Vyxeos Liposomal

(44 mg/100 mg powder for concentrate for solution for infusion Daunorubicin/Cytarabine)

Clinical Overview

Vyxeos Liposomal is indicated for the treatment of adults with newly diagnosed, therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).[1]

1. Vyxeos Liposomal. European Summary of Product Characteristics. January 2021.

INT-VYX-2100026
Date of Preparation: April 2021

Vyxeos® Liposomal

44 mg/100 mg Powder for concentrate for solution for infusion

daunorubicin / cytarabine

Prescribing information is available at the end of this presentation

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Please refer to the full publications for further information.

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Clinical evidence for Vyxeos Liposomal vs conventional chemotherapy* – Phase III Pivotal trial

Trial	Patient Population	Objectives	Size	Vyxeos Liposomal demonstrated, vs conventional chemotherapy:
Phase III randomised, multicentre, open-label, parallel arm, superiority study[1]	Untreated high-risk AML	Evaluate overall survival (primary endpoint), CR+CRi, EFS, safety (secondary endpoints)	309 patients	• Significantly improved overall survival[1] • Superior rates of CR / CRi[1] • OS benefit maintained to 5 years[2] • Superior OS post-HSCT[1] • Lower rates of early mortality[1] • Similar frequency and severity of Grade 3-5 AEs[1]

Please see the following slides in this deck for further information on these results

1. Lancet JE, et al. *J Clin Oncol* 2018;36(26): 2684-2692.
2. Lancet JE et al. Presented at the Congress of the European Hematological Association (EHA) 2020, EP556.

*Conventional chemotherapy is defined as 7+3 in induction, 5+2 in second induction and consolidation, where given

AE, adverse event; CR, complete response; CRi, CR with incomplete blood count recovery; EFS, event-free survival.

Phase III randomised, open-label, multicentre study[1,2]

- Older patients: aged 60-75

  - Therapy-related AML
  - AML with history of MDS
  - AML with history of CMML
  - *De novo* AML with MDS karyotype

- Previously untreated
- Able to tolerate intensive therapy (ECOG PS 0-2)

1. Lancet JE, et al. *J Clin Oncol* 2018;36(26): 2684-2692..
2. Vyxeos Liposomal. European Summary of Product Characteristics. January 2021.

ECOG PS: The Eastern Cooperative Oncology Group Performance Status

Phase III trial design[1]

309 PATIENTS

Patient characteristics were balanced across the 2 treatment arms

Vyxeos Liposomal n=153	**Conventional chemotherapy*** n=156
Induction 44 mg/100 mg/m^2 on days 1, 3 and 5	**Induction** 7 days cytarabine 100 mg/m^2/day 3 days daunorubicin 60 mg/m^2/day
Subsequent induction 44 mg/100 mg/m^2 on days 1 and 3	**Subsequent induction** 5 days cytarabine 100 mg/m^2/day 2 days daunorubicin 60 mg/m^2/day
Consolidation (1-2 cycles) 29 mg/65 mg/m^2 on days 1 and 3	**Consolidation** (1-2 cycles) 5 days cytarabine 100 mg/m^2/day 2 days daunorubicin 60 mg/m^2/day

