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Dual resistance to asparaginase and PD-1 blockade in extranodal natural killer/T-cell lymphoma: dismal outcomes from a multicenter cohort

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Short Title: Dual Resistance in ENKTL

Declarations

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Author contributions

L.F., D.K., M.S., and C.W. conceptualized and designed the study, supervised the data analysis, and reviewed and revised the manuscript critically. R.L., L.S., J.M., X.L., and X.W. acquired data, conducted statistical analysis, and drafted the paper. X.W., H.L., L.C., H.S., Y.X., J.Z., H.H., J.S., X.Z., X.X., and W.W. acquired data, helped analyze and interpret the data, and reviewed and revised the manuscript. All authors approved the submitted and final versions.

Competing interests

The authors declare that they have no competing interests.

Data availability statement

The datasets analyzed during the current study are available from the corresponding authors on reasonable request.

Abstract

Asparaginase-based regimens and anti-PD-1 therapies have significantly improved survival in patients with extranodal natural killer/T-cell lymphoma (ENKTL) and are now increasingly incorporated into earlier treatment lines. However, clinical outcomes for patients with dual resistance to asparaginase and PD-1 inhibitors remain poorly defined. We conducted a multicenter retrospective study of 61 patients with dual resistance from a cohort of 900 ENKTL patients across 12 academic centers in China. Among 61 patients, median overall survival from initial diagnosis (OS-1) was 21.9 months (95% CI: 14.7 – 43.1). After the onset of dual resistance, the median post-resistance survival (OS-2) was 4.9 months (95% CI: 2.8 – 9.9). Rechallenge with asparaginase-based regimens or anti-PD-1 agents resulted in only limited benefit, yielding median progression-free survival (PFS) of 3.2 months (95% CI: 1.4 – 5.0) and 2.7 months (95% CI: 2.1 – 3.3), respectively. Chidamide-containing regimens were associated with a significantly longer OS-2 compared to regimens without chidamide (HR, 0.46; 95% CI: 0.24 – 0.88; P = 0.019). Other novel agents, including inhibitors of XPO1, PI3K, and JAK1, along with brentuximab vedotin, did not demonstrate a significant survival benefit in patients with dual-resistant ENKTL. This is the first comprehensive analysis of dual-resistant ENKTL, revealing poor prognosis and suggesting a potential signal of benefit associated with chidamide-containing regimens.

Keywords: ENKTL, dual resistance, asparaginase, PD-1 inhibitors, novel therapies

Introduction

Extranodal natural killer/T-cell lymphoma (ENKTL) is a rare subtype of peripheral T/NK-cell lymphoma closely associated with Epstein-Barr virus (EBV) infection, with distinct geographic predominance in East Asia and Latin America.[1, 2] ENKTL is characterized by male predominance, aggressive clinical behavior, and poor overall survival.[3]

ENKTL is highly resistant to CHOP-like regimens (cyclophosphamide, doxorubicin, vincristine, and prednisone), historically contributing to poor prognosis.[4, 5] The introduction of asparaginase-based regimens marked a significant therapeutic advance, substantially improving survival.[6-8] Current NCCN guidelines recommend frontline asparaginase-containing protocols such as SMILE, P-GemOx, and DDGP.[9-11] Nevertheless, 20%-40% of patients still fail to respond to asparaginase-based therapy.[12-14] EBV-infected lymphoma cells frequently upregulate programmed death-ligand 1 (PD-L1),[15] providing a biological rationale for immune checkpoint blockade. In relapsed or refractory (R/R) ENKTL, anti-PD-1 agents have shown notable activity. Pembrolizumab achieved a 100% overall response in a small cohort,[16] and the ORIENT-4 trial reported a 75% overall response rate with sintilimab (complete response rate 21.4%) among 28 R/R ENKTL patients.[17]

With the increasing incorporation of asparaginase-based regimens and anti-PD-1 therapies into earlier treatment lines for ENKTL,[18-20] characterizing outcomes after dual resistance has become critical. However, outcomes for patients who develop dual resistance remain poorly defined, and no consensus salvage strategies exist for this high-risk population. To address this evidence gap, we conducted a multicenter retrospective study across 12 academic centers to characterize clinical outcomes and evaluate the efficacy of salvage therapies in patients with dual-resistant ENKTL. Acquiring a cohort of 61 such patients from 900 ENKTL patients is significant, as studying this specific population prospectively would be extremely challenging. This is the first multicenter effort to systematically delineate the natural history and therapeutic outcomes of dual-resistant ENKTL.

Methods

Patient population

A cohort of 900 ENKTL patients from 12 academic medical centers in China was

analyzed. All enrolled patients were selected according to the following inclusion criteria: (1) histologically confirmed ENKTL diagnosis according to the World Health Organization classification; (2) received a standard, asparaginase-containing combination chemotherapy regimen; (3) received anti-PD-1 therapy either as monotherapy or in combination; (4) either disease progression, confirmed by imaging or biopsy, or within three months after the last dose of both asparaginase-based and anti-PD-1 therapies. Exclusion criteria: (1) Inadequate clinical follow-up data to determine treatment response or survival status; (2) Discontinuation of either asparaginase-based therapy or PD-1 blockade primarily due to intolerable toxicity, financial reasons, or patient preference rather than confirmed disease progression. All 61 enrolled patients were aged 18 years or older. The study protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Jiangsu Province Hospital (approval No. 2025-SR-121). After securing data-sharing agreements, clinical data were retrospectively abstracted from electronic medical records at each site.

