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Real-world Evidence of Duvelisib and Romidepsin in Relapsed/Refractory Peripheral and Cutaneous T-cell Lymphomas

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Abstract:
Patients with R/R PTCL require lineage-specific therapies to bridge them to HSCT. A prior phase I/II study of duvelisib/romidepsin (duv/romi) reported ORR of 58% and CRR of 42% with reduced grade 3-4 transaminitis (14%). We report real-world outcomes on a multicenter cohort of 38 patients with R/R PTCL treated with duv/romi. The median age at diagnosis was 64y, with histological subtypes including nTFH (n=17), PTCL-NOS (n=14), CTCL (n=3), ENKTCL (n=1), ALK- ALCL (n=1), ATLL (n=1), and HSTCL (n=1). Median prior therapies were 1 (IQR, 1-2); 15 patients relapsed and 23 were refractory to prior treatment with 8 having prior HSCT (5 auto, 3 allo). Patients received a median of 3 cycles (IQR, 2-4). Among 38 evaluable patients, ORR and CRR were 61% and 47%, respectively, with higher ORR (82% vs 43%) and CRR (71% vs 29%) in nTFH compared to non-nTFH. Median PFS and OS (HSCT-censored) were 11m (HR 0.31, 95%CI: 0.11-0.87; p=0.03) and 16m (HR 0.66, 95%CI: 0.23-1.87; p=0.4) for nTFH versus 3.3m and 8.3m for non-nTFH patients. The median TTR was 1.9m (IQR, 1.7-2.6), DoR was 21m (95%CI, 11-NR) and TTNT was 17m (95%CI, 6.4-NR). Post duv/romi, 11 patients were immediately bridged to allo-HSCT. Treatment was well tolerated, with most common grade 3-4 toxicities being lymphopenia (n=15), neutropenia (n=15), thrombocytopenia (n=10), ALT/AST-transaminitis (n=6), among others. Treatment-related adverse events seldom led to discontinuation (n=4) and death (n=1). These findings reinforce duv/romi's efficacy and role as a bridge to curative HSCT in high-risk R/R PTCL.

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RUNNING TITLE: Duvelisib and romidepsin affirms efficacy in PTCL

KEY WORDS: Peripheral T-cell lymphomas, cutaneous T-cell lymphomas, phosphatidylinositol 3-kinase delta/gamma inhibitor, histone deacetylase inhibitor

KEY POINTS:

1.Duvelisib and romidepsin combination in real-world confirms efficacy, tolerability and safety for patients with R/R PTCL.
2.Duvelisib and romidepsin combination offers a novel strategy to bridge eligible patients with R/R PTCL to allogeneic transplantation.

DATA SHARING STATEMENT: For original data please contact salvia.jain@mgh.harvard.edu. De-identified patient data can be shared. External data requests will be answered within 1 month.

The preliminary results from this study were presented at the 66th American Society of Hematology annual meetings held in San Diego, California on 9th December 2024 and the 15th T-Cell Lymphoma Forum Annual Conference in La Jolla, California on 6th June 2024.

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ABSTRACT:

Patients with R/R PTCL require lineage-specific therapies to bridge them to HSCT. A prior phase I/II study of duvelisib/romidepsin (duv/romi) reported ORR of 58% and CRR of 42% with reduced grade 3-4 transaminitis (14%). We report real-world outcomes on a multicenter cohort of 38 patients with R/R PTCL treated with duv/romi. The median age at diagnosis was 64y, with histological subtypes including nTFH (n=17), PTCL-NOS (n=14), CTCL (n=3), ENKTCL (n=1), ALK- ALCL (n=1), ATLL (n=1), and HSTCL (n=1). Median prior therapies were 1 (IQR, 1-2); 15 patients relapsed and 23 were refractory to prior treatment with 8 having prior HSCT (5 auto, 3 allo). Patients received a median of 3 cycles (IQR, 2-4). Among 38 evaluable patients, ORR and CRR were 61% and 47%, respectively, with higher ORR (82% vs 43%) and CRR (71% vs 29%) in nTFH compared to non-nTFH. Median PFS and OS (HSCT-censored) were 11m (HR 0.31, 95%CI: 0.11-0.87; p=0.03) and 16m (HR 0.66, 95%CI: 0.23-1.87; p=0.4) for nTFH versus 3.3m and 8.3m for non-nTFH patients. The median TTR was 1.9m (IQR, 1.7-2.6), DoR was 21m (95%CI, 11-NR) and TTNT was 17m (95%CI, 6.4-NR). Post duv/romi, 11 patients were immediately bridged to allo-HSCT. Treatment was well tolerated, with most common grade 3-4 toxicities being lymphopenia (n=15), neutropenia (n=15), thrombocytopenia (n=10), ALT/AST-transaminitis (n=6), among others. Treatment-related adverse events seldom led to discontinuation (n=4) and death (n=1). These findings reinforce duv/romi's efficacy and role as a bridge to curative HSCT in high-risk R/R PTCL.

INTRODUCTION:

Among patients with relapsed or refractory (R/R) peripheral T-cell lymphomas (PTCL), overall survival (OS) and progression-free survival (PFS) range from 2.5-29.1m and 3.1-9.6m, respectively, highlighting poor outcomes.[1] Thus, there is a critical unmet need to develop novel treatments to improve response quality, duration, and ability to safely bridge to allogeneic hematopoietic stem-cell transplantation (allo-HSCT), which can be curative for a subset of patients, ultimately leading to improved survival. Duvelisib is an oral phosphatidylinositol 3-kinase (PI3K)-δ and PI3K-γ dual inhibitor which demonstrated overall response rates (ORR) of 50.0% and 31.6% in patients with PTCL and

cutaneous T-cell lymphoma (CTCL), respectively, in a phase I trial.[2] In a heavily pretreated phase 2 PRIMO-EP trial, duvelisib single agent (SA) confirmed a robust ORR of 48% and complete response rate (CRR) of 33%, but adverse events (AEs) necessitated a dose hold in 44.7% of patients.[3] Combinatorial strategies with histone deacetylase inhibitors (HDACi) were hypothesized to improve response and survival. In a recent phase 1b/2a trial of R/R TCL, the addition of HDACi romidepsin to duvelisib increased efficacy and attenuation of PI3Ki-driven toxicity.[4] This trial demonstrated an ORR of 55% and CRR of 34% with event-free survival (EFS) not reached in patients with CR.[4-5] Notably, the incidence of grade 3-4 transaminitis (ALT/AST) rate was only 14%.[4]

Duvelisib and romidepsin (duv/romi) combination therapy is emerging as a guideline-recommended treatment for R/R PTCL and CTCL, though the supporting evidence is currently limited. Affirmation of superior responses and abrogation of AEs in real-world patient population is needed to gain more knowledge about the efficacy and toxicity of this doublet to facilitate clinical decisions. This in turn would potentially increase access to this combination through expedited insurance and regulatory agency approvals for at least a subset of patients with R/R PTCL and CTCL. It will also support further design and development of several planned phase II studies of combinations of PI3K, HDAC and DNA methyl transferase inhibitors in TCL.

Herein, we report a multicenter descriptive experience of duv/romi efficacy and toxicity in patients with R/R PTCL and CTCL, which demonstrates that the addition of duvelisib to romidepsin is safe, well-tolerated, and induces high response rates, particularly in the nTFH subtype. We also discuss management of AEs and their functional consequences and compare this regimen to other varied double drug combinations of PI3K, HDAC, DNMT inhibitors and IMIDs.

METHODS:

Study Design and Patient Eligibility

This multi-institution retrospective and prospective observational study was approved by the Dana-Farber Cancer Institute Institutional Review Board (DFCI protocol #22-355). It included patients who received care at the Massachusetts General Hospital (MGH) Cancer Center, MGH-affiliated community practices, and Dana-Farber Cancer Institute. This study was conducted in accordance with the Declaration of Helsinki.

Eligible patients had pathologically-confirmed PTCL and/or CTCL that had relapsed or progressed after at least one systemic therapy per the 2016 (4th edition) or 2022 (5th edition) WHO classification of lymphoid neoplasms. Patients should have received combination duvelisib/romidepsin (duv/romi) between January 2016 and November 2024. Most of the patients were treated as per the previously reported phase 1b/2a MTD dose and schedule, which included romidepsin at 10mg/m^2 intravenously on days 1, 8 and 15 of a 28-day cycle. Relapsed status was defined as disease recurrence after achieving CR to previous therapy, while refractory status was failure to achieve CR to the end of previous therapy. Patients who received duv/romi as part of a clinical trial were excluded. Patients were screened and enrolled in this study both prospectively and retrospectively. Data was collected via EMR through January 15, 2025. Responses were assessed based on the 2014 Consensus of the International Conference on Malignant Lymphomas Imaging Working Group and their 5-point Deauville scale for PET/CT interpretation, which was performed at baseline and as clinically indicated. Patients achieving remission were evaluated every 6 months for 2 years or until disease progression. Patients were followed to capture treatment courses, response, and survival status long-term regardless of their response (or lack of) or ability to proceed to allo-HSCT. Electronic chart

review of AEs was continuous throughout treatment and AEs were graded per the National Cancer Institute Common Terminology Criteria for AEs (CTCAE) version 5.0. Only grade three and four AEs and their management were reported. Time to AE onset was defined from treatment start to the first of grade 3 or 4 AE. The maximum AE grade per patient was reported irrespective of causality and its attribution to the duv/romi combination. Pre-existing abnormalities (clinical or laboratory) that significantly worsened during duv/romi treatment were considered AEs while neutrophilic leukocytosis in the setting of granulocyte colony-stimulating factor (G-CSF) was not counted. Primary objectives included assessment of ORR including CRR and PRR and grade 3/4 hematologic or non-hematologic AEs. Kaplan-Meier method was used to estimate PFS, OS, DoR, TTNT, TTR, and time to AE onset. Further details of the methods section is included in the supplmenetary information.

RESULTS:

Baseline and treatment characteristics

We prospectively and retrospectively identified 38 patients who were treated with duv/romi, including 17 patients with nodal T-follicular helper cell lymphoma (nTFH) and 21 patients with non-nTFH lymphomas, including 14 with PTCL-not otherwise specified (NOS), 3 with cutaneous T-cell lymphoma (1 mycosis fungoides (MF), 1 Sezary syndrome (SS) and 1 primary cutaneous gamma-delta (GD)), 1 with anaplastic lymphoma kinase negative (ALK) anaplastic large cell lymphoma (ALCL), 1 extranodal natural killer-T cell lymphoma (ENKTCL), 1 hepatosplenic T-cell lymphoma (HSTCL) and 1 adult T-cell leukemia/lymphoma (ATLL) (Table 1). Their clinical characteristics are presented in Table 1. Notably, the median age was 62 years, and patients were equally distributed by sex (male, n=17/38; 50%) and white (n=28/38; 74%). The most common histologies were angio-immunoblastic T-cell lymphoma (AITL, subtype of nTFH, n=13/17; 76%) and PTCL-NOS, subtype of non-nTFH (n=14/21; 67%). For majority of the patients, IPI (International Prognostic Index) and PIT (Prognostic Indicator for T-cell lymphoma) were intermediate to high risk and comparable between nTFH and non-nTFH subtypes, whereas patients with nTFH patients had lower PIRT (Prognostic Index for Relapsed/Refractory mature T and NK-cell lymphoma) scores compared to non-nTFH (p=0.009).[7] Seventy-six percent (n=29/38) of patients were initially treated with an anthracycline-based therapy, and 21% (n=8/38) patients received an HSCT, autologous (auto; n=6) or allogeneic (allo; n=2), before study inclusion. Thirty-nine percent (n=15/38) of patients had relapsed whereas 61% (n=23/38) had primary refractory lymphoma. Median number of prior therapies was 1 with no statistical difference between the two major (nTFH vs non-nTFH) subgroups. The most common salvage therapies in second and third line prior to duv/romi included chemotherapy and HDACis such as romidepsin.