PRIMARY ENDPOINT: OVERALL SURVIVAL

SECONDARY ENDPOINTS INCLUDED: CR, EFS, RATE OF MLFS, PROPORTION OF HSCT

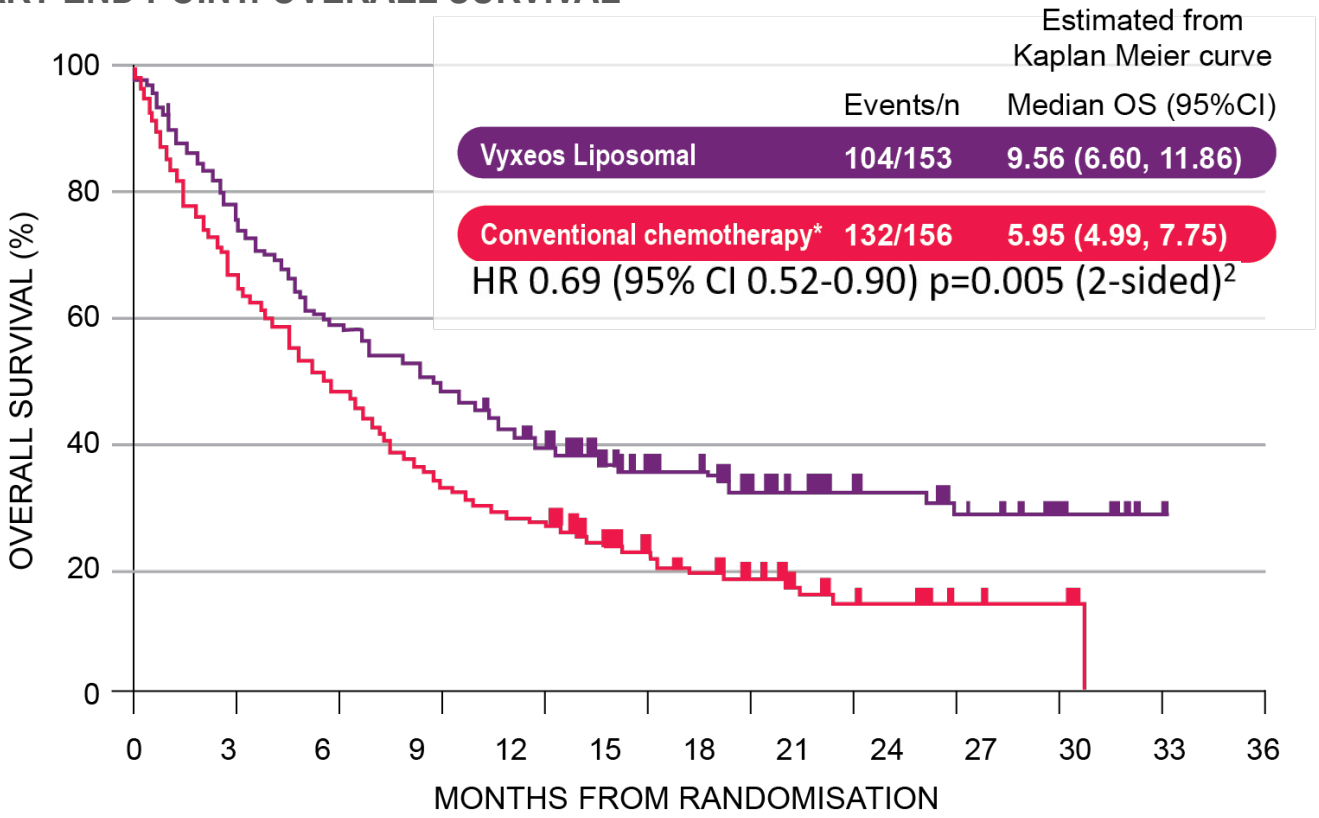
*Conventional chemotherapy is defined as 7+3 in induction, 5+2 in second induction and consolidation where given.

CR: Complete Remission
EFS: Event-Free Survival
MLFS: Morphologic Leukaemia-free State
HSCT: Haematopoietic Stem Cell Transplantation

1. Lancet JE et al. *J Clin Oncol* 2018, 10;36(26):2684-2692.

The first chemotherapy to significantly increase overall survival vs conventional chemotherapy* for patients with high-risk AML**[1,2]

PRIMARY END POINT: OVERALL SURVIVAL[1]



NO. AT RISK

Vyxeos Liposomal	153	122	92	79	62	46	34	21	16	11	5	1
Conventional chemotherapy*	156	110	77	56	43	31	20	12	7	3	2	0

- **31%** reduction in the relative risk of death for patients treated with **Vyxeos Liposomal** vs **conventional chemotherapy** *[1]