Data Collection

Data were extracted, including baseline clinical characteristics, response to first-line therapy, features at initiation of asparaginase-based and anti-PD-1 treatment regimens and responses, details of disease progression, and overall survival. Treatment responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to imaging assessments and clinical documentation.[21]

Endpoints

Primary endpoints were OS from diagnosis (OS-1) and OS from the onset of dual resistance (OS-2). Secondary endpoints included characterization of clinical features among patients with dual resistance (demographic, disease stage, PINK-E scores, first-line regimens, and treatment responses) and comparison of OS across salvage therapies administered after dual resistance. Progression-free survival analyses included PFS-1—defined as the interval from initial diagnosis to first progression or death, and PFS-2—defined as the interval from development of dual resistance to subsequent progression or death. Comparative analyses of PFS across treatment groups were performed to evaluate therapeutic efficacy.

Statistical Analysis

Time-to-event analyses were conducted using the Kaplan-Meier method, and

survival curves were compared with the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. All statistical analyses were performed using R version 4.3.3. Two-sided P values <0.05 were considered statistically significant.

Results

Patient characteristics

Between January 2011 and May 2024, 61 patients were included in this analysis. Median age was 51 years (range, 21-80); 45 patients (73.8%) were male, and 16 (26.2%) were female; all patients were Asian. Baseline demographic and clinical characteristics are summarized in **Table 1**. Forty patients (65.6%) had advanced-stage disease, and 32 (52.5%) had high PINK-E scores. For frontline therapy, 43 patients (70.5%) received asparaginase-based chemotherapy, 15 (24.6%) received asparaginase combined with anti-PD-1 therapy, and 3 (4.9%) received other therapies. Forty-seven patients (77%) had primary refractory ENKTL after frontline therapy.

Initial asparaginase and anti-PD-1 therapy

Characteristics of patients who received initial asparaginase-based therapy are summarized in **Table 2**. In the initial pegaspargase group, 46 of 61 patients received chemotherapy-containing regimens, including P-GemOx (n=19), PMED (n=12), P-GOD (n=6), P-GDP (n=3), and other regimens (n=6). In the initial anti-PD-1 group, 23 of 61 patients received chemotherapy-based strategies, with GemOx administered in 14 cases and the remaining 9 receiving various regimens such as GDP, DEP, liposomal mitoxantrone, among others. Across all lines of therapy, oxaliplatin was used in 42 patients, cisplatin in 7 and nedaplatin in 1. Regarding PD-1 inhibitors, the initial agents used were: sintilimab (n=23), tislelizumab (n=22), penpulimab (n=8), camrelizumab (n=6), pembrolizumab (n=1), and pucotenlimab (n=1).

Among patients with primary resistance to either asparaginase or PD-1 blockade (n=39), median OS-1 was 14.4 months (95% CI, 10.9 – 40.1). In contrast, patients who achieved prior response before developing resistance (n=22) had a longer median OS-1 of 45.3 months (95% CI, 30.9 – not reached). However, no significant difference in OS-1 (HR, 0.62; 95% CI, 0.33 – 1.18; P=0.147, Figure S1A) and OS-2 (HR, 0.84; 95% CI, 0.45 – 1.58; P=0.588, Figure S1B) was observed in this subgroup analysis.

Dual resistance

At the time of dual resistance, the median age was 52 years (range 24–85). Patients had received a median of 2 prior lines of therapy (range 1–4). After development of dual resistance, 44 patients (72.1%) underwent further treatments; the median number of subsequent lines was 1 (range 0-6). 15 patients (24.6%) were rechallenged with asparaginase-based regimens, and 24 (39.3%) with anti-PD-1 therapy. The ORR to asparaginase-based rechallenge was 15% (no CRs; PR 8%), with a median PFS of 3.2 months (95% CI, 1.4–5.0). The ORR upon anti-PD-1 rechallenge was 10% (all PRs), with a median PFS of 2.7 months (95% CI, 2.1-3.3) (**Table 3**).

Outcomes

At data cutoff, 45 patients had experienced an OS-1 event. Median OS-1 was 21.9 months (95% CI, 14.7–43.1); estimated OS-1 rates at 12-, 36-, and 60-months were 71.7% (95% CI, 61.1-84.0), 39.9% (95% CI, 28.7-55.5), and 20.6% (95% CI, 11.3-37.6), respectively (**Figure 1A**). Univariate and multivariate Cox analyses revealed that advanced tumor stage (Univariate analysis: HR, 1.942; 95% CI, 0.918 - 4.108; P = 0.083; Multivariate Cox: HR, 9.378; 95% CI, 1.571 - 55.995; P = 0.014) and lymph node involvement (Univariate analysis: HR, 1.939; 95% CI, 1.023 - 3.674; P = 0.042; Multivariate Cox: HR, 4.211; 95% CI, 1.544 - 11.484; P = 0.005) were significantly associated with poorer OS-1 (**Table S1**). Median OS from the onset of dual resistance (OS-2) was 4.9 months (95% CI, 2.8–9.9); estimated OS-2 rates at 12 and 24 months were 27.7% (95% CI,17.6-43.4) and 14.0% (95% CI,6.0-32.8), respectively (**Figure 1B**). Univariate and multivariate Cox analyses identified lymph node involvement (Univariate analysis: HR, 2.267; 95% CI, 1.172 - 4.386; P = 0.015; Multivariate Cox: HR, 2.006; 95% CI, 0.999 - 4.028; P = 0.05) as an independent predictor of reduced OS-2 (Table S2). By data cutoff, median PFS-1 was 5.3 months (95% CI, 3.5 – 8.1), and 26.2% (95% CI,17.2-40.0) of patients remained progression-free at 12 months (**Figure 1C**). Fifty-three patients experienced a PFS-2 event after dual resistance; median PFS-2 was 2.8 months (95% CI, 1.5–3.5), and the estimated 6-month PFS-2 was 19.2% (95% CI,11.1-33.3, **Figure 1D**).

