



P2.378: Intrathecal Pemetrexed Plus EGFR-TKI for Osimertinib-Refractory Leptomeningeal Metastasis in EGFR-Mutant NSCLC

Ying-Ting Liao^{1,2}, Chi-Lu Chiang^{1,2}, Cheng-Chia Lee³, Ruei-Lin Sun^{2,4}, Hsu-Ching Huang^{1,2}, Chia-I Shen^{1,2}, Yen-Han Tseng^{1,2}, Heng-Sheng Chao^{1,2}, Tsu-Hui Shiao^{1,2}, Yung-Hung Luo^{1,2}, Yuh-Min Chen^{2,4,5}
¹Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ²School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ³Department of Neurosurgery, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan, ⁴Division of Pulmonology, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, ⁵Clinical Research Center, Shin Kong Wu Ho-Su Memorial Hospital
Correspondence: ytliao6@vghtpe.gov.tw



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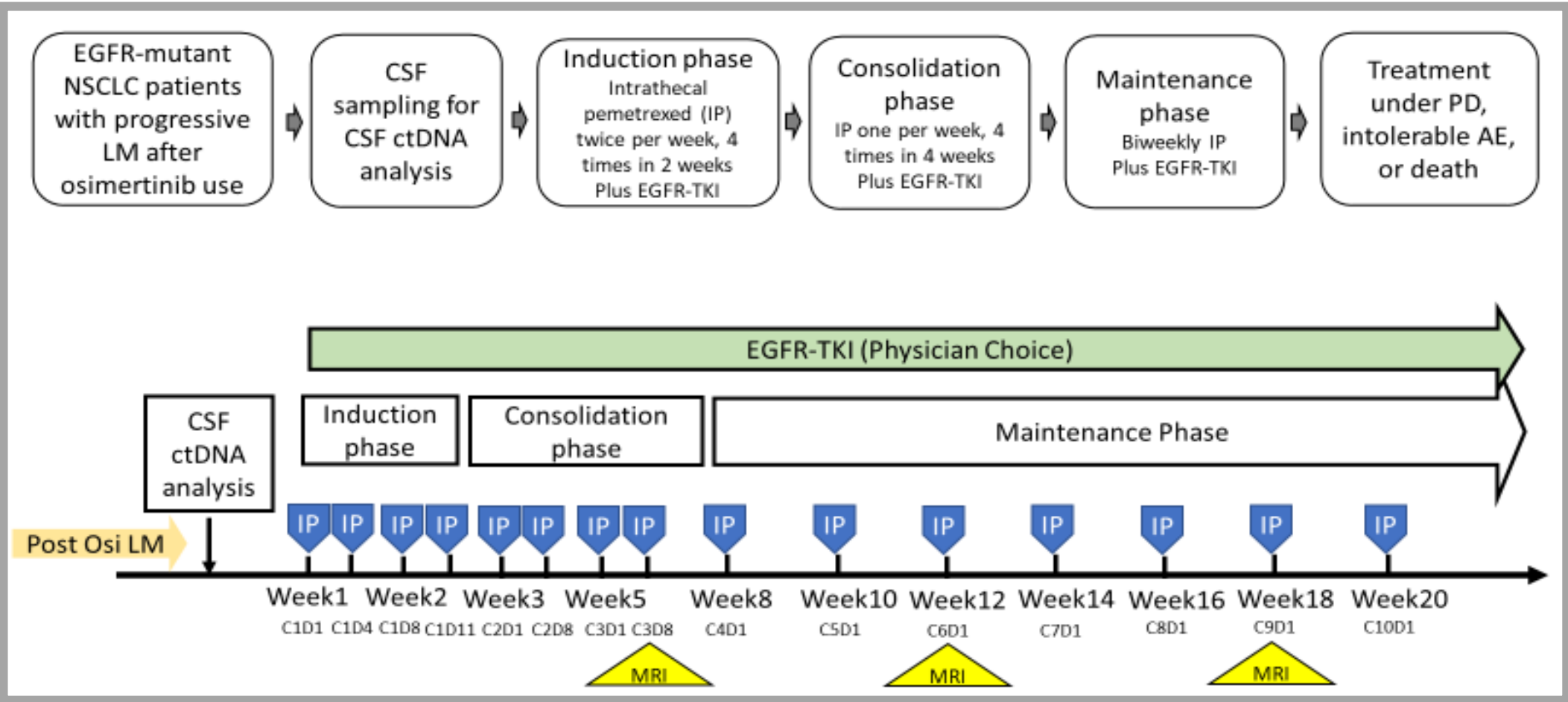
INTRODUCTION

