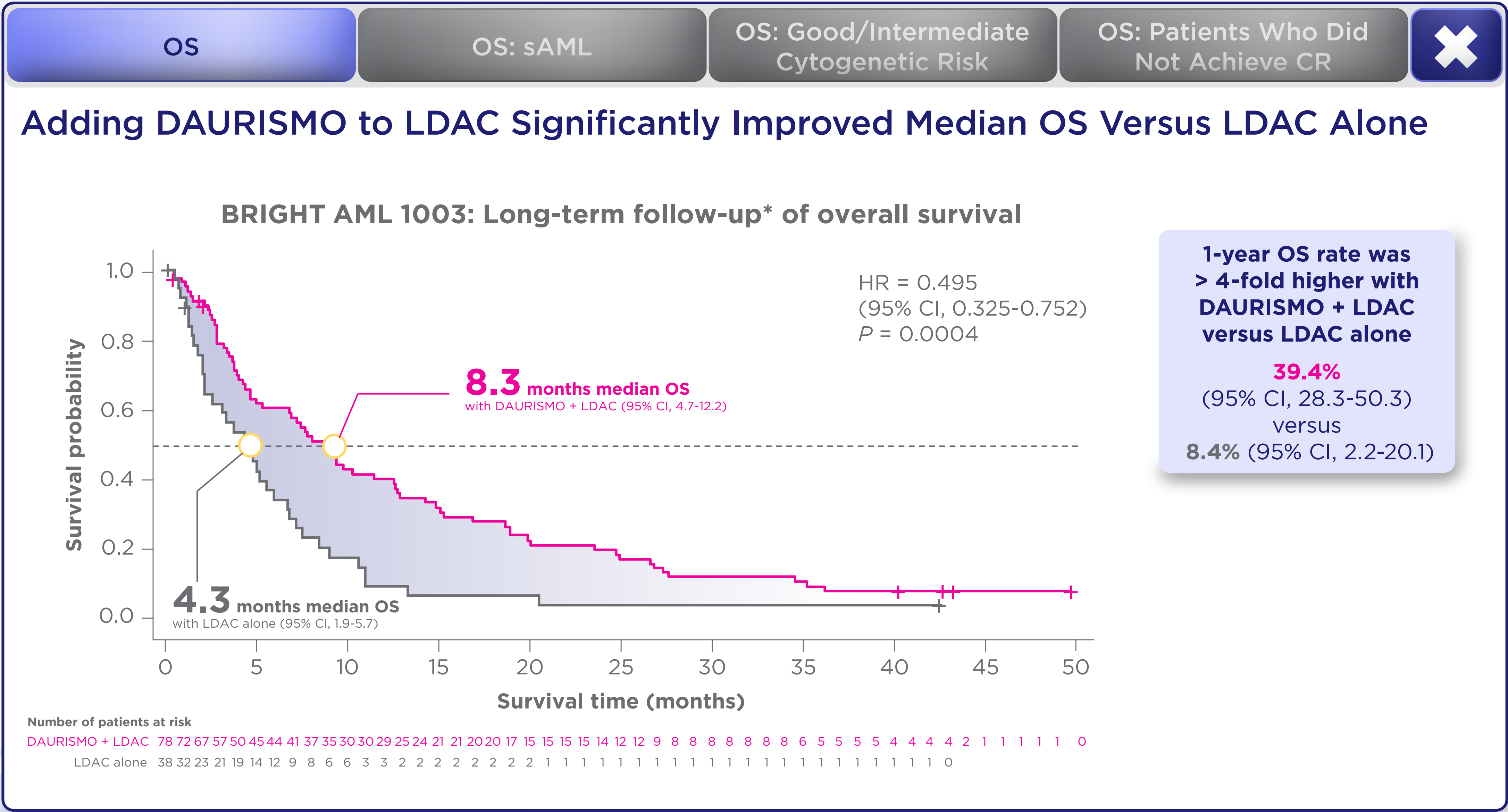
How Does Elsie's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Diagnosis

Initial Treatment

Follow-up



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*Approximately 20 additional months of follow-up from the primary completion date.
AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival; sAML=secondary acute myeloid leukemia.
Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194.

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glasdegib tablets

OS: Patients Who Did Not Achieve CR

How Does Elsie's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Diagnosis

Initial Treatment

Follow-up

OS

OS: sAML

OS: Good/Intermediate Cytogenetic Risk

OS: Patients Who Did Not Achieve CR

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

There is a slight imbalance towards 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

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	

Median OS in patients with good/intermediate cytogenetic risk who received DAURISMO + LDAC was > **2-fold greater** than in patients who received LDAC alone

*HR based on the Cox proportional hazards model stratified by prognosis stratum.†One-sided P-value from stratified log-rank test based on cytogenetic risk. AML=acute myeloid leukemia; CI, confidence interval; CR=complete remission; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival; sAML=secondary acute myeloid leukemia. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.

How Does Elsie's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Diagnosis

Initial Treatment

Follow-up

OSOS: sAMLOs: Good/Intermediate Cytogenetic RiskOS: Patients Who Did Not Achieve CR

Improvement in OS Was Observed With DAURISMO + LDAC, Even Among Patients Who Did Not Achieve CR

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

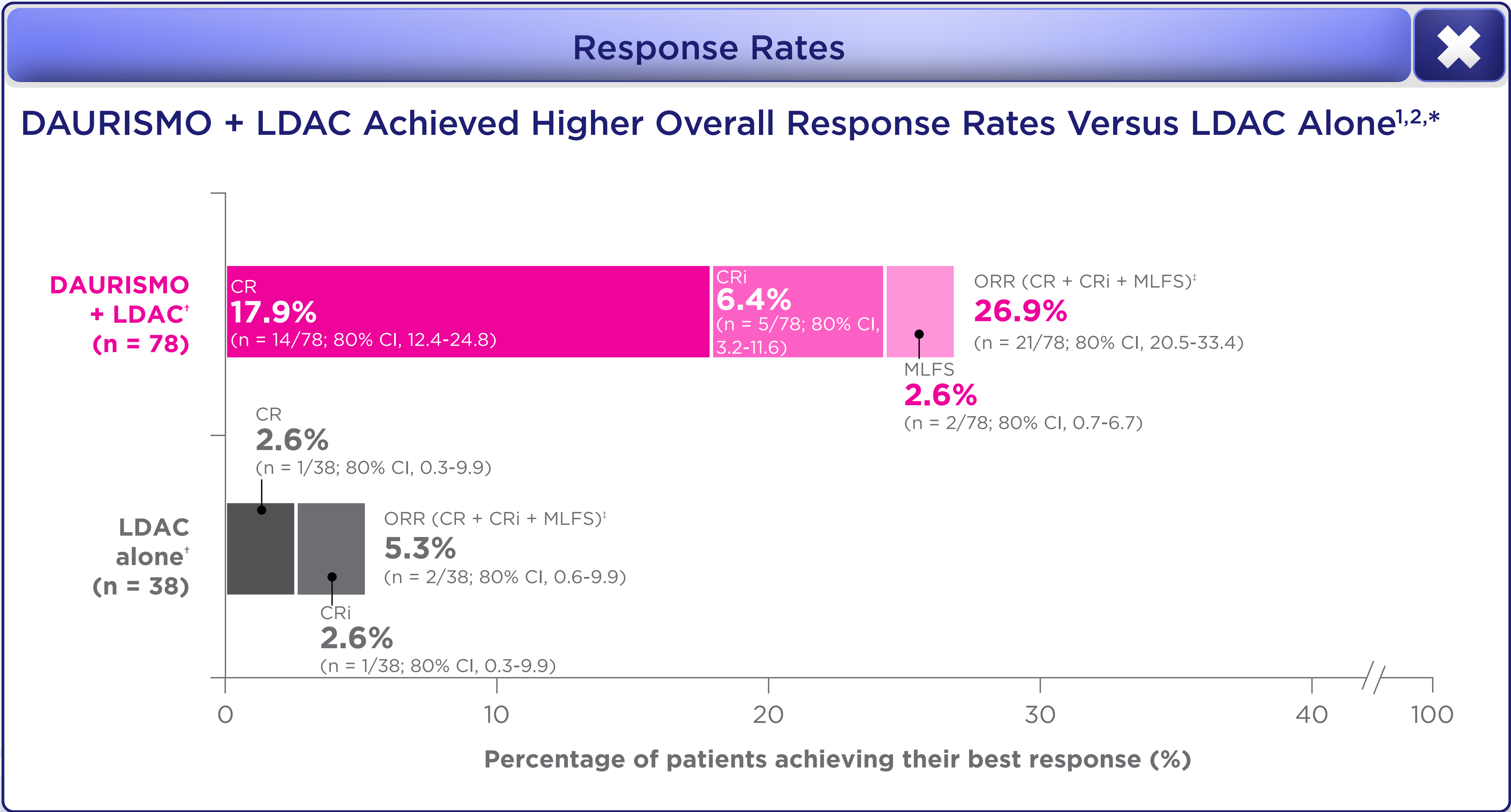
OS	DAURISMO + LDAC (n = 78)	LDAC alone (n = 38)
Patients who did not achieve CR		
n	63	37
Median OS, months (95% CI)	5.0 (3.5-8.3)	4.1 (1.9-5.3)
HR (95% CI)	0.63 (0.41-0.98)	
P-value	0.0182	

In patients who did not achieve CR, 1-year OS rates were higher in the DAURISMO + LDAC versus LDAC alone arm

27.3% (95% CI, 16.7-39.0) versus **5.7%** (95% CI, 1.0-16.8)

Adapted from Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. Data cut-off: October 2018.
AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival;
sAML=secondary acute myeloid leukemia.
Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92.

How Does Elsie's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Data cut-off: January 3, 2017.
*Using exact method based on binomial distribution and CIs expressed in percentages.² [†]In the DAURISMO + LDAC and LDAC alone arms, 24 and 16 patients, 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.² [‡]Using normal approximation for further endpoints of interest and CIs expressed in percentages.²
AE=adverse event; AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; LDAC=low-dose cytarabine; MLFS=morphologic leukemia-free state; ORR=overall response rate.
1. Cortes JE, et al. *Leukemia*. 2019;33(2):379-389. 2. Cortes JE, et al. *Leukemia*. 2019;33(2):379-389 (supplementary appendix).

