Supplemental Digital Content (SDC) for Döhner et al. Adjunctive Volasertib in Patients With Acute Myeloid Leukemia not Eligible for Standard Induction Therapy: A Randomized, Phase 3 Trial

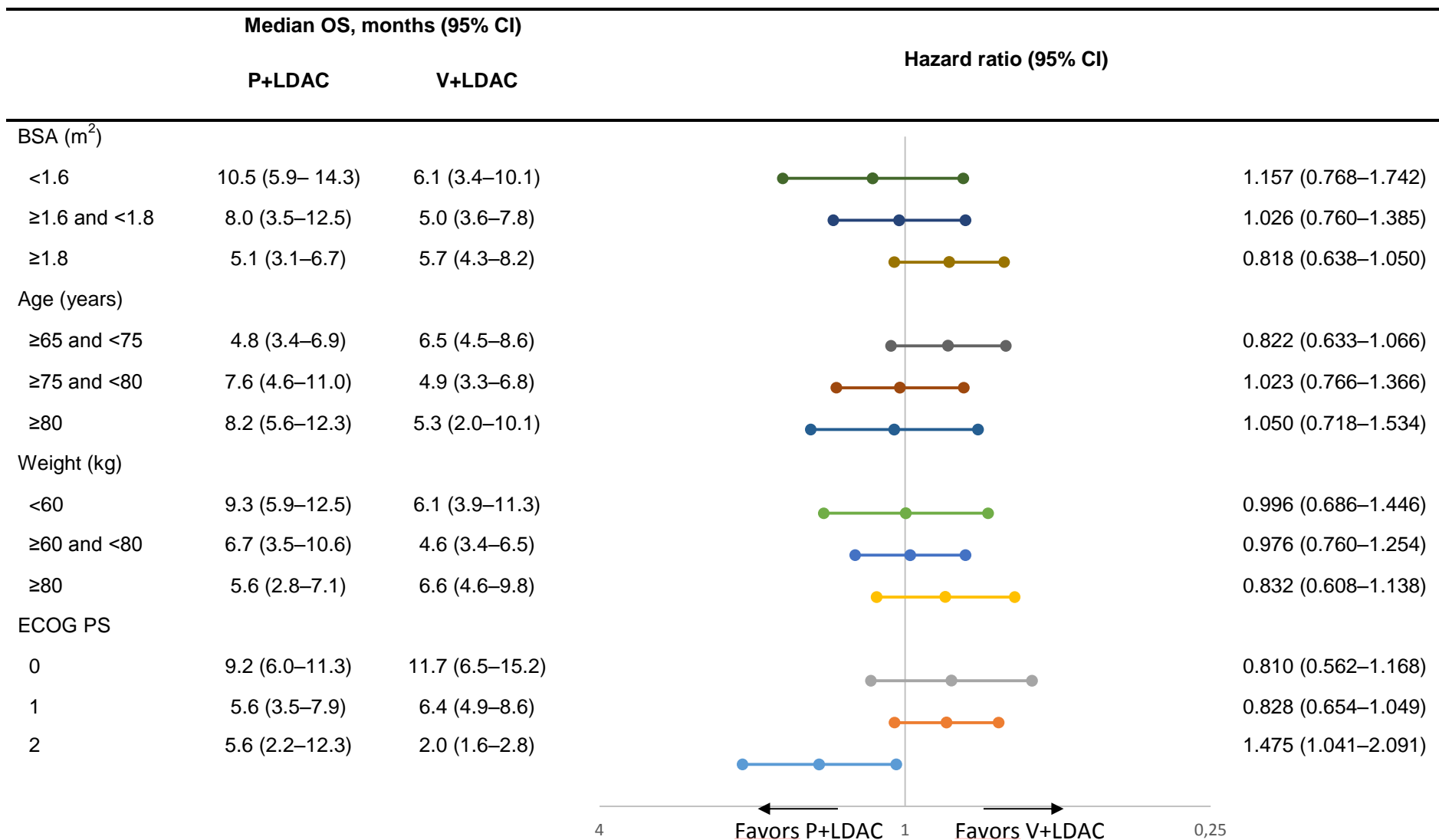**SDC Methods. Unplanned, exploratory, post hoc analysis to compare the phase 2 and phase 3 results**