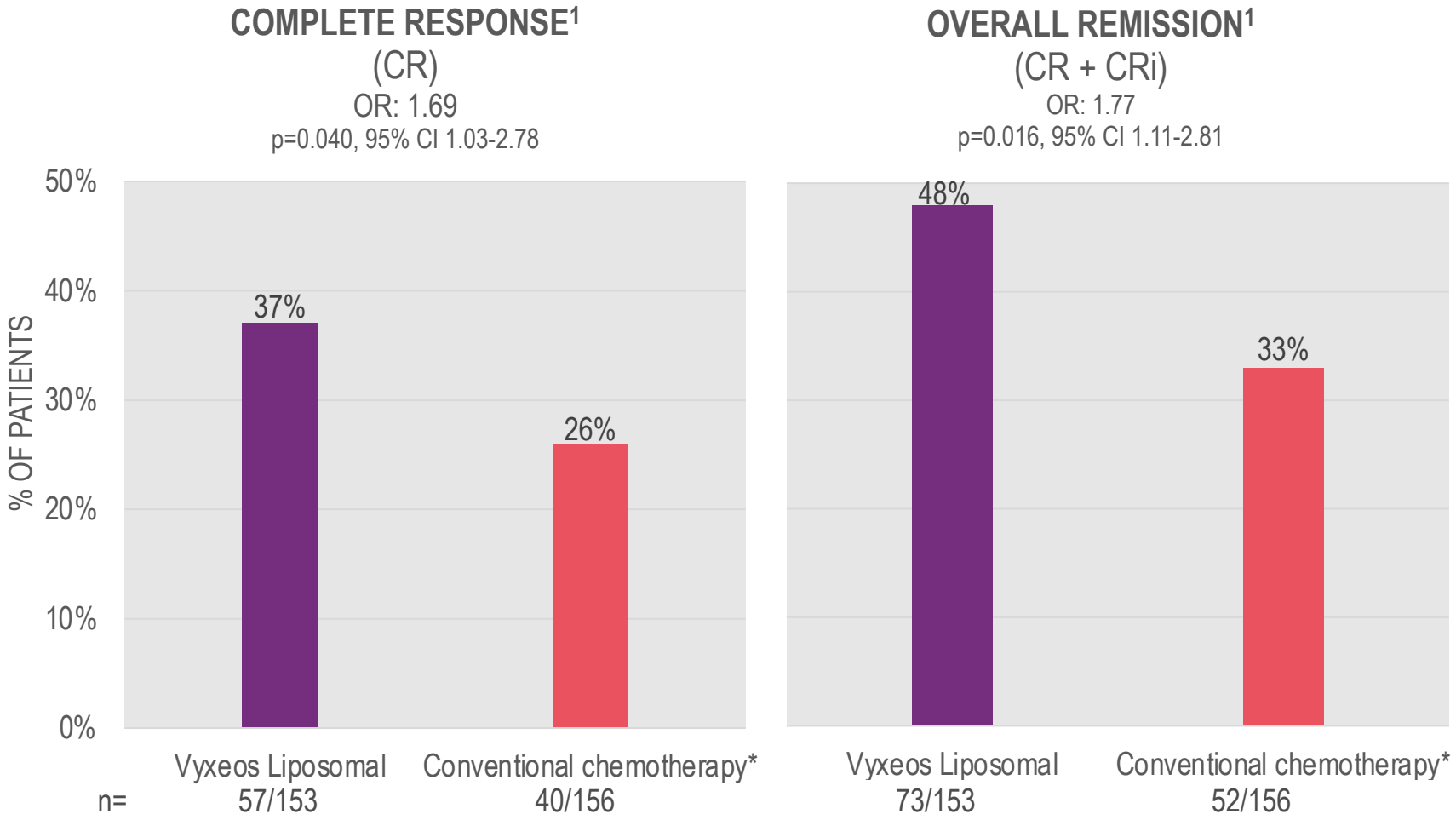
(HR 0.69, 95% CI 0.52-0.90, p=0.005, 2-sided[2])

Median duration of follow up: 20.7 months

*Conventional chemotherapy is defined as 7+3 in induction, 5+2 in second induction and consolidation where given; **High-risk AML defined as t-AML or AML-MRC

1. Lancet JE et al. *J Clin Oncol* 2018, 10;36(26):2684-2692. 2. Vyxeos Liposomal. European Summary of Product Characteristics. January 2021.

Patients receiving Vyxeos Liposomal achieve significantly greater response rates vs conventional chemotherapy*[1]



Overall remission (CR + CRi) rates after 1 induction cycle:[1]

- **55% Vyxeos Liposomal** (58/105)
- **34% Conventional chemotherapy*** (34/100)