How Does Elsie's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Adverse Reactions

DAURISMO + LDAC Has a Tolerable and Manageable Safety Profile^{1,2}

TEAEs* occurring after the first 90 days of treatment in patients who did not achieve CR²

MedDRA term n (%)	DAURISMO + LDAC (n = 29)	LDAC alone (n = 13)	MedDRA term n (%)	DAURISMO + LDAC (n = 29)	LDAC alone (n 13)
Anemia	8 (27.6)	3 (23.1)	Constipation	4 (13.8)	1 (7.7)
Nausea	5 (17.2)	0	Edema peripheral	1 (3.4)	0
Febrile neutropenia	4 (13.8)	1 (7.7)	Dysgeusia	2 (6.9)	0
Decreased appetite	8 (27.6)	3 (23.1)	Vomiting	2 (6.9)	0
Thrombocytopenia	8 (27.6)	2 (15.4)	Cough	2 (6.9)	1 (7.7)
Diarrhea	5 (17.2)	1 (7.7)	Dizziness	3 (10.3)	0
Fatigue	2 (6.9)	2 (15.4)	Dyspnea	2 (6.9)	2 (15.4)
Pneumonia	5 (17.2)	3 (23.1)	Muscle spasm	3 (10.3)	0
Pyrexia	5 (17.2)	1 (7.7)	Weight decreased	1 (3.4)	0

The safety profile of DAURISMO + LDAC is consistent with the toxicities reported for elderly patients receiving chemotherapy and the toxicities reported for other marketed smoothed inhibitors¹

Adapted from Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92 (supplementary appendix). Data cut-off: October 2018.

*Any-Grade all-causality TEAEs occurring in ≥ 20% of patients with AML (receiving DAURISMO + LDAC or LDAC alone in the BRIGHT AML 1003 study. DAURISMO + LDAC, n = 75; LDAC alone, n = 36).

AML=acute myeloid leukemia; CR=complete remission; LDAC=low-dose cytarabine; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

1. Cortes JE, et al. *Leukemia.* 2019;33(2):379-389. 2. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92 (supplementary appendix).



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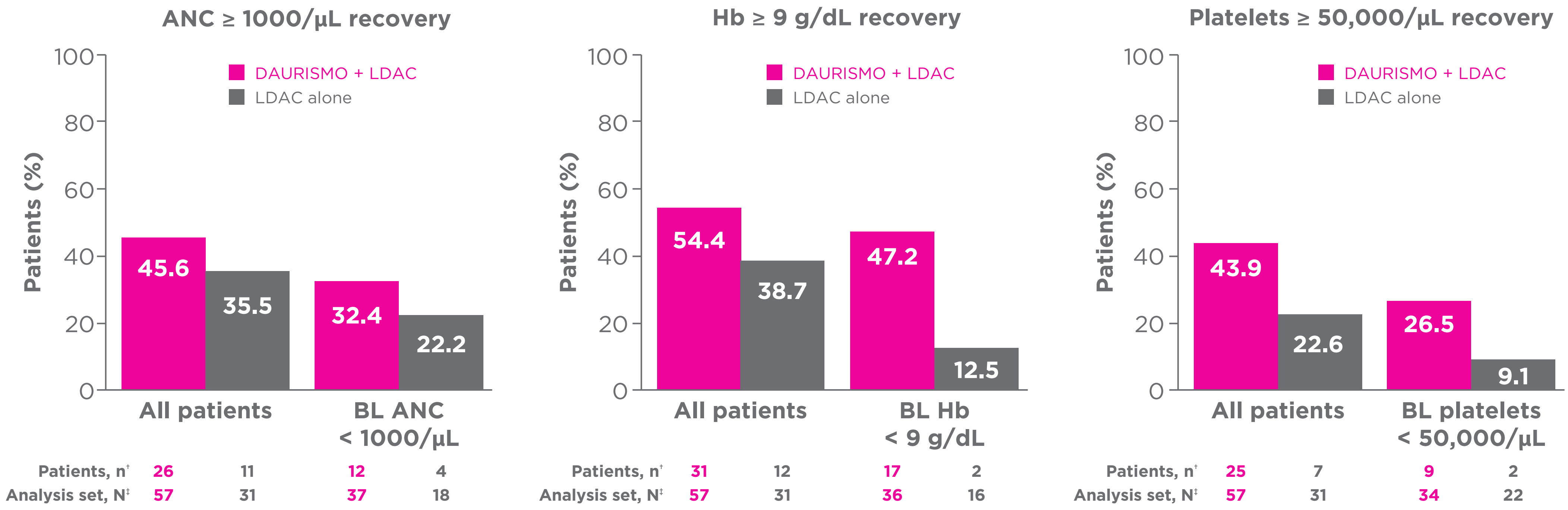


Bone Marrow Recovery

In Patients Who Did Not Achieve CR, Rates of Bone Marrow Recovery Were Consistently Higher With DAURISMO + LDAC Versus LDAC Alone Across All Three Cell Lineages

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

Durable ANC, Hb, and platelet recovery at any time on study in patients who did not achieve CR*



Adapted from Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. Data cut-off: October 2018.
*Required threshold measurement at ≥ 2 consecutive visits. [†]Number of patients meeting recovery criteria in the cycle. [‡]Number of patients with ANC/Hb or platelet results in the cycle.
AML=acute myeloid leukemia; ANC=absolute neutrophil count; BL=baseline; CR=complete remission; Hb=hemoglobin; LDAC=low-dose cytarabine.
Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92.



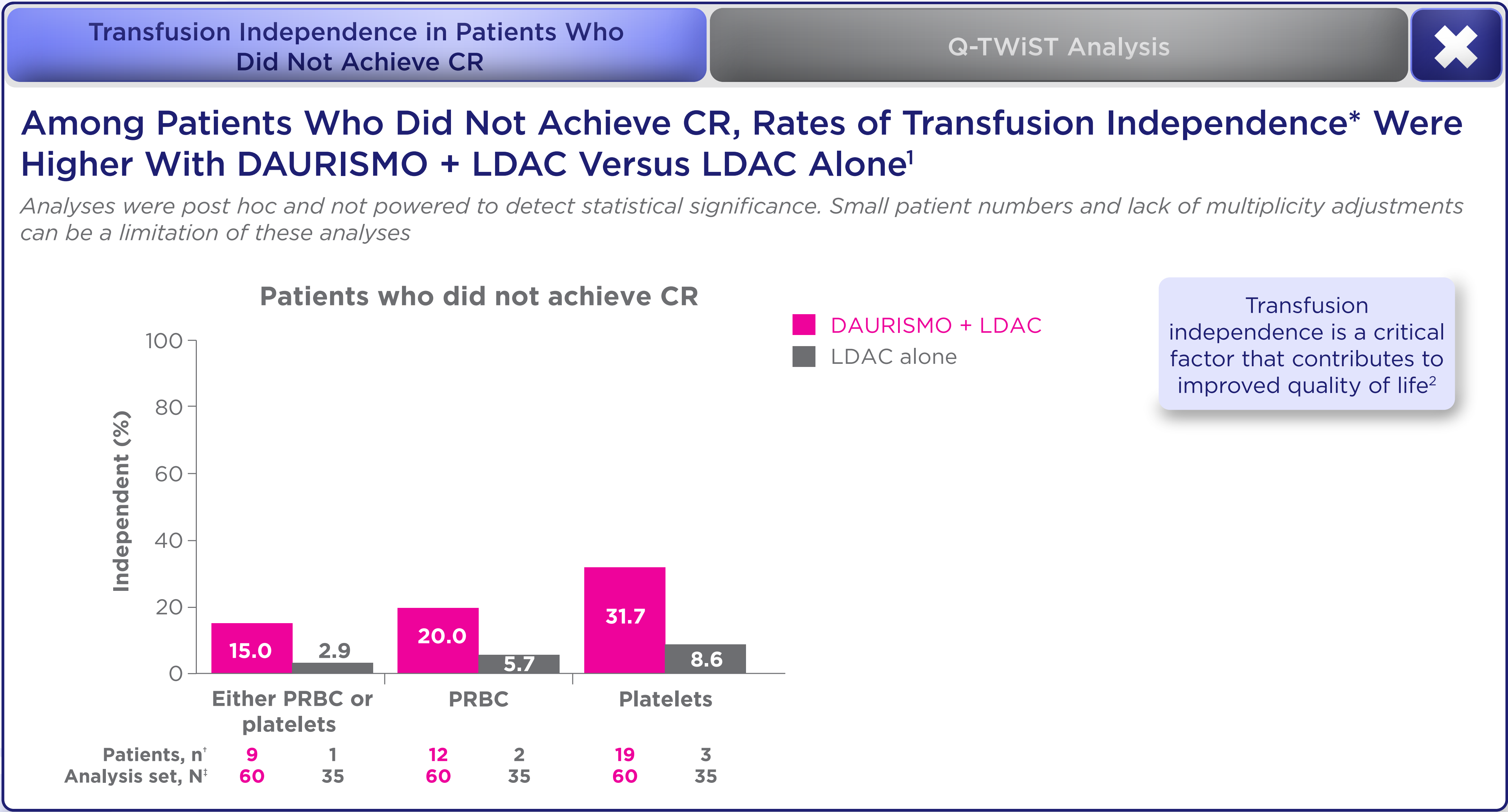
How Does Elsie's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Diagnosis

Initial Treatment

Follow-up



Adapted from Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. Data cut-off: October 2018.
*Transfusion-independent patients were defined as those who had ≥ 8 weeks (56 days) without any type of transfusion at any point of the study. All other patients are considered transfusion dependent. [†]Number of patients meeting recovery criteria in the cycle. [‡]Number of patients with results in the cycle.
AML=acute myeloid leukemia; CR=complete remission; LDAC=low-dose cytarabine; PRBC=packed red blood cells;
Q-TWiST=quality-adjusted time without symptoms of disease progression or toxicity.
1. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. 2. Wang ES, et al. EHA 2019. Poster presentation (Abstract PF272).

How Does Elsie's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?

