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.

INT-VYX-2200189
Date of Preparation: September 2022

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.

Jazz Pharmaceuticals

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. Lancet Haematol 2021;8:e481–491.

*Conventional chemotherapy is defined as 7+3 in induction, 5+2 in second induction and consolidation, where given
AML, acute myeloid leukaemia; AE, adverse event; CR, complete response; CRi, CR with incomplete neutrophil or platelet recovery; EFS, event-free survival; OS, overall survival; HSCT, haematopoietic stem cell transplantation .

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.

AML, acute myeloid leukaemia; MDS, Myelodysplastic syndromes; CMML, Chronic myelomonocytic leukaemia; ECOG PS, 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
Second induction (where given) 44 mg/100 mg/m^2 on days 1 and 3	**Second induction** (where given) 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, REMISSION DURATION, EFS

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

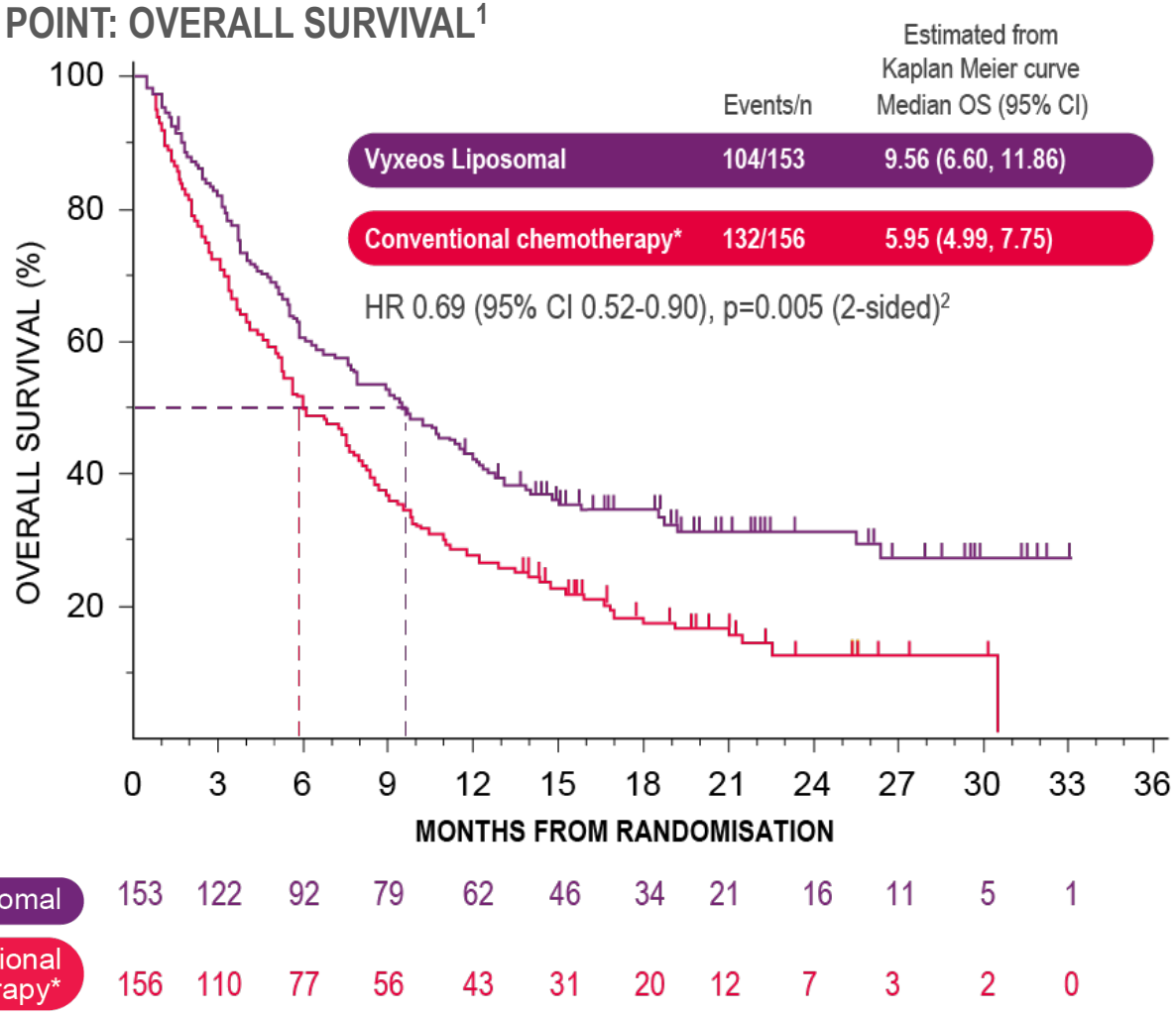
CR: complete remission
EFS: event free survival