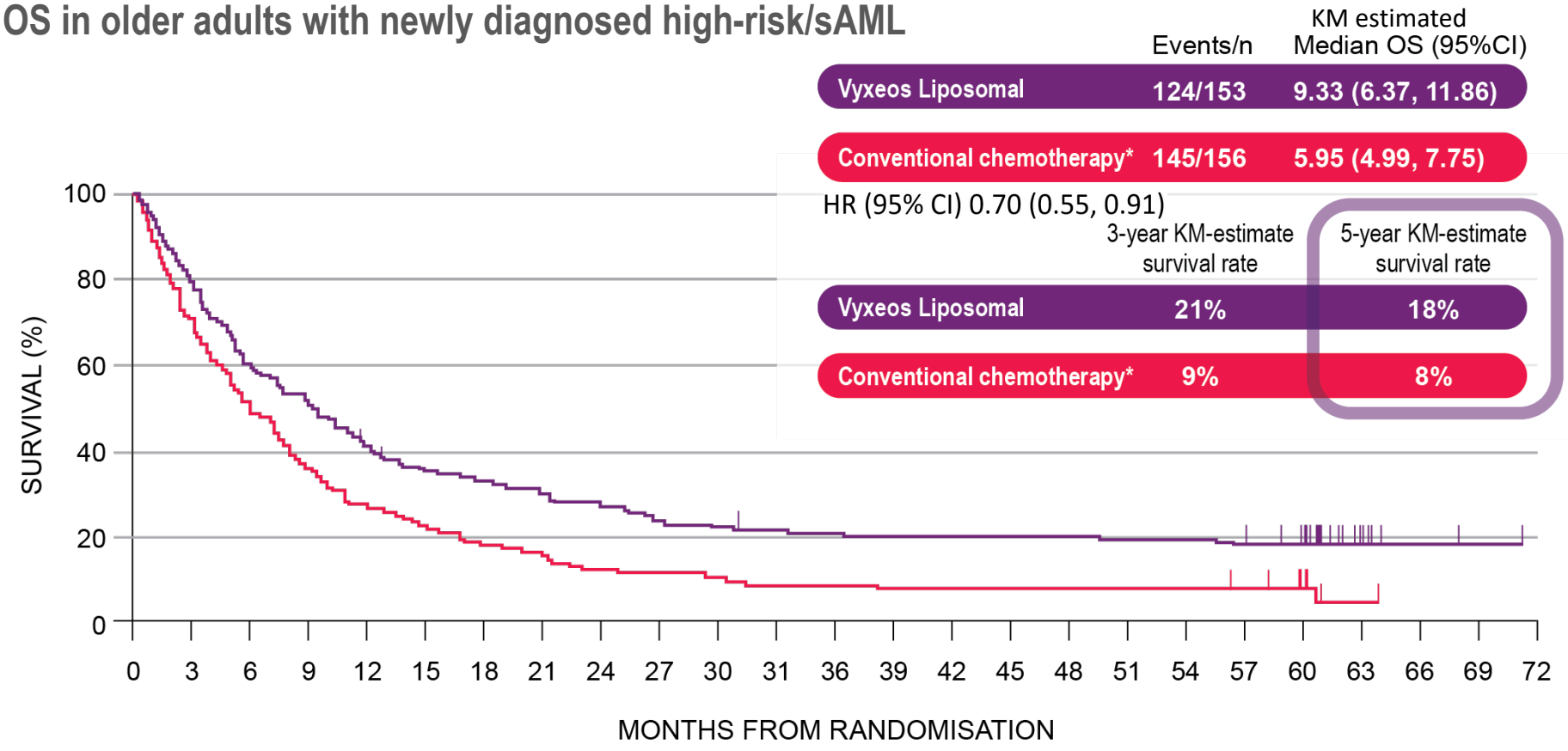
p-values are 2-sided
CRi, complete response with incomplete platelet or neutrophil recovery

*Conventional chemotherapy is defined as 7+3 in induction, 5+2 in second induction and consolidation where given

1. Lancet JE et al. *J Clin Oncol* 2018, 10;36(26):2684-2692.

At a pre-specified 5-year analysis, improved overall survival with Vyxeos Liposomal vs conventional chemotherapy* was maintained and consistent with the primary endpoint analysis

KM OS in older adults with newly diagnosed high-risk/sAML



The KM estimated 5-year survival rate for **Vyxeos Liposomal** was **more than double** that of **conventional chemotherapy**.

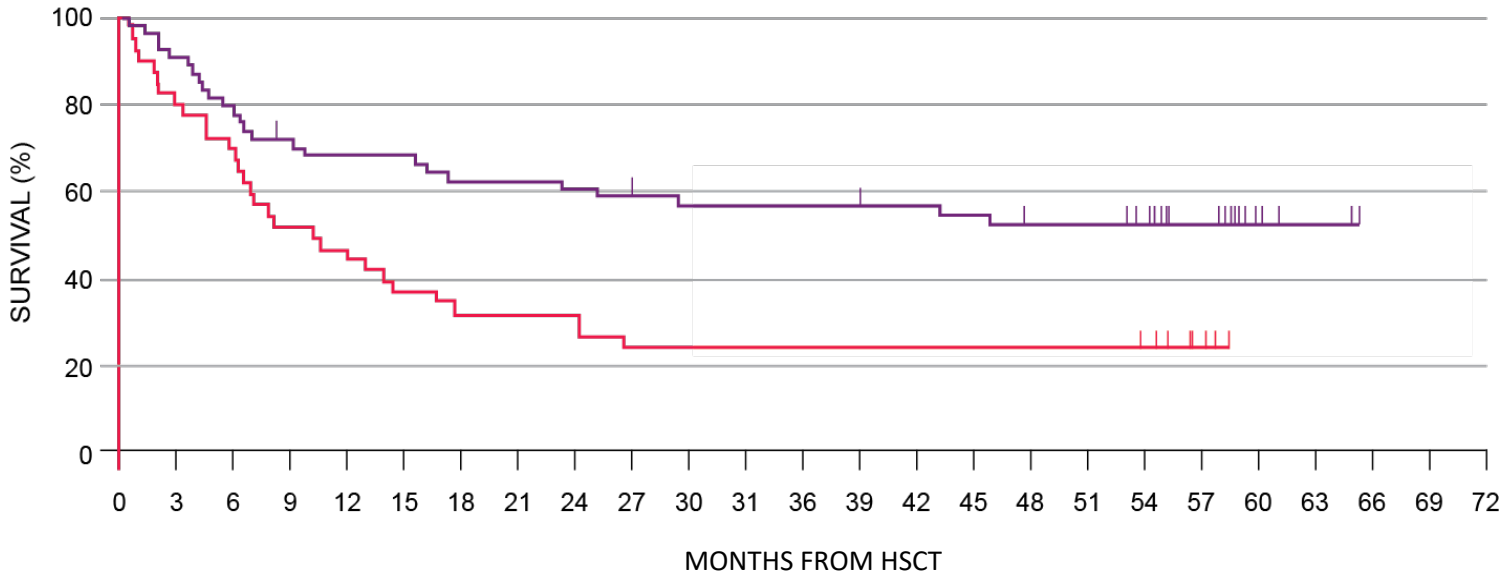
*Conventional chemotherapy is defined as 7+3 in induction, 5+2 in second induction and consolidation where given.