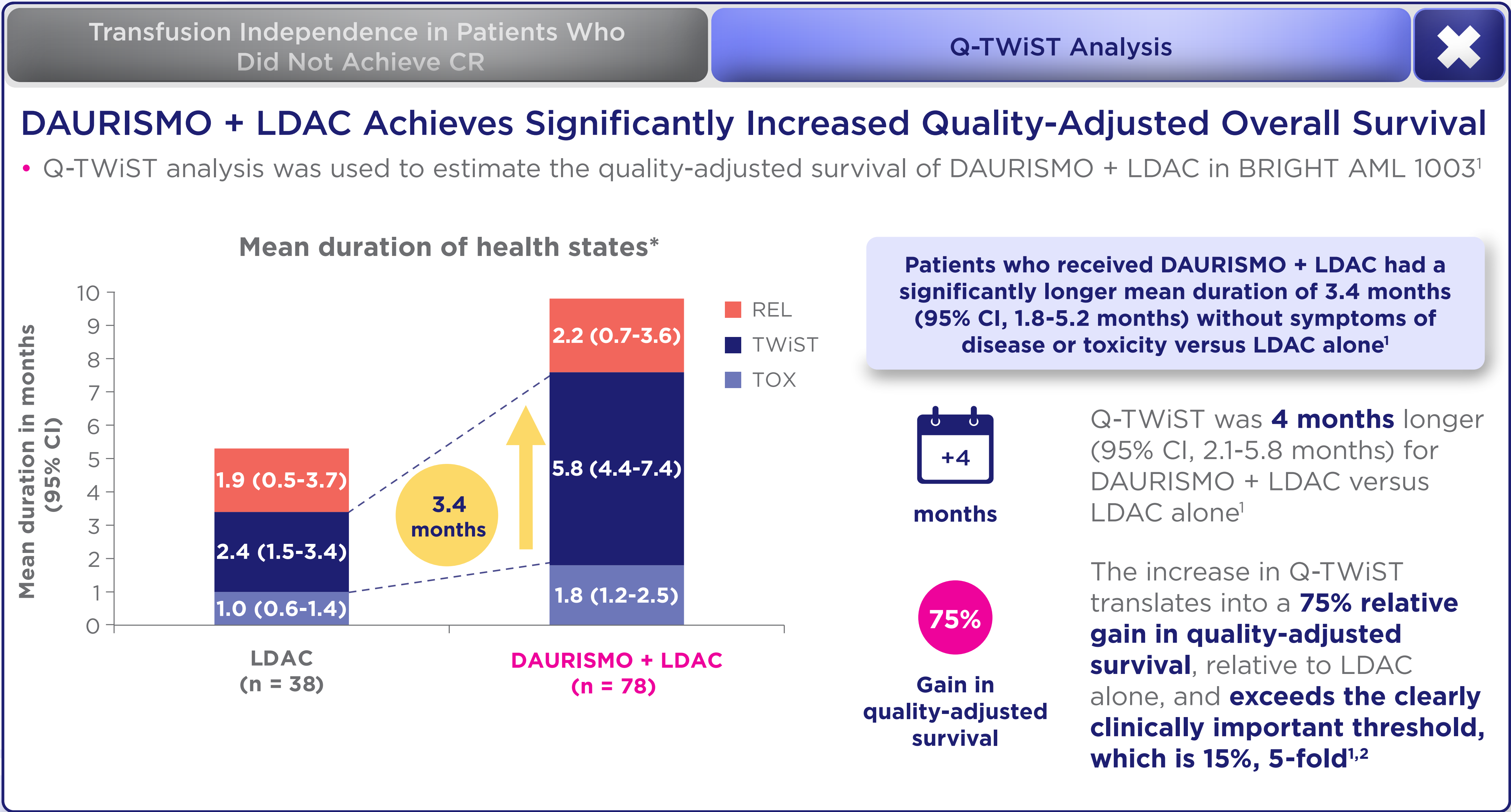
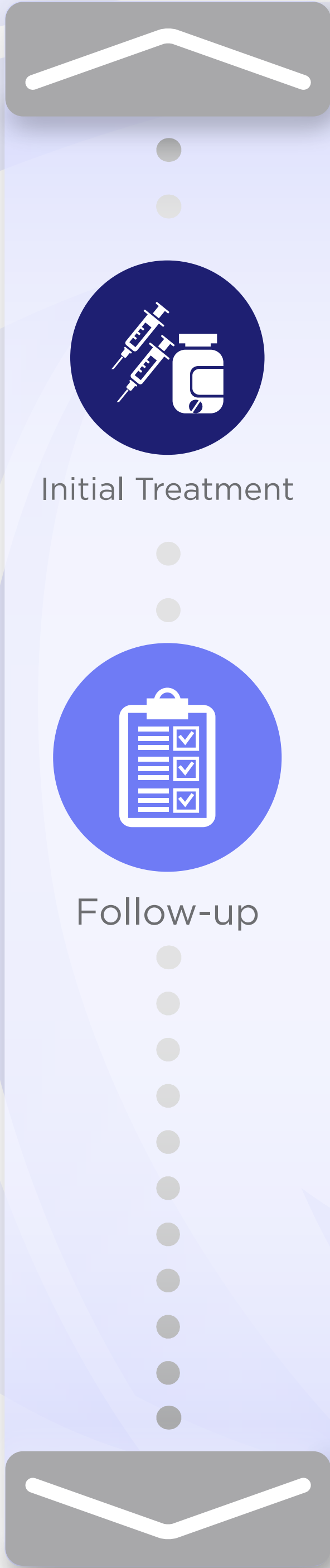


Figure adapted from Solem C, et al. *Cancer*. 2020;126(19):4315-4321.
*OS restricted to a follow-up of 20 months.
AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; LDAC=low-dose cytarabine; OS=overall survival; Q-TWiST=quality-adjusted time without symptoms of disease progression or toxicity; REL=time after treatment discontinuation due to insufficient clinical response, relapse or death; TOX=time with any Grade ≥ 3 treatment-emergent adverse event; 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.

Elsie's Examination and Laboratory Findings After 12 Cycles of DAURISMO + LDAC Treatment



Response

Adverse reactions

Bone marrow recovery

Quality of life

- Relapse after Cycle 12
- BM aspirate/biopsy: blast count = 20%
- WBC count = 4000/ μ L

- Anemia (Grade 3)
- Hemorrhages (Grade 2)
- Thrombocytopenia (Grade 2)
- Febrile neutropenia (Grade 3)

- Hemoglobin = 7.1 g/dL
- Platelet count = 23,000/ μ L
- ANC = 900/ μ L

- Intermittent RBC and platelet transfusions were required for 2 years
- Hemoglobin levels and platelet counts decreased, which meant that more frequent transfusions were required
- Was able to stay at home for the majority of treatment duration to spend quality time with family

How does Elsie compare with patients in the BRIGHT AML 1003 study?

- sAML
- Intermediate-risk cytogenetics
- CRi after Cycle 4

	Elsie	BRIGHT AML 1003 DAURISMO + LDAC arm
Duration of treatment	12 cycles	Median duration of treatment: two cycles (range: 1-43) in patients who did not achieve CR (n = 63) ¹
OS following initiation of treatment	14 months	Median OS for patients who did not achieve CR: 5.0 months (95% CI, 3.5-8.3) (n = 63) ^{1,*}
		Median OS for patients with good/intermediate cytogenetic risk: 11.1 months (95% CI, 7.1-14.9) (n = 49) ^{2,*}
		Median OS for patients with sAML: 9.1 months (95% CI, 4.4-16.5) (n = 40) ^{2,*}

*Analyses were exploratory, without adequate power to detect the difference between arms, and should be interpreted with caution.
AML=acute myeloid leukemia; ANC=absolute neutrophil count; BM=bone marrow; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; LDAC=low-dose cytarabine; OS=overall survival; RBC=red blood cell; sAML=secondary acute myeloid leukemia; WBC=white blood count.
1. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. 2. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.

Francesco: Diagnosis

Patient evaluation

- 87-year-old retired teacher
- Lives far from the treatment center, has difficulty traveling



Clinical presentation

- ECOG PS = 2
- Dyspnea
- Fatigue
- A number of infections, including pulmonary infiltrates over the past 2 months (on and off antibiotics)
- Pancytopenic (risk of myelosuppression)



Medical history

- History of coronary artery disease
- Angina
- Diabetes
- Hepatic dysfunction



Examination and laboratory findings

Cytogenetic and molecular profile

- Intermediate cytogenetic risk status
- *IDH1*/2wt, *FLT3*wt

Blood tests

- BM aspirate/biopsy:blast count = 25%
- WBC count = 1500/ μ L
- Hemoglobin = 8 g/dL
- Platelet count = 30,000/ μ L
- ANC = 900/ μ L
- Serum creatinine = 0.8 mg/dL



Diagnosis

De novo AML, not suitable for intensive induction chemotherapy

Which **clinical characteristics would impact your first-line treatment decision** for Francesco?



Diagnosis



Initial Treatment

AML=acute myeloid leukemia; ANC=absolute neutrophil count; BM=bone marrow; ECOG PS= Eastern Cooperative Oncology Group performance status; WBC=white blood count; wt=wild-type.



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Which Clinical Characteristics Would Impact Your First-Line Treatment Decision for Francesco?



Most patients in the BRIGHT AML 1003 study were aged ≥ 75 years and had multiple comorbidities that made them difficult to treat^{1,2}

Francesco	BRIGHT AML 1003 DAURISMO + LDAC arm ¹
Aged 87 years	62% of patients were aged ≥ 75 years
Newly diagnosed de novo AML	49%
Good/intermediate cytogenetic risk	63%
ECOG PS = 2	53%
Baseline severe cardiac disease	67%

- Patients were **not eligible for intensive chemotherapy**, as defined by meeting ≥ 1 of the following criteria³
 - Aged ≥ 75 years
 - ECOG PS = 2
 - Serum creatinine > 1.3 mg/dL
 - Severe cardiac disease
- At baseline, **two-thirds of patients met ≥ 2 criteria for nonintensive treatment²**



Diagnosis



Initial Treatment

AML=acute myeloid leukemia; ECOG PS= Eastern Cooperative Oncology Group performance status; LDAC=low-dose cytarabine.
1. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021. 2. Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194.
3. Cortes JE, et al. *Leukemia.* 2019;33(2):379-389.



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Francesco

Initial Treatment Choice: DAURISMO + LDAC



Francesco's Examination and Laboratory Findings After Two Cycles of DAURISMO + LDAC Treatment



Response

- Clinical benefit without CR after Cycle 2
- BM aspirate/biopsy: blast count = 6%
- WBC count = 3100/ μ L



Adverse reactions

- Anemia (Grade 2)
- Nausea (Grade 1)
- Grade 3 muscle-related AE (serum creatinine $\leq$ ULN; CK elevation $7 \times$ ULN) requiring DAURISMO dose reduction



Bone marrow recovery

- Hemoglobin = 9.8 g/dL
- Platelet count = 90,000/ μ L
- ANC = 1200/ μ L



Quality of life

- Treatment well tolerated following dose reduction
- Able to receive treatment at home
- Improved quality of life

How does Francesco compare with patients in the **BRIGHT AML 1003** study?

After Cycle 2, Francesco experienced **Grade 3 muscle spasms**. What would your **treatment considerations** be?

AE=adverse event; AML=acute myeloid leukemia; ANC=absolute neutrophil count; BM=bone marrow; CK=creatinine kinase; CR=complete remission; LDAC=low-dose cytarabine; ULN=upper limit of normal; WBC=white blood count.



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How Does Francesco's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Overall survival

Response rates

Adverse reactions

Bone marrow recovery

Quality of life



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glasdegib tablets

OS: Patients Who Did Not Achieve CR

[illegible]

Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194.