After development of dual resistance, patients were treated with rechallenged strategies (anti-PD-1 or asparaginase) or with novel agents, including HDACi inhibitors, XPO1 inhibitors, PI3K inhibitors, JAK1 inhibitors, or BV. All 61 patients were assessed for OS-2 and PFS-2 according to subsequent treatment groups.

Compared with those who did not receive anti-PD-1 therapy, patients who received anti-PD-1 therapy had similar OS-2 (HR, 0.58; 95% CI, 0.32 - 1.06; P=0.078, **Figure 2A**). OS-2 was also comparable between patients who received asparaginase and those who did not (HR, 0.62; 95% CI, 0.31 - 1.23; P=0.169, **Figure 2B**). A statistically significant difference in OS-2 was observed between the chidamide-treated and control groups (HR, 0.46; 95% CI, 0.24-0.88; P=0.019, **Figure 2C**). Novel therapies (XPO1, PI3K, and JAK1 inhibitors, and BV) did not significantly improve OS-2 relative to the control group (HR, 0.62; 95% CI, 0.32 - 1.21; P=0.160, **Figure 2D**). No significant differences in PFS were observed across groups stratified by subsequent anti-PD-1 therapy, asparaginase, chidamide, or novel therapies (**Figure S2A-S2D**). Next, Univariate and multivariate Cox analyses identified chidamide treatment (Univariate analysis: HR, 0.46; 95% CI, 0.24 - 0.88; P = 0.019; Multivariate Cox: HR, 0.482; 95% CI, 0.235 - 0.990; P = 0.047) as an independent predictor of prolonged OS-2 (**Table S3**).

Discussion

This is the first multicenter study to characterize clinical outcomes in patients with ENKTL who developed dual resistance to asparaginase and PD-1 inhibitors. In a cohort of 61 patients from 12 academic centers in China, we evaluated overall survival from diagnosis (OS-1) and survival after onset of dual resistance (OS-2). The most common post-resistance strategies were rechallenge with anti–PD-1 agents or asparaginase-based regimens, which yielded a median PFS of less than 4 months. Novel agents—including XPO1, PI3K, and JAK1 inhibitors, as well as BV—did not improve OS-2 in our series. By contrast, patients who received chidamide-containing regimens demonstrated a statistically significant improvement in OS-2.

Integration of asparaginase into combined-modality treatment (chemotherapy plus radiotherapy) has substantially improved outcomes for patients with early-stage ENKTL.[22, 23] By contrast, patients with advanced-stage disease continue to have a poor prognosis, with 5-year survival rates of 30–40%.[3, 24] Although asparaginase-containing regimens provide effective salvage after anthracycline failure, outcomes are particularly unfavorable for patients who relapse after non-anthracycline regimens, with reported median PFS and OS of approximately 4.1 and 6.4 months, respectively.[25] PD-1 inhibitors have introduced important therapeutic options for

relapsed/refractory ENKTL, with preclinical and clinical data suggesting that combining ICIs with chemotherapy, radiotherapy, targeted agents, or epigenetic modulators can produce synergistic antitumor effects.[26, 27] Nevertheless, responses to ICIs are heterogeneous, and our data reveal poor prognosis for patients with dual resistance to asparaginase and PD-1 blockade, highlighting the urgent need for novel targeted strategies in this high-risk subgroup.

The apparent benefit of chidamide-containing salvage regimens in our cohort is consistent with prior reports. A recent phase II study in relapsed/refractory ENKTL reported overall response and complete response rates of 39% and18%, respectively, with chidamide.[28] A case report described durable remission when chidamide is combined with PD-1 blockade.[29] These data, together with our findings, suggest that epigenetic modulation with chidamide may restore or enhance sensitivity to immunotherapy in some patients. Although chidamide-containing regimens were associated with longer OS-2, this finding should be interpreted with caution given the absence of a corresponding PFS benefit and the potential for selection bias inherent to retrospective analyses.

We observed a notably durable response in one patient who achieved CR after liposomal mitoxantrone monotherapy; maintenance chidamide sustained remission and yielded OS-2 exceeding 36 months. These results raise the hypothesis that novel formulations of conventional cytotoxic agents could potentially overcome drug-resistance mechanisms. Traditional anthracyclines are largely ineffective in ENKTL due to P-glycoprotein–mediated multidrug resistance,[30] whereas liposomal encapsulation of mitoxantrone could potentially bypass efflux mechanisms.[31, 32] In a small retrospective series of 12 heavily pretreated R/R ENKTL patients who received liposomal mitoxantrone-based combinations after asparaginase failure, an ORR of 83.4% was reported, with a median PFS of approximately 5 months and median OS of approximately 7 months.[33]