For full list of secondary endpoints, please see Lancet JE, et al. J Clin Oncol 2018;36(26):2684-2692

1. Lancet JE, et al. J Clin Oncol 2018;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]



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

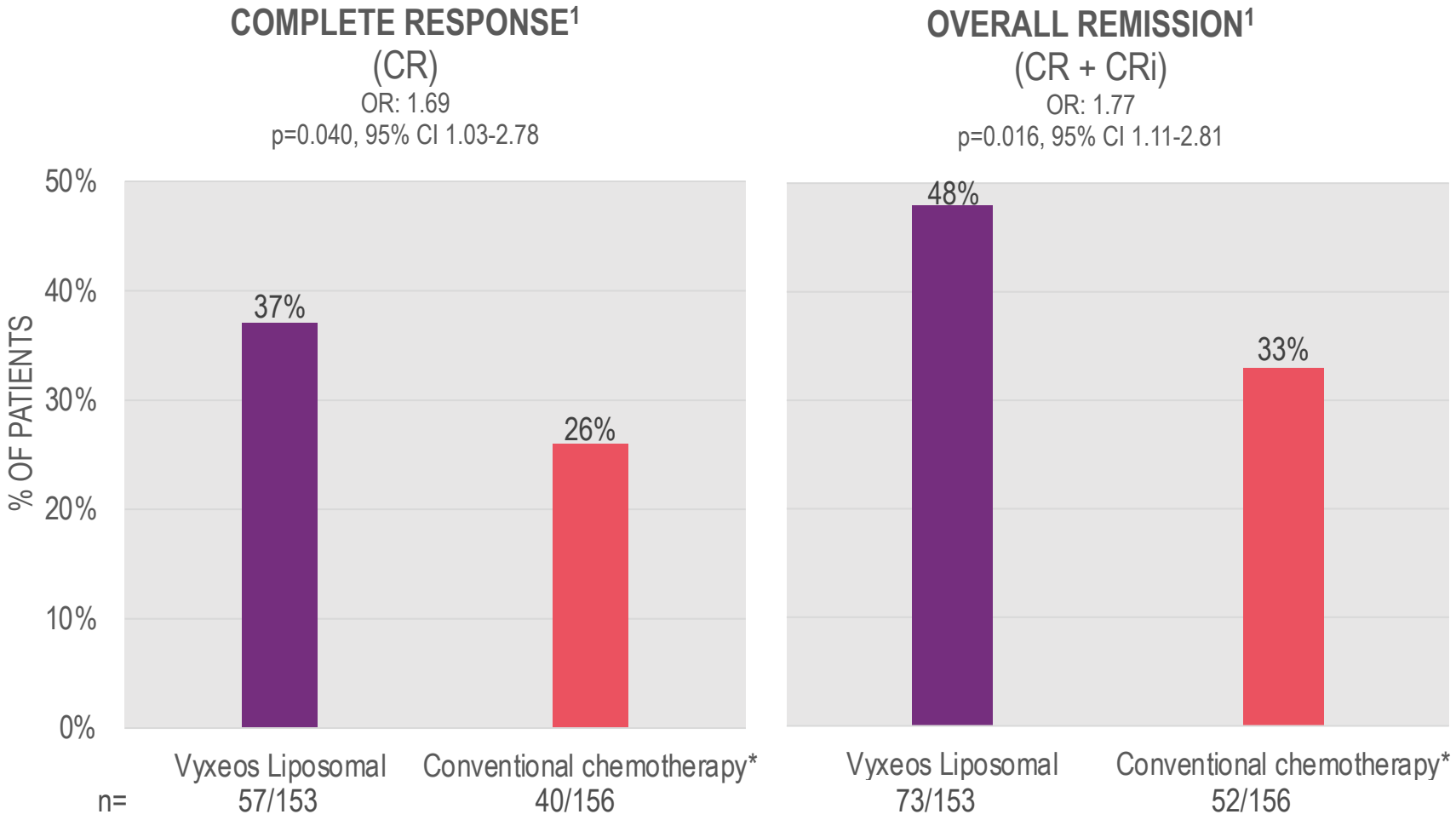
Median duration of follow up: 20.7 months[1]