DAURISMO Dose Reduction



Resources

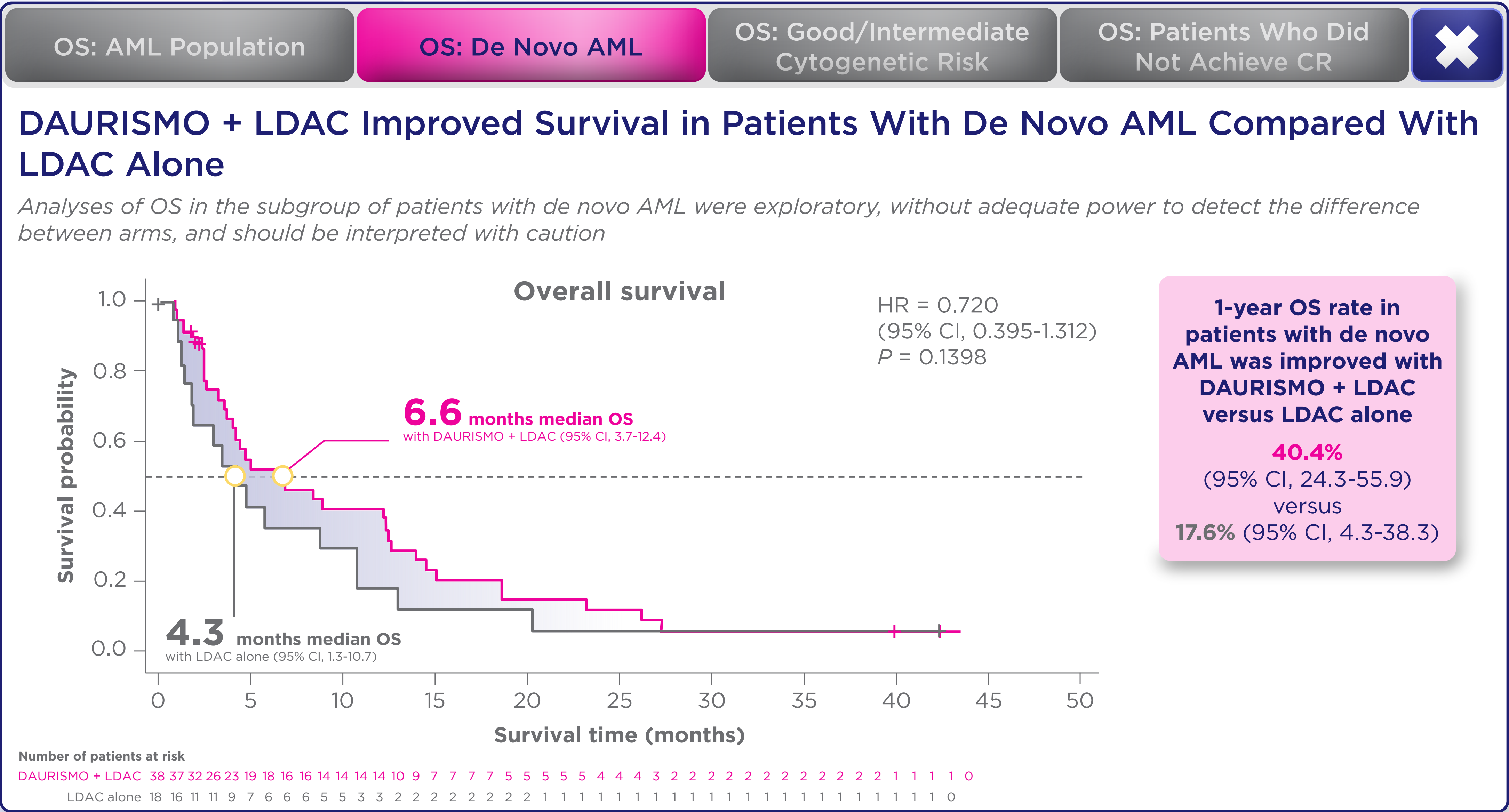
How Does Francesco's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Diagnosis

Initial Treatment

DAURISMO Dose Reduction



++ censored. Data cut-off: October 11, 2018.
AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival.
Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194.

How Does Francesco's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



OS: AML Population

OS: De Novo AML

OS: Good/Intermediate
Cytogenetic Risk

OS: Patients Who Did
Not Achieve CR



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

There is a slight imbalance towards 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

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	

Median OS in patients with good/intermediate cytogenetic risk who received DAURISMO + LDAC was > 2-fold greater than in patients who received LDAC alone

*HR based on the Cox proportional hazards model stratified by prognosis stratum. †One-sided P-value from stratified log-rank test based on cytogenetic risk. AML=acute myeloid leukemia; CI, confidence interval; CR=complete remission; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.



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How Does Francesco's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Diagnosis

Initial Treatment

DAURISMO Dose Reduction

OS: AML Population

OS: De Novo AML

OS: Good/Intermediate Cytogenetic Risk

OS: Patients Who Did Not Achieve CR

Improvement in OS Was Observed With DAURISMO + LDAC, Even Among Patients Who Did Not Achieve CR

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 + LDAC (n = 78)	LDAC alone (n = 38)
Patients who did not achieve CR		
n	63	37
Median OS, months (95% CI)	5.0 (3.5-8.3)	4.1 (1.9-5.3)
HR (95% CI)	0.63 (0.41-0.98)	
P-value	0.0182	

In patients who did not achieve CR, 1-year OS rates were higher in the DAURISMO + LDAC versus LDAC alone arm

27.3% (95% CI, 16.7-39.0) versus **5.7%** (95% CI, 1.0-16.8)

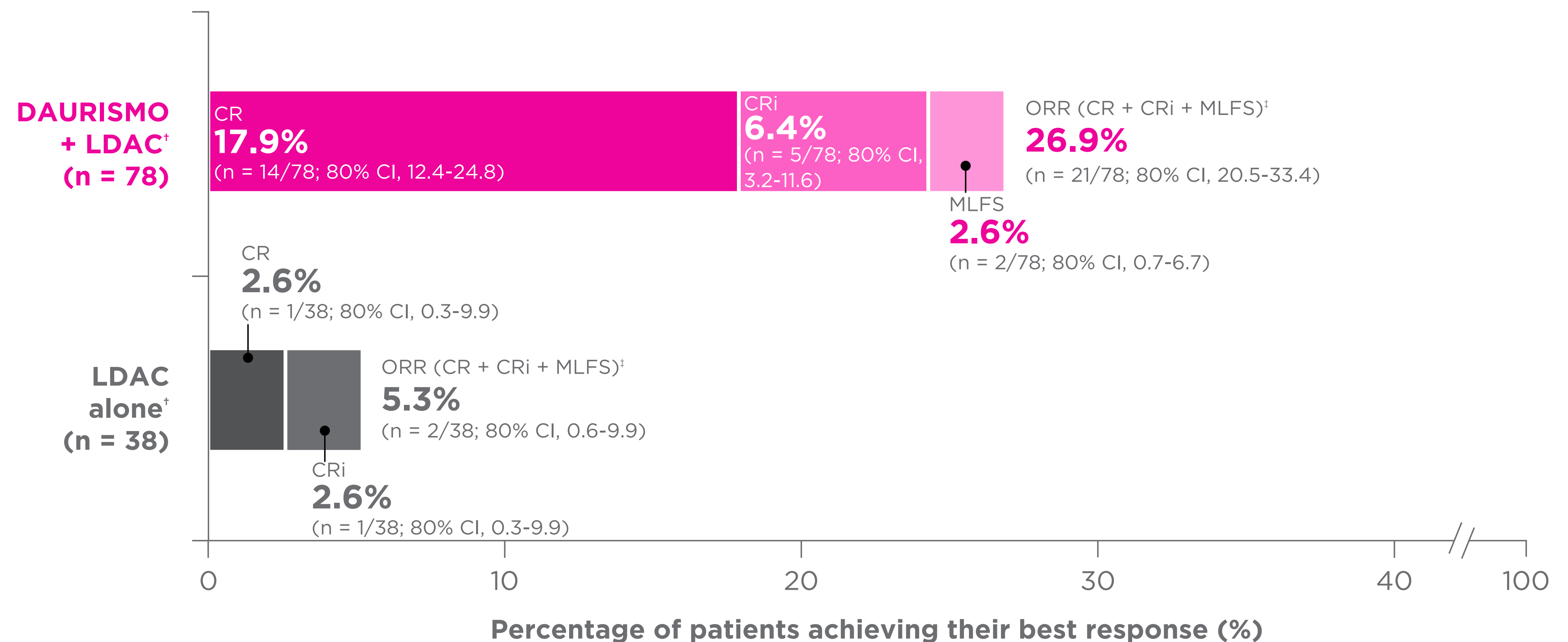
Adapted from Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. Data cut-off: October 2018. AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; HR=hazard ratio; LDAC=low-dose cytarabine; OS=overall survival. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92.

How Does Francesco's Treatment Journey Compare With Patients in the BRIGHT AML 1003 Study?



Response Rates

DAURISMO + LDAC Achieved Higher Overall Response Rates Versus LDAC Alone^{1,*}



Data cut-off: January 3, 2017.

*Using exact method based on binomial distribution and CIs expressed in percentages.² [†]In the DAURISMO + LDAC and LDAC alone arms, 24 and 16 patients, 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.² [‡]Using normal approximation for further endpoints of interest and CIs expressed in percentages.²

AE=adverse event; AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery of peripheral blood counts; LDAC=low-dose cytarabine; MLFS=morphologic leukemia-free state; ORR=overall response rate.

1. Cortes JE, et al. *Leukemia*. 2019;33(2):379-389. 2. Cortes JE, et al. *Leukemia*. 2019;33(2):379-389 (supplementary appendix).



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Adverse Reactions

DAURISMO + LDAC Has a Tolerable and Manageable Safety Profile^{1,2}

TEAEs* occurring after the first 90 days of treatment in patients who did not achieve CR²

MedDRA term n (%)	DAURISMO + LDAC (n = 29)	LDAC alone (n = 13)	MedDRA term n (%)	DAURISMO + LDAC (n = 29)	LDAC alone (n 13)
Anemia	8 (27.6)	3 (23.1)	Constipation	4 (13.8)	1 (7.7)
Nausea	5 (17.2)	0	Edema peripheral	1 (3.4)	0
Febrile neutropenia	4 (13.8)	1 (7.7)	Dysgeusia	2 (6.9)	0
Decreased appetite	8 (27.6)	3 (23.1)	Vomiting	2 (6.9)	0
Thrombocytopenia	8 (27.6)	2 (15.4)	Cough	2 (6.9)	1 (7.7)
Diarrhea	5 (17.2)	1 (7.7)	Dizziness	3 (10.3)	0
Fatigue	2 (6.9)	2 (15.4)	Dyspnea	2 (6.9)	2 (15.4)
Pneumonia	5 (17.2)	3 (23.1)	Muscle spasm	3 (10.3)	0
Pyrexia	5 (17.2)	1 (7.7)	Weight decreased	1 (3.4)	0

In the overall population, there were no treatment discontinuations due to Hedgehog-inhibitor class-effect AEs³

Dose modification and management recommendations for muscle-related AEs

Adapted from Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92 (supplementary appendix). Data cut-off: October 2018.