Emerging therapies in development for ENKTL can be broadly classified as immunotherapeutic (cell-surface antibodies, ICIs, EBV-specific cytotoxic T lymphocytes, immunomodulators, and CAR-T cells) or targeted (signaling pathway inhibitors and epigenetic agents).[34-36] Because relatively few patients in our cohort received XPO1, PI3K, or JAK1 inhibitors or BV, we grouped these agents into a single “novel therapy” category (n = 16). In our series, novel therapies as a group did not significantly improve OS-2 compared with non-novel therapies (HR, 0.62; 95%

CI, 0.32 - 1.21; P=0.160). Large trials of targeted agents offer some optimism—for example, the phase 2 multinational study of the JAK1 inhibitor golidocitinib reported ORR 44.3% (39/88) with CR 24% and PR 20% in R/R PTCL patients.[37] However, in our real-world cohort, only one of four patients treated with golidocitinib had a prolonged OS-2 (approximately 77.4 months), whereas others had OS-2 less than 6 months. Brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate linked to monomethyl auristatin E, has shown efficacy across several non-Hodgkin lymphoma subtypes,[38] and ECHELON-2 demonstrated the benefit of BV-CHP over CHOP in PTCL,[39] supporting further exploration of BV in ENKTL. Exportin-1 (XPO1) is frequently overexpressed in NHL and associated with poor prognosis.[40] Combination regimens such as ATG-010 plus GemOx showed promising activity in a phase Ib trial, with ORR of 48.6% and CRR of 22.9% among 35 evaluable patients.[41]

Several limitations should be acknowledged. First, its retrospective, multicenter design may introduce selection bias, unmeasured confounding, and heterogeneity in treatment approaches and data collection. Second, heterogeneity of post-resistance treatment regimens prevents definitive conclusions about the efficacy of any single therapy. Third, the absence of a randomized control group and limited biomarker data (eg, PD-L1 expression, EBV viral dynamics, and comprehensive genomic profiling) constrained our ability to investigate mechanisms of dual resistance or identify predictive biomarkers. Prospective studies with larger, standardized cohorts and integrated biomarker analyses are needed to validate these observations and elucidate the biological basis of resistance in this high-risk population.

In conclusion, dual resistance to asparaginase and PD-1 blockade constitutes a major therapeutic challenge in ENKTL and is associated with dismal survival outcomes in our multicenter cohort of 61 patients. Chidamide-containing regimens demonstrated promising efficacy as a salvage therapy in this setting. Future prospective trials are needed to directly compare chidamide-based strategies with other approaches in this specific population. The present study serves as a crucial foundation for this essential subsequent research.

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Tables

Table 1. Baseline patient characteristics (n = 61)

	All patients (n=61)
Age, median (range)	51 (21-80)
Sex, n (%)	
Female	16 (26.2)
Male	45 (73.8)
Race, n (%)	
Asian	61 (100.0)
AASS at diagnosis, n (%)	
Limited (I-II)	15 (24.6)
Advanced (III-IV)	40 (65.6)
Unknown	6 (9.8)
PINK-E Score, n (%)	
Low	12 (19.7)
Intermediate	10 (16.4)
High	32 (52.5)
Unknown	7 (11.5)
Frontline Therapy, n (%)	
PEG-Asp+Chemo	43 (70.5)
PEG-Asp+Anti-PD-1	15 (24.6)
Other	3 (4.9)
Frontline CR, n (%)	
Yes	23 (37.7)
No	38 (62.3)
Primary Refractory, n (%)	
Yes	47 (77.0)
No	14 (23.0)

AASS, Ann Arbor stage system

Table 2. Initial pegaspargase (PEG-Asp) and anti–PD-1 therapy details.

	Pegaspargase (n=61)		**Anti-PD-1 (n=61)**
Prior LOT (median, range)	0 (0-1)	**Prior LOT (median, range)**	1 (0-3)
Regimen		**Regimen**	
PEG-Asp+Chemo	46 (75.4)	Anti-PD-1	5 (8.2)
PEG-Asp+Anti-PD-1	15 (24.6)	Anti-PD-1+Chemo	23 (37.7)
		Anti-PD-1+PEG-Asp	24 (39.3)
		Other Combination	9 (14.8)
Best Response		**Best Response**	
CR	21 (34.4)	CR	6 (9.8)
PR	0	PR	6 (9.8)
SD	1 (1.6)	SD	2 (3.3)
PD	39 (64.0)	PD	47 (77.0)

LOT, lines of therapy; PEG-Asp, Pegaspargase; Chemo, Chemotherapy.

Table 3. Characteristics at dual resistance and subsequent treatments (n = 61).