*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;36(26):2684-2692.
2. Vyxeos Liposomal. European Summary of Product Characteristics.

Adapted from Lancet JE, et al. J Clin Oncol 2018

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



Overall remission (CR + CRi) rates among patients with 1 induction cycle:[1]

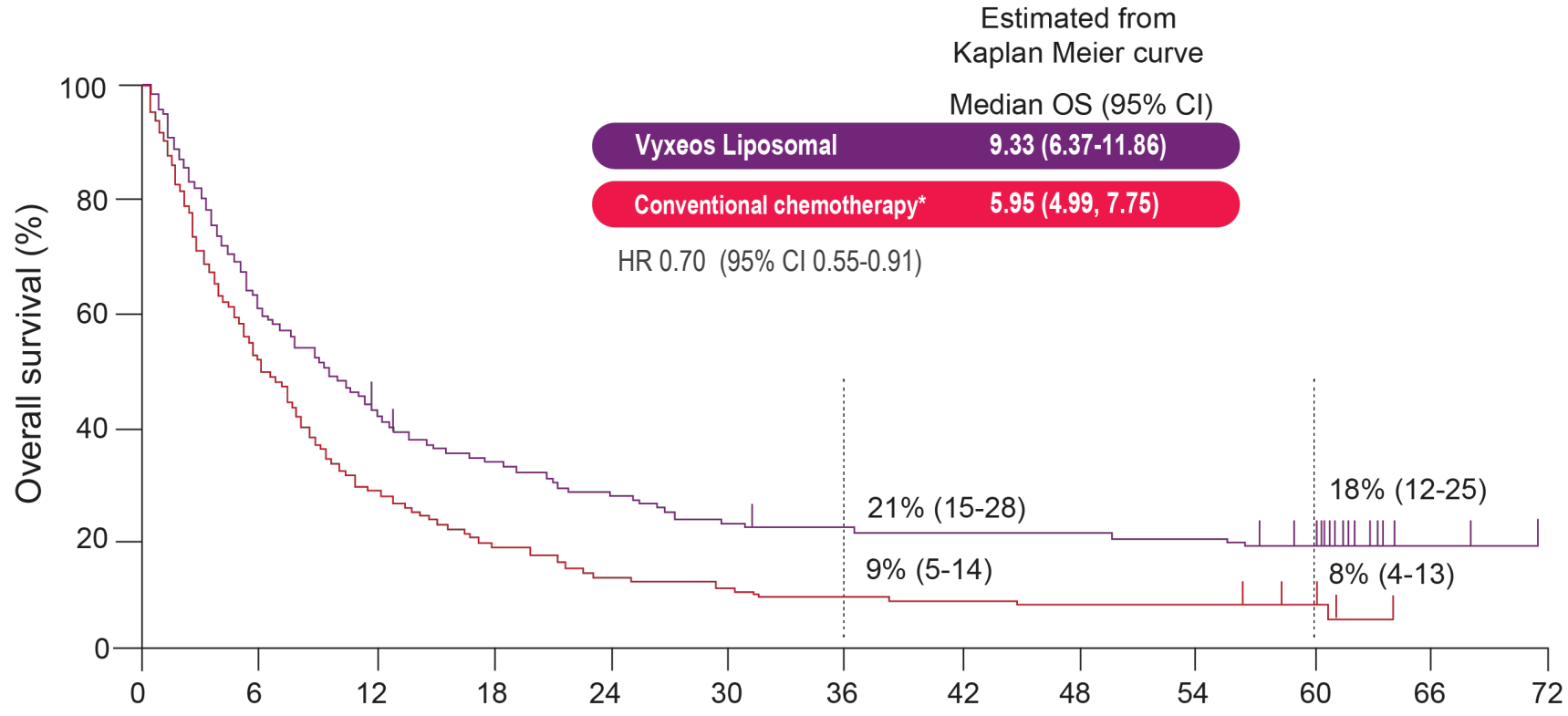
- **55% Vyxeos Liposomal** (n=58/105)
- **34% Conventional chemotherapy*** (n=34/100)