*Any-Grade all-causality TEAEs occurring in ≥ 20% of patients with AML (receiving DAURISMO + LDAC or LDAC alone in the BRIGHT AML 1003 study. DAURISMO + LDAC, n = 75; LDAC alone, n = 36).

AE=adverse event; AML=acute myeloid leukemia; CR=complete remission; LDAC=low-dose cytarabine; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

1. Cortes JE, et al. *Leukemia.* 2019;33(2):379-389. 2. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92 (supplementary appendix). 3. Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194.



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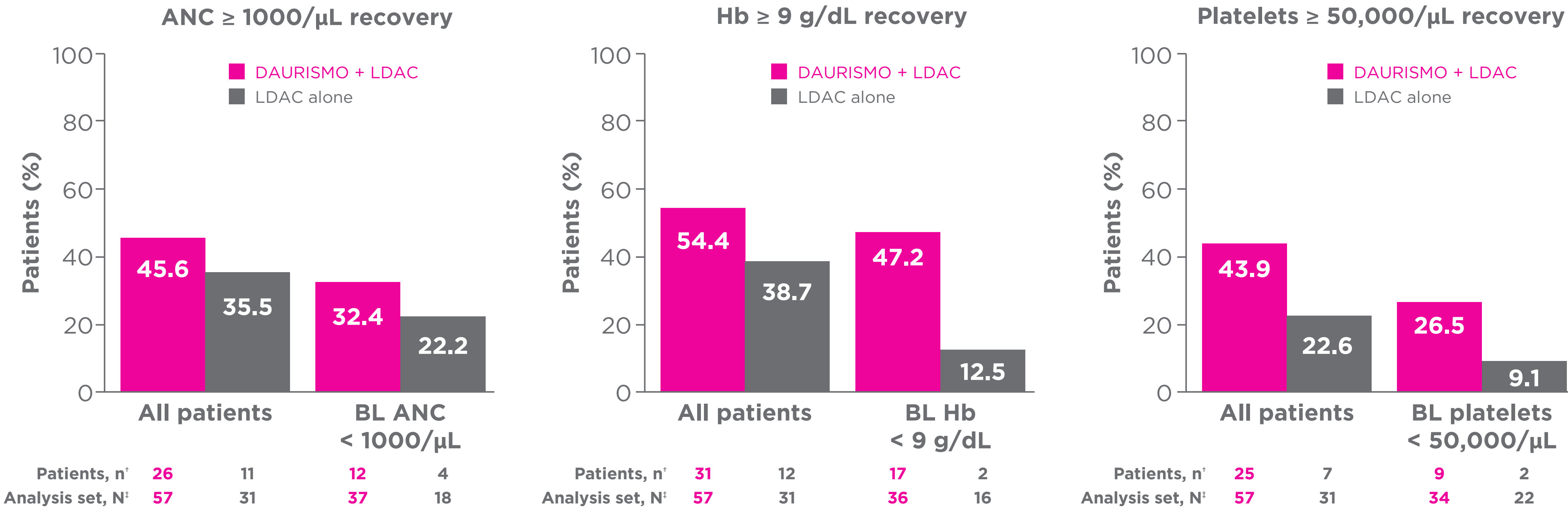


Bone Marrow Recovery

In Patients Who Did Not Achieve CR, Rates of Bone Marrow Recovery Were Consistently Higher With DAURISMO + LDAC Versus LDAC Alone Across All Three Cell Lineages

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

Durable ANC, Hb, and platelet recovery at any time on study in patients who did not achieve CR*



Adapted from Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. Data cut-off: October 2018.
*Required threshold measurement at ≥ 2 consecutive visits. [†]Number of patients meeting recovery criteria in the cycle. [‡]Number of patients with ANC/Hb or platelet results in the cycle.
AML=acute myeloid leukemia; ANC=absolute neutrophil count; BL=baseline; CR=complete remission; Hb=hemoglobin; LDAC=low-dose cytarabine.
Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92.



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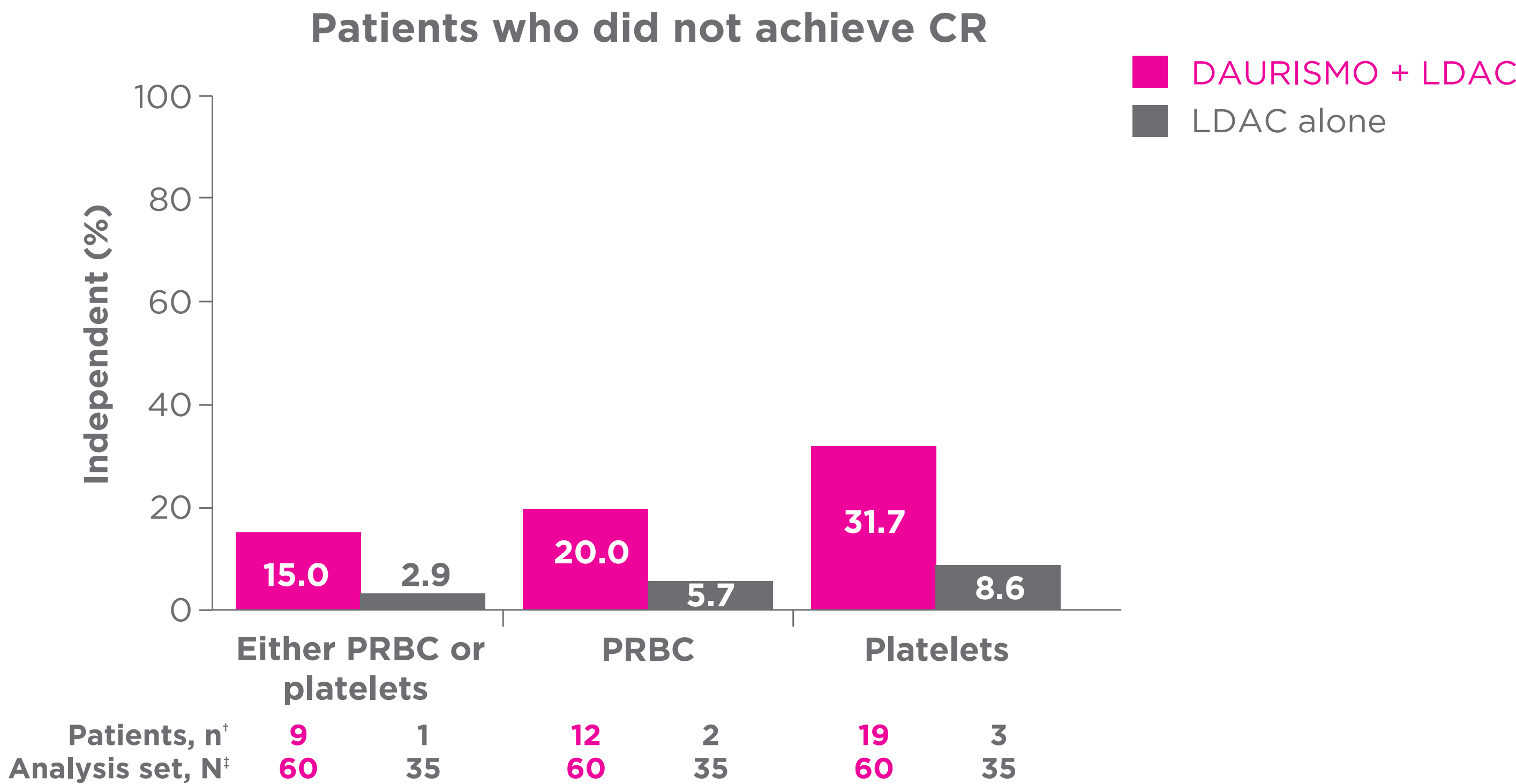
Transfusion Independence in Patients Who Did Not Achieve CR

Q-TWiST Analysis



Among Patients Who Did Not Achieve CR, Rates of Transfusion Independence* Were Higher With DAURISMO + LDAC Versus LDAC Alone¹

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



Transfusion independence is a critical factor that contributes to improved quality of life²

Adapted from Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. Data cut-off: October 2018.

*Transfusion-independent patients were defined as those who had ≥ 8 weeks (56 days) without any type of transfusion at any point of the study. All other patients are considered transfusion-dependent. [†]Number of patients meeting recovery criteria in the cycle. [‡]Number of patients with results in the cycle. AML=acute myeloid leukemia; CR=complete remission; LDAC=low-dose cytarabine; PRBC=packed red blood cells; Q-TWiST=quality-adjusted time without symptoms of disease progression or toxicity.

1. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. 2. Wang ES, et al. EHA 2019. Poster presentation (Abstract PF272).



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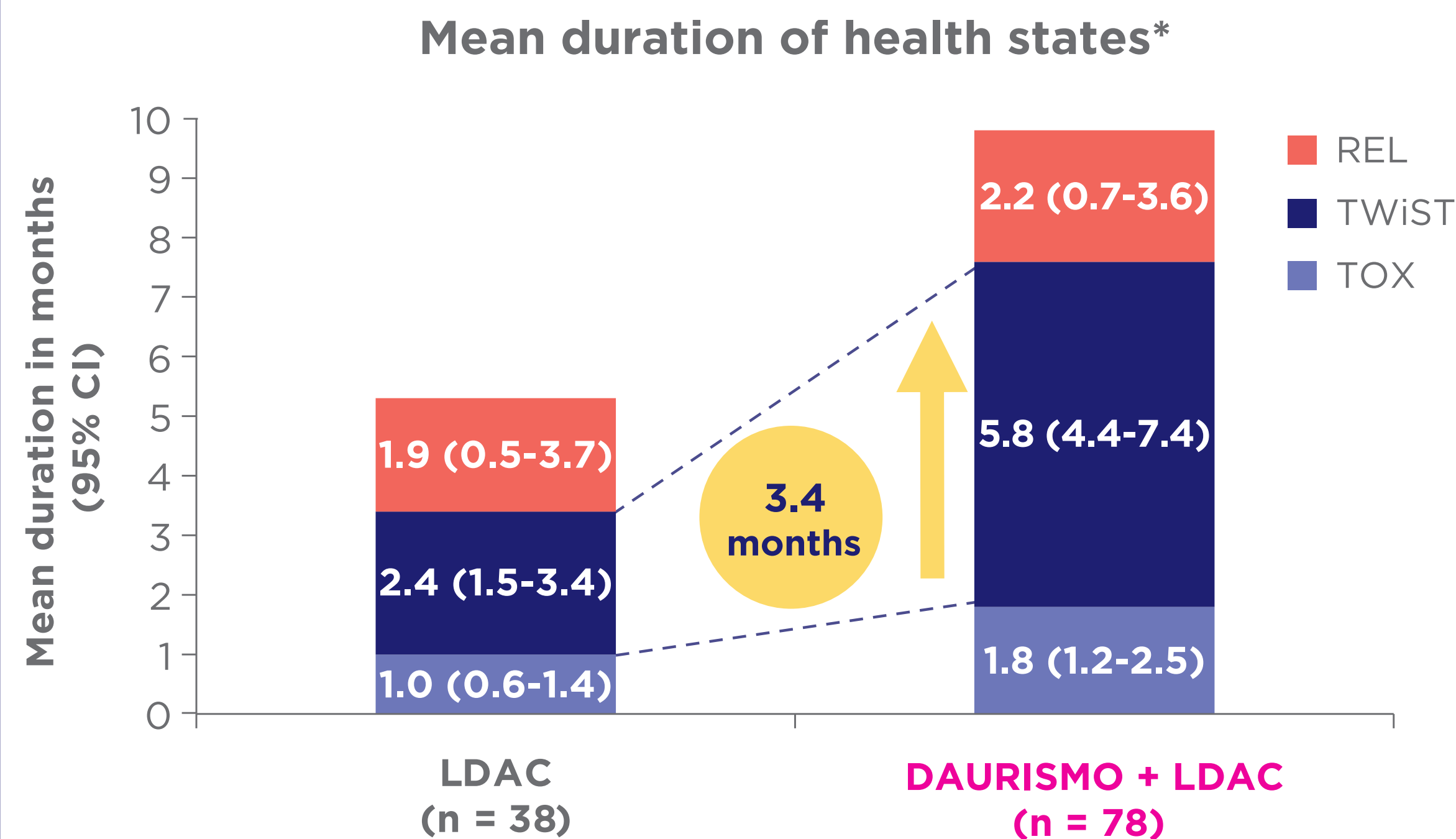
Transfusion Independence in Patients Who Did Not Achieve CR