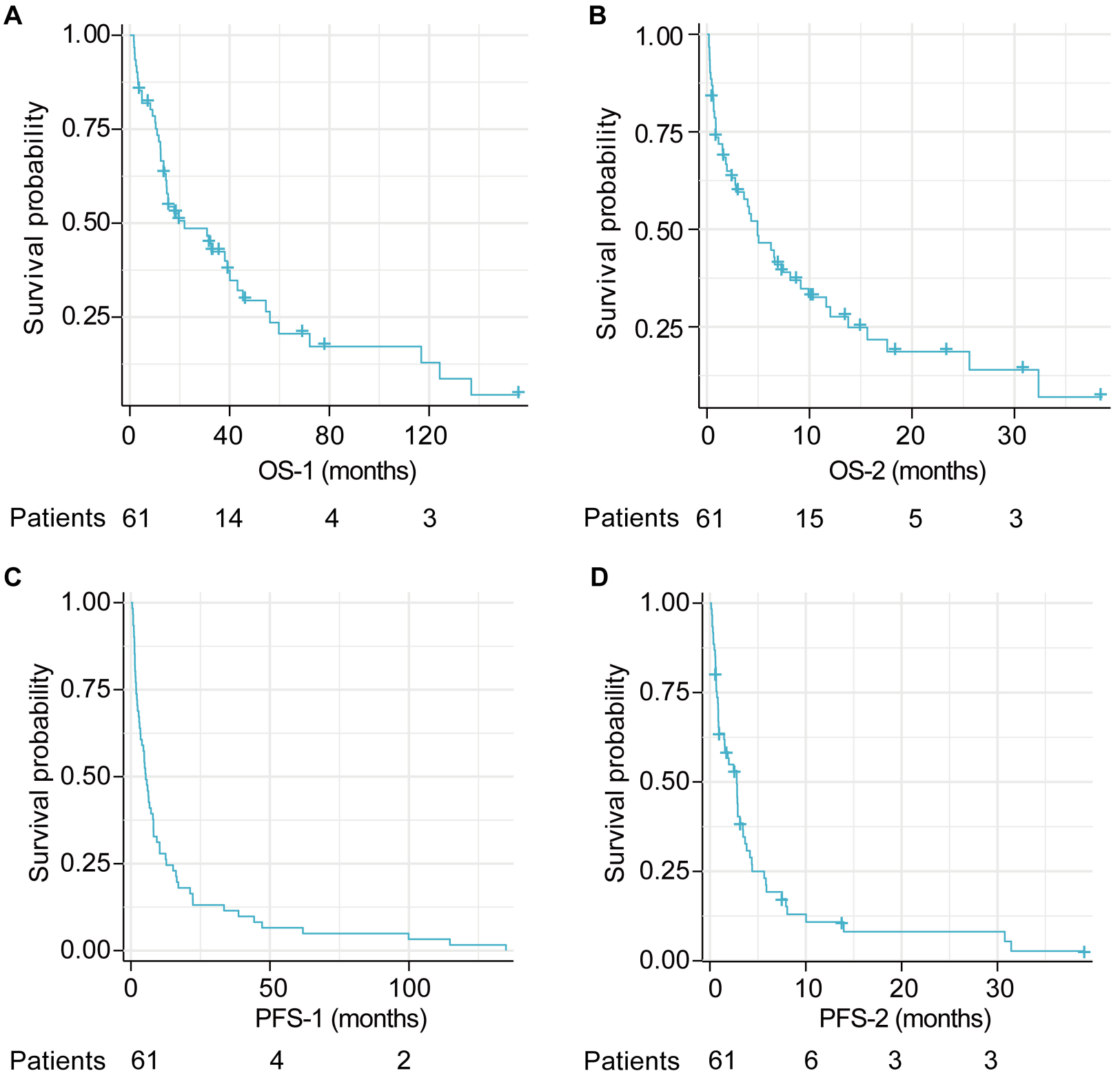
	All patients (n=61)
Age at DR (median, range)	52 (24-85)
Prior LOT (median, range)	2 (1-4)
LOT after DR (median, range)	1 (0-6)
PEG-Asp therapy after DR	
Yes	15 (24.6)
No	46 (75.4)
Anti-PD-1 therapy after DR	
Yes	24 (39.3)
No	37 (60.7)
ORR (%)	
PEG-Asp-based rechallenge	15
Anti-PD-1-based rechallenge	10
PFS (months, median,95% CI)	
PEG-Asp-based rechallenge	3.2 (1.4–5.0)
Anti-PD-1-based rechallenge	2.7 (2.1-3.3)