Leptomeningeal metastasis (LM) is a devastating complication of EGFR-mutant non–small cell lung cancer (NSCLC). Although osimertinib improves central nervous system (CNS) control, intracranial progression frequently develops, and survival after LM progression remains poor. Systemic therapies are limited by blood-brain barriers, and effective treatment options following osimertinib failure are lacking. Intrathecal pemetrexed (IP) has shown preliminary activity in early-phase studies. We conducted a prospective clinical trial to evaluate the efficacy and safety of IP combined with oral EGFR tyrosine kinase inhibitors (TKIs) in patients with osimertinib-refractory LM.

METHODS

Design:

- Patients diagnosed with (i) metastatic EGFR+ NSCLC, (ii) Newly developed or progressive LM after osimertinib with or without previous chemotherapy, (iii) stable extracranial disease, are eligible for screening.
- Intrathecal pemetrexed (10 mg) was administered via induction (twice weekly ×2 weeks), consolidation (weekly ×4 weeks), and maintenance (biweekly) phases until progression or unacceptable toxicity.
- Concomitant oral EGFR-TKI was allowed per physician's choice.



DISCUSSION AND CONCLUSION

Take Away Message

- Intrathecal pemetrexed plus EGFR-TKI showed CNS activity in patients with osimertinib-refractory LM and stable extracranial disease.
- CNS disease control was achieved in 55.5%, with a CNS ORR of 33.3% and cytological clearance rate of 62.5%.
- Manageable toxicity
- Significant molecular compartmentalization between CSF and plasma underscores the importance of CSF-directed therapy and molecular profiling.

Future Direction for Research

- Define clinical and molecular predictors of benefit from intrathecal pemetrexed.
- Perform longitudinal paired CSF and plasma ctDNA to characterize CNS-specific resistance mechanisms and treatment response.
- Evaluate whether CSF molecular response/clearance can serve as an early biomarker.
- Investigate the optimal EGFR-TKI partner, treatment duration, and maintenance strategy.
- Larger prospective and comparative studies to define the role of intrathecal pemetrexed in the treatment algorithm for osimertinib-refractory LM.

REFERENCES & ACKNOWLEDGEMENTS

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RESULTS

Table 1. Patient characteristics

Variable	n (%)
Total patients, n	9
Female	9 (100)
Never smoker	9 (100)
Median age, years, range	66.0 (47 – 73)
Initial staging (AJCC 9 th)	
Recurrence	5 (55.6)
Stage IVA	0 (0)
Stage IVB	4 (44.4)
ECOG PS during IT	
0-1	0 (0)
2	7 (77.8)
3	2 (22.2)
EGFR	
Exon 19 deletion	5 (55.6)
L858R	4 (44.4)
T790M before IT	2 (22.2)

Table 2. Treatment pattern and LM presentation

Treatment lines during IT, median (range)	2 (1-3)
Chemotherapy before IT	2 (22.2)
Immune checkpoint inhibitor before IT	0 (0)
Whole brain radiotherapy before IT	2 (22.2)
Time from diagnosis to IT, months, median (range)	46.5 (19.8 – 81.1)
Time from osimertinib to IT, months, median (range)	12.9 (5.7 – 33.1)
Time from LM diagnosis to IT, months, median (range)	8.8 (0.4 – 31.5)
Neurological symptoms	9 (100)
CSF cytology positive	8 (88.9)