Objective response rate (ORR), overall survival (OS), time to fatal adverse events (AEs), and time to fatal infections were analyzed retrospectively by dose intensity. Dose intensity was calculated by dividing the dose of volasertib or placebo administered in Cycle 1 by the interval (days) from start of Cycle 1 to start of Cycle 2 (with the dose intensity per protocol [2 x 350 mg in a 28-day cycle] being 25 mg/d). Higher and lower dose intensities were defined as a calculated dose of either volasertib or placebo of ≥25 mg/d and <25 mg/d, respectively, with dose intensities <25 mg/d resulting from skipped doses or delays in the start of the next cycle; of note, skipped or delayed doses will also have reduced the dose intensity of LDAC in parallel. Differences in dose intensities were the result of medical assessment and decision making by the investigator, and imbalances in patient and/or disease characteristics between the dose intensity groups were expected. Therefore, to minimize the confounding effect from baseline imbalance, propensity score methodology was used to identify a subset of patients with similar baseline factors between the dose intensity groups. Competing risk modeling was conducted to compare treatment effect and determine to what extent the OS results observed in this trial were caused by the intolerability or lack of efficacy of volasertib. Several approaches were taken to identify the OS events caused by lack of efficacy, treatment intolerability, or neither of the two. Survival analysis with competing risks was conducted using the categorized data based on two standard models: the cause-specific hazard model and the subdistribution model.[1,2]
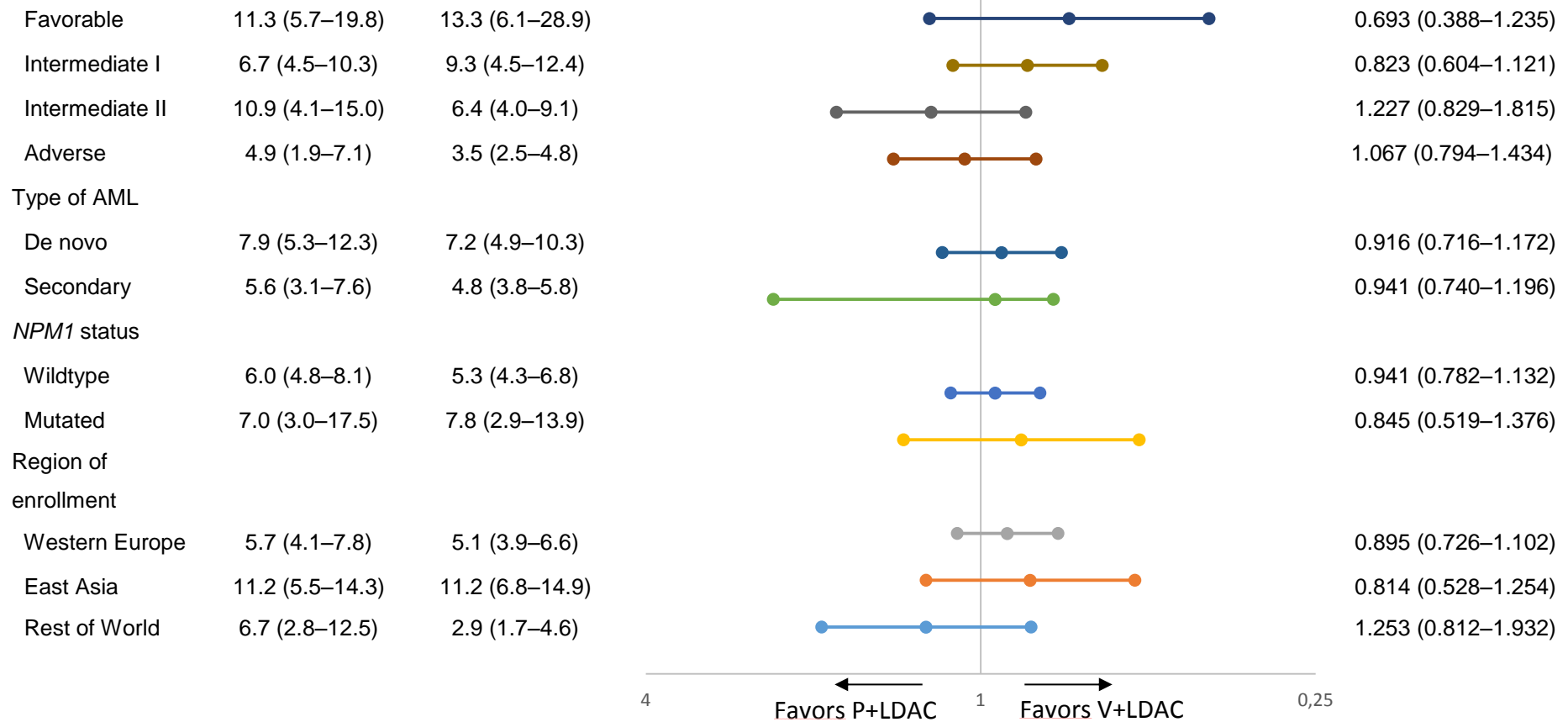
SDC References

1. Prentice RL, Kalbfleisch JD, Peterson AV, Jr., Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics.* 1978;34:541–554.

2. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;94:496–509.

SDC Table 1

Overall Survival Rate by Treatment Arm and in Various Subgroups: Final Analysis.

	Median OS, months (95% CI)		Hazard ratio (95% CI)
	P+LDAC	**V+LDAC**	
BSA (m^2)			
<1.6	10.5 (5.9– 14.3)	6.1 (3.4–10.1)	1.157 (0.768–1.742)
≥1.6 and <1.8	8.0 (3.5–12.5)	5.0 (3.6–7.8)	1.026 (0.760–1.385)
≥1.8	5.1 (3.1–6.7)	5.7 (4.3–8.2)	0.818 (0.638–1.050)
Age (years)			
≥65 and <75	4.8 (3.4–6.9)	6.5 (4.5–8.6)	0.822 (0.633–1.066)
≥75 and <80	7.6 (4.6–11.0)	4.9 (3.3–6.8)	1.023 (0.766–1.366)
≥80	8.2 (5.6–12.3)	5.3 (2.0–10.1)	1.050 (0.718–1.534)
Weight (kg)			
<60	9.3 (5.9–12.5)	6.1 (3.9–11.3)	0.996 (0.686–1.446)
≥60 and <80	6.7 (3.5–10.6)	4.6 (3.4–6.5)	0.976 (0.760–1.254)
≥80	5.6 (2.8–7.1)	6.6 (4.6–9.8)	0.832 (0.608–1.138)
ECOG PS			
0	9.2 (6.0–11.3)	11.7 (6.5–15.2)	0.810 (0.562–1.168)
1	5.6 (3.5–7.9)	6.4 (4.9–8.6)	0.828 (0.654–1.049)
2	5.6 (2.2–12.3)	2.0 (1.6–2.8)	1.475 (1.041–2.091)

Favors P+LDAC   1   Favors V+LDAC

4   0,25

2010 ELN genetic group			
Favorable	11.3 (5.7–19.8)	13.3 (6.1–28.9)	0.693 (0.388–1.235)
Intermediate I	6.7 (4.5–10.3)	9.3 (4.5–12.4)	0.823 (0.604–1.121)
Intermediate II	10.9 (4.1–15.0)	6.4 (4.0–9.1)	1.227 (0.829–1.815)
Adverse	4.9 (1.9–7.1)	3.5 (2.5–4.8)	1.067 (0.794–1.434)
Type of AML			
De novo	7.9 (5.3–12.3)	7.2 (4.9–10.3)	0.916 (0.716–1.172)
Secondary	5.6 (3.1–7.6)	4.8 (3.8–5.8)	0.941 (0.740–1.196)
NPM1 status			
Wildtype	6.0 (4.8–8.1)	5.3 (4.3–6.8)	0.941 (0.782–1.132)
Mutated	7.0 (3.0–17.5)	7.8 (2.9–13.9)	0.845 (0.519–1.376)
Region of enrollment			
Western Europe	5.7 (4.1–7.8)	5.1 (3.9–6.6)	0.895 (0.726–1.102)
East Asia	11.2 (5.5–14.3)	11.2 (6.8–14.9)	0.814 (0.528–1.254)
Rest of World	6.7 (2.8–12.5)	2.9 (1.7–4.6)	1.253 (0.812–1.932)

4   1   0,25

←Favors P+LDAC   Favors V+LDAC→

AML=acute myeloid leukemia, BSA=body surface area, CI=confidence interval, ECOG PS=Eastern Cooperative Oncology Group Performance Status, ELN=European LeukemiaNet, P+LDAC=placebo plus low-dose cytarabine, V+LDAC=volasertib plus low-dose cytarabine.