The majority of the patients (n=31/38; 82%) received prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) and VZV (n=32/38; 84%), whereas 3% (n=1) of the patients received anti-fungal prophylaxis with fluconazole (Table 2). Sixteen (16/38; 42%) patients received G-CSF once or more during duv/romi treatment, 9 (24%) with filgrastim and 7 (18%) with pegfilgrastim (Table 2). Twenty-four percent of the patients (n=9/38) received duvelisib lead-in cycles ranging from 1-5. The median number of cycles of duv/romi received was 3, with the nTFH subtype receiving a higher number (median of 4) compared to the most common non-nTFH subtypes like PTCL-NOS who received a median of 2 cycles. Four patients received 1 cycle or less of the combination, twelve received 2 cycles and 22 received greater than 2 cycles.

Efficacy

Duvelisib plus romidepsin showed varied efficacy across disease subtypes, with an ORR of 61% (47% CRR, 13% PRR) with or without duvelisib lead-in. Patients with nTFH subtype exhibited a significantly higher ORR of 82% (71% CRR, 12% PRR; p= 0.02 by Fisher's exact test) compared to non-nTFH subtypes like PTCL-NOS (36% ORR, 29% CRR, 7% PRR) with a median follow-up of 11m (95% CI: 9.5-17 (Table 3). Of note, 11 of the 13 (85%) patients with AITL under the nTFH category demonstrated a CRR. Median OS since treatment initiation was 16m in the cohort (95% confidence interval (CI): 9.5–Not Reached (NR)) upon standard censoring, versus 9.7m (95% CI: 8.3-NR) after censoring patients who underwent allo-HSCT (Figure 1A-B; Table 3). It was 16m for nTFH subtype (95% CI: 9.5-NR) in comparison with NR (95% CI: 8.0-NR) for the non-nTFH subtype (Figure 1C). When censored by allo-HSCT, the median OS was for patients with nTFH (16m, 95% CI: 9.5–NR) was higher relative to non-nTFH subtype (8.3m, 95% CI: 8.0–NR) but not statistically significant (Figure 1D). The median PFS of nTFH subtype (23m, 95% CI: 8.6–NR) was comparable to non-nTFH subtype (3.3m, 95% CI: 2.2–NR) in standard censoring, but was significantly higher with allo-HSCT censoring (11m, 95% CI: 8.6–NR vs. 3.3m, 95% CI: 2.2–NR; p=0.03), respectively (Figure 2A-F; Table 3-4). When stratified by response type, patients with ORR (CRR+PRR) demonstrated significantly longer OS (p<0.0001) than those who demonstrated progression of disease (SD+PD) regardless of censoring (Figure 3; Table 4). The median EFS showed very similar pattern to the median PFS in overall cohort, and histological subgroup comparisons were only significant between nTFH and non-nTFH groups with allo-HSCT censoring (Figure 4A-F; Table 4).

The overall median time to first response for responding patients was 1.9m (IQR, 1.7–2.6) with median DoR of 21m (95% CI: 11–NR) and higher in nTFH (21m, 95% CI: 8.6-NR) as opposed to the non-nTFH subtype (11m, 95% CI: 11-NR) but not statistically significant with comparable time of follow up and TTNT. At the time of data cut-off, 3 of the 17 (18%) responders remained on active treatment (Table 5). Eleven (33%) patients (6 nTFH and 5 non-nTFH) immediately proceeded to allo-HSCT following combination treatment with duv/romi with curative intent. Among these eleven patients, the median age was younger (50 vs. 66, p = 0.008), with no significant difference in PIT score compared to those who did not undergo allo-HSCT (p = 0.5); they had received a median of one prior line of therapy (IQR: 1–2), and their survival rate at the last follow-up was 100% compared to 45% in the non-allo-HSCT group (p = 0.002) with a median follow-up time of 7.5m (IQR, 4.2-12.2). Ten out of the 11 (91%) patients who proceeded to allo-HSCT were in remission at day 100 post HSCT, 3 of the 10 (30%) continued to remain in remission at day +290. Two patients demonstrated disease progression after day 200 and 1 patient was not yet evaluable. Two (2/11; 18%) patients experienced graft-versus-host disease (GVHD) (acute stage 1 and 2 progressing to chronic) after allo-HSCT immediately following duv/romi, and GVHD was managed with institutional standards. One patient with a CR to duv/romi died secondary to bacterial sepsis. Out of 21 patients who developed progressive disease (PD) on duv/romi, 6 died of lymphoma progression, 1 transitioned to hospice, and 14 proceeded to subsequent salvage therapies. The most commonly used next line treatment was CFT74455 (Ikaros 1/3 degrader) in 3 patients, of whom 1 (nTFH) achieved a CR followed by allo-HSCT and two (PTCL-NOS) demonstrated PD, azacitidine and lenalidomide combination in 1 patient (nTFH) who achieved a CR but eventually died of infectious complication (EBV reactivation leading to ENKTCL), and alemtuzumab in 1 (SS) who achieved a CR and proceeded to allo-HSCT. Three patients were unevaluable on their next line of therapy as they were transitioned to hospice soon after (nTFH on azacitidine alone, PTCL-NOS on gemcitabine, carboplatinum and dexamethasone and PTCL-NOS on duvelisib and ruxolitinib). Seven patients demonstrated PD on various different

regimens spanning conventional chemotherapy, CFT74455, and mogamulizumab. A swimmer plot depicting responses of the cohort patients over time is shown in Figure 5.

Adverse Events

Treatment was overall well-tolerated with no cases of gr 3-4 elevated bilirubin, or elevated alkaline phosphatase in 36 evaluable patients (Table 6). Notable AEs were mostly hematologic, affecting 72% (26/36) of patients. Neutropenia occurred in 42% (15/36) of patients, with gr 3 and 4 occurring in 14% and 28%, respectively. The median time to onset of neutropenia was 0.5m (IQR, 0.2–1.4). Febrile neutropenia was less common, occurring in 11% (4/36) of patients, with a median onset of 2.2m (IQR, 2.1–2.7). Gr 3 anemia was observed in 17% (6/36) of patients, with a median time to onset of 1.9 m (IQR, 0.2–4.2). Thrombocytopenia occurred in 28% (10/36) of patients, with gr 3 and 4 comprising 6% and 22%, respectively, with a median onset of 1.6m (IQR, 0.4-1.9). Lymphopenia was seen in 42% (15/36) of patients, with gr 3 (28%) more common than gr 4 (14%) events. The median time to lymphopenia onset was 2.2m (IQR, 0.8–3.0). Leukocytosis was mostly gr 3 (8%; 3% gr 4) and was noted in 11% (4/36) of patients with a median onset of 0.2m (IQR, 0–1.2).

Gastrointestinal AEs occurred in 25% (9/36) of patients with ALT elevation observed in 17% (6/36), and most cases were gr 3 (n=5) with a single gr 4 case. The median time to onset was 2m (IQR, 1.7–2.6). Similarly, AST elevation was seen in 17% (6/36), was entirely of gr 3 severity, and had a median time to onset of 1.1m (IQR, 1.0–1.7). Drug-mediated non-infectious gr 3 enterocolitis was observed in 2 patients, and non-infectious diarrhea in 3% (1/36), with an onset at 2.8m (IQR: 2.5-3.2) and 3.4m. Among infectious AEs, observed in 38% (9/38) of patients, cytomegalovirus (CMV) viremia without organ involvement was the most common and noted in 17% (5/29) of evaluable patients, with a median onset of 1.2m (IQR, 1.1–1.4). Tuberculosis (TB) reactivation was reported in 1 patient from a TB endemic region (3%), COVID-19 infection occurred in 2 patients (7%), and Pseudomonas bacteremia and Klebsiella bacteremia occurred in 1 patient (3%) each. Other notable Gr 3 and 4 AEs observed in 28% (10/36) of patients included rash in 14% (5/36), with a notably delayed median onset of 9.5m (IQR, 1.2–9.9) and gr 3 fatigue in 17% (6/36) of patients, with a median onset of 2.1m (IQR, 1.5–2.4). No cases of anorexia were reported.

Overall, hematologic toxicities were the most prevalent AEs, with neutropenia and leukocytosis occurring early in the treatment course. Gastrointestinal and infectious complications were less frequent but remained clinically relevant. Rash, although less common, was a late-onset toxicity.

Dose Delays/Reductions/Discontinuations

Sixteen patients experienced dose interruptions due to gr 3-4 adverse events, most commonly ALT and AST transaminitis (14%; 5/36 and 8%; 3/36, respectively) and thrombocytopenia (11%; 4/36). Grade 3 transaminitis led to varying periods of duvelisib-only interruption for 3 patients, ranging from three to 28 days. 1 patient with gr 3 AST and gr 4 ALT transaminitis experienced 1 week of interruption for both duv/romi followed by a 3-week duv interruption, and 1 patient discontinued duv then romi due to gr 3 colitis. No dose reductions occurred due to transaminitis.

Thrombocytopenia led to dose interruptions in both duv and romi in 2 patients (1 gr 3 and 1 gr 4), one of whom also had neutropenia, led to romi-only delay in 1 patient (gr 4) who also had neutropenia, and led to elimination of romi D8 dose for the remainder of therapy in 1 patient (gr 4). Thrombocytopenia was associated with romi-only dose reduction from 10 to 8mg/m^2 in cycle 2 and 4 in 2 patients (1 gr 3 and 1 gr 4), one of whom (gr 4) also had a romi dose interruption. Thrombocytopenia did not lead to duv-only interruption in the cohort. Thrombocytopenia (gr 4) and

neutropenia (gr 4) during duv lead-in in 1 patient led to duv delay for one week and dose reductions from 75mg to 25mg twice daily. Remaining duv-only dose reductions to 50mg were observed in cycle 1 and primarily due to pancytopenia (gr 4) and neutropenia (gr 3) in 1 patient each. Remaining dose reductions for romi only to 8mg/m^2 was due to gr 3 fatigue in cycle 4 for 1 patient.

Dose interruptions from infectious complications included COVID-19 (6%; 2/32) in which duv/romi was held for one cycle (n=1) and one dose each per cycle for two cycles (n=1), and tuberculosis reactivation (3%; 1/32) where one dose of romi was withheld. Four patients had duv-romi treatment discontinuation, including gr 3 autoimmune enterocolitis and associated gr 4 non-infectious diarrhea in cycle 4 (n=1), and grade 3 ALT transaminitis in cycle 3 (duv) then colitis in cycle 4 (romi) (n=1). The remaining two discontinuations were due to gr 3 febrile neutropenia and gr 4 neutropenia, one in cycle 1 (following 5 cycles duv-lead in) with *Pseudomonas* bacteremia, and one in cycle 2 with *Klebsiella* bacteremia. One death occurred due to septic shock secondary to duvelisib-associated pancytopenia for which they had been dose-reduced in C1 from 75 to 50mg duv.

Dose Schedule

Twenty-eight (74%) patients started at 75mg twice daily duv, and the majority (19/28; 68%) received this dose for half or more of the total treatment (lead-in or combination) cycles they received. Eight (8/28; 29%) patients received 75mg twice daily for cycles 1-2 and 25mg twice daily in cycle 3 per the PRIMO-EP dosing schedule. At cycle 3 day 1, 35% (9/26) of patients on treatment continued to receive 75mg twice daily duv, of which 1 started duv cycle 1 day 14, 1 received 25mg duv during cycle 1, and 1 was status-post 6-week duv dose interruption in cycles 1-2 due to motor vehicle trauma. In the remaining 6 patients receiving 75mg twice daily duv at cycle 3 day 1, no specific reason for the sustained 75mg dose was cited in provider notes. By cycle 4 day 1, 18% (3/17) of patients still on the doublet received duv 75mg twice daily, while the remaining 76% (13/16) received 25mg (n=12) or 50mg (n=1). Seven (18%; 7/38) patients started at 25mg twice daily duv in cycle 1, but 3/7 increased to 75mg by cycle 2. Three patients (3/38) started at 50mg twice daily and remained on this dose (n=2) or lower (n=1) until treatment end.