Q-TWiST Analysis



DAURISMO + LDAC Achieves Significantly Increased Quality Adjusted Overall Survival

- Q-TWiST analysis was used to estimate the quality-adjusted survival of DAURISMO + LDAC in BRIGHT AML 1003¹

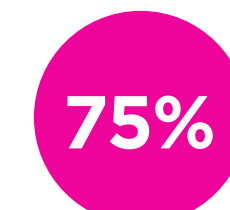


Patients who received DAURISMO + LDAC had a significantly longer mean duration of 3.4 months (95% CI, 1.8-5.2 months) without symptoms of disease or toxicity versus LDAC alone¹



months

Q-TWiST was **4 months** longer (95% CI, 2.1-5.8 months) for DAURISMO + LDAC versus LDAC alone¹



Gain in quality-adjusted survival

The increase in Q-TWiST translates into a **75% relative gain in quality-adjusted survival**, relative to LDAC alone, and **exceeds the clearly clinically important threshold, which is 15%, 5-fold^{1,2}**

Figure adapted from Solem C, et al. *Cancer*. 2020;126(19):4315-4321.

*OS restricted to a follow-up of 20 months.

AML=acute myeloid leukemia; CI=confidence interval; CR=complete remission; 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 treatment-emergent adverse event; 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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DAURISMO Dose Reduction to 50 mg Once Daily



DAURISMO Dose Modification and Management Recommendations: CK Elevations and Muscle-Related Adverse Events (Grade 3-4)



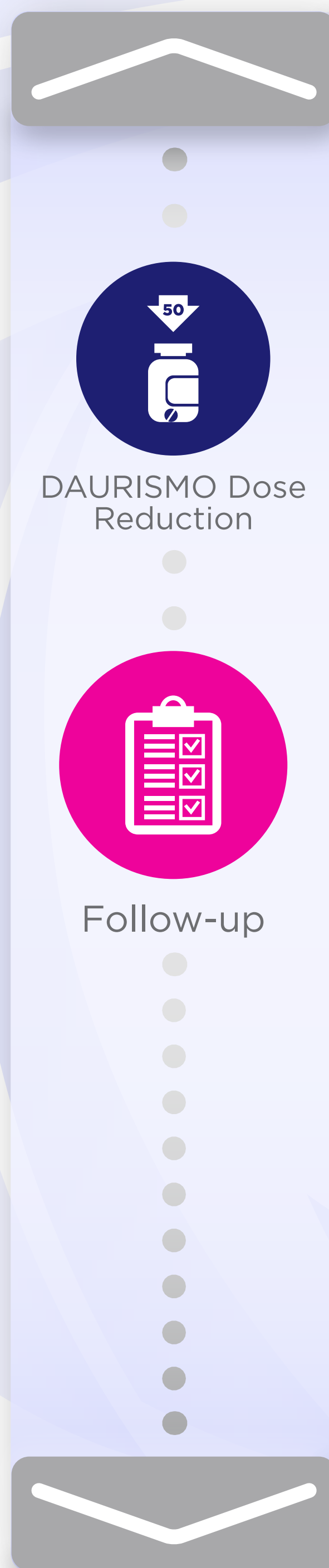
 Adverse event	 Recommended actions	 DAURISMO dose reduction	 Continued monitoring recommendations
Grade 3 or 4 muscle-related AE without renal impairment (serum creatinine $\leq$ ULN) (Grade 3 [CK elevation $> 5 \times$ ULN - $10 \times$ ULN]) (Grade 4 [CK elevation $> 10 \times$ ULN])	- Interrupt DAURISMO and monitor CK levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline - Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated	If renal function is not impaired and CK resolves to baseline, consider resuming DAURISMO at 50 mg daily	CK levels should be measured weekly for 2 months after re-administration of DAURISMO and monthly thereafter

 If dose reduction is necessary, then DAURISMO should be reduced to 50 mg taken orally once daily. For more information, please click the 'Dosing and Administration' tab below

Francesco	BRIGHT AML 1003 DAURISMO + LDAC arm ¹
DAURISMO dose reduction to 50 mg once daily following Grade 3 muscle spasms	Muscle spasms were the most frequently reported AR leading to dose reduction (4.7%)

AE=adverse event; AML=acute myeloid leukemia; AR=adverse reaction; CK=creatine kinase; LDAC=low-dose cytarabine; ULN=upper limit of normal. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.

Francesco's Examination and Laboratory Findings After Seven Cycles of DAURISMO + LDAC Treatment



Response	Adverse reactions	Bone marrow recovery	Quality of life
- Relapsed after Cycle 5 - BM aspirate/biopsy = 25% - WBC count = 2100/μL	- Anemia (Grade 3) - Pneumonia (Grade 3) - Nausea (Grade 1)	- Hemoglobin = 7 g/dL - Platelet count = 40,000/μL - ANC = 800/μL	Hospitalized for last 2 weeks of life but was able to spend most of treatment time at home with family

How does Francesco compare with patients in the BRIGHT AML 1003 study?

	Francesco	BRIGHT AML 1003 DAURISMO + LDAC arm
Duration of treatment	5 cycles	Median duration of treatment: two cycles (range: 1-43) in patients who did not achieve CR (n = 63) ¹
OS following initiation of treatment	6 months	Median OS for patients with de novo AML: 6.6 months (95% CI, 3.7-12.4) (n = 38) ^{2,*}
		Median OS for patients who did not achieve CR: 5.0 months (95% CI, 3.5-8.3) (n = 63) ^{1,*}
		Median OS for patients with good/intermediate cytogenetic risk: 11.1 months (95% CI, 7.1-14.9) (n = 49) ^{3,*}

*Analyses were exploratory, without adequate power to detect the difference between arms, and should be interpreted with caution.
 AML=acute myeloid leukemia; ANC=absolute neutrophil count; BM=bone marrow; CI=confidence interval; CR=complete remission; LDAC=low-dose cytarabine; OS=overall survival; WBC=white blood count.
 1. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92. 2. Heuser M, et al. *Ann Hematol.* 2021;100(5):1181-1194. 3. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.

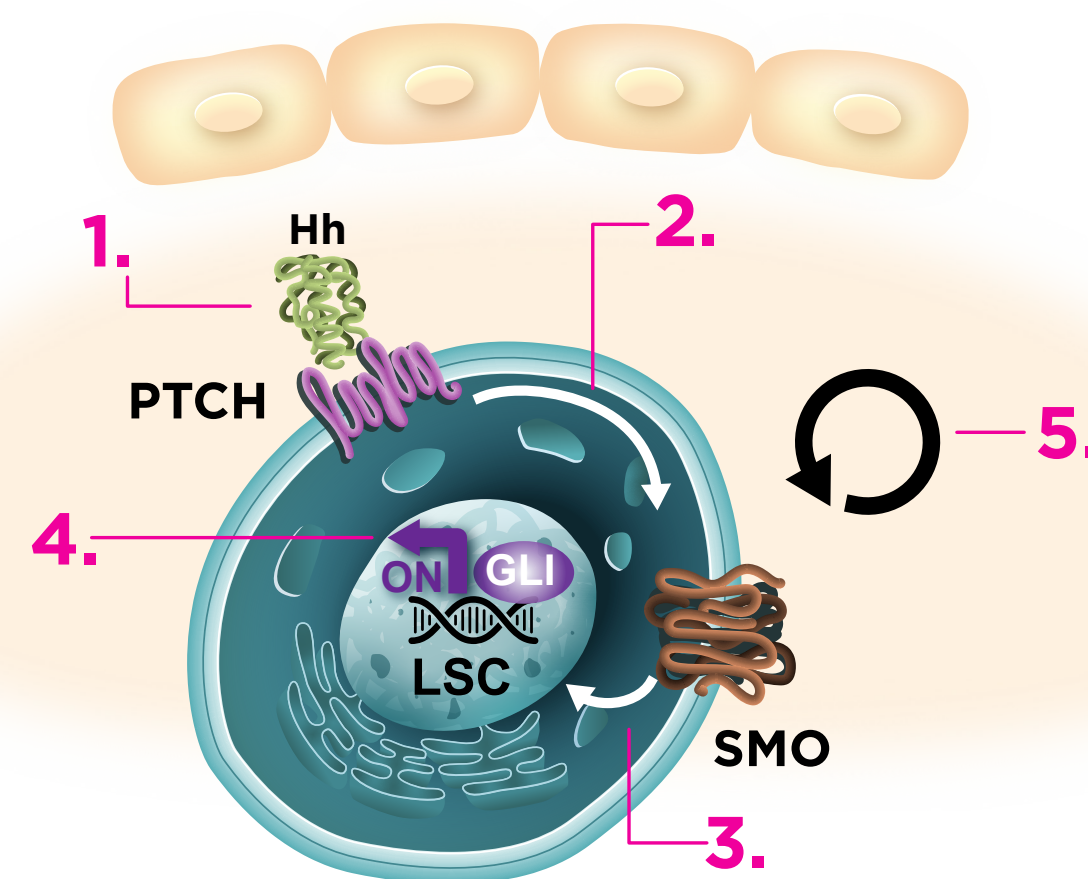
DAURISMO Mechanism of Action

Hh Pathway

DAURISMO + LDAC

DAURISMO Is a Selective Inhibitor of SMO, a Key Component of the Hh Signaling Pathway in LSCs^{1,2}