Vyxeos Liposomal	153	122	92	79	62	52	49	45	40	35	33	31	30	29	29	29	29	28	28	26	22	6	2	1	0
Conventional chemotherapy*	156	110	77	56	43	35	28	25	20	19	17	14	14	13	13	12	12	12	12	11	5	1	0	0	0

1. Lancet JE, et al. *EHA* 2020; Poster EP556

In patients who received Vyxeos Liposomal and underwent HSCT, overall survival was maintained above 50% at 5 years in a post-hoc analysis

KM OS landmarked from HSCT in older adults with newly diagnosed high-risk/sAML



	Events/n	KM estimated Median OS (95%CI)
Vyxeos Liposomal	25/53	Not reached
Conventional chemotherapy*	30/39	10.25 (6.21, 16.69)

HR (95% CI) 0.51 (0.28, 0.90)

	3-year KM-estimate survival rate	5-year KM-estimate survival rate
Vyxeos Liposomal	56%	52%
Conventional chemotherapy*	23%	Not estimable

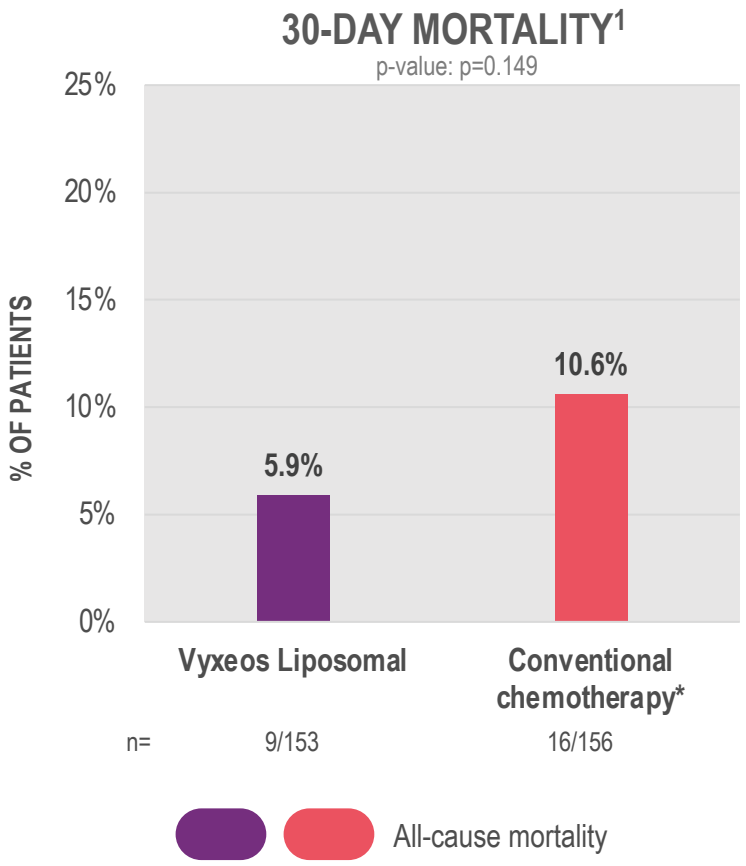
Vyxeos Liposomal	53	48	42	37	35	35	32	32	31	29	28	28	28	27	27	26	24	24	21	15	6	2	0	0	0
Conventional chemotherapy*	39	31	27	20	18	14	12	12	12	9	9	9	9	9	9	9	9	9	8	2	0	0	0	0	0