In cycle 1, 15 (15/31, 48%) of patients receiving romi started at 10mg/m^2, with the rest receiving greater doses ranging to 14mg/m^2. By cycle 2, the majority (18/32; 56%) on romi received 10mg/m^2. Romi modifications due to gr 3-4 AEs were more commonly dose delays over dose reductions.

DISCUSSION:

In this less-selected, real-world patient population, the data confirm the earlier observations regarding the safety, tolerability, and high overall and complete response rates with the combination of romidepsin and duvelisib for treatment of relapsed or refractory TCLs, which remains a challenging group of malignancies to date. Specifically, the responses seen in patients with nTFH subtype are noteworthy and in line with previous observations from early phase clinical trial data utilizing the combination and from single agent studies. While the robust responses in patients with nTFH subtype is not surprising albeit higher than the phase 1b/2a trial data, demonstration of a relatively high ORR of 43% in the non-nTFH subtype including 29% CRR positions duv/romi favorably as a novel strategy for patients with a broad range of nodal PTCLs including the common PTCL-NOS subtype.[4] The difference in ORR between the nTFH and non-nTFH groups held even with comparable baseline prognostic indices such as IPI, PIT and PIRT within the limitations of a small sample size. Our data demonstrate the efficacy and safety of this regimen in patients up to the age of 89 years, having received up to 8 prior lines of therapy with intermediate to high-risk risk features. This further

highlights its potential as another viable strategy for patients >60 years of age, a subset with reportedly poor outcomes due to advancing age and comorbidities. Of note are responses seen in patients previously exposed to epigenetic modifiers including romidepsin and azacitidine administered as single agents and as a combination. All three patients with previous refractoriness to azacitidine and romidepsin achieved a durable CR on duv/romi. One patient bridged to allo-HSCT and remains in remission at 11m post HSCT with no GVHD, and two remain in CR on active therapy with one patient planned to undergo allo-HSCT and the last declined future HSCT. For two patients who experienced relapsed lymphoma after their first allo-HSCT, duv/romi led to a durable remission and enabled a second allo-HSCT with both patients alive at day +100.

Our study, which employed broader inclusion criteria than the phase 1b/2a trial—including patients with cytopenias, prior treatment toxicities, and no mandated washout period—demonstrates comparable ORR and CRR, thereby enhancing the generalizability of these findings to real-world, high-risk patient populations.[4] It is worth noting that despite brief interruptions and dose reductions in the dose of duvelisib from cycle 3 onwards in many patients in this multicenter cohort as opposed to the higher doses which were permissible in the phase 1b/2a trial, we did not see any reduction in overall efficacy such as ORR or CRR. This suggests an alternative plausible approach whereby a decrease in dose could be permitted if a CR has been achieved after 2 cycles of therapy to mitigate toxicity. It is foreseeable that this strategy could allow a potentially longer duration of treatment for patients who are transplant ineligible. Adverse event profiles noted with duv/romi suggest that among gr 3-4 toxicities, hematologic ones are the most common with gr 3-4 lymphopenia and neutropenia each observed in 42% of patients, similar to the phase 1b/2a trial.[4] Bacteremia secondary to gr 3 febrile neutropenia and gr 4 neutropenia led to discontinuation in two patients. While we observed a higher incidence of gr 3-4 transaminitis than previously reported, it led to discontinuation of therapy only in 1 patient, suggesting that appropriate management with dose interruptions, reductions, use of short-term steroids and growth factor support can enable continued use. With appropriate prophylactic use of antibiotics and preemptive CMV monitoring when feasible, no cases of disseminated viral infections with organ involvement were observed. No instance of fungal infection was observed despite lack of prophylactic anti-fungal antibiotics for most patients. However, 1 case of TB reactivation in a patient from a TB endemic region warrants consideration of chemoprophylaxis with INH-like antibiotics to prevent active tuberculosis disease in high-risk populations. Thus, our manuscript provides robust data on on observed grade 3-4 AEs, timeline of occurrence, and the associated dose changes, delays, discontinuations, management and ouctomes post treatment with the combination. This renders valuable information and facilitates clinical decisions and optimization of therapy in this high-risk population. It is worth pointing out that no patients who experienced PRs after cycle 2 went onto achieve a CR, despite continuation of therapy. In fact, all patients with PR displayed progression of their lymphoma within 6 weeks, leading to alternative strategies. Thus, based on our small multicenter cohort with a median TTR of 1.9m, a CR after cycle 2 might serve as a surrogate of a meaningful response to this combination.

We reviewed the literature of other contemporary combinations in R/R PTCL and CTCL in phase I-III and real-world studies as reported in Table 7. The OS ranged from 10.2-32.9m, PFS from 2.2-23.2m, and DoR from 8.2-25.3m.[8-18] ORRs ranged from 35.7 to 78% and CRRs from 13-55%.[8-18] In 4/11 studies which reported them, nTFH subtype response rates were consistently superior to the overall cohort, except in duvelisib/ruxolitinib where CRR was inferior but ORR superior in nTFH.[8,13-15] Of the 8/11 studies that mentioned allo-HSCT, histology was rarely reported and rate of allo-HSCT ranged from 0-55%.[8-11,13-14,17-18] The most commonly reported grade 3-4 adverse events were thrombocytopenia (range of event rates, 11-53%) and neutropenia (8-45%).[8-18] While no direct comparison can be made between across these doublets, we do believe that duv/romi combination

poses a tolerable and effective option for patients with R/R PTCL. However, randomized studies will be critical in identifying one superior regimen over others for R/R patients. Further, systematic NGS-based studies will play a critical role in defining subpopulations likely to benefit from combination over another based on inherent molecular vulnerabilities and heterogeneity across the three nTFH subtypes. Thus, it is also foreseeable that enrollment of patients in a biomarker-driven master trial will aid in the nomination of ideal doublets tailored to nTFH subsets across the available options. Prospective longitudinal samples including cfDNA from diagnosis through treatment including relapse and post allo-HSCT have been collected for our cohort. Diagnostic and relapsed tumor tissues are undergoing whole exome and cfDNA-based sequencing and analyses for non-invasive tracking of personalized somatic variants underlying response and resistance. These will be reported soon as part of larger multicenter effort to define molecular residual disease in nPTCL and will provide a layer of genomic information which will be integral to precision therapy in PTCL. Nevertheless, the robust reporting of responses leading to curative intent allo-HSCT with no greater incidence of GVHD or toxicity post-HSCT relative to under-reporting and lack of details in other doublet studies positions duv/romi as another novel option for transplant eligible patients with R/R PTCL.

The study has several limitations. These include systematic errors based on the partial retrospective nature of the analyses specifically with varied documentation over the span of 8 years, lack of centralized pathology and response to treatment review among others. This is a small, prospective and retrospective real-world study and is therefore insufficient on its own to draw broader conclusions. It is, however, an additional piece of data that supports the overall activity of this regimen in a patient population with very limited treatment options. We note that definitive conclusions cannot be drawn in the absence of a randomized trial, and further research is needed, such as a randomized phase 3 trial of duv/romi versus investigator's choice in the upfront and/or relapsed/refractory setting. To ascertain the role of this combination in CTCL, further studies or observations from use in real-world are warranted. Until these studies reveal more data including insight into the mechanisms that are overcome by duv/romi in patients with previous failures to epigenetic modifiers, we believe that this combination is a very viable prospect for transplant eligible and even ineligible patients with R/R PTCL who cannot be enrolled into clinical trials. We believe these data also point to further investigation of this combination or single agents as a regimen in transplant ineligible patients, preferably guided by MRD-based assays.

AUTHOR CONTRIBUTIONS:

J.G.F., M.K., A.W.L., C.M., K.C., M.N.S., A.M., M.M., A.B.R., A.R.S., S.M.M., R.A.N., M.I., K.M.K., S.C., J.B., S.M., Y.C., E.J., and S.J. designed the research. J.G.F., M.K., M.N.S., A.W.L., C.M., K.C., A.M., and S.J. analyzed data. J.G.F., M.K., and S.J. wrote the manuscript. All authors contributed to and performed the research and reviewed the manuscript.

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Table 1. Baseline Demographic and Clinical Characteristics of the Multi-Center R/R Cohort Treated with Combination Duv/Romi

Characteristic	All[1] (n = 38)	nTFH (n = 17)	Non-nTFH (n = 21)	P-value[a]
Age at Diagnosis, Median (IQR)	62 (53 - 72)	65 (61 - 71)	56 (50 - 72)	0.4
Biological Sex, No. (%)				
Female	19 (50)	9 (53)	10 (48)	>0.99
Male	19 (50)	8 (47)	11 (52)	
Race, Self-Identified, No. (%)				
White	28 (74)	13 (76)	15 (71)	0.7
African American or Black	1 (3)	1 (6)	0	
Asian	3 (8)	2 (12)	1 (5)	
Other	1 (3)	0	1 (5)	
Unknown	3 (8)	01 (6)	34 (19)	
Ethnicity, Self-Identified, No. (%)				
Hispanic	4 (11)	3 (18)	1 (5)	0.2
Non-Hispanic	32 (84)	13 (76)	19 (90)	
Other	1 (3)	0	1 (5)	
Unknown	1 (3)	1 (6)	0	
Histological Subtype, No. (%)				
nTFH	17 (48)	17 (100)	0	-
AITL	13 (34)	13 (76)	0	
ALK- ALCL	1 (3)	0	1 (5)	
ATLL	1 (3)	0	1 (5)	
CTCL	3 (8)	0	3 (14)	
MF	1 (3)	0	1 (6)	
Sezary Syndrome	1 (3)	0	1 (5)	
Gamma Delta	1 (3)	0	1 (5)	
ENKTCL	1 (3)	0	1 (5)	
HSTCL	1 (3)	0	1 (5)	
PTCL-NOS	14 (37)	0	14 (67)	
IPI at Diagnosis, No. (%)				
0	0	0	0	0.2
1	5 (13)	1 (6)	4 (19)	
2	14 (37)	9 (53)	5 (24)	
3	10 (26)	3 (18)	7 (33)	
4	4 (11)	2 (12)	2 (10)	
5	0	0	0	
NA	5 (13)	2 (12)	3 (14)	
PIT at Diagnosis, No. (%)				
0	1 (3)	0	1 (5)	0.6
1	14 (37)	6 (35)	8 (38)	
2	14 (37)	8 (47)	6 (29)	
3	4 (11)	1 (6)	3 (14)	
4	0	0	0	
NA	5 (13)	2 (12)	3 (14)	
PIRT at Diagnosis, No. (%)				
Low (0 - 1)	1 (3)	1 (6)	0	0.009
Intermediate (2 – 3)	16 (42)	11 (65)	5 (24)	
High (4 – 6)	6 (16)	0	6 (29)	
NA	15 (39)	5 (29)	10 (48)	
Prior Lines of Therapy, Median (IQR)	1 (1 - 2)	1 (1 – 2)	1 (1 – 2)	0.1
Prior Therapies Received, Frontline, No. (%)	**38 (100)**	**17/17 (100)**	**21/21 (100)**	
CHOP	12 (32)	7 (41)	5 (24)	
mini-CHOP	2 (5)	1 (6)	1 (65	
CHOEP	9 (24)	3 (17)	6 (29)	
CEOP[2]	1 (3)	1 (6)	0	