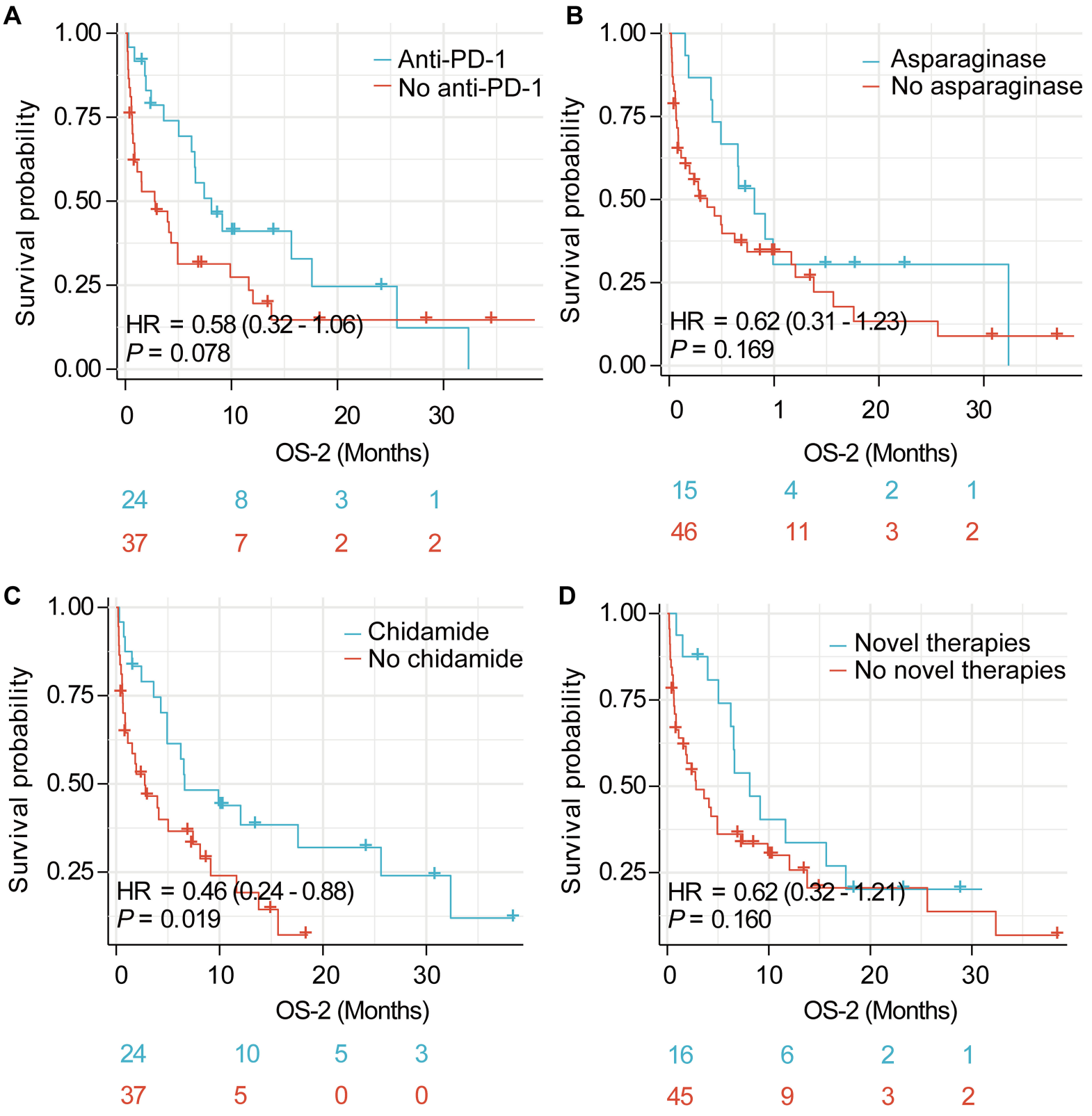
DR, dual resistance; LOT, lines of therapy; PEG-Asp, Pegaspargase.

Figure legends

Figure 1. Kaplan‐Meier estimates of investigator-assessed survival outcomes. (A) Overall survival from diagnosis (OS-1) in the full cohort. (B) Overall survival from onset of dual resistance (OS-2) in the full cohort. (C) Progression-free survival from diagnosis (PFS-1) in the full cohort. (D) Progression-free survival from onset of dual resistance (PFS-2) in the full cohort.

Figure 2. Overall survival from onset of dual resistance (OS-2), stratified by subsequent therapy: (A) anti‐PD-1, (B) asparaginase, (C) chidamide, and (D) novel therapies (pooled: XPO1, PI3K, JAK1 inhibitors, or BV).


A
1.00
0.75
0.50
0.25
Survival probability
0
40
80
120
OS-1 (months)
Patients 61 14 4 3
B
1.00
0.75
0.50
0.25
Survival probability
0
10
20
30
OS-2 (months)
Patients 61 15 5 3
C
1.00
0.75
0.50
0.25
0.00
Survival probability
0
50
100
PFS-1 (months)
Patients 61 4 2
D
1.00
0.75
0.50
0.25
0.00
Survival probability
0
10
20
30
PFS-2 (months)
Patients 61 6 3 3


A
Survival probability
1.00
0.75
0.50
0.25
0.00
Anti-PD-1
No anti-PD-1
HR = 0.58 (0.32 - 1.06)
P = 0.078
0
10
20
30
OS-2 (Months)
24 8 3 1
37 7 2 2
B
Survival probability
1.00
0.75
0.50
0.25
0.00
Asparaginase
No asparaginase
HR = 0.62 (0.31 - 1.23)
P = 0.169
0
1
20
30
OS-2 (Months)
15 4 2 1
46 11 3 2
C
Survival probability
1.00
0.75
0.50
0.25
Chidamide
No chidamide
HR = 0.46 (0.24 - 0.88)
P = 0.019
0
10
20
30
OS-2 (Months)
24 10 5 3
37 5 0 0
D
Survival probability
1.00
0.75
0.50
0.25
Novel therapies
No novel therapies
HR = 0.62 (0.32 - 1.21)
P = 0.160
0
10
20
30
OS-2 (Months)
16 6 2 1
45 9 3 2