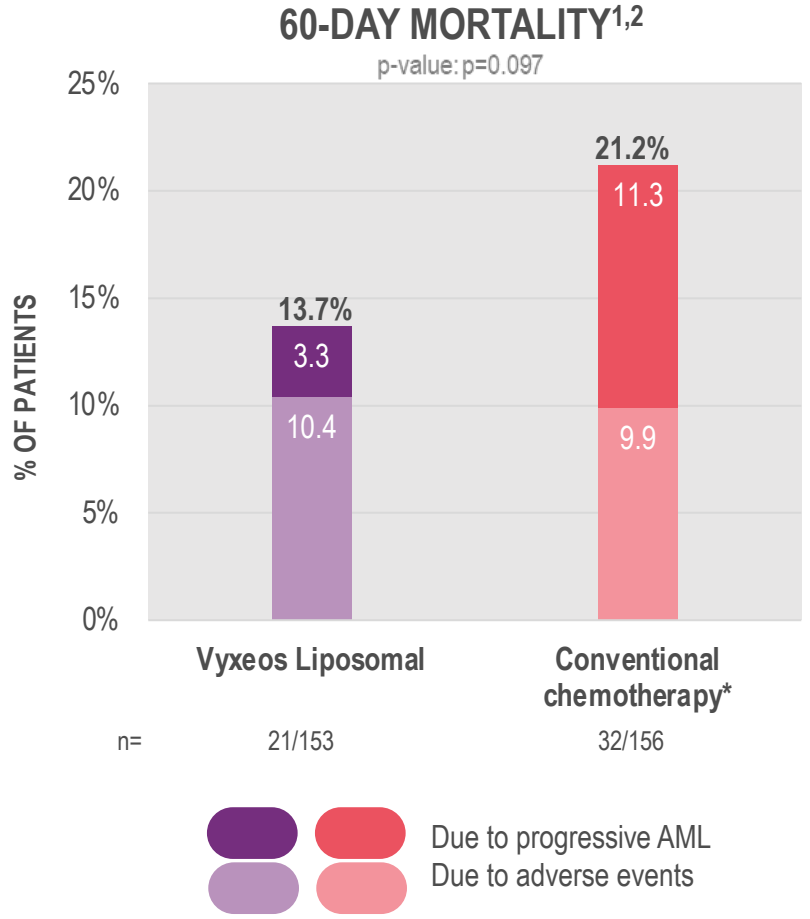
*Conventional chemotherapy is defined as 7+3 in induction, 5+2 in second induction and consolidation where given

HSCT, haematopoietic stem cell transplant

1. Lancet JE, et al. *EHA* 2020; Poster EP556

Early mortality rates were lower with Vyxeos Liposomal than with conventional chemotherapy*[1,2]