SDC Table 2

Summary of Adverse Events at Final Analysis.

AE, n (%)	P+LDAC (n=222)	V+LDAC (n=439)
Any AE	217 (97.7)	437 (99.5)
Drug-related AEs[a]	163 (73.4)	352 (80.2)
AE leading to dose reduction[b]	16 (7.2)	33 (7.5)
AEs leading to discontinuation of study drugs	30 (13.5)	74 (16.9)
Due to progressive disease	12 (5.4)	15 (3.4)
Due to other AE	18 (8.1)	59 (13.4)
Serious AEs	163 (73.4)	380 (86.6)
Fatal AEs	40 (18.0)	137 (31.2)
CTCAE grade ≥3	192 (86.5)	419 (95.4)

AE=adverse event, CTCAE=Common Terminology Criteria for Adverse Events,

P+LDAC=placebo plus low-dose cytarabine, V+LDAC=volasertib plus low-dose cytarabine.

[a]As assessed by the investigator.

[b]All AEs leading to dose reduction are assumed to be AEs leading to a reduction of the volasertib/placebo dose.

SDC Table 3

Adverse Events Occurring in >10% of Patients at the Preferred Term Level in Patients in Either Treatment Arm: Final Analysis.

AE, n (%)	P+LDAC (n=222)				V+LDAC (n=439)			
	All grades	Grade 3	Grade 4	Grade 5	All grades	Grade 3	Grade 4	Grade 5
Any AE	217 (97.7)	63 (28.4)	89 (40.1)	40 (18.0)	437 (99.5)	84 (19.1)	198 (45.1)	137 (31.2)
Infections and infestations	141 (63.5)	51 (23.0)	20 (9.0)	14 (6.3)	357 (81.3)	136 (31.0)	44 (10.0)	75 (17.1)
Pneumonia	44 (19.8)	23 (10.4)	8 (3.6)	6 (2.7)	124 (28.2)	59 (13.4)	18 (4.1)	23 (5.2)
Sepsis	10 (4.5)	4 (1.8)	1 (0.5)	3 (1.4)	51 (11.6)	18 (4.1)	14 (3.2)	17 (3.9)
Blood and lymphatic system disorders	138 (62.2)	56 (25.2)	73 (32.9)	1 (0.5)	351 (80.0)	113 (25.7)	225 (51.3)	5 (1.1)
Febrile neutropenia	65 (29.3)	58 (26.1)	4 (1.8)	1 (0.5)	265 (60.4)	202 (46.0)	51 (11.6)	5 (1.1)
Thrombocytopenia	66 (29.7)	12 (5.4)	53 (23.9)	-	177 (40.3)	14 (3.2)	155 (35.3)	-
Anemia	61 (27.5)	41 (18.5)	13 (5.9)	-	148 (33.7)	85 (19.4)	44 (10.0)	-
Neutropenia	36 (16.2)	9 (4.1)	27 (12.2)	-	132 (30.1)	9 (2.1)	119 (27.1)	-
Leukopenia	23 (10.4)	8 (3.6)	9 (4.1)	-	44 (10.0)	3 (0.7)	40 (9.1)	-
Gastrointestinal disorders	156 (70.3)	25 (11.3)	3 (1.4)	-	330 (75.2)	57 (13.0)	4 (0.9)	1 (0.2)
Nausea	79 (35.6)	3 (1.4)	-	-	122 (27.8)	4 (0.9)	-	-
Constipation	55 (24.8)	1 (0.5)	-	-	121 (27.6)	3 (0.7)	-	-
Diarrhea	49 (22.1)	4 (1.8)	-	-	121 (27.6)	8 (1.8)	-	-
Stomatitis	16 (7.2)	3 (1.4)	-	-	80 (18.2)	10 (2.3)	-	-
Vomiting	27 (12.2)	-	-	-	71 (16.2)	-	-	-
Abdominal pain	26 (11.7)	-	-	-	47 (10.7)	2 (0.5)	-	-

General disorders and administration site conditions	154 (69.4)	25 (11.3)	3 (1.4)	-	302 (68.8)	63 (14.4)	17 (3.9)	8 (1.8)
Pyrexia	72 (32.4)	3 (1.4)	1 (0.5)	-	102 (23.2)	17 (3.9)	-	-
Peripheral edema	42 (18.9)	1 (0.5)	-	-	76 (17.3)	4 (0.9)	-	-
Asthenia	44 (19.8)	7 (3.2)	-	-	69 (15.7)	17 (3.9)	2 (0.5)	-
Mucosal inflammation	11 (5.0)	1 (0.5)	-	-	68 (15.5)	7 (1.6)	4 (0.9)	-
Fatigue	33 (14.9)	7 (3.2)	-	-	64 (14.6)	9 (2.1)	1 (0.2)	-
Metabolism and nutrition disorders	99 (44.6)	15 (6.8)	6 (2.7)	-	229 (52.2)	74 (16.9)	15 (3.4)	1 (0.2)
Hypokalemia	38 (17.1)	6 (2.7)	3 (1.4)	-	120 (27.3)	37 (8.4)	4 (0.9)	-
Decreased appetite	45 (20.3)	2 (0.9)	-	-	82 (18.7)	10 (2.3)	-	-
Respiratory, thoracic and mediastinal disorders	103 (46.4)	17 (7.7)	5 (2.3)	5 (2.3)	234 (53.3)	43 (9.8)	19 (4.3)	9 (2.1)
Cough	21 (9.5)	-	-	-	92 (21.0)	4 (0.9)	-	-
Dyspnea	32 (14.4)	10 (4.5)	1 (0.5)	-	77 (17.5)	17 (3.9)	3 (0.7)	-
Epistaxis	28 (12.6)	1 (0.5)	-	-	77 (17.5)	4 (0.9)	2 (0.5)	-
Skin and subcutaneous disorders	93 (41.9)	1 (0.5)	1 (0.5)	-	222 (50.6)	27 (6.2)	2 (0.5)	-
Petechiae	24 (10.8)	-	-	-	73 (16.6)	4 (0.9)	-	-
Rash	30 (13.5)	1 (0.5)	-	-	68 (15.5)	8 (1.8)	-	-
Nervous system disorders	65 (29.3)	11 (5.0)	1 (0.5)	2 (0.9)	144 (32.8)	22 (5.0)	5 (1.1)	5 (1.1)
Headache	23 (10.4)	-	-	-	48 (10.9)	1 (0.2)	-	-
Vascular disorders	60 (27.0)	8 (3.6)	-	-	137 (31.2)	23 (5.2)	4 (0.9)	1 (0.2)
Hematoma	20 (9.0)	-	-	-	56 (12.8)	2 (0.5)	-	-
Musculoskeletal and connective tissue	81 (36.5)	15 (6.8)	-	-	150 (34.2)	13 (3.0)	-	-