Supplementary Figure

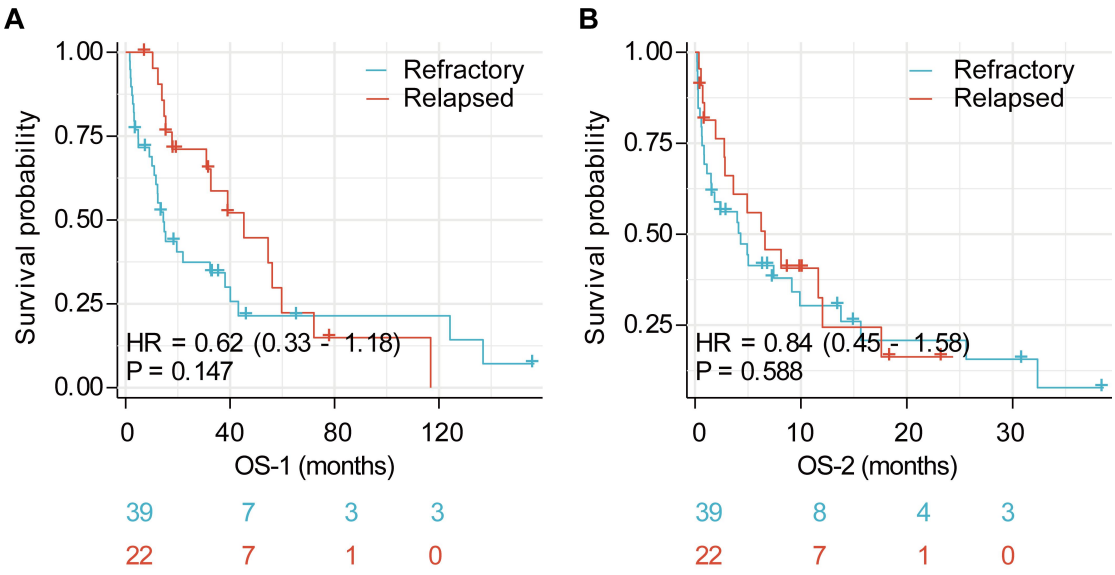


Figure S1. Subgroup analyses of OS-1 (A) and OS-2 (B) comparing patients with primary resistance to either asparaginase or PD-1 blockade versus those who achieved prior response before developing resistance.

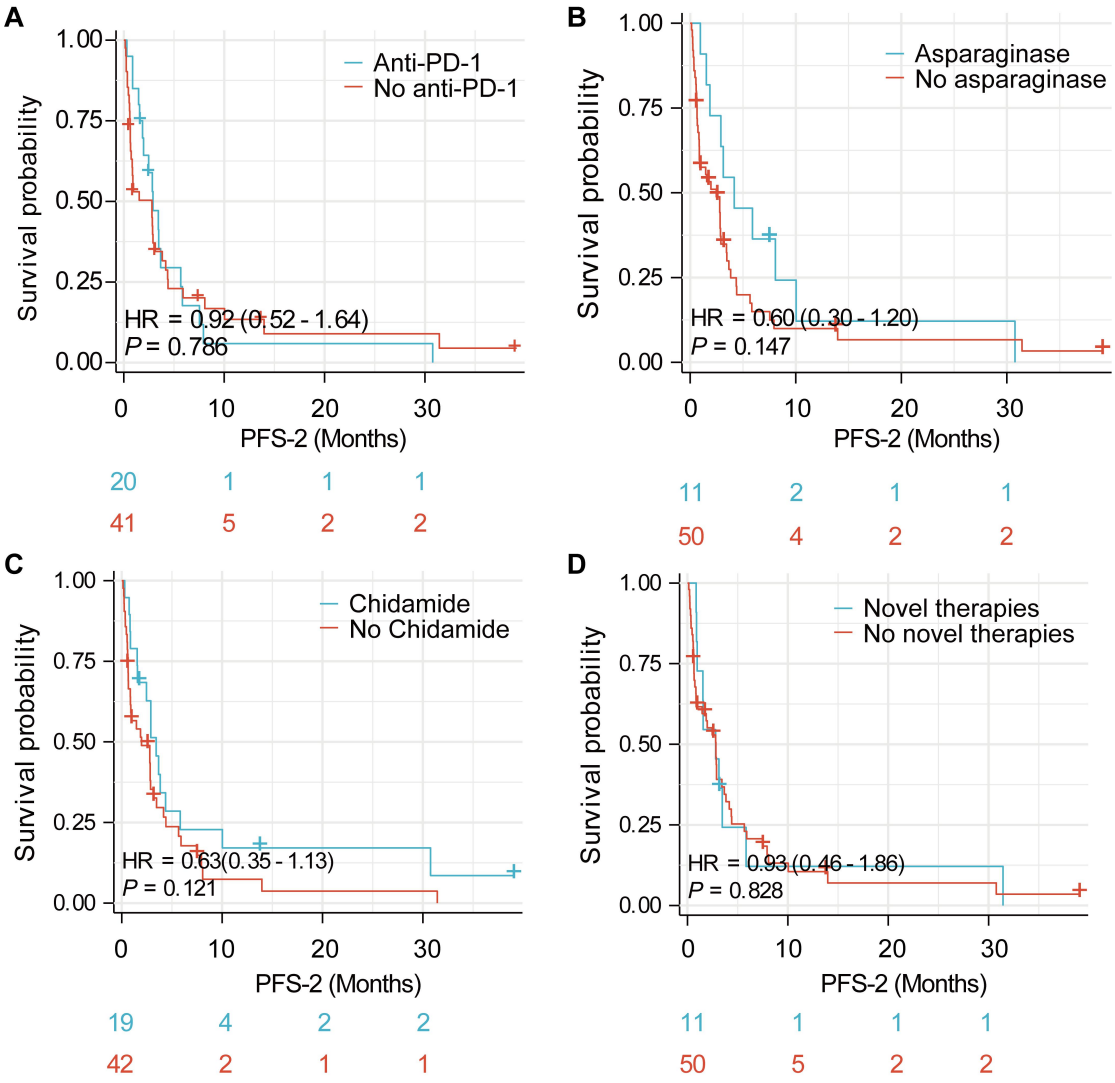


Figure S2. Progression-free survival from onset of dual resistance (PFS-2), stratified by subsequent therapy: (A) anti–PD-1, (B) asparaginase, (C) chidamide, and (D) novel therapies (pooled: XPO1, PI3K, JAK1 inhibitors, or BV).