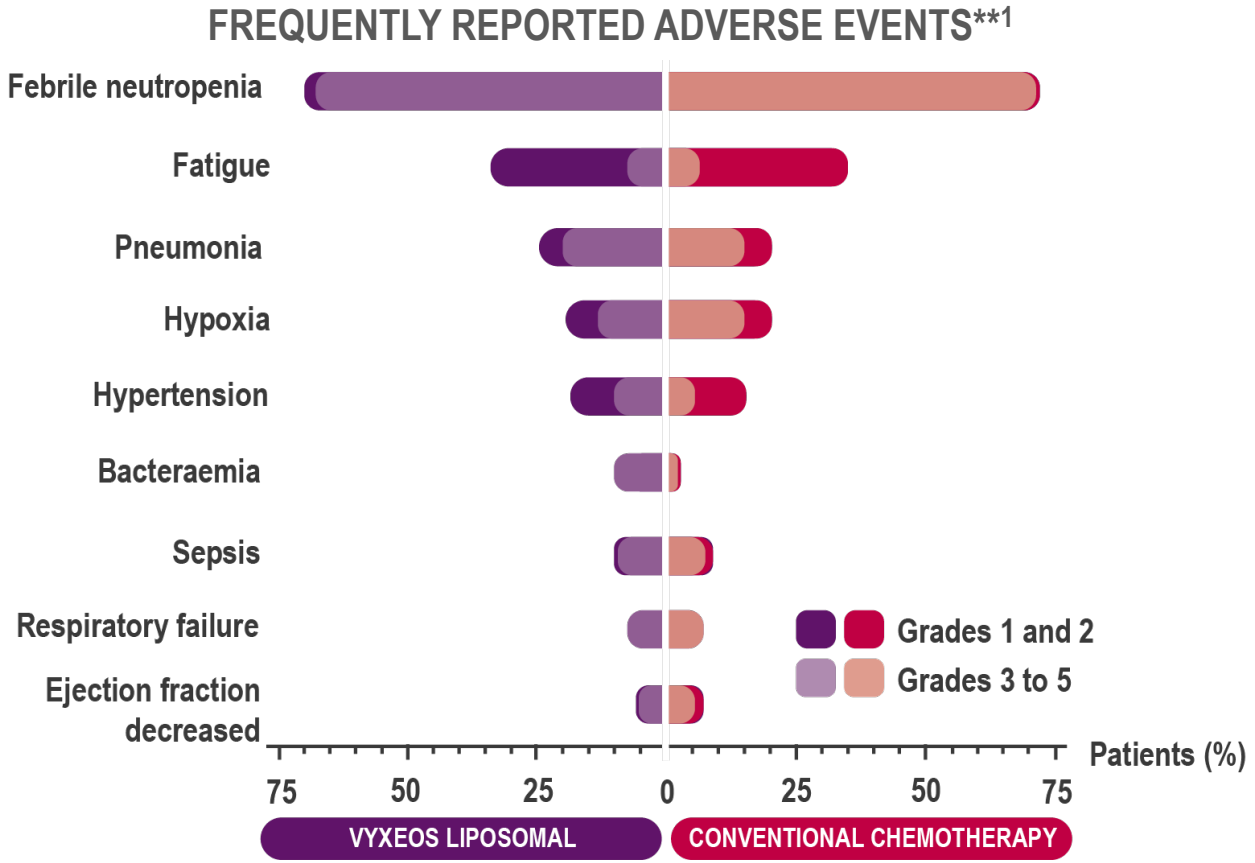


- 60-day mortality due to disease progression was lower for **Vyxeos Liposomal** than **conventional chemotherapy***
- 60-day mortality due to adverse events was comparable

*Conventional chemotherapy is defined as 7+3 in induction, 5+2 in second induction and consolidation where given

1. Lancet JE et al. *J Clin Oncol* 2018, 10;36(26):2684-2692. 2. Jazz Pharmaceuticals. Data on File.

The overall frequency and severity of adverse events was comparable for Vyxeos Liposomal and conventional chemotherapy*[1,2]



*Conventional chemotherapy is defined as 7+3 in induction, 5+2 in second induction and consolidation where given

**The percentages of patients with grade 1-2 and 3-5 events are shown for all adverse events occurring in >5% of patients in either treatment group as grade 3-5 events.

1. Adapted from Lancet JE et al. *J Clin Oncol* 2018, 10;36(26):2684-2692.
2. Vyxeos Liposomal. European Summary of Product Characteristics. January 2021.

Thrombocytopaenia and neutropaenia with Vyxeos Liposomal

Vyxeos Liposomal is associated with prolonged thrombocytopaenia and neutropaenia vs **conventional chemotherapy***, so patients may require additional monitoring[1,2]

	Vyxeos Liposomal	Conventional chemotherapy*
Median time to recovery from thrombocytopaenia (≥ 50,000/µl) after first induction for patients who had achieved CR/CRi[1]	36.5 days	29 days
Median time to recovery from neutropaenia (ANC value ≥ 500/µl) after first induction for patients who had achieved CR/CRi[1]	35 days	29 days

1. Lancet JE et al. *J Clin Oncol* 2018, 10;36(26):2684-2692.
2. Vyxeos Liposomal. European Summary of Product Characteristics. January 2021.

*Conventional chemotherapy is defined as 7+3 in induction, 5+2 in second induction and consolidation where given

Jazz Pharmaceuticals®

Vyxeos® Liposomal
44 mg /100 mg Powder for concentrate for solution for infusion
daunorubicin / cytarabine

International Core Prescribing Information

Vyxeos® Liposomal 44mg/100mg powder for concentrate for solution for infusion
(Daunorubicin and cytarabine)
Please refer to the Summary of Product Characteristics before prescribing.