| disorders | | | | | | | | |
| Back pain | 18 (8.1) | 1 (0.5) | - | - | 50 (11.4) | 3 (0.7) | - | - |

AE=adverse event, P+LDAC=placebo plus low-dose cytarabine, V+LDAC=volasertib plus low-dose cytarabine.

SDC Table 4

Objective Response by Treatment and Cycle 1 Dose Intensity – Primary Analysis.

	P+LDAC	V+LDAC
Lower dose intensity in Cycle 1		
Patients randomized, n (%)	52 (100.0)	117 (100.0)
Objective response, n (%)	6 (11.5)	48 (41.0)
Higher dose intensity in Cycle 1		
Patients randomized, n (%)	41 (100.0)	42 (100.0)
Objective response, n (%)	15 (36.6)	12 (28.6)

P+LDAC=placebo plus low-dose cytarabine, V+LDAC=volasertib plus low-dose cytarabine.

SDC Figure 1. Kaplan–Meier plots of overall survival by baseline ECOG PS in the final analysis. CI=confidence interval, ECOG PS=Eastern Cooperative Oncology Group Performance Status, LDAC=low-dose cytarabine.
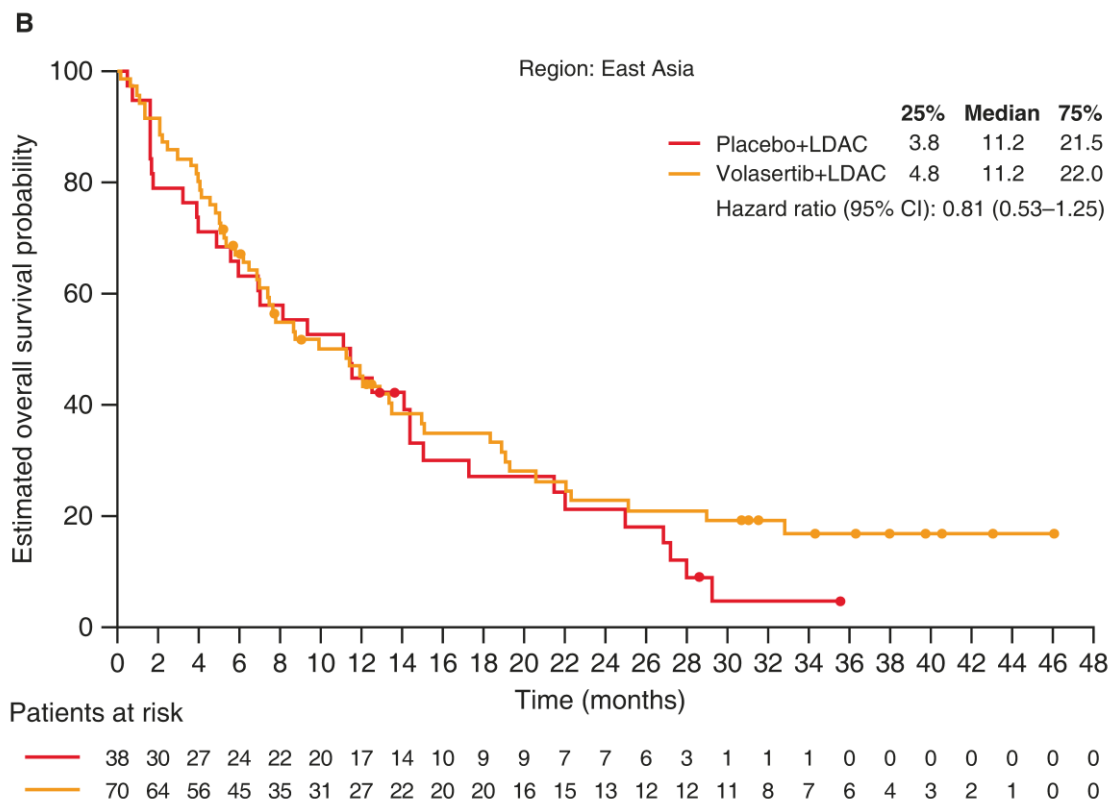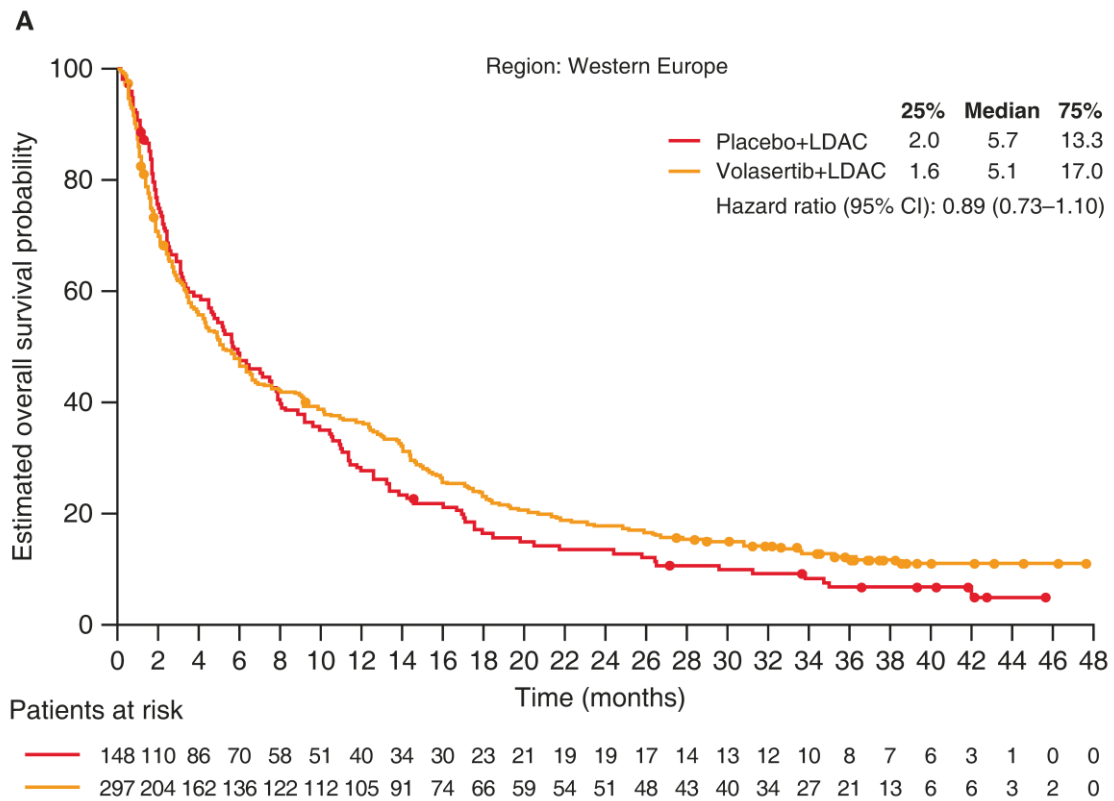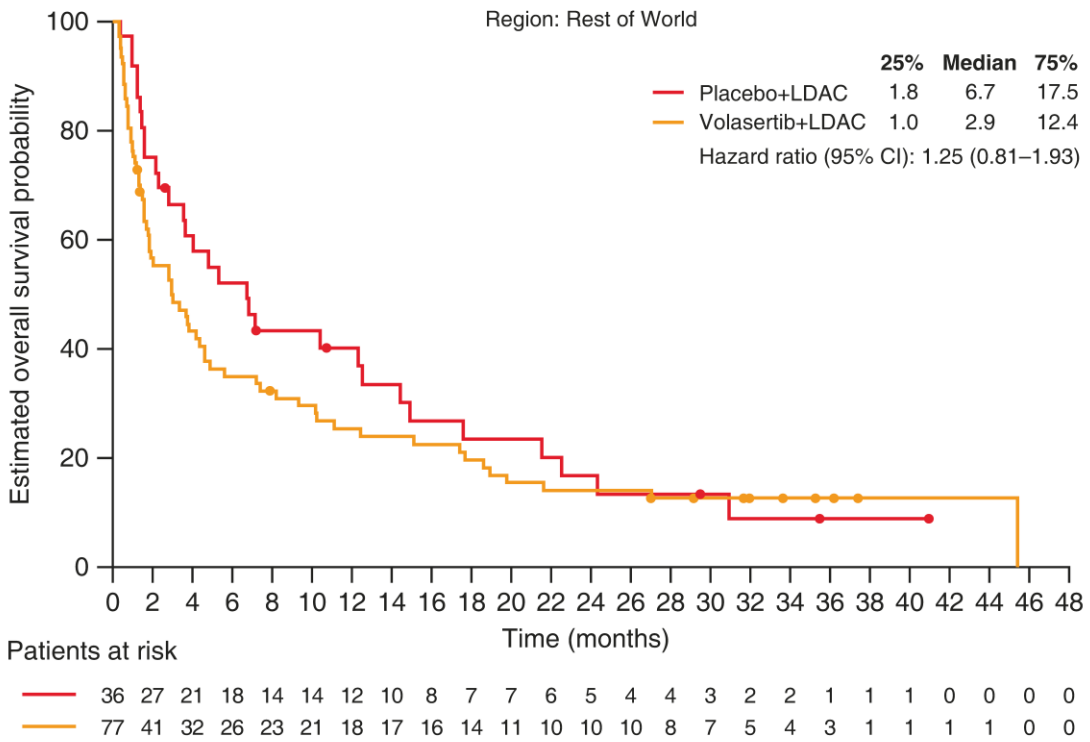

A

Baseline ECOG Score: 0

	25%	Median	75%
Placebo+LDAC	4.4	9.2	18.4
Volasertib+LDAC	3.6	11.7	23.4

Hazard ratio (95% CI): 0.81 (0.56–1.17)

Patients at risk

| 53 | 45 | 40 | 34 | 28 | 23 | 18 | 16 | 14 | 13 | 12 | 12 | 12 | 10 | 7 | 5 | 4 | 3 | 2 | 2 | 2 | 0 | 0 | 0 | 0 |