Supplementary Tables

Table S1. Univariate and multivariate Cox regression analysis for OS-1

Characteristics	Total (N)	HR (95% CI) Univariate analysis	P-value Univariate analysis	HR (95% CI) Multivariate analysis	P-value Multivariate analysis
Age	61				

⩽60	44	Reference			
> 60	17	1.064 (0.551 - 2.055)	0.853		
Sex	61				
Male	45	Reference			
Female	16	0.617 (0.293 - 1.298)	0.203		
AASS	55				
I+II	15	Reference		Reference	
III+IV	40	1.942 (0.918 - 4.108)	0.083	9.378 (1.571 - 55.995)	**0.014**
ECOG	50				
Good (0-1)	33	Reference		Reference	
Intermediate (2)	12	2.915 (1.250 - 6.796)	**0.013**	1.778 (0.658 - 4.800)	0.256
Poor (⩾3)	5	2.233 (0.749 - 6.655)	0.149	1.276 (0.258 - 6.323)	0.765
PINK-E	54				
Low (0-1)	12	Reference		Reference	
Intermediate (2)	10	2.745 (0.841 - 8.959)	0.094	0.550 (0.126 - 2.396)	0.426
High (⩾3)	32	3.161 (1.267 - 7.890)	**0.014**	0.208 (0.031 - 1.377)	0.103
Primary site	60				
Nasal type	44	Reference		Reference	
Non-Nasal type	16	2.683 (1.366 - 5.269)	**0.004**	1.863 (0.745 - 4.656)	0.183
Lymph node involvement	57				
Absent	35	Reference		Reference	
Present	22	1.939 (1.023 - 3.674)	**0.042**	4.211 (1.544 - 11.484)	**0.005**
Bone marrow involvement	52				
Absent	37	Reference			
Present	15	1.407 (0.674 - 2.935)	0.364		

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Table S2. Univariate and multivariate Cox regression analysis for OS-2

Characteristics	Total (N)	HR (95% CI) Univariate analysis	P-value Univariate analysis	HR (95% CI) Multivariate analysis	P-value Multivariate analysis

Age	61				
⩽60	44	Reference			
> 60	17	0.960 (0.500 - 1.844)	0.902		
Sex	61				
Male	45	Reference			
Female	16	0.968 (0.475 - 1.970)	0.928		
AASS	55				
I+II	15	Reference		Reference	
III+IV	40	2.113 (0.963 - 4.635)	0.062	1.905 (0.819 - 4.428)	0.134
ECOG	50				
Good (0-1)	33	Reference			
Intermediate (2)	12	1.922 (0.864 - 4.276)	0.109		
Poor (⩾3)	5	1.269 (0.432 - 3.725)	0.664		
PINK-E	54				
Low (0-1)	12	Reference			
Intermediate (2)	10	1.004 (0.347 - 2.901)	0.995		
High (⩾3)	32	1.483 (0.661 - 3.324)	0.339		
Primary site	60				
Nasal type	44	Reference			
Non-Nasal type	16	1.251 (0.664 - 2.356)	0.489		
Lymph node involvement	57				
Absent	35	Reference		Reference	
Present	22	2.267 (1.172 - 4.386)	**0.015**	2.006 (0.999 - 4.028)	**0.05**
Bone marrow involvement	52				
Absent	37	Reference			
Present	15	1.555 (0.743 - 3.251)	0.241		

AASS, Ann Arbor stage system

Table S3. Univariate and multivariate Cox regression analysis of chidamide treatment for OS-2

Characteristics	Total(N)	HR(95% CI) Univariate analysis	P value Univariate analysis	HR(95% CI) Multivariate analysis	P value Multivariate analysis
Age	61				
≤60	44	Reference			
> 60	17	0.960 (0.500 - 1.844)	0.902		
Sex	61				
Female	16	Reference			
Male	45	1.033 (0.508 - 2.104)	0.928		
AASS	55				
I+II	15	Reference		Reference	
III+IV	40	2.113 (0.963 - 4.635)	0.062	1.906 (0.820 - 4.433)	0.134
ECOG	50				
Good	33	Reference			
Intermediate	12	1.922 (0.864 - 4.276)	0.109		
Poor	5	1.269 (0.432 - 3.725)	0.664		
PINK-E	54				
Low	12	Reference			
Intermediate	10	1.004 (0.347 - 2.901)	0.995		
High	32	1.483 (0.661 - 3.324)	0.339		

Primary site	60				
Nasal type	44	Reference			
Non-Nasal type	16	1.251 (0.664 - 2.356)	0.489		
Lymph node involvement	57				
Present	22	Reference		Reference	
Absent	35	0.441 (0.228 - 0.854)	0.015	0.561 (0.279 - 1.131)	0.106
Bone marrow involvement	52				
Absent	37	Reference			
Present	15	1.555 (0.743 - 3.251)	0.241		
Chidamide treatment	61				
No	37	Reference		Reference	
Yes	24	0.461 (0.242 - 0.881)	**0.019**	0.482 (0.235 - 0.990)	**0.047**

AASS, Ann Arbor stage system