p-values are 2-sided
CRi, CR with incomplete neutrophil or platelet 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;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



NO. AT RISK

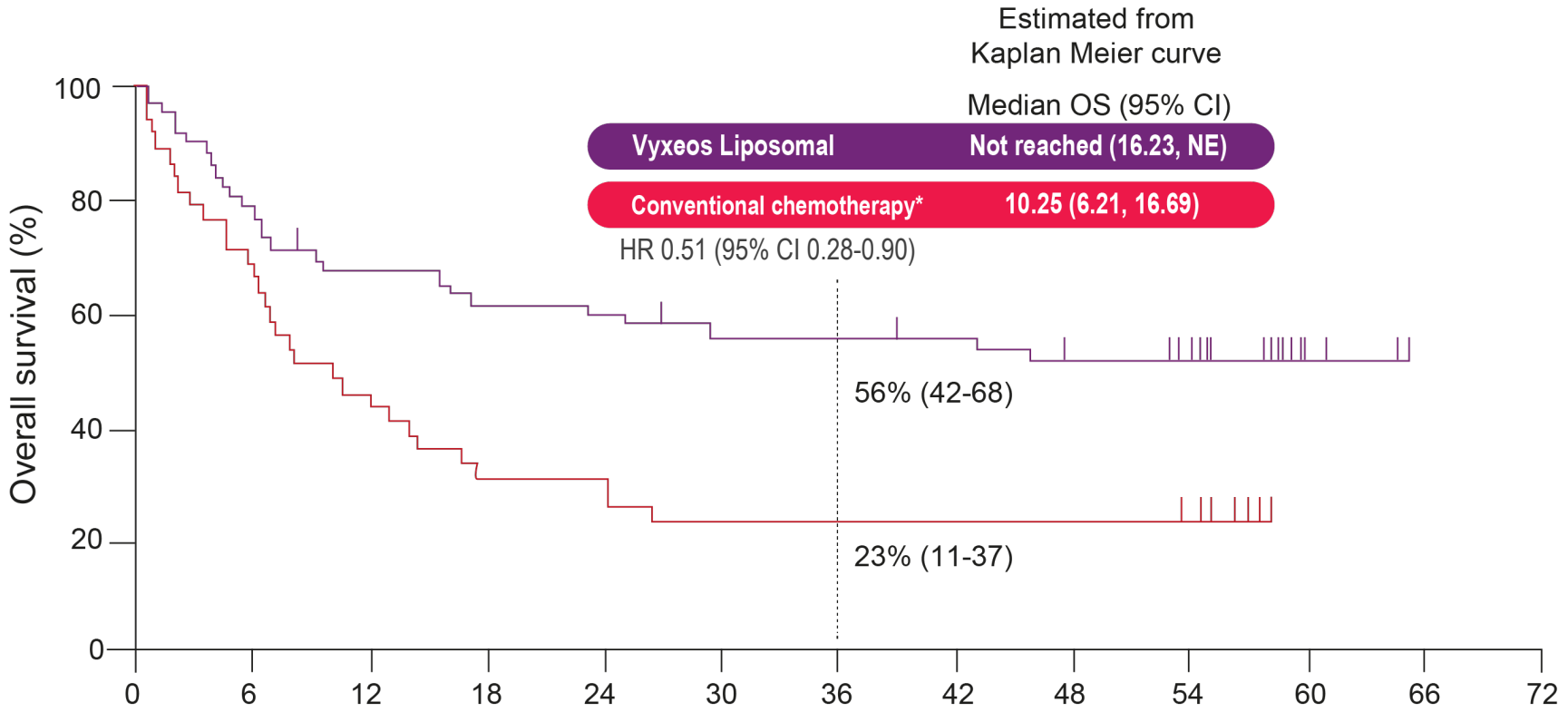
Vyxeos Liposomal	153	92	62	49	40	33	30	29	29	28	22	2	0
	(0)	(0)	(1)	(2)	(2)	(2)	(3)	(3)	(3)	(3)	(7)	(27)	(29)
Conventional chemotherapy*	156	77	43	28	20	17	14	13	12	12	5	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(7)	(11)	(11)