CHOP + Azacitidine	2 (5)	2 (12)	0	
BV-CHP	3 (8)	0	3 (14)	
Alemtuzumab	1 (3)	0	1 (5)	
Azacitidine + Romidepsin	2 (5)	2 (12)	0	
Extracorporeal Photopheresis + Bexarotene	1 (3)	0	1 (5)	
Methotrexate + Prednisolone	2 (5)	0	2 (10)	
ICE	2 (5)	0	2 (10)	
Pola-R-CHP[3]	2 (5)	2 (12)	0	
CHP[4]	1 (3)	1 (6)	0	
Prior Therapies Received, Second Line, No. (%)	**10/38 (26)**	**4/17 (24)**	**6/21 (29)**	
BV-CHP	2 (5)	0	2 (10)	
Alemtuzumab	1 (3)	0	1 (5)	
Azacitidine	1 (3)	1 (6)	0	-
Romidepsin	2 (5)	1 (6)	1 (5)	
Azacitidine + Romidepsin	2 (5)	2 (12)	0	
Gemcitabine + Oxaliplatinum	1 (3)	0	1 (5)	
Pegasparaginase	1 (3)	0	1 (5)	
Prior Therapies Received, Third Line and Onwards, No. (%)	**5/38 (13)**	**0**	**5/21 (24)**	
Romidepsin	2 (5)		2 (10)	
Pralatrexate	1 (3)		1 (5)	
Alemtuzumab	1 (3)		1 (5)	
Pembrolizumab	1 (3)		1 (5)	
Ruxolitinib	1 (3)		1 (5)	
IVAC	1 (3)		1 (5)	-
DHAP + Cytarabine	2 (5)		2 (10)	
Gemcitabine + Oxaliplatinum	2 (5)		2 (10)	
Nivolumab	1 (3)		1 (5)	
Brentuximab vedotin	1 (3)		1 (5)	
Brentuximab vedotin + Gemcitabine	1 (3)		1 (5)	
Denileukin Difitox (NCT01871727)	1 (3)		1 (5)	
Received HSCT Prior to Duv/Romi, No. (%)	**8/38 (21)**	**5/17 (29)**	**3/21 (14)**	
Autologous	5 (13)	4 (24)	(5)	-
Allogeneic	3 (8)	1 (6)	2 (10)	
Response to Therapy Preceding Duv/Romi[5], No. (%)				
Relapsed	15 (39)	6 (35)	9 (43)	0.9
Primary Refractory	23 (61)	11 (65)	12 (57)	

Abbreviation: AITL-Angioimmunoblastic T-cell lymphoma, ALCL-Anaplastic large cell lymphoma, ALK-Anaplastic lymphoma kinase, ATLL-Adult T-cell leukemia/lymphoma, CTCL-Cutaneous T-cell lymphoma, ENKTCL-Extranodal NK/T-cell lymphoma, HSTCL-Hepatosplenic T-cell lymphoma, IPI-International Prognostic Index, IQR-Inter Quartile range, MF-Mycosis fungoides, PIT-Prognostic Index for T-cell lymphoma, PIRT-Prognostic Index for R/R Mature T-Cell and NK-Cell Lymphomas, PTCL-NOS-Peripheral T-cell lymphoma-not otherwise specified, nTFH-nodal T follicular helper cell, CHOP-cyclophosphamide, adriamycin, oncovin/vincristine, and prednisone, mini-CHOP-CHOP administered at abbreviated doses, CHOEP-cyclophosphamide, adriamycin, oncovin/vincristine, etoposide and prednisone, CEOP-cyclophosphamide, etoposide, vincristine and prednisone, CHP-cyclophosphamide, doxorubicin and prednisone, BV-CHP-brentuximab vedotin, cyclophosphamide, adriamycin and prednisone, ICE- ifosphamide, carboplatinum and etoposide, IVAC-ifosphamie, vinblastine and cytarabine, DHAP-dexamethasone, adriamycine and cisplatinum, Pola-R-CHP-polatuzumab, rituximab, cyclophosphamide, adriamycin and prednisone.

[a]P values for the comparison between patients in different national cohorts were calculated using Kruskal-Wallis and chi-square tests for non-normally distributed continuous variables and categorical variables, respectively.

[b]P values based on Fisher's exact test due to some small cell counts.

[1]Two patients received re-treatment with duv/romi in discrete lines of therapy, and treatment response was assessed independently for each line of therapy. Hence, 38 lines of therapy were evaluated among 36 patients.

[2]One patient received CHOP in the first cycle followed by CEOP in cycles 2-6.

[3]One patient was treated with frontline R-CHOP for diffuse large B-cell lymphoma (DLBCL). Upon relapse, they received 4 cycles Pola-R-CHP, 2 cycles Pola-R-CEP to which they were primary refractory and subsequently diagnosed with AITL. Another received frontline Pola-R-CHP for primary cutaneous DLBCL and second-line duv/romi for nodal TFH.

[4]One patient received CHOP for 5 weeks which was complicated by PJP, respiratory failure requiring mechanical ventilation, anuric acute kidney injury status-oist dialysis, pseudomonas urinary tract infection, and sepsis requiring pressors and thus was switched to CHP chemotherapy after 5 weeks. They received CHP for two weeks before switching to second line azacitidine + romidepsin.

[5]Relapsed defined as disease recurrence after achieving CR to previous therapy and primary refractory defined as failure to achieve CR to end of previous therapy

Table 2. Treatment Characteristics of Combination Duv/Romi in Multi-Center R/R Cohort

Treatment Characteristics	All[1] (n = 38)
***Pneumocystis jirovecii* Pneumonia Prophylaxis, No. (%)**	**31 (82)**
Atovaquone	12 (32)
Trimethoprim-Sulfamethoxazole	21 (55)
Varicella Zoster Virus Prophylaxis, No. (%)	**32 (84)**
Acyclovir	25 (66)
Valacyclovir	8 (21)
Valganciclovir	1 (3)
Anti-Fungal Prophylaxis, No. (%)	
Fluconazole	1 (3)
Granulocyte Colony-Stimulating Factor, No. (%)	16 (42)
Filgrastim	9 (24)
Pegfilgrastim	7 (18)
Number of Lead-In Duvelisib Cycles Received by Subtype, No. (%)	**9 (24)**
AITL	2 (5)
1	1 (3)
2	1 (3)
3	
PTCL-NOS	2 (6)
3	1 (3)
5	
CTCL	1 (3)
1	
ENKTCL	1 (3)
1	
Number of Lead-In Romidepsin Cycles Received by Subtype, No. (%)	**2 (5)**
AITL	1 (3)
4	
PTCL/CTCL-MF	1 (3)
4	
Number of Combination Duv/Romi Cycles Received, Median (IQR)	**3 (2-4)**
nTFH including AITL	4 (3-5)
PTCL-NOS	2 (2-3)
CTCL	2 (2-3)
ALK- ALCL	4
ENKTCL	4
ATLL	3
HSTCL	2
Duration of Combination Duv/Romi Treatment at Full/Abbreviated Doses (Mo), Median (IQR)	**2.9 (1.8-4.1)**
nTFH including AITL	3.9 (3.1-4.9)
PTCL-NOS	2.0 (1.3-2.8)
CTCL	1.8 (1.7-3.0)
ALK- ALCL	3.4
ENKTCL	3.7
ATLL	2.0
HSTCL	1.4

Abbreviation: AITL-Angioimmunoblastic T-cell lymphoma, ALCL-Anaplastic large cell lymphoma, ALK-Anaplastic lymphoma kinase, ATLL-Adult T-cell leukemia/lymphoma, CTCL-Cutaneous T-cell lymphoma, ENKTCL-Extranodal NK/T-cell lymphoma, HSTCL-Hepatosplenic T-cell lymphoma, PTCL-NOS-Peripheral T-cell lymphoma-not otherwise specified, nTFH-nodal T follicular helper cell, IQR- inter-quartile range

[1]Lead-in duv, cycles of combination duv/romi and duration of treatment were reported in all lines of therapy (n=38).