Presentation: Purple lyophilised cake of powder for concentrate for solution for infusion.
Each vial contains 44 mg of daunorubicin and 100 mg of cytarabine. After reconstitution the solution contains 2.2 mg/mL daunorubicin and 5 mg/mL cytarabine encapsulated in liposomes in a fixed combination in a 1:5 molar ratio. **Indication**: For the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC). **Dosage and administration**: For intravenous infusion use only. An in-line membrane filter may be used provided the minimum pore diameter of the filter is greater than or equal to 15 µm. It must not be administered via an intramuscular, intrathecal, or subcutaneous route. *Refer to the full SmPC for detailed information on preparation of solution for infusion.* Treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products. *Recommended dosing schedule for induction of remission*: 44 mg/100 mg/m^2, administered intravenously over 90 minutes on days 1, 3, and 5 as the first course of induction therapy; then on days 1 and 3 as subsequent course of induction therapy, if needed. *Recommended dosing schedule for consolidation:* The first consolidation cycle should be administered 5 to 8 weeks after the start of the last induction. The recommended dosing schedule is 29 mg/65 mg/m^2, administered intravenously over 90 minutes on days 1 and 3 as subsequent courses of consolidation therapy, if needed. Dose adjustments during treatment may be required in hypersensitivity symptoms and cardiotoxicity. Assessment of cardiac function prior to start of treatment is recommended. *Renal impairment*: Dose adjustment is not required for patients with mild (creatinine clearance [CrCL] 60 mL/min to 89 mL/min by Cockcroft Gault equation [C-G]) or moderate (CrCL 30 mL/min to 59 mL/min) renal impairment. There is no experience in patients with severe renal impairment (CrCL 15 mL/min to 29 mL/min) or end-stage renal disease. It should only be used in patients with severe renal impairment if the benefits outweigh the risks. *Hepatic impairment:* Dose adjustment is not required for patients with a bilirubin level less than or equal to 50 µmol/L. There is no experience in patients with hepatic impairment resulting in a bilirubin level greater than 50 µmol/L. It should only be used in patients with severe hepatic impairment if the benefits outweigh the risks. *Elderly population (≥65 years):* No dose adjustment is required. *Paediatric population*: The safety and efficacy in children aged 0–18 years has not yet been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings, precautions and interactions**: Do not substitute or interchange with other daunorubicin and/or cytarabine-containing products. Severe myelosuppression and serious or fatal haemorrhagic events have been reported. Due to the long plasma half-life of Vyxeos liposomal, time to recovery of ANC and platelets may be prolonged and require additional monitoring. Prophylactic anti-infectives may be administered during the period of profound neutropenia until ANC returns to 500/µL or greater. If myelosuppressive complications occur, appropriate supportive measures should be used. Blood counts should be regularly monitored until recovery. As cardiotoxicity is a known risk prior therapy with anthracyclines, pre-existing cardiac disease, previous radiotherapy of the mediastinum, or concomitant use of cardiotoxic products may increase the risk. Hepatotoxic medicinal products may impair liver function and increase toxicity. Evaluation of hepatic and renal function is recommended prior to administration and periodically during treatment. Blood uric acid levels should be monitored and appropriate therapy initiated if hyperuricemia develops. Each vial of Vyxeos liposomal contains 100 mg of copper gluconate. It should only be used in patients with a history of Wilson's disease or other copper-related disorder if the benefits outweigh the risks. To avoid local tissue necrosis care should be taken to ensure that there is no extravasation of Vyxeos liposomal during administration. Administration of live or live-attenuated vaccines should be avoided. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. The absorption of oral accompanying medicinal products may be considerably influenced by gastrointestinal mucositis and/or diarrhoea frequently occurring in association with intensive chemotherapy. **Pregnancy, lactation and fertility:** There are no data on use in pregnant women. It should not be used during pregnancy unless the benefit of treatment outweighs the risk. It is not known if Vyxeos liposomal is excreted in human milk therefore mothers should be advised to discontinue breastfeeding during therapy. Patients should be advised to avoid becoming pregnant while receiving Vyxeos liposomal. Male patients and women of childbearing potential must use an effective method of contraception during treatment and for 6 months following the last dose. Male fertility may be compromised by treatment. **Undesirable effects**: ***Please refer to the full SmPC for the complete list of undesirable effects.*** The most frequently occurring adverse reactions were hypersensitivity, febrile neutropenia, oedema, diarrhoea/colitis, mucositis, fatigue, musculoskeletal pain, abdominal pain, decreased appetite, cough, headache, chills, arrhythmia, pyrexia, sleep disorders, and hypotension. The most serious and frequently occurring ADRs were infection, cardiotoxicity and haemorrhage. **Overdose**: There is no specific antidote for overdose and treatment should be symptomatic. **Storage and Handling**: Store in a refrigerator (2°C - 8°C). Shelf life of unopened vials: 2 years. Keep vial in the original carton to protect from light and store in an upright position. Vyxeos liposomal is a cytotoxic medicinal product intended for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents. **Legal category**: POM. **Marketing authorisation number**: EU/1/18/1308/001 **Package quantity and Cost**: carton containing 1 × 50 mL vial. Price differs across countries. Further information is available from the **Marketing Authorisation Holder**: Jazz Pharmaceuticals Ireland Ltd., 5th Floor, Waterloo Exchange, Waterloo Road, Dublin D04 E5W7, Ireland. **Date of preparation:** November 2019.
INT-VYX-1900009

For country specific information please refer to your local SmPC or Product Monograph

Adverse events should be reported. Healthcare professionals are asked to report any suspected adverse events via their national reporting system. Adverse events should be reported to Jazz Pharmaceuticals by email to aereporting@jazzpharma.com or by fax to +44 (0) 1865 598765