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

1. Lancet JE, et al. Lancet Haematol 2021;8:e481–491.

Adapted from Lancet JE, et al. Lancet Haematol 2021

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



NO. AT RISK

Vyxeos Liposomal	53	42	35	32	31	28	28	27	24	21	6	0	0
	(0)	(0)	(1)	(1)	(1)	(2)	(2)	(3)	(4)	(7)	(22)	(28)	(28)
Conventional chemotherapy*	(39)	27	18	12	12	9	9	9	9	8	0	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(9)	(9)	(9)

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

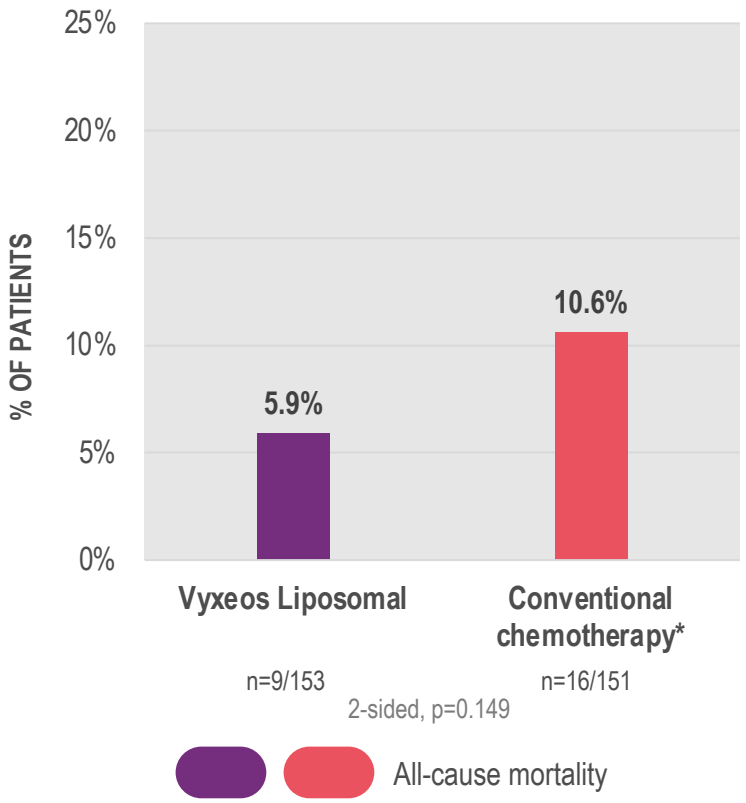
1. Lancet JE, et al. Lancet Haematol 2021;8:e481–491.