| 100 | 79 | 69 | 61 | 56 | 52 | 47 | 44 | 35 | 35 | 28 | 25 | 23 | 23 | 20 | 18 | 12 | 11 | 11 | 6 | 3 | 2 | 1 | 0 | 0 |

Baseline ECOG Score: 1

	25%	Median	75%
Placebo+LDAC	1.9	5.6	13.3
Volasertib+LDAC	2.0	6.4	18.9

Hazard ratio (95% CI): 0.83 (0.65–1.05)

Patients at risk

| 117 | 86 | 66 | 53 | 44 | 41 | 32 | 26 | 21 | 17 | 17 | 15 | 14 | 13 | 11 | 9 | 8 | 7 | 6 | 5 | 4 | 2 | 1 | 0 | 0 |
| 241 | 179 | 149 | 121 | 102 | 94 | 87 | 73 | 66 | 59 | 52 | 48 | 45 | 41 | 37 | 35 | 31 | 24 | 17 | 10 | 7 | 7 | 4 | 2 | 0 |

B

Axis labels: Estimated overall survival probability; Time (months)

C

Baseline ECOG Score: 2

	25%	Median	75%
Placebo+LDAC	1.7	5.6	16.9
Volasertib+LDAC	1.0	2.0	6.6

Hazard ratio (95% CI): 1.48 (1.04–2.09)

Estimated overall survival probability

Time (months)

Patients at risk

| 52 | 36 | 28 | 25 | 22 | 21 | 19 | 16 | 13 | 9 | 8 | 5 | 5 | 4 | 3 | 3 | 3 | 3 | 1 | 1 | 1 | 1 | 0 | 0 | 0 |
| 103 | 51 | 32 | 25 | 22 | 18 | 16 | 13 | 9 | 6 | 6 | 6 | 6 | 6 | 6 | 5 | 4 | 3 | 2 | 2 | 0 | 0 | 0 | 0 | 0 |

SDC Figure 2. Kaplan–Meier plots of overall survival by geographical location in the final analysis. CI=confidence interval, LDAC=low-dose cytarabine.