Table 3. Efficacy of Combination Duv/Romi (Duv/Romi) in Multi-Center R/R Cohort

Outcome Measure	All (n = 38)	Lead-In Duv (n = 10)	No Lead-In Duv (n = 28)	nTFH Subtype (incl. AITL) (n = 17)	Non-nTFH Subtype (n = 21)	AITL (n = 13)	PTCL-NOS (n = 14)	CTCL (n = 3)	ALK-ALCL (n = 1)	ENKTCL (n = 1)	ATLL (n = 1)	HSTCL (n = 1)
Treatment Response												
OR[1], No. (%)	23 (61)	5 (50)	18 (64)	14 (82)	9 (43)	11 (85)	5 (36)	2 (67)	1 (100)	1 (100)	0	0
CR, No. (%)	18 (47)	4 (40)	14 (50)	12 (71)	6 (29)	11 (85)	4 (29)	0	1 (100)	1 (100)	0	0
PR, No. (%)	5 (13)	1 (10)	4 (14)	2 (12)	3 (14)	0	1 (7)	2 (67)	0	0	0	0
SD, No. (%)	2 (5)	1 (10)	1 (4)	0	2 (10)	0	2 (14)	0	0	0	0	0
PD, No. (%)	13 (34)	4 (40)	9 (32)	3 (18)	10 (48)	2 (15)	7 (50)	1 (33)	0	0	1 (100)	1 (100)
Survival Probability (Mo)												
T=0: Best response date												
OS								All Other Subtypes:				
Median (95% CI)	13 (6.9-NR)			13 (3.2-NR)	7.3 (4.1-NR)	13 (3.2-NR)	NR (1.6-NR)	6.9 (1.8-NR)				
S(t) at t = 6 (95% CI)	0.7 (0.5-0.8)			0.7 (0.5-1.0)	0.6 (0.5-0.9)	0.7 (0.5-1.0)	0.6 (0.4-0.9)	0.7 (0.4-1.0)				
S(t) at t = 12 (95% CI)	0.6 (0.4-0.8)			0.7 (0.5-1.0)	0.5 (0.3-0.8)	0.7 (0.5-1.0)	0.5 (0.3-0.9)	0.4 (0.1-1.0)				
S(t) at t = 24 (95% CI)	0.5 (0.3-0.8)			0.5 (0.2-1.0)	0.5 (0.3-0.8)	0.5 (0.2-1.0)	-	0.4 (0.1-1.0)				
OS, Allo-HSCT-Censored												
Median (95% CI)	7.3 (4.1-NR)			13 (3.2-NR)	6.9 (4.1-NR)	13 (3.2-NR)	7.3 (1.6-NR)	6.9 (1.8-NR)				
S(t) at t = 6 (95% CI)	0.6 (0.4-0.8)			0.6 (0.3-1.0)	0.6 (0.4-0.9)	0.6 (0.3-1.0)	0.5 (0.3-1.0)	0.7 (0.4-1.0)				
S(t) at t = 12 (95% CI)	0.4 (0.3-0.8)			0.6 (0.3-1.0)	0.3 (0.1-0.9)	0.6 (0.3-1.0)	0.4 (0.1-1.0)	-				
PFS												
Median (95% CI)	2.8 (1.1-NR)			21 (2.3-NR)	1.7 (0-NR)	21 (8.6-NR)	0.9 (0-NR)	NR (0-NR)				
S(t) at t = 6 (95% CI)	0.5 (0.4-0.7)			0.7 (0.5-1.0)	0.3 (0.2-0.6)	0.8 (0.6-1.0)	0.3 (0.1-0.7)	0.5 (0.3-1.0)				
S(t) at t = 12 (95% CI)	0.3 (0.2-0.6)			0.6 (0.3-1.0)	0.2 (0.1-0.6)	0.6 (0.4-1.0)	0.1 (0.02-0.7)	0.5 (0.3-1.0)				
S(t) at t = 24 (95% CI)	0.2 (0.04-0.8)			-	0.2 (0.1-0.6)	-	-	0.5 (0.3-1.0)				
PFS, Allo-HSCT-Censored												
Median (95% CI)	1.8 (1.1-NR)			8.6 (1.3-NR)	1.1 (0-NR)	8.6 (2.3-NR)	0.9 (0-NR)	1.1 (0-NR)				
S(t) at t = 6 (95% CI)	0.4 (0.2-0.6)			-	-	-	-	-				
S(t) at t = 12 (95% CI)	0.2 (0.04-0.8)			-	-	-	-	-				
T=0: Treatment start date												
OS												
Median (95% CI)	16 (9.5-NR)			16 (9.5-NR)	NR (8.0-NR)	16 (9.5-NR)	NR (8.3-NR)	NR (3.6-NR)				
S(t) at t = 6 (95% CI)	0.7 (0.6-0.9)			0.8 (0.6-1.0)	0.7 (0.5-0.9)	0.8 (0.6-1.0)	0.7 (0.5-1.0)	0.7 (0.4-1.0)				
S(t) at t = 12 (95% CI)	0.6 (0.4-0.8)			0.7 (0.5-1.0)	0.5 (0.3-0.8)	0.7 (0.5-1.0)	0.5 (0.3-0.9)	0.5 (0.3-1.0)				
S(t) at t = 24 (95% CI)	0.5 (0.3-0.8)			0.5 (0.2-1.0)	0.5 (0.3-0.8)	0.4 (0.2-1.0)	0.5 (0.3-0.9)	0.5 (0.3-1.0)				
OS, Allo-HSCT-Censored												
Median (95% CI)	9.7 (8.3-NR)			16 (9.5-NR)	8.3 (8.0-NR)	16 (9.5-NR)	9.7 (3.3-NR)	8.0 (3.6-NR)				
S(t) at t = 6 (95% CI)	0.7 (0.6-0.9)			0.8 (0.6-1.0)	0.7 (0.5-0.9)	0.8 (0.6-1.0)	0.7 (0.5-1.0)	0.7 (0.4-1.0)				
S(t) at t = 12 (95% CI)	0.5 (0.3-0.8)			0.6 (0.4-1.0)	0.4 (0.2-0.8)	0.6 (0.3-1.0)	0.3 (0.1-1.0)	-				
S(t) at t = 24 (95% CI)	0.3 (0.1-0.8)			0.3 (0.1-1.0)	0.4 (0.2-0.8)	0.3 (0.1-1.0)	0.3 (0.1-1.0)	-				
PFS												
Median (95% CI)	8.6 (3.0-NR)			23 (8.6-NR)	3.3 (2.2-NR)	23 (11-NR)	3.0 (1.7-NR)	NR (2.2-NR)				
S(t) at t = 6 (95% CI)	0.5 (0.4-0.7)			0.8 (0.6-1.0)	0.4 (0.2-0.6)	0.8 (0.7-1.0)	0.2 (0.1-0.6)	0.6 (0.3-1.0)				
S(t) at t = 12 (95% CI)	0.4 (0.2-0.6)			0.6 (0.3-0.9)	0.2 (0.1-0.6)	0.6 (0.4-1.0)	0.1 (0.02-0.7)	0.6 (0.3-1.0)				
S(t) at t = 24 (95% CI)	0.3 (0.1-0.6)			0.3 (0.1-1.0)	0.2 (0.1-0.6)	0.3 (0.1-1.0)	-	0.6 (0.3-1.0)				
PFS, Allo-HSCT-Censored												
Median (95% CI)	5.0 (3.0-NR)			11 (8.6-NR)	3.3 (2.2-NR)	11 (8.6-NR)	3.0 (1.7-NR)	6.5 (2.2-NR)				
S(t) at t = 6 (95% CI)	0.5 (0.3-0.7)			0.7 (0.5-1.0)	0.3 (0.1-0.7)	0.8 (0.7-1.0)	-	0.6 (0.3-1.0)				
S(t) at t = 12 (95% CI)	0.2 (0.1-0.6)			0.3 (0.1-1.0)	-	0.4 (0.2-1.0)	-	-				
S(t) at t = 24 (95% CI)	0.2 (0.1-0.6)			0.3 (0.1-1.0)	-	0.4 (0.2-1.0)	-	-				
EFS												

Median (95% CI)	4.5 (2.8-NR)			23 (8.6-NR)	3.0 (2.2-NR)	23 (8.6-NR)	2.8 (1.7-NR)	NR (2.2-NR)
S(t) at t = 6 (95% CI)	0.5 (0.3-0.7)			0.7 (0.5-1.0)	0.3 (0.1-0.6)	0.8 (0.6-1.0)	0.2 (0.04-0.6)	0.6 (0.3-1.0)
S(t) at t = 12 (95% CI)	0.3 (0.2-0.6)			0.5 (0.3-0.9)	0.2 (0.03-0.7)	0.6 (0.3-1.0)	-	0.6 (0.3-1.0)
S(t) at t = 24 (95% CI)	0.2 (0.1-0.6)			0.3 (0.1-1.0)	0.2 (0.03-0.7)	0.3 (0.1-1.0)	-	0.6 (0.3-1.0)
EFS, Allo-HSCT-Censored								
Median (95% CI)	5.0 (3.0-NR)			11 (8.6-NR)	3.3 (2.2-NR)	11 (8.6-NR)	3.0 (1.7-NR)	6.5 (2.2-NR)
S(t) at t = 6 (95% CI)	0.5 (0.3-0.7)			0.7 (0.5-1.0)	0.3 (0.1-0.1)	0.8 (0.7-1.0)	-	0.6 (0.3-1.0)
S(t) at t = 12 (95% CI)	0.2 (0.1-0.6)			0.3 (0.1-1.0)	-	0.4 (0.2-1.0)	-	-
S(t) at t = 24 (95% CI)	0.2 (0.1-0.6)			0.3 (0.1-1.0)	-	0.4 (0.2-1.0)	-	-
Duration (Mo)								
TTNT[2], Median (95% CI)	**17 (6.4-NR)**	**11 (11-NR)**	**17 (3.7-NR)**	**25 (11-NR)**	**6.4 (2.5-NR)**	**25 (25-NR)**	**6.4 (3.5-NR)**	**6.5 (2.3-NR)**
Time of Follow Up[3], Median (95% CI)	11 (9.5-17)	18 (10-NR)	11 (8.5-17)	11 (8.5-NR)	11 (8.2-NR)	12 (9.5-NR)	14 (7.5-NR)	10 (8.2-NR)
	(n = 23)	(n = 5)	(n = 18)	(n = 14)	(n = 9)	(n = 11)	(n = 5)	(n = 4)
TTR[4], Median (IQR)	1.9 (1.7-2.6)	2.4 (2.3-5.6)	1.8 (1.7-2.2)	2.0 (1.8-2.8)	1.8 (1.5-2.3)	2.1 (1.7-2.6)	1.5 (1.4-1.8)	2.1 (1.8-3.1)
DoR[5], Median (95% CI)	21 (11-NR)	8.6 (2.3-NR)	21 (11-NR)	21 (8.6-NR)	11 (11-NR)	21 (8.6-NR)	11 (1.8-NR)	NR (0.9-NR)
Allo-HSCT Consolidation Post-Duv/Romi, No. (%)								
Immediately following (incl. bridging therapy)	11 (29)	1 (10)	10 (36)	6 (35)	5 (24)	5 (38)	3 (21)	2 (29)
Any time following (incl. future therapy lines)	14 (37)	2 (20)	12 (43)	7 (41)	7 (33)	5 (38)	4 (29)	3 (43)

Abbreviation: AITL-Angioimmunoblastic T-cell lymphoma, ALCL-Anaplastic large cell lymphoma, ALK-Anaplastic lymphoma kinase, Allo-Allogeneic, ATLL-Adult T-cell leukemia/lymphoma, CR-Complete Response, CTCL-Cutaneous T-cell lymphoma, DoR- Duration of response, Duv-Duvelisib, EFS-Event-free survival, ENKTCL-Extranodal NK/T-cell lymphoma, HSCT-Hematopoietic Stem Cell Transplantation, HSTCL-Hepatosplenic T-cell lymphoma, incl.-including, Mo-Month, NR-Not Reached, OR-Overall Response, OS-Overall Survival, PD-Progressive Disease, PR-Partial Response, PFS-Progression Free Survival, PTCL-NOS-Peripheral T-cell lymphoma-not otherwise specified, R/R-Relapsed and Refractory, SCT-Stem Cell Transplantation, SD-Stable Disease, S(t)-Survival probability, nTFH-nodal T follicular helper cell, TTNT-Time to next therapy, TTR-Time to response.

[1]Response rates were measured at best PET response to duv/romi.

[2]Time to next therapy was measured from treatment start date to initiation of next line of therapy after duv/romi, only in patients who received a subsequent line of therapy after duv/romi. Patients who went on to stem cell transplantation were censored at that event date.

[3]Time of follow-up was measured from treatment initation date to date of latest clinical update.

[4]Time to response was reported from treatment start date to date of first response, only in patients who achieved CR/PR to duv/romi.

[5]Duration of response was measured from date of first evaluable PET response to date of progression or last follow-up, only in patients who achieved CR/PR to duv/romi.

Table 4. Survival Estimates and Hazard Ratios of Combination Duv/Romi in Multi-Center R/R Cohort

		HR [95% CI] (p-value)		
		nTFH vs. Non-nTFH (ref)	**nTFH vs. PTCL-NOS vs. All Other** (ref)	**CRR/PRR** (ref) **vs. Progression**
OS[#]	**Standard censoring**	0.72 [0.26, 2.02] (0.5)	**nTFH**: 0.74 [0.18, 3.0] (0.7) **PTCL-NOS**: 1.0 [0.26, 4.2] (0.96)	17.9 [3.9, 82] (0.0002)
	Allo-HSCT-censored	0.66 [0.23, 1.87] (0.4)	**nTFH**: 0.66 [0.16, 2.7] (0.6) **PTCL-NOS**: 0.99 [0.25, 4.0] (0.99)	13.0 [2.9, 58] (0.0008)
PFS[#]	**Standard censoring**	0.44 [0.18, 1.09] (0.07)	**nTFH**: 0.82 [0.21, 3.2] (0.8) **PTCL-NOS**: 2.50 [0.68, 9.2] (0.2)	-
	Allo-HSCT-censored	0.31 [0.11, 0.87] (0.03)	**nTFH**: 0.45 [0.12, 1.7] (0.2) **PTCL-NOS**: 1.84 [0.57, 6.0] (0.3)	-
EFS[#]	**Standard censoring**	0.45 [0.19, 1.07] (0.07)	**nTFH**: 0.93 [0.25, 3.5] (0.9) **PTCL-NOS**: 2.9 [0.80, 11] (0.1)	
	Allo-HSCT-censored	0.31 [0.11, 0.87] (0.03)	**nTFH**: 0.45 [0.12, 1.7] (0.2) **PTCL-NOS:** 1.84 [0.57, 6.0] (0.3)	
Treatment response and duration				
Overall Response Rate		$P^1 = 0.02$		
Time to next therapy		$P^2 = 0.2$		
Time of follow-up		$P^2 = 0.9$		
Time to response		$P^3 = 0.3$		
Duration of response		$P^2 = 0.8$		

Abbreviation: HR-Hazard ratio, OS-Overall survival, nTFH-nodal T follicular helper cell, PTCL-NOS-Peripheral T-cell lymphoma-not otherwise specified, CR-Complete response rate, PR-Partial response rate, PFS-PFS-Progression free survival, Allo-HSCT- allogeneic hematopoietic stem cell transplantation, ref-reference