Adapted from Lancet JE, et al. Lancet Haematol 2021

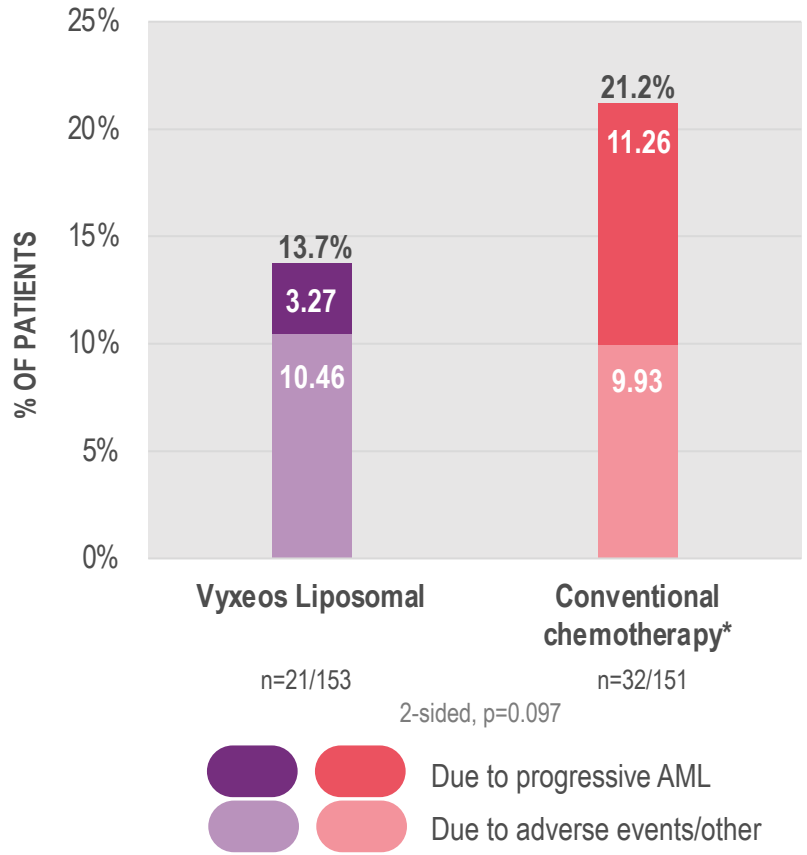
Increased overall survival without increasing the toxicity burden[1]

While the overall safety profile was comparable between Vyxeos Liposomal and conventional chemotherapy, early mortality rates were lower with Vyxeos Liposomal[1,2]

30-DAY MORTALITY[1]



60-DAY MORTALITY[1,2]