The Hh pathway is implicated in the maintenance of LSC dormancy and resistance to chemotherapy and targeted therapy¹⁻³

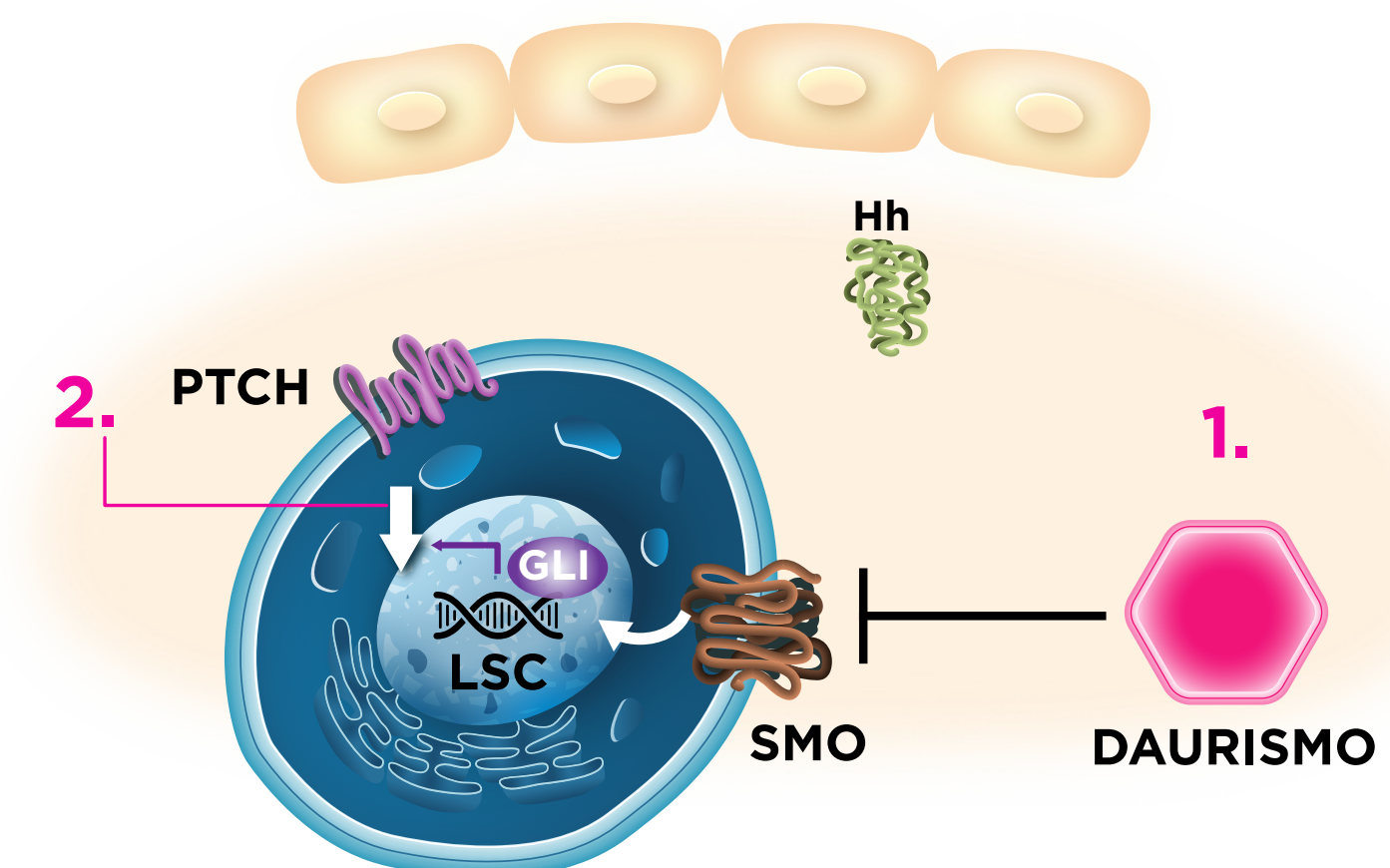


The Hh pathway: Active state^{2,4-6}

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

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 signaling¹



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

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

3. Irvine DA, et al. *Blood*. 2012;119(10):2196-2204. 4. Amakye D, et al. *Nat Med*. 2013;19(11):1410-1422. 5. Rimkus TK, et al. *Cancers (Basel)*. 2016;8(2):e22.

6. Cochrane CR, et al. *Cancers (Basel)*. 2015;7(3):1554-1585.



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DAURISMO Mechanism of Action



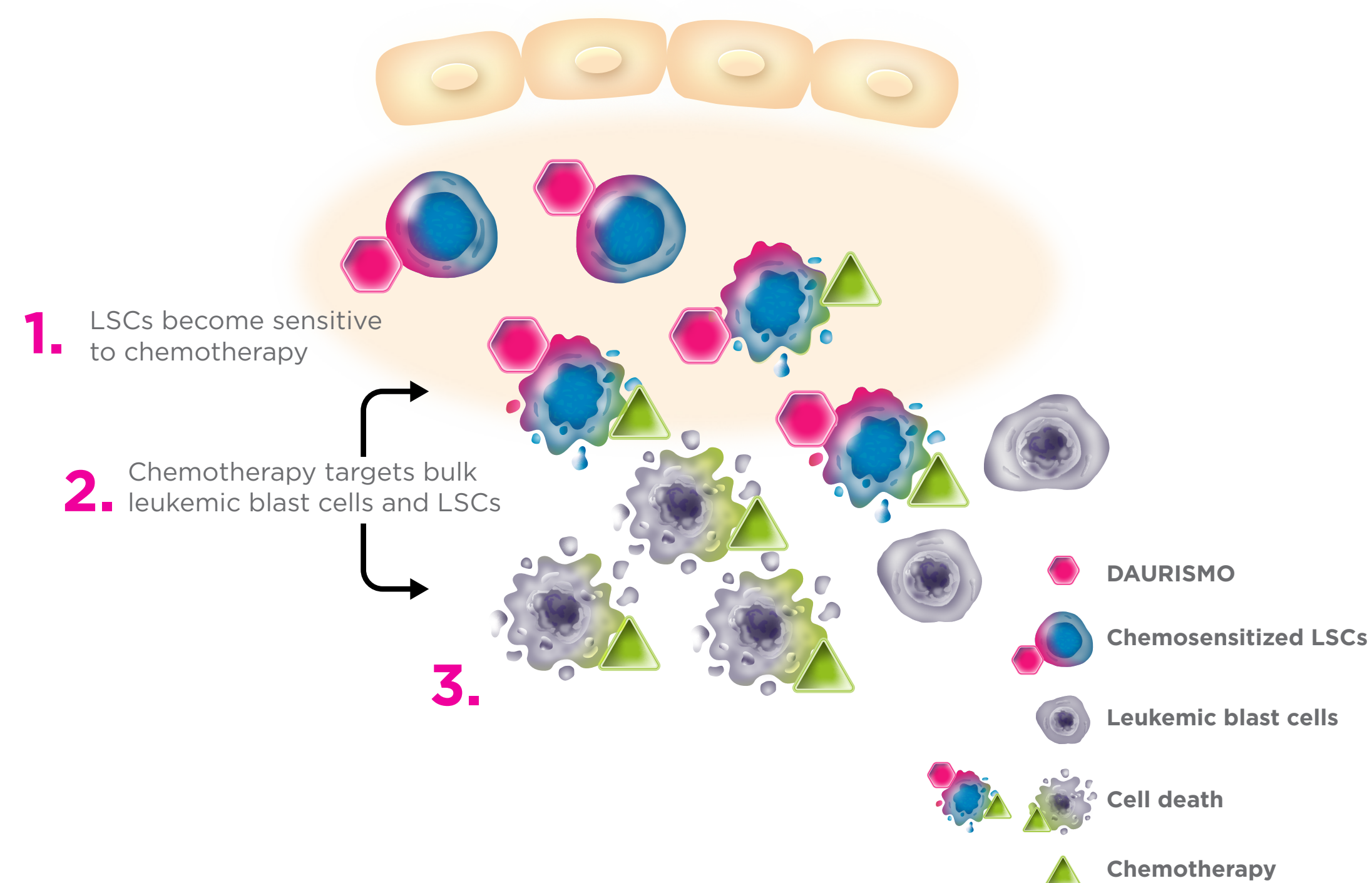
Hh Pathway

DAURISMO + LDAC

DAURISMO Is a Selective Inhibitor of SMO, a Key Component of the Hh Signaling Pathway in LSCs^{1,2}

In preclinical studies, DAURISMO has been shown to inhibit LSC dormancy and limit LSC self-renewal¹

The mechanism of action of the combination of Hh pathway inhibition and cytarabine is not fully understood²



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 alone²

AML=acute myeloid leukemia; 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. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.

3. Siveen KS, et al. *Mol Cancer.* 2017;16(1):13.



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BRIGHT AML 1003: A Phase 2 Open-Label, Randomized, Multicenter Study That Evaluated DAURISMO + LDAC in Patients Who Were Not Eligible for Intensive Chemotherapy^{1,2}

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 chemotherapy¹

Treatment arms and administration schedule for the AML population³

Eligibility criteria

Adults aged ≥ 55 years 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 endpoints: OS, response assessments, safety and tolerability, PK/PD, effect on corrected QT (QTc) interval³

- Patients were stratified at randomization by cytogenetic risk (good/intermediate or poor)³
- Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent³

*sAML included AML evolving from MDS or other AHD and AML after previous cytotoxic therapy or radiation.³

AHD=antecedent hematologic disorder; AML=acute myeloid leukemia; ECOG PS=Eastern Cooperative Oncology Group performance status; LDAC=low-dose cytarabine; MDS=myelodysplastic syndrome; OS=overall survival; PD=pharmacodynamics; PK=pharmacokinetics; sAML=secondary acute myeloid leukemia.

1. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021. 2. Cortes JE, et al. *J Hematol Oncol.* 2020;13(1):92.

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

Study Design

Patient Characteristics

Most Patients in the BRIGHT AML 1003 Study Were Aged ≥ 75 Years and Had Multiple Comorbidities That Made Them Difficult to Treat¹

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), ¹ n (%)		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)

Key patient characteristics across treatment arms

- **52%** of patients had sAML¹
- **15% of patients had received prior AZA or DEC therapy¹**
- **51%** had an ECOG PS of 2¹
- **35%** of patients had adverse-risk disease²

^{*}Baseline ECOG PS was not reported for one patient in the DAURISMO + LDAC arm.
AML=acute myeloid leukemia; AZA=azacitidine; DEC=decitabine; ECOG PS=Eastern Cooperative Oncology Group performance status; ELN=European LeukemiaNet; HMA=hypomethylating agent; LDAC=low-dose cytarabine; sAML=secondary acute myeloid leukemia.
1. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021. 2. Cortes JE, et al. *Leukemia*. 2019;33(2):379-389.