C

Region: Rest of World

	25%	Median	75%
Placebo+LDAC	1.8	6.7	17.5
Volasertib+LDAC	1.0	2.9	12.4

Hazard ratio (95% CI): 1.25 (0.81–1.93)

Estimated overall survival probability

Time (months)

Patients at risk

36	27	21	18	14	14	12	10	8	7	7	6	5	4	4	3	2	2	1	1	1	0	0	0	0
77	41	32	26	23	21	18	17	16	14	11	10	10	10	8	7	5	4	3	1	1	1	1	0	0

SDC Figure 3. Kaplan–Meier plot of time to fatal infections by dose intensity of V+LDAC in the primary analysis set. C1=cycle 1, DD=dose density, LDAC=low-dose cytarabine.
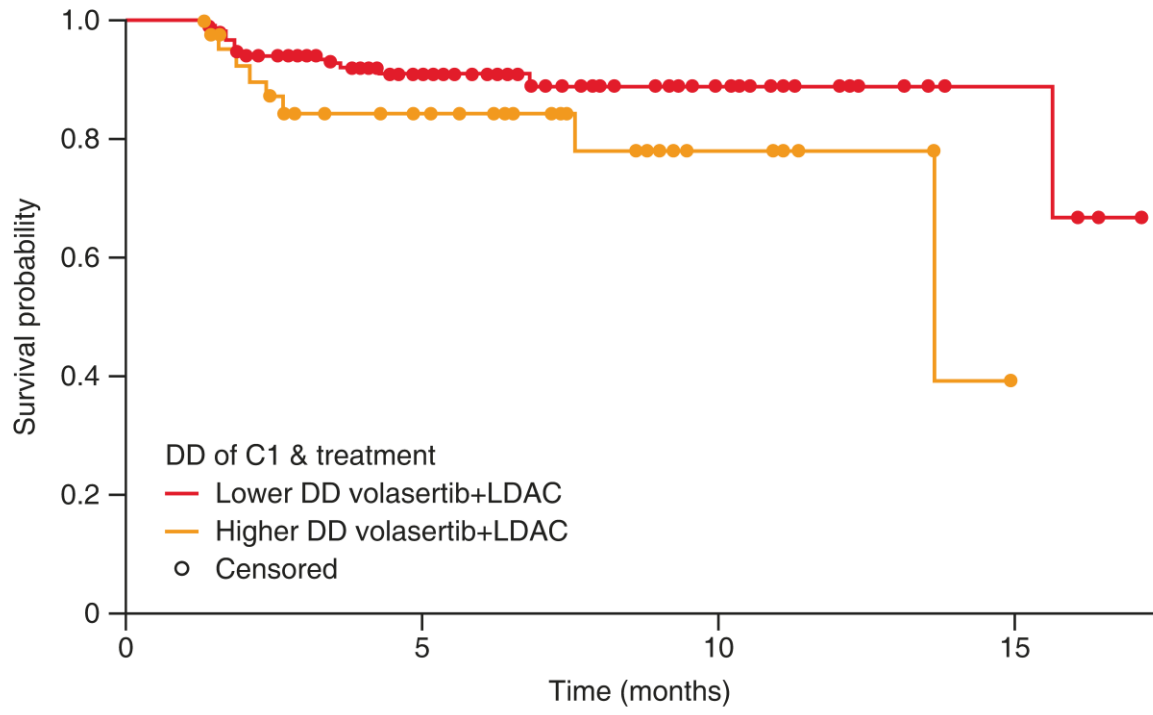
SDC Figure 4. Kaplan–Meier plot of time to fatal adverse events by dose intensity of V+LDAC in the primary analysis. C1=cycle 1, DD=dose density, LDAC=low-dose cytarabine.
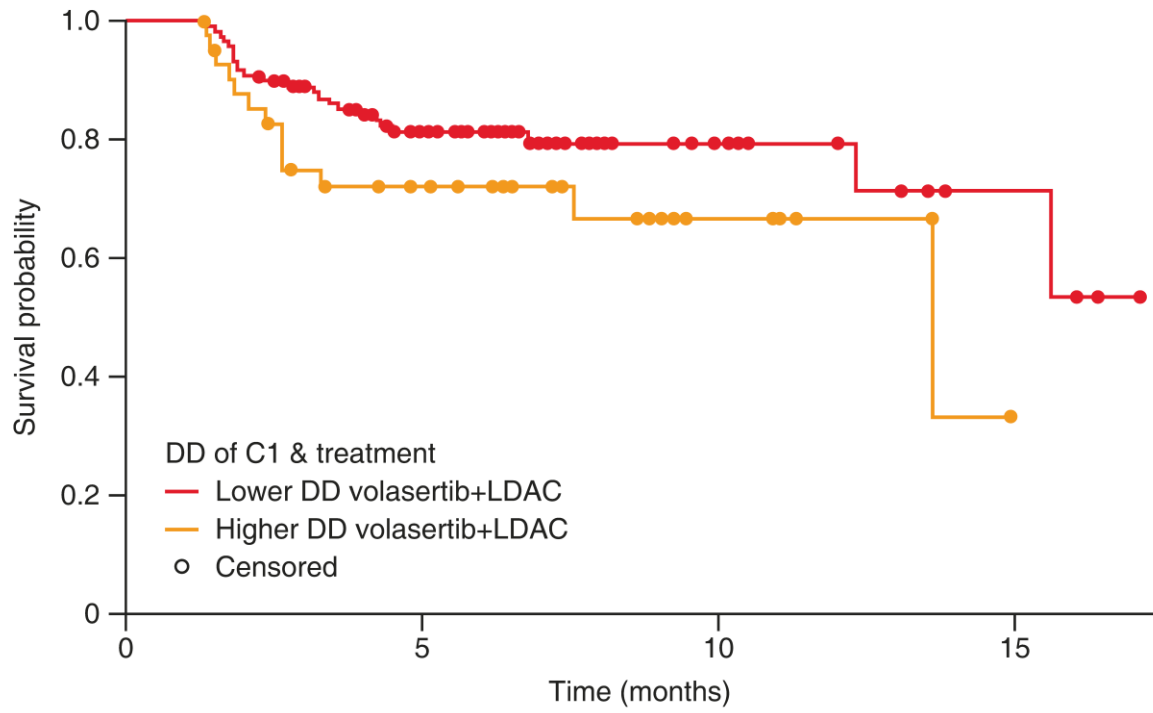
SDC Figure 5. Kaplan–Meier plot of overall survival by dose intensity of V+LDAC in the primary analysis. C1=cycle 1, DD=dose density, LDAC=low-dose cytarabine.
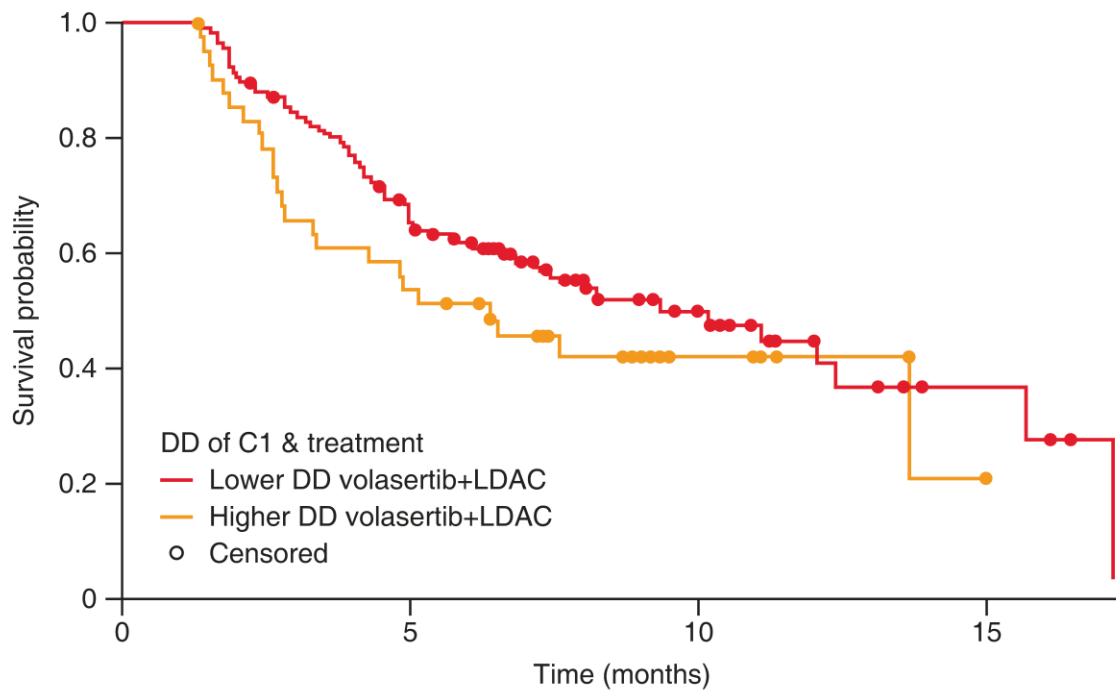