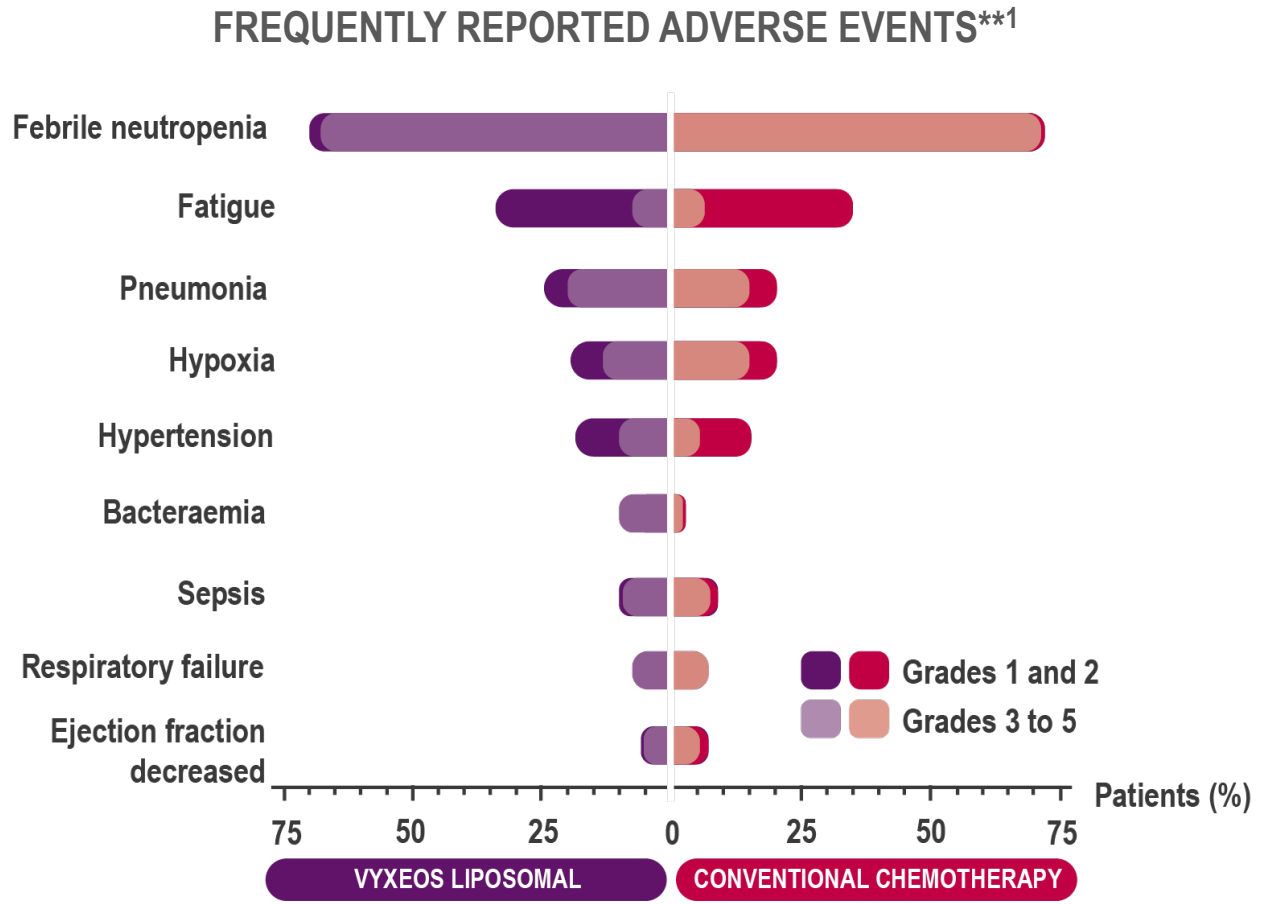


- **Lower 60-day mortality** due to disease progression vs conventional chemotherapy*[2]
- **60-day mortality** due to adverse events was **comparable**[2]

*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;36(26):2684-2692.
2. Data on File (VYX-2021-066). Jazz Pharmaceuticals, Inc.

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



Please refer to SmPC for full safety and tolerability information

*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.

Adapted from Lancet JE, et al. J Clin Oncol 2018

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

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;36(26):2684-2692.
2. Vyxeos Liposomal. European Summary of Product Characteristics.

*Conventional chemotherapy is defined as 7+3 in induction, 5+2 in second induction and consolidation, where given
CR, complete response; CRi, CR with incomplete neutrophil or platelet recovery; ANC, absolute neutrophil count.