Dosing and Administration



Dosing Schedule

Dose Modifications and Management Recommendations for ARs

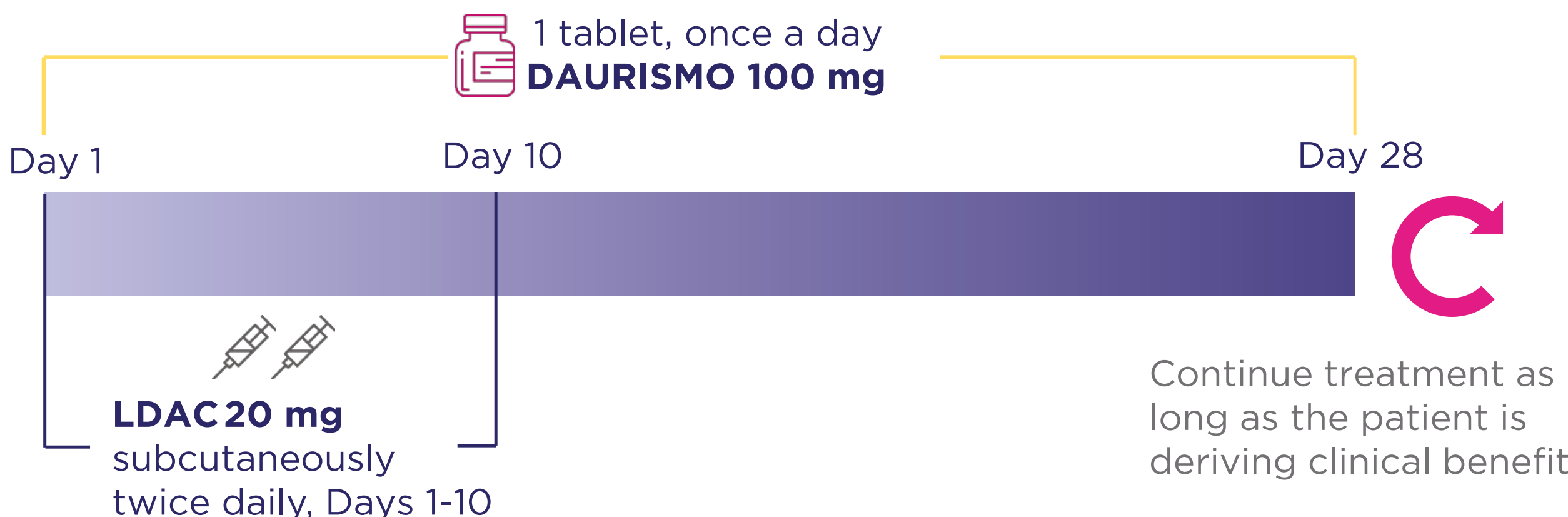
QT Interval Prolongation

CK Elevations and
Muscle-Related AEs

Hematologic and
Nonhematologic Toxicity

Oral, Once-Daily¹

DAURISMO + LDAC 28-day dosing schedule¹



Dosing and administration considerations



DAURISMO may be taken with or without food¹



DAURISMO + LDAC can be administered as an outpatient or at-home treatment^{1-3,*}

Dose modifications



DAURISMO is available in 100 mg and 25 mg film-coated tablets, offering dose flexibility for treatment management¹



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 daily¹

*Per institutional guidelines.

AE=adverse event; AR=adverse reaction; CK=creatinine kinase; LDAC=low-dose cytarabine.

1. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 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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Dose Modifications and Management Recommendations for ARs

QT Interval Prolongation

CK Elevations and Muscle-Related AEs

Hematologic and Nonhematologic Toxicity

In BRIGHT AML 1003,¹ Grade 3/4 ECG QT Prolonged Was Reported in 3.5% of Patients Treated With DAURISMO + LDAC Compared With 2.4% of Patients Treated With LDAC Alone²

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 daily²

Adverse reaction: QT interval prolongation (corrected QT interval prolongation on at least two separate ECGs) ²	Recommended actions ²
Corrected QT interval 480-500 ms	• Assess electrolyte levels and supplement as clinically indicated • Review and adjust concomitant medicinal products with known QT prolonging effects • Monitor ECGs at least weekly for 2 weeks following resolution of QT prolongation to ≤ 480 ms
Corrected QT interval > 500 ms	• Assess electrolyte levels and supplement as clinically indicated • Review and adjust concomitant medicinal products with known QT prolonging effects • Interrupt DAURISMO • Resume DAURISMO at a reduced dose of 50 mg once daily when corrected QT interval returns to within 30 ms of baseline or ≤ 480 ms • Monitor ECGs at least weekly for 2 weeks following resolution of QT prolongation • Consider re-escalating the dose of DAURISMO to 100 mg daily if an alternative etiology for the QT prolongation can be identified
Corrected QT interval prolongation and life-threatening arrhythmia	• Discontinue DAURISMO permanently

Click here for guidance on monitoring laboratory and QT abnormalities with DAURISMO



AE=adverse event; AML=acute myeloid leukemia; AR=adverse reaction; CK=creatinine kinase; ECG=electrocardiogram; LDAC=low-dose cytarabine.
1. Cortes JE, et al. *J Hematol Oncol*. 2020;13(1):92. 2. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.

Dosing and Administration



Dosing Schedule

Dose Modifications and Management Recommendations for ARs

QT Interval Prolongation

CK Elevations and
Muscle-Related AEs

Hematologic and
Nonhematologic Toxicity

In BRIGHT AML 1003,¹ Muscle Spasms Were Observed in 22.6% of Patients Treated With DAURISMO + LDAC Compared With 4.8% of Patients Treated With LDAC Alone²

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 daily²

Adverse reaction: CK elevations and muscle-related AEs ²	Recommended actions ²
Grade 1 (CK elevation > ULN - 2.5 × ULN)	• Continue DAURISMO at the same dose and monitor CK levels weekly until resolution to baseline level and then monthly thereafter • Monitor muscle symptoms for changes until resolution to baseline • Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated
Grade 2 without renal impairment (serum creatinine ≤ ULN) (CK elevation > 2.5 × ULN - 5 × ULN)	• Interrupt DAURISMO and monitor CK levels weekly until resolution to baseline level • Monitor muscle symptoms for changes until resolution to baseline. Upon resolution, resume DAURISMO at the same dose level and measure CK monthly thereafter • Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated • If symptoms re-occur, interrupt DAURISMO until resolution to baseline. Re-introduce DAURISMO at 50 mg daily and follow the same monitoring recommendations. If symptoms persist, consider discontinuing DAURISMO
Grade 3 or 4 without renal impairment (serum creatinine ≤ ULN) (Grade 3 [CK elevation > 5 × ULN - 10 × ULN]) (Grade 4 [CK elevation > 10 × ULN])	• Interrupt DAURISMO and monitor CK levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline • Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated • If renal function is not impaired and CK resolves to baseline, consider resuming DAURISMO at 50 mg daily. CK levels should be measured weekly for 2 months after re-administration of DAURISMO and monthly thereafter
Grade 2, 3, or 4 with renal impairment (serum creatinine > ULN per CTCAE 4.0)	• If renal function is impaired, interrupt DAURISMO and ensure that the patient is adequately hydrated and evaluate other secondary causes of renal impairment • Monitor CK and serum creatinine levels weekly until resolution to baseline. Monitor muscle symptoms for changes until resolution to baseline • If CK and serum creatinine levels return to baseline consider resuming DAURISMO at 50 mg daily and measure CK levels weekly for 2 months and monthly thereafter; otherwise discontinue treatment permanently

AE=adverse event; AML=acute myeloid leukemia; AR=adverse reaction; CK=creatine kinase; CTCAE=Common Terminology Criteria for Adverse Events; LDAC=low-dose cytarabine; ULN=upper limit of normal.

1. Cortes JE, et al. *J Hematol Oncol*. 2020;13(1):92. 2. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.



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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

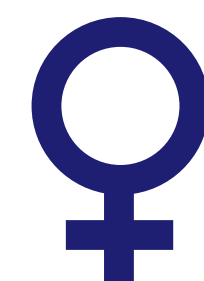
Adverse reaction: Hematologic toxicity	Recommended actions
Platelets < $10 \times 10^9/L$ for > 42 days in the absence of disease	• Discontinue DAURISMO and LDAC permanently
Neutrophil count < $0.5 \times 10^9/L$ for > 42 days in the absence of disease	• Discontinue DAURISMO and LDAC permanently
Adverse reaction: Nonhematologic toxicity	Recommended actions
	If AR is attributed to LDAC and not to DAURISMO, LDAC may be modified while DAURISMO dosing should be continued
Grade 3*	• Interrupt DAURISMO and/or LDAC until symptoms improve to Grade ≤ 1 or return to baseline • Resume DAURISMO at the same dose level, or at a reduced dose of 50 mg • Resume LDAC at the same dose level, or at a reduced dose of 15 mg or 10 mg • If toxicity recurs, discontinue DAURISMO and/or LDAC[†]
Grade 4*	• Withhold DAURISMO until symptoms improve to Grade ≤ 1 or return to baseline • Upon recovery, resume DAURISMO at a dose of 50 mg or discontinue treatment at the discretion of the prescriber

*Grading according to CTCAE 4.0: Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening. [†]If a decision is made to permanently discontinue LDAC, DAURISMO should also be discontinued, unless the individual patient is deriving clinical benefit and is tolerating treatment with DAURISMO. AE=adverse event; AR=adverse reaction; CK=creatinine kinase; CTCAE=Common Terminology Criteria for Adverse Events; LDAC=low-dose cytarabine. DAURISMO® [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.

Special Warnings and Precautions: Embryo-Fetal Toxicity

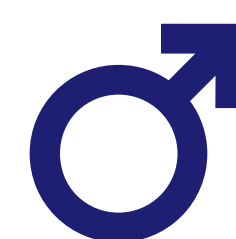
Adverse Reactions

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



Click [here](#) for other special warnings and precautions with DAURISMO

HCP=healthcare professional.
DAURISMO[®] [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.

Special Warnings and Precautions:
Embryo–Fetal Toxicity

Adverse Reactions

DAURISMO + LDAC Has a Tolerable and Manageable Safety Profile¹

ARs reported in clinical studies^{2,*}

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 overall safety profile of DAURISMO is based on data from clinical studies, including BRIGHT AML 1003. AML=acute myeloid leukemia; AR=adverse reaction; LDAC=low-dose cytarabine.
1. Cortes JE, et al. *Leukemia*. 2019;33(2):379-389. 2. DAURISMO[®] [summary of product characteristics]. Brussels, Belgium: Pfizer; 2021.

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