SDC Figure 6. Kaplan–Meier plot, from an unplanned exploratory analysis, of time to fatal infections in patients receiving V+LDAC by duration of prophylactic antibiotic use in the primary analysis set. The extent of prophylactic antibiotic treatment was calculated as the percentage of days in the risk period (from the first treatment to the last treatment, +21 days) on which prophylactic antibiotics were given: no use, 0%; some use, >0 to ≤60%; frequent use, >60%. Prophylactic antibiotics administered in the V+LDAC arm included fluconazole (36.4%); ciprofloxacin (27.4%); levofloxacin (25.4%); aciclovir (21.2%); ciprofloxacin hydrochloride (16.1%); and vancomycin (11.6%). LDAC=low-dose cytarabine.
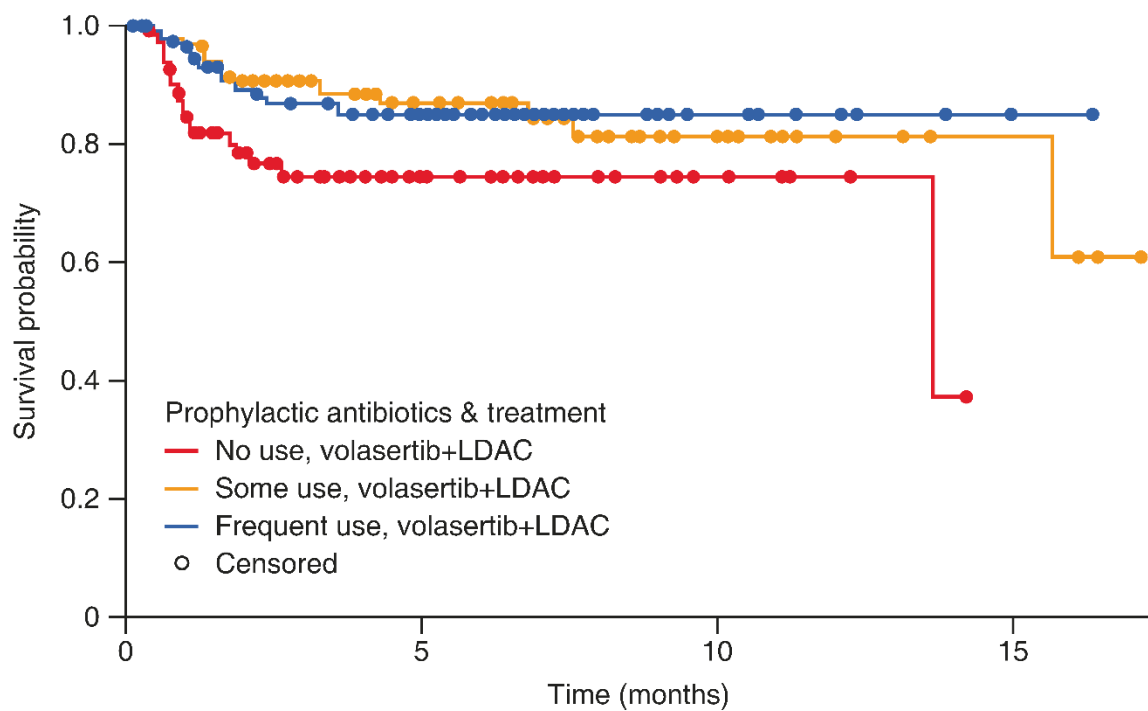
SDC Figure 7. Kaplan–Meier survival plots, from an unplanned exploratory analysis using the cause-specific hazard model for competing risk, of deaths potentially due to lack of treatment efficacy (a) and potentially due to treatment intolerability (b).