[1]P value calculated by Fisher's exact test

[2]P value calculated by log-rank test

[3]P value calculated by Kruskal-Wallis test

[#]OS, PFS, and EFS calculated since treatment initiation

Table 5. Patient Outcomes Status-Post Combination Therapy with Duv/Romi (Duv/Romi in Multi-Center R/R Cohort

Clinical Outcomes	All (n = 38)
Outcomes in Responders Following Duv/Romi, No. (%)	**17/38 (45)**
On Active Duv/Romi Therapy	3/17 (18)
PR on Duv/Romi, PD Despite Switch to Pralatrexate	1/17 (6)
Discontinued Duv/Romi Due to Patient Preference	1/17 (6)
Bridged to Allogeneic Hematopoietic Stem Cell Transplant (Allo-HSCT)	11/17 (65)
CR at Day 100	10/11 (91)
CR at Day 290+	3/10 (30)
PD after Day 200	2/10 (20)[1]
Not Yet Evaluable (Day <100)	1/11 (9)
Death Due to Duv/Romi AE	1/17 (6)
Outcomes in Progressive Disease (PD), No. (%)	**21/38 (55)**
Salvage Therapy s/p Duv/Romi	14/21 (67)
Death Due to Lymphoma	6/21 (29)
Hospice Care, No Known Death at Data Cutoff	1/21 (5)
Therapy Received Directly Following Duv/Romi Progression, No. (%)	**14/21 (66)**
CFT74455 (IKZF1/3 Degrader)	**3/21 (14)**
CR + Bridge to Allo-HSCT	1 (5)
PD	2 (10)
Azacitidine	**1/21 (5)**
Not Evaluable- Transition to Hospice	
Azacitidine + Lenalidomide	**1/21 (5)**
CR[2]	
Alemtuzumab	**1/21 (5)**
CR + Bridge to Allo-HSCT	
Brentuximab Vedotin + Gemcitabine	**1/21 (5)**
PD	
Dexamethasone + Methotrexate[3]	**1/21 (5)**
PD	
GVD	**1/21 (5)**
PD	
GCD	**1/21 (5)**
Not Evaluable- Transition to Hospice	
GemDOx	**1/21 (5)**
PD	
Gemcitabine	**1/21 (5)**
PD	
Mogamulizumab	**1/21 (5)**
PD	
Duvelisib + Ruxolitinib	**1/21 (5)**
Not Evaluable - Transition to Hospice	

Abbreviation: CR-complete remission, PD-progressive disease, GVD-gemcitabine, vinorelbine, and doxorubicin with pralatrexate in cycle 1 only, GCD-gemcitabine, carboplatin, and dexamethasone, GemDOx-gemcitabine, oxaliplatin, and dexamethasone.

[1]One patient had relapsed disease after bridging to allo-HSCT for which they were re-treated with combination duv/romi. They achieved a response to re-treatment, bridged to a second allo-HSCT, and remain in remission.

[2]Patient developed EBV viremia related extranodal NK/T-cell lymphoma from severe immunocompromise during cycle 2 and thus was not bridged to allo-HSCT.

[3]Patient developed central nervous system involvement and hence methotrexate was added.

Table 6. Grade 3-4 Adverse Events (AEs) Associated with Combination Therapy with Duv/Romi (Duv/Romi) in Multi-Center R/R Cohort

Adverse Event	No. (%) (n = 36)	Time to Event[1] (Mo), Median (IQR)	Dose Delay[2] Due to AE, No. (%)
Hematologic	**26 (72)**		**5/36 (14)**
Neutropenia	**15 (42)**	0.5 (0.2-1.4)	**2/36 (6)**
Grade 3	5 (14)		1* (3)
Grade 4	10 (28)		1*, 1[D] (6)
Febrile Neutropenia	**4 (11)**	2.2 (2.1-2.7)	**0**
Grade 3	3 (8)		2*[4] (6)
Grade 4	1 (3)		
Anemia		1.9 (0.2-4.2)	**0**
Grade 3	**6 (17)**		
Thrombocytopenia	**10 (28)**	1.6 (0.4-1.9)	**4/36 (11)**
Grade 3	2 (6)		1* (3)
Grade 4	8 (22)		1*,2[R] ()
Lymphopenia	**15 (42)**	2.2 (0.8-3.0)	**0**
Grade 3	10 (28)		
Grade 4	5 (14)		
Leukocytosis	**4 (11)**	0.2 (0-1.2)	**0**
Grade 3	3 (8)		
Grade 4	1 (3)		
		-	
Gastrointestinal	**9 (25)**		**5/36 (14)**
Transaminitis (ALT Elevation)	**6 (17)**	2.0 (1.7-2.6)	**5/36 (14)**
Grade 3	5 (14)		2*[5], 2[D] (6)
Grade 4	1 (3)		1*[D] (3)
Transaminitis (AST Elevation)		1.1 (1.0-1.7)	**3/36 (8)**
Grade 3	**6 (17)**		1*[D], 2[D] (8
Enterocolitis		2.8 (2.5-3.2)	**1/36 (3)**
Grade 3	**2 (6)**		1[D3] (3)
Non-Infectious Diarrhea		3.39	**1/36 (3)**
Grade 4	**1 (3)**		1[D3] (3)
Alkaline Phosphatase Elevation	**0**		0
Infectious	**9/29 (38)**		**3/36 (8)**
Cytomegalovirus viremia[6]	5/29 (17)	1.2 (1.1-1.4)	0
Tuberculosis reactivation	1 (3)	-	1[R] (3)
COVID-19 Infection	2 (6)	-	2* (6)
Pseudomonas bacteremia	1 (3)		0
Klebsiella bacteremia	1 (3)		0
Other Grade 3 and 4 AEs	**10 (28)**		**3/36 (8)**
Rash	5 (14)	9.5 (1.2-9.9)	1[R] (3)
Fatigue (Grade 3)	6 (17)	2.1 (1.5-2.4)	1[D], 1* (6)
Anorexia	0	-	0

*=Romidepsin and duvelisib delay
[D]=Duvelisib delay
[R]= Romidepsin delay
[1]Time to event was measured from treatment start date to date of adverse event and only reported in patients who had an adverse event.
[2]Dose delays were defined as a held dose due to AE resulting in a deviation from the treatment plan in either duv, romi, or both in any treatment cycle. If a patient experienced dose delays in multiple treatment cycles due to a single adverse event (AE), they were counted as one delay. Dose delays often but did not always coincide with dose changes.
[3]Duvelisib-associated gr 3 enterocolitis and gr 4 non-infectious diarrhea led to duv-romi treatment discontinuation (n=1).
[4]Febrile neutropenia gr 3 and neutropenia gr 4 with secondary Pseudomonas (n=1) and Klebsiella bacteremia (n=1) led to discontinuation of duv-romi therapy in two patients.
[5]Transaminitis with ALT elevation led to discontinuation of duv-romi therapy (n=1).

[6]Nine patients had no CMV PCR values available during duv/romi regimen and therefore 29 patients were evaluable.

Table 7. Efficacy and Safety of Two-Drug Combination Therapies in R/R PTCL and CTCL

Drug Combination	Drug Targets	Trial Phase	T-Cell Lymphoma Patients Enrolled (n)	Previous Treatment Lines, Median (Range)	Patients Evaluated (n)	Overall Response Rate (%)	Complete Response Rate (%)	Overall Survival, Median (mo)	Progression-Free Survival, Median (mo)	Duration of Response, Median (mo)	Most Prevalent Gr 34 Adverse Events (AEs)	AEs, No (%)	Reference
Romidepsin + Azacytidine[a]	HDAC + DNMT1	Real-World	Overall: 27[b] AITL: 19 TFH: 3 PTCL NOS:1 ATLL: 2 TFH-PTCL + DLBCL: 1 ALK- ALCL + FL: 1	1 (0-5)	Overall: 26 AITL + TFH: 23	76.9 69.5	53 60.8	NR	7.07	NR	Thrombocytopenia* Nausea* Neutropenia* Fatigue* Anemia*	14 (51) 11 (40) 10 (37) 8 (29) 6 (22)	Kalac et al.[8]
Romidepsin + Azacytidine[b]	HDAC + DNMT1	2	Overall: 14 AITL: 9 PTCL NOS: 2 ALCL: 1: EATL: 1 ENKTCL: 1	2 (1-6)	Overall: 13	54	38	20.6	8.0	13.5	Thrombocytopenia Neutropenia Lymphopenia Anemia Febrile Neutropenia	12 (48) 10 (40) 8 (32) 4 (16) 3 (12)	Falchi et al.[9]
Romidepsin + Azacytidine[c]	HDAC + DNMT1	1	Overall: 11 AITL: 3 PTCL NOS: 2 ATLL: 2 ALCL: 1 CTCL: 1 EATL: 1 ENKTCL: 1	6 (1-15)	Overall: 11	73	55	-	NR	-	Lymphopenia Neutropenia Thrombocytopenia Leukopenia Anemia	11 (42) 11 (42) 7 (27) 6 (23) 5 (19)	O'Connor et al.[10]
Romidepsin + Lenalidomide[d]	HDAC + E3 Ubiquitin	2	Overall: 27 AITL: 3 PTCL NOS: 5 ATLL: 7 ENKTCL: 1 T-PLL: 1 CTCL, MF: 7 CTCL- Sezary Syndrome: 3	3 (1-12)	Overall: 24 PTCL: 15 CTCL: 9	50 53 44	13 13 11	18.3	4.8	15.7	Thrombocytopenia Lymphopenia Neutropenia Leukopenia Anemia	26 (53) 25 (51) 24 (49) 22 (45) 13 (27)	Ruan et al.[11]
Romidepsin + Pembrolizumab	HDAC + PD1	2	Overall: 38	2 (1-6)	Overall: 38	47.3	37.3	21.3	-	-	Infection, NOS*[e] Thrombocytopenia	11 (28) 10 (26)	Iyer et al.[12]
Romidepsin + Pralatrexate[f]	HDAC + DHFR	2	Overall: 18 PTCL NOS: 8 PTCL w TFH Phenotype/AITL: 4 ATLL: 2 ENKTCL: 1 CTCL: 1 Subcutaneous Panniculitis PTCL: 2	2 (0-7)	Overall: 14 PTCL NOS: 6 PTCL w TFH Phenotype/AITL: 3 ATLL: 2 ENKTCL: 1 CTCL: 1	35.7	14.3 33 50	20.2	3.56	8.2	Infection[g] Sepsis Anemia Heart Failure Sinus Tachycardia	4 (24) 1 (6) 1 (6) 1 (6) 1 (6)	Ryu et al.[13]

					Subcutaneous Panniculitis PTCL: 1								
Duvelisib + Azacytidine	PI3K δ + DNMT1	1	Overall: 14 TFH: 4 CTCL: 2	2 (1-21)	Overall: 14 TFH: 4	46 100	31 100	10.2	2.2	-	Neutropenia* Anemia* Transaminitis Thrombocytopenia* Leukopenia*	4 (28) 3 (21) 2 (14) 2 (14) 1 (7)	Saeed et al.[14]
Duvelisib + Ruxolitinib[h]	PI3K δ + JAK	1	Overall: 49 PTCL NOS: 13 TFH: 14 T-PLL: 3 T-LGL: 3 MF: 7 ATLL: 1 ALCL, ALK-: 3 ALCL, ALK+: 1 MEITL: 1	*	Overall: 49 PTCL NOS: 13 TFH: 14 T-PLL: 3 T-LGL: 3 MF: 7	41 23 79 60 67 14	24 15 64 0 33 0	-	-	NR	Neutropenia Anemia Thrombocytopenia Transaminitis Hypertension	(38) (16) (12) (4) (4)	Moskowitz et al.[15]
Durvalumab + Lenalidomide	PD1 + E3 Ubiquitin	2	Overall: 13 CTCL: 13	3[i]	Overall: 12 CTCL: 12	75 75	-	-	NR	-	Neutropenia	1 (8)	Querfeld et al.[16]
Chidamide + Sintilimab	HDAC + PD1	1b/2	Overall: 38 ENKTCL, Phase 1b: 9 ENKTCL, Phase 2: 28	1 (1-2)	Overall: 37 ENKTCL, Phase 1b: 9 ENKTCL, Phase 2: 28	59.5 66.7 57.1	48.6 55.6 46.4	32.9	23.2	25.3	Neutropenia Leukopenia Lymphopenia Thrombocytopenia	11 (29) 3 (8) 3 (8) 4 (11)	Gao et al.[17]
Azacytidine + Nivolumab	PD1 + DNMT1	N/A	Overall: 9 AITL: 9	1 (1-2)	Overall: 9 AITL: 9	78 78	33 33	-	-	-	Neutropenia Anemia Colitis	1 (11) 1 (11) 1 (11)	Ricard et al.[18]

Abbreviation: EATL-enteropathy-associated T-cell lymphoma, DLBCL-diffuse large B-cell lymphoma, FL-follicular lymphoma, T-PLL-T-cell prolymphocytic leukemia, MEITL-monomorphic epitheliotropic intestinal T cell lymphoma.