Table 3. Treatment exposure, outcome and survival

Median IT treatment duration, months (range)	5.1 (0.3 – 13.7)
Median number of IT cycles (range)	10 (1 – 28)
Median survival since LM	11.9 (5.2 – 40.9)
CNS Objective response rate	33.3%
CNS Disease control rate	55.5%
Improved Level of function score after IT	22.2%
Radiological response improvement	44.4%
CSF cytological clearance	62.5%

Figure 1. Oncoplot of detected genomic alterations in (a) CSF (b) plasma samples at baseline

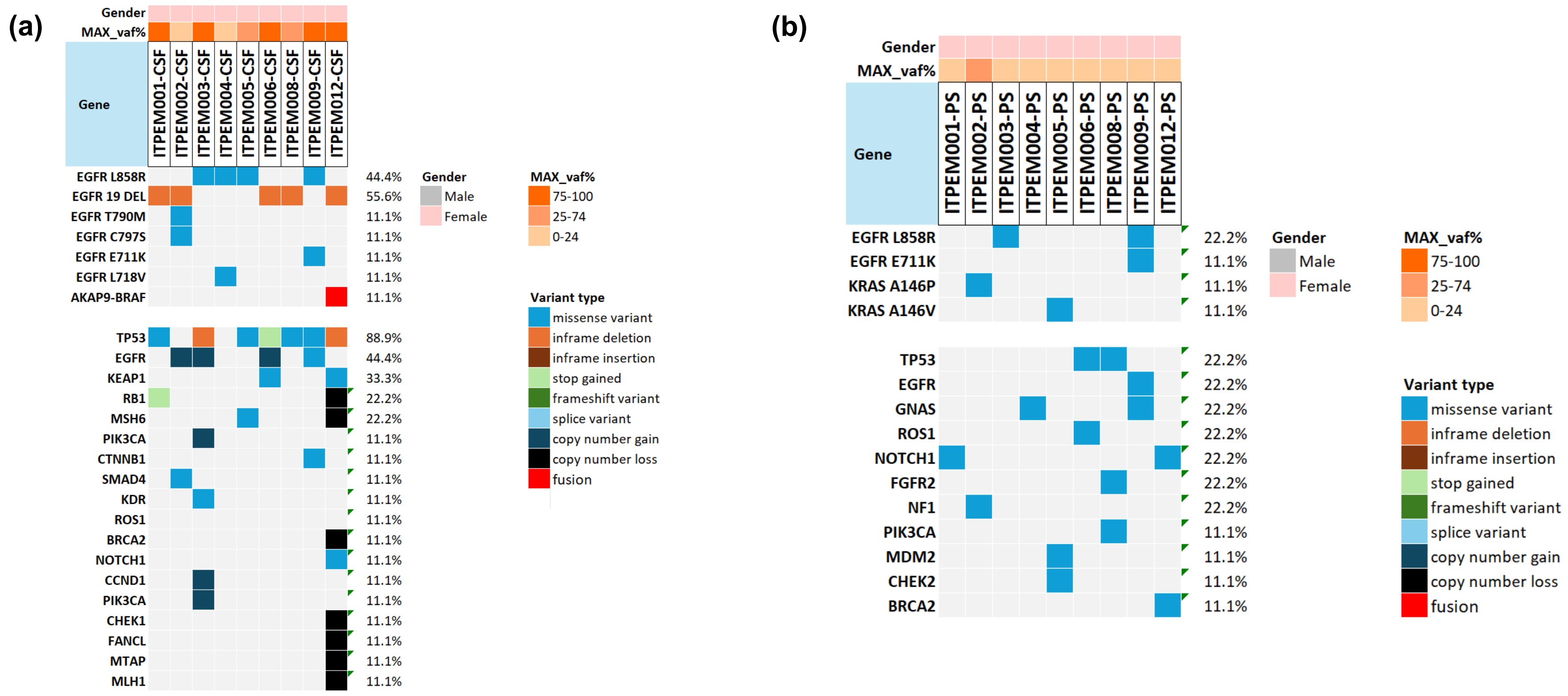