Jazz Pharmaceuticals

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

EU Prescribing Information

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

Presentation: Purple lyophilised cake of powder for concentrate for solution for infusion. Each vial contains 44 mg daunorubicin and 100 mg 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:** Treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Do not interchange Vyxeos liposomal with other daunorubicin and/or cytarabine containing products. For intravenous infusion use only. An in-line membrane filter may be used provided the minimum pore diameter is greater than or equal to 15 µm. Do not administer via an intramuscular, intrathecal, or subcutaneous route. Refer to full SmPC for detailed information on preparation of solution for infusion. Recommended dosing schedule for induction of remission: 44 mg/100 mg/m2, 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: Administer first consolidation cycle 5 to 8 weeks after the start of the last induction. Recommended dosing schedule is 29 mg/65 mg/m2, 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. Patients should be monitored for haematologic response and toxicities. Renal impairment: No dose adjustment required in mild, moderate or severe renal impairment. There is no experience in end-stage renal disease managed with dialysis. Hepatic impairment: No dose adjustment required for bilirubin level less than or equal to 50 µmol/L. There is no experience in hepatic impairment resulting in a bilirubin level greater than 50 µmol/L. Elderly population (≥65 years): No dose adjustment required. **Contraindications**: Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions**:
Do not substitute or interchange with other daunorubicin and/or cytarabine-containing products. Severe myelosuppression and serious or fatal haemorrhagic events have been reported. Time to recovery of ANC and platelets may be prolonged and require additional monitoring. Monitor blood counts regularly until recovery.
Prophylactic anti-infectives may be administered during the period of profound neutropenia until ANC returns to 500/µL or greater. 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. Hepatic impairment may increase the risk of toxicity. Evaluation of hepatic function is recommended prior to administration and periodically during treatment. Monitor blood uric acid levels and initiate appropriate therapy if hyperuricemia develops. Each vial of Vyxeos liposomal contains 100 mg of copper gluconate. Only use in patients with a history of Wilson's disease or other copper-related disorder if the benefits outweigh the risks. Serious hypersensitivity reactions including anaphylactic reactions have been reported with daunorubicin and cytarabine. Avoid administration of live or live-attenuated vaccines. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. Gastrointestinal mucositis and/or diarrhoea frequently occur and may influence the absorption of oral **accompanying** medicinal products.
Interactions: Do not administer in combination with cardiotoxic agents unless cardiac function is closely monitored. Monitor hepatic function more frequently if co-administered with hepatotoxic agents. **Pregnancy, lactation and fertility**: There are no data on use in pregnant women. Do not use during pregnancy unless the benefit of treatment outweighs the risk. It is not known if Vyxeos liposomal is excreted in human milk therefore advise mothers to discontinue breastfeeding during therapy. Advise patients 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**. Hypersensitivity, febrile neutropenia, oedema, diarrhoea/colitis, mucositis, fatigue, musculoskeletal pain, abdominal pain, decreased appetite, cough, headache, chills, arrhythmia, pyrexia, sleep disorders, and hypotension are the most frequently occurring adverse reactions (ADRs). Infection, cardiotoxicity and haemorrhage are the most serious and frequently occurring ADRs. **Storage and Handling**: Store in a refrigerator (2°C - 8°C). Vyxeos liposomal is cytotoxic; unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents**. Legal category**: Prescription only medicine (POM). **Marketing authorization number**: EU/1/18/1308/001 **Package quantity and Cost**: carton containing 1 × 50 mL vial. Refer to local prescribing information for price. **Further information** is available from **Marketing Authorisation Holder**: Jazz Pharmaceuticals Ireland Ltd., 5th Floor, Waterloo Exchange, Waterloo Road, Dublin D04 E5W7, Ireland. **Date of revision**: July 2022. INT-VYX-1900009

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

ADVERSE EVENTS REPORTING
Adverse events should be reported. Healthcare professionals are asked to report any adverse events via their national reporting system (see Section 4.8 of SmPC). Adverse events should also be reported to Jazz Pharmaceuticals by email to **medinfo-int@jazzpharma.com** or phone via **+353 1 968 1631** (may include an international call charge).