*=Grade of AE not reported.

[a]Three (3/27) patients of unspecified histology were treatment-naive and included in all treatment response and AE measures. R/R-specific outcomes were not reported by the authors.

[b]AE rates include treatment-naive patients.

[c]Median lines of therapy and AE rates include treatment-naive patients and those with Hodgkin and B-cell lymphomas.

[d]Median lines of therapy and duration of response include patients with R/R Hodgkin and B-cell lymphomas.

[e]Infection type not reported.

[f]Three (3/18) patients of unspecified histology were treatment-naive and included in all treatment response and AE measures. R/R-specific outcomes were not reported by the authors.

[g]Grade 3-4 infection included staph infection, lymph node infection, and upper respiratory infection, and appendicitis.

[h]Treatment response and AE measures include treatment-naive patients of unknown count.

[i]Median lines of therapy included systemic therapies only. Authors did not report range.

Figure Legends:

Figure 1. OS for real-world patients with R/R PTCL and CTCL receiving combination Duv/Romi (Duv/Romi). Kaplan-Meier curves show OS estimates since duv/romi treatment initiation (A) Overall cohort with standard censoring. (B) Overall cohort with allogeneic hematopoietic stem cell transplants (allo-HSCT) post-duv/romi as censoring events. (C) Comparison by histological subtype (nTFH vs. non-nTFH) with standard censoring. (D) Comparison by histological subtype (nTFH vs. non-nTFH) and allo-HSCT-censored. P-values calculated by log-rank test.

Figure 2. PFS for real-world patients with R/R PTCL and CTCL receiving combination Duv/Romi (Duv/Romi). Kaplan-Meier curves show PFS estimates since duv/romi treatment initiation (A) Overall cohort with standard censoring. (B) Overall cohort with allogeneic hematopoietic stem cell transplants (allo-HSCT) post-duv/romi as censoring events. (C) Comparison by histological subtype (nTFH vs. non-nTFH) with standard censoring. (D) Comparison by histological subtype (nTFH vs. non-nTFH) and HSCT-censored. (E) Comparison by histological subtype (PTCL-NOS, nTFH subtype, and Other) with standard censoring. (F) Comparison by histological subtype (PTCL-NOS, nTFH Subtype, and Other) and allo-HSCT-censored. P-values calculated by log-rank test.

Figure 3. OS for real-world patients with R/R PTCL and CTCL receiving combination Duv/Romi (Duv/Romi). Kaplan-Meier curves show OS estimates since duv/romi treatment initiation (A) Comparison by best response (CR + PR) vs. best response: progression (PD + SD) on duv/romi with standard censoring. (B) Comparison by best response (CR + PR) vs. best response: progression (PD + SD) on duv/romi and allo-HSCT-censored. P-values calculated by log-rank test. CR-complete response, PR-partial response, PD-progressive disease, SD-stable disease

Figure 4. EFS for real-world patients with R/R PTCL and CTCL receiving combination Duv/Romi (Duv/Romi). Kaplan-Meier curves show EFS estimates since duv/romi treatment initiation (A) Overall cohort with standard censoring. (B) Overall cohort with allogeneic hematopoietic stem cell transplants (HSCT) post-duv/romi as censoring events. (C) Comparison by histological subtype (nTFH vs. non-nTFH) with standard censoring. (D) Comparison by histological subtype (nTFH vs. non-nTFH) and allo-HSCT-censored. (E) Comparison by histological subtype (PTCL-NOS, nTFH subtype, and Other) with standard censoring. (F) Comparison by histological subtype (PTCL-NOS, nTFH Subtype, and Other) and allo-HSCT-censored. P-values calculated by log-rank test.

Figure 5. Swimmer plot of patient outcomes over time for real-world patients with R/R PTCL and CTCL receiving combination Duv/Romi (Duv/Romi). Each horizontal bar represents an individual patient's treatment timeline, with the x-axis denoting time (months since duv/romi treatment initiation) and the y-axis listing individual patients. Colored segments within the bars indicate different responses (blue denotes progression free and gray denotes progression). Symbols indicate key clinical events (yellow square denotes complete response, dark blue triangle denotes allogeneic-HSCT, and green line denotes alive patient status at the time of data cutoff).