CI=confidence interval, LDAC=low-dose cytarabine.
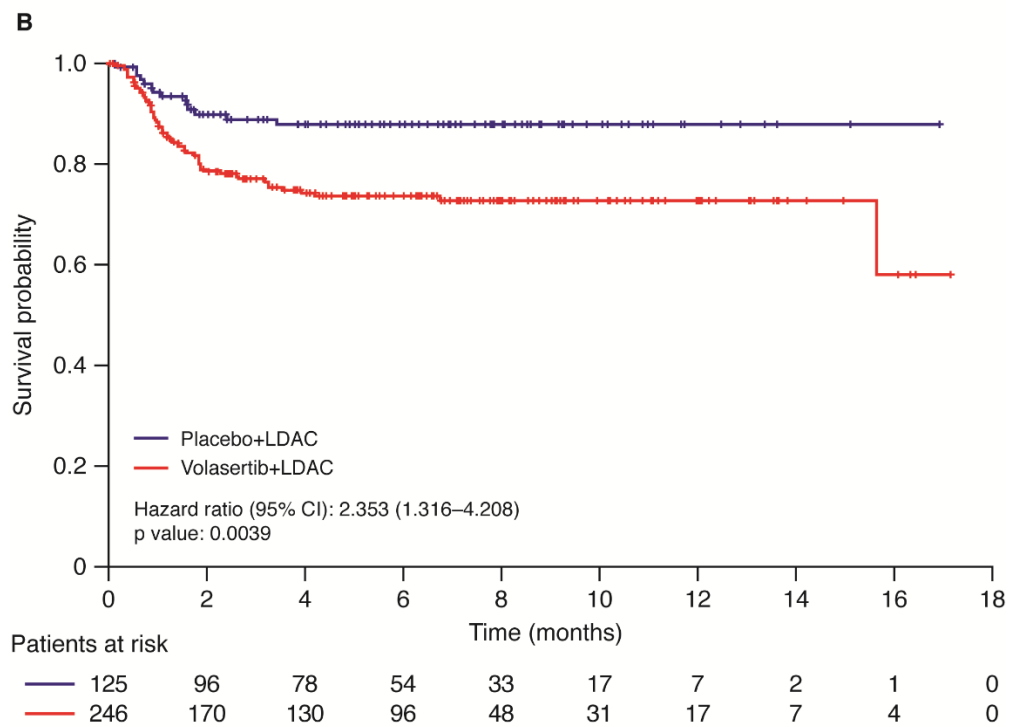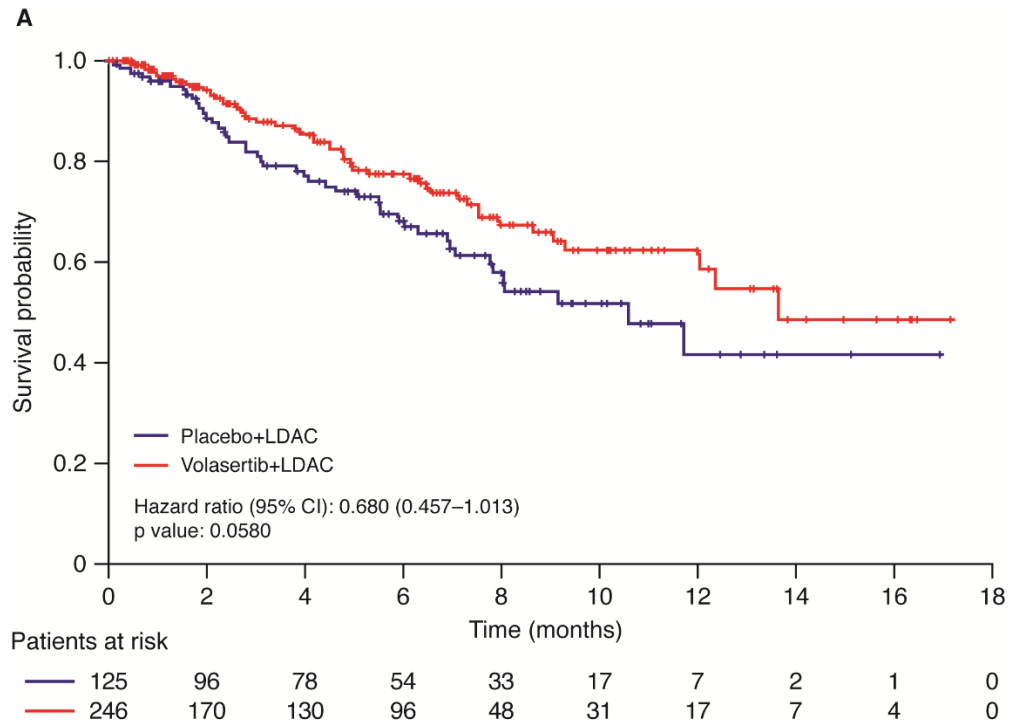
SDC Figure 8. Cumulative incidence curves of deaths potentially due to lack of treatment efficacy (A) and treatment intolerability (B), from an unplanned exploratory analysis, using the subdistribution model for competing risk. CI=confidence interval, LDAC=low-dose cytarabine.

A

B