Figure 2. (a) Progression-free survival (b) Survival since IT

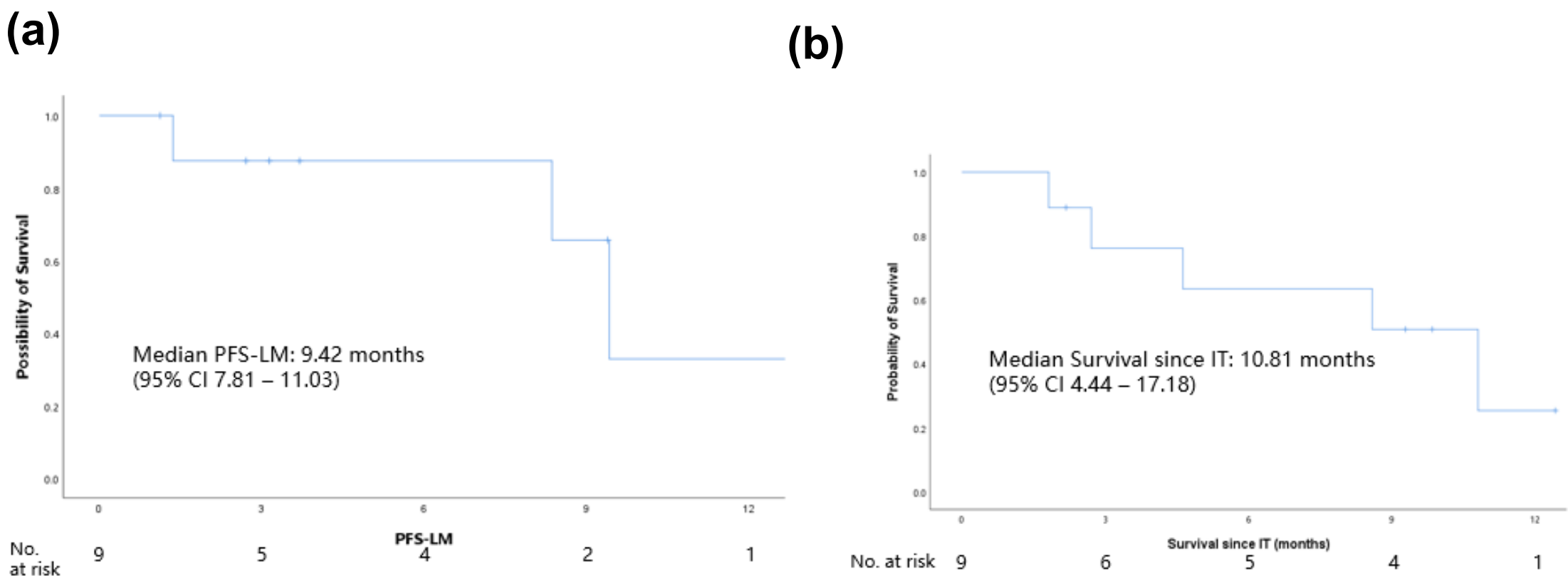


Table 4. Treatment-related adverse events

	Any grade n (%)	Grade ≥3 n (%)
Hematological AEs		
Neutropenia	3 (33.3)	1 (11.1)
Anemia	1 (11.1)	0 (0)
Thrombocytopenia	2 (22.2)	1 (11.1)
Non-Hematological AEs		
Nausea	0 (0)	0 (0)
Diarrhea	2 (22.2)	0 (0)
Elevated ALT/AST	2 (22.2)	1 (11.1)
Fatigue	3 (33.3)	0 (0)
Anorexia	2 (22.2)	0 (0)
Insomnia	1 (11.1)	0 (0)
Events that led to discontinuation	1 (11.1)	0 (0)