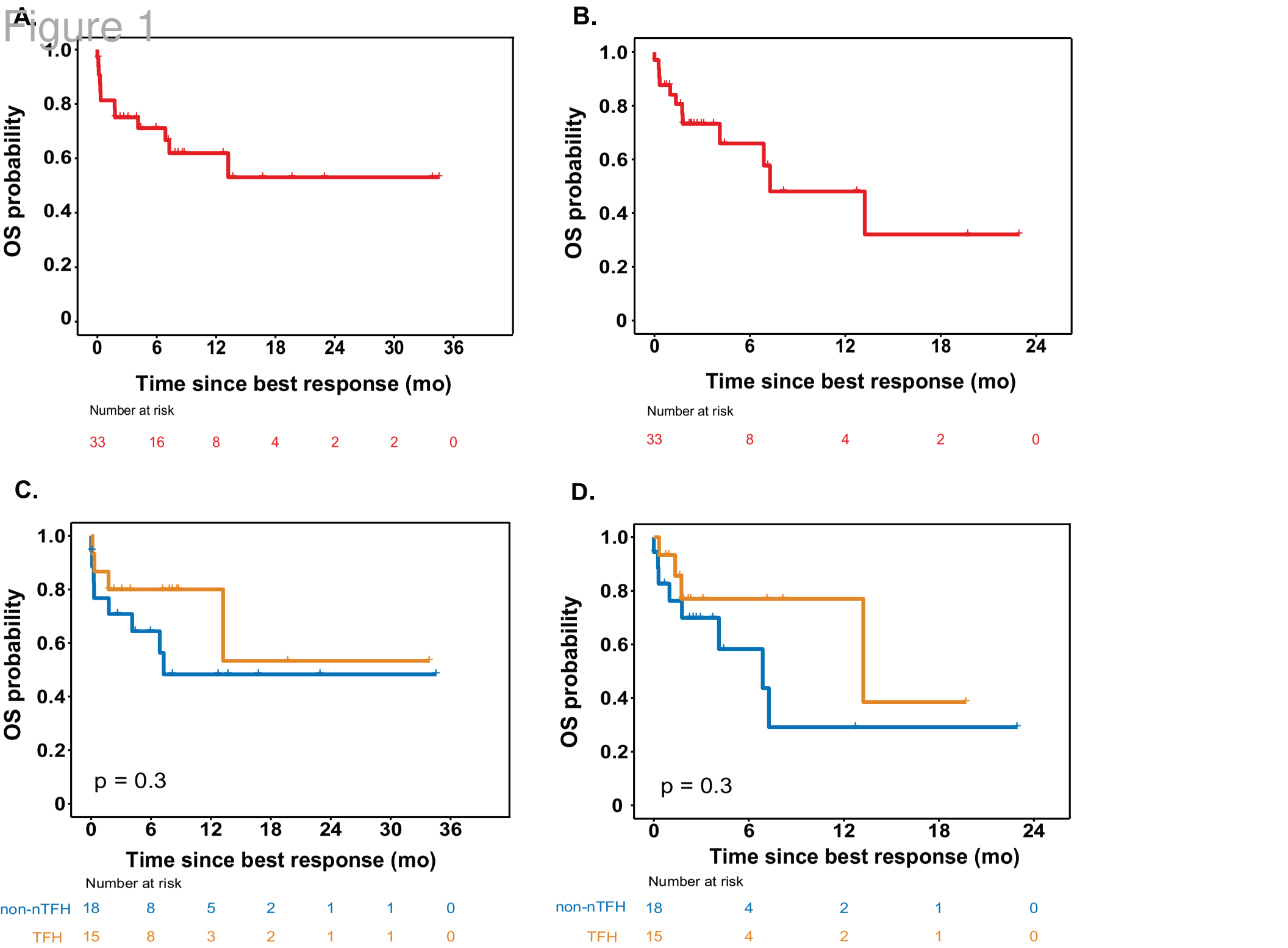


Figure 1

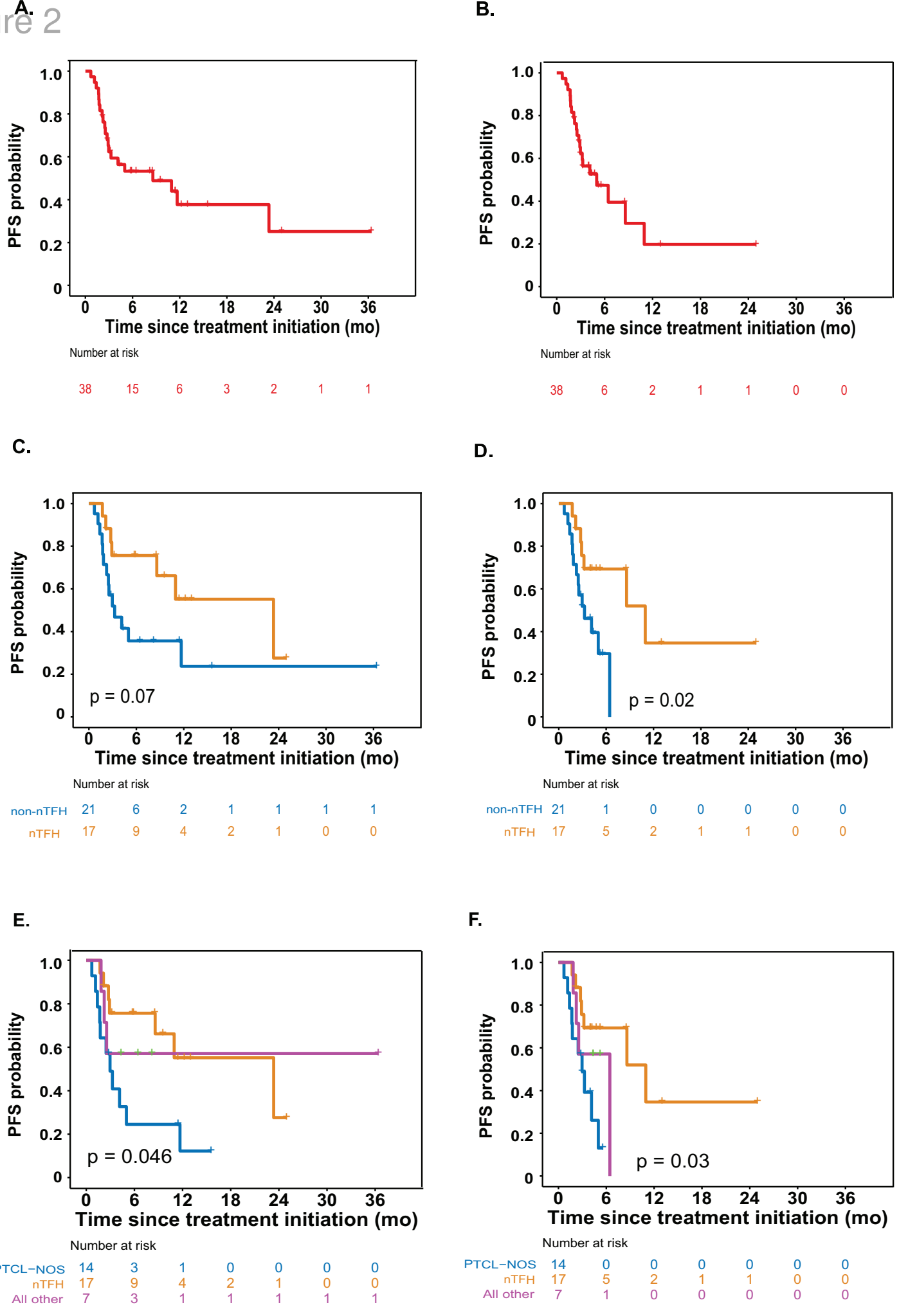
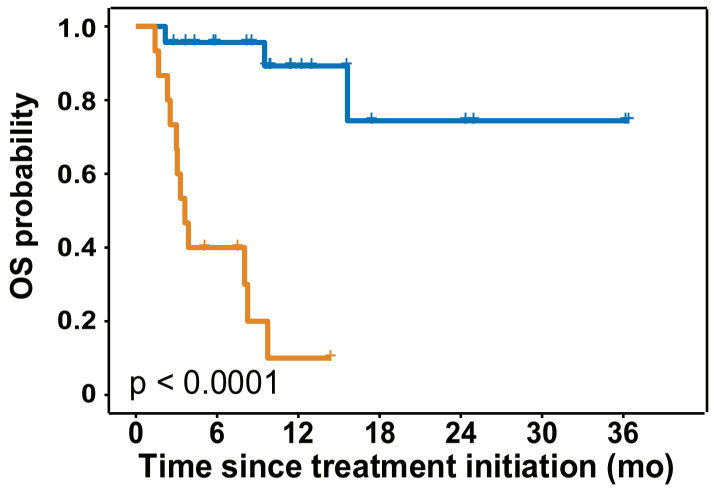


Figure 2

Figure 3



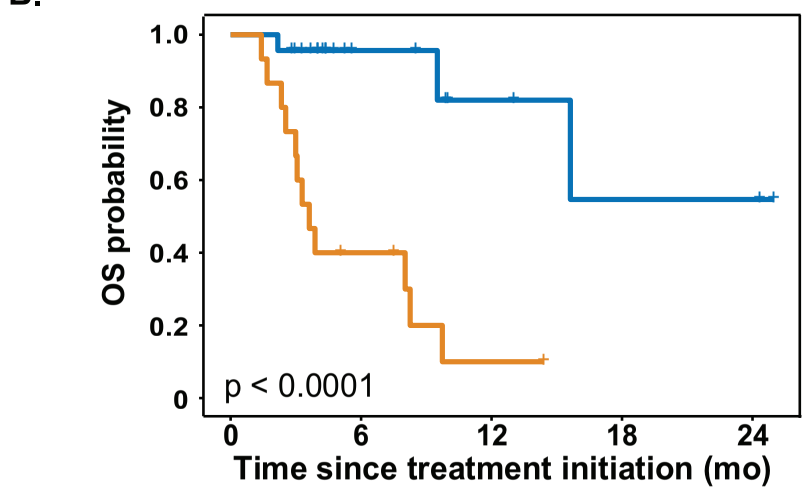


Figure 3

Figure 4

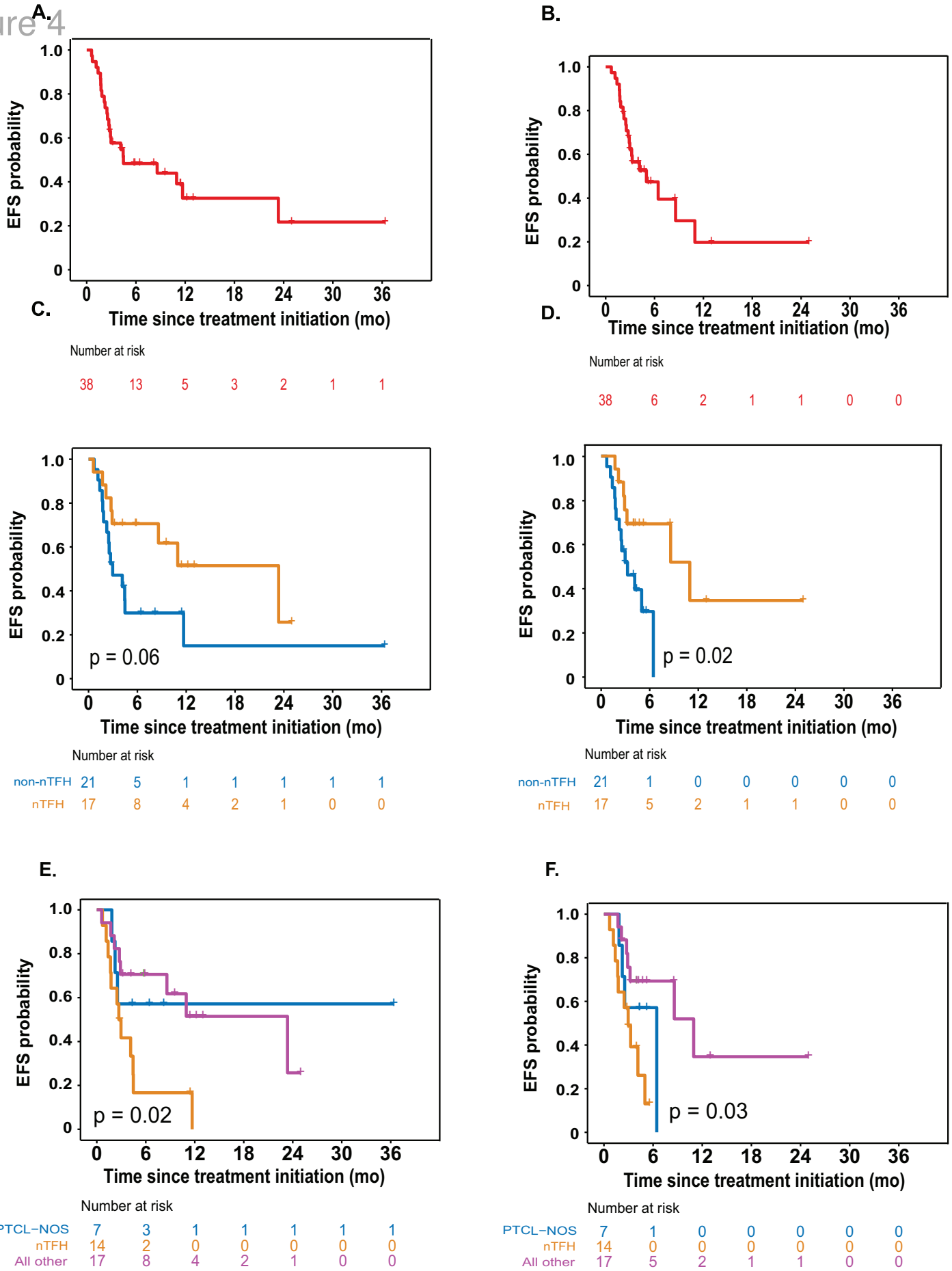


Figure 4

Figure 5

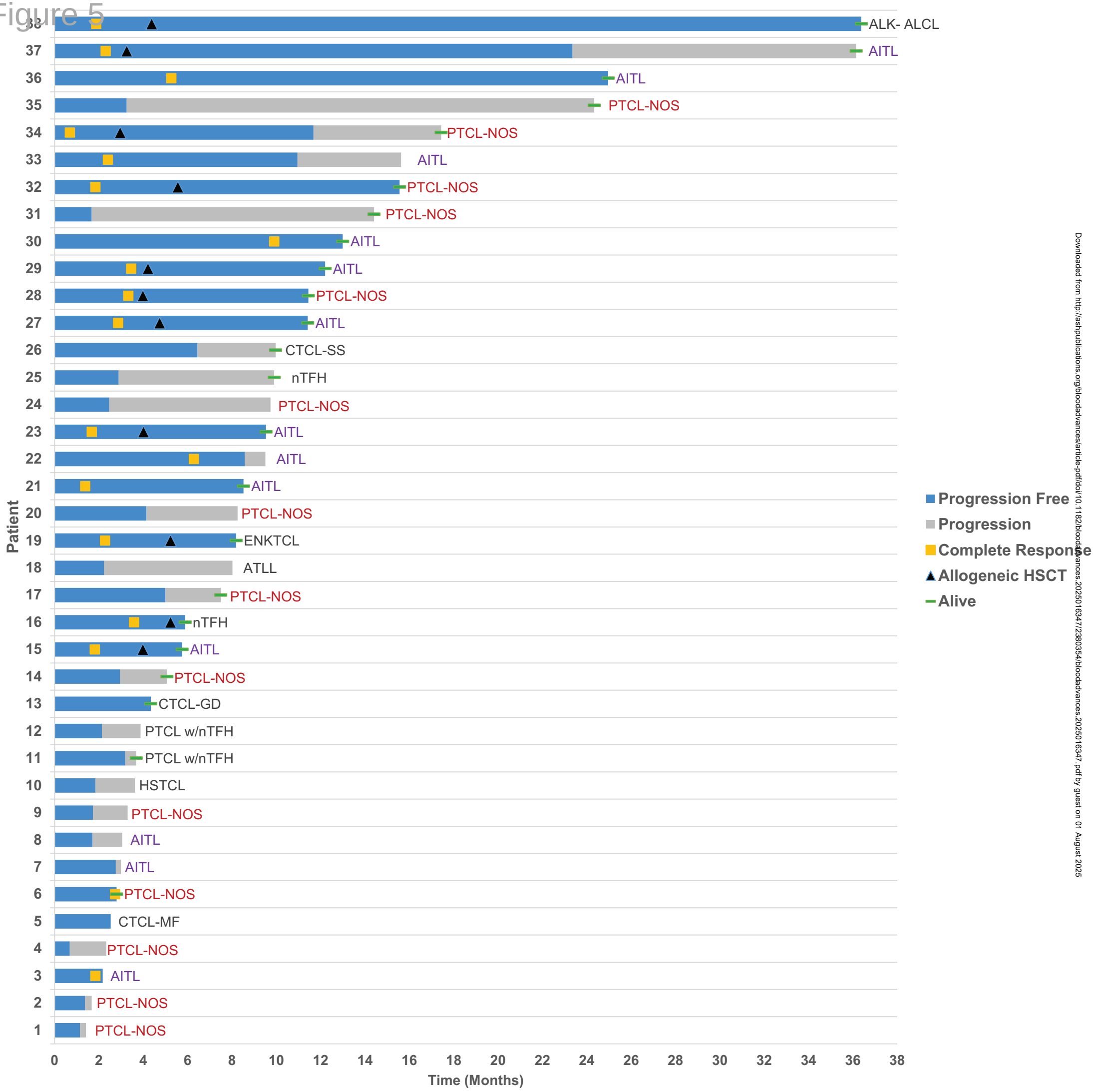


Figure 5