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Final results of UK NCRI phase II trial of pembrolizumab and radiotherapy in cutaneous T cell lymphoma

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Author Contributions

TI conceptualized the study, developed the methodology, performed investigations, secured funding, provided supervision, and contributed to the original draft and review & editing of the manuscript. WW contributed to the methodology, performed formal statistical analysis, managed data curation, and contributed to the original draft and review and editing of the manuscript. JP contributed to writing the original draft and executing the review & editing of the manuscript. SM contributed to study conceptualization, methodology, clinical investigation, and writing the original draft and review and editing. JS and SW contributed to study conceptualization, clinical investigations, and manuscript review & editing. EC contributed to data curation, study validation, investigations, and manuscript review and editing. AB, GC, EG-E, EJ, WO, NO'R, JPa, and JW participated in clinical investigations and contributed to manuscript review and editing. RC contributed to project administration and clinical investigations. NE-M contributed to project administration, study supervision, resources, data curation, and investigations. TA contributed to project administration and study supervision. All authors read and approved the final version of the manuscript.

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- WW, JP, SM, EG-E, SW, JPa, EC, NE-M, TA, EJ, AB, NO'R, and JW declare no competing financial interests or conflicts of interest to disclose.

Data Sharing Statement

Data sets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Abstract:

The outlook for patients with advanced cutaneous T-cell lymphomas (CTCL); mycosis fungoides (MF) and Sézary syndrome (SS) remains poor and most systemic treatments provide short-lived remissions. Immunotherapy has provided a major cancer breakthrough, and the PORT trial was designed to investigate the efficacy of Pembrolizumab and whether the addition of Radiotherapy (RT) could further enhance systemic “abscopal” anti-tumour immune responses. Pembrolizumab followed by 12Gy in 3 fractions RT to a localized lesion was investigated in a single-arm, multicentre phase II trial for relapsed/refractory CTCL. Primary endpoint was overall response rate (ORR), secondary endpoints included duration of response (DOR), abscopal response, progression-free survival (PFS), overall survival (OS). 46 patients (41 MF, 5 SS) were registered, median age 63 (24-83), 24% stage IV. Median follow-up was 24.8 months. 24% of patients remained on treatment for >1 year whilst 57% received <9 infusions (all stage IV disease / SS). Although the primary endpoint was not met, ORR 20%, best ORR 26% (95% CI 14-41), DOR rates at 1 and 2-years were 75% (95% CI 41-91) and 57% (95% CI 25-80) resulting in median PFS of 12.6 months and abscopal mSWAT scores suggested a RT induced “abscopal” effect. The treatment was well tolerated with infections most common (17%), 21 deaths were reported (11 CTCL, 3 Covid-19, 1 Sepsis, 6 Other). 2-year OS was 62%. Pembrolizumab in combination with RT resulted in durable clinical responses with evidence of a RT induced abscopal effect in a subset of relapsed CTCL patients.

Introduction

Mycosis fungoides (MF) and Sézary syndrome (SS) are two of the most common subtypes of cutaneous T-cell lymphoma (CTCL). The annual incidence of MF and its variants is estimated at between 1/350,000 and 1/110,000, with classical MF accounting for about 50-70% of CTCL cases. The male to female ratio is 2:1. Classical MF predominantly affects adults and the elderly (median age at diagnosis: 55-60 years). MF is a mature T-cell non-Hodgkin lymphoma that presents in the skin but can involve the lymph nodes, blood, and other organs. SS is defined as a distinctive erythrodermic CTCL with a leukemic burden of malignant T-cells with identical T-cell clones in the skin and blood with worse prognosis. [1, 2]

The prognosis of MF and SS varies with disease stage and patients with advanced stages have a higher risk of disease progression and much shorter median overall survival. A large international study showed a median OS in advanced stage MF/SS of just 63 months with 52% 5-year survival [3] Skin directed therapies are effective in patients with early-stage disease but those with advanced stage or refractory disease require systemic therapies, none of which are considered curative and relapses with progressive disease expected [2,3]. Systemic therapies used include immunomodulators (interferon-alpha , bexarotene) anti-folates (low dose methotrexate) [4, 5, 6], pegylated liposomal doxorubicin [7], gemcitabine [8] and HDAC inhibitors (romidepsin [9], vorinostat [10]) as well as extracorporeal Cellular Phototherapy (ECP) [11] . These treatments are used as single agents or as combinations e.g. IFN-alpha and retinoids, ECP and IFN alpha/ retinoids. More recently the anti-CD30 antibody drug conjugate, brentuximab vedotin and anti-CCR4 antibody mogamulizumab have demonstrated higher response rates, improving patient outcomes with longer durations of response [12,13] . However, the majority of patients relapse and require further lines of therapy, leading to a major unmet clinical need for novel approaches to further improve outcomes. Allogeneic stem cell transplantation (HCT) remains the only potentially curative treatment for advanced stage MF and SS, which is associated with a substantial morbidity and mortality risk and reserved for medically fit patients with high-risk disease. [14, 15]

Immune checkpoint inhibitors (ICI) have achieved major “breakthrough” status and have established immunotherapy as a routine part of cancer therapy providing durable responses in a variety of malignancies refractory to conventional chemotherapy [16, 17, 18]. ICI targeting programmed cell death protein (PD-1), expressed by exhausted T cells aims to reinvigorate exhausted T cells and provide anti-tumour immunity. The PD-1 inhibitors such as nivolumab [19] and pembrolizumab [20] have transformed treatment approaches to Hodgkin lymphoma but have had less impact in the treatment of other haematological malignancies [21]. PD-1 is often expressed by malignant T cells in certain subtypes of T cell lymphomas including MF and SS [22, 23, 24]. Furthermore, a small Phase II study involving 24 patients demonstrated that pembrolizumab had efficacy in CTCL with a 38% ORR, with some durable responses and manageable toxicity [25].

Radiotherapy (RT) also plays an important part of the routine treatment of CTCL by providing durable local control for tumours as well as the use of Total Skin Electron Beam (TSEB) for more generalized skin disease [26]. RT can generate local immunogenic cell death leading to anti-tumour immunity and numerous preclinical studies have confirmed the potential for clinical translation of RT in combination with immunomodulatory agents [27, 28]. More recently in other pre-clinical in vivo studies it has been demonstrated that the combination of RT and anti-PD-1/PD-L1 can be synergistic and result in long term clearance of T cell lymphoma and in other cancer models with responses seen outside of the RT field [29, 30].

Therefore, the aim of this trial was to investigate the novel approach of radiotherapy in combination with the anti-PD-1 mAbs pembrolizumab in patients with advanced CTCL to potentially enhance anti-tumour immunity and improve outcomes in relapsed/refractory CTCL.

Methods

This study was conducted according to the modified Declaration of Helsinki. The study was approved by the Northeast – Tyne & Wear South REC (18/NE/0077) and the MHRA (EudraCT 2017-000433-30) and was managed by the Cancer Research UK and University College London Cancer Trials Centre. Informed consent was obtained for all patients.

Trial design and eligibility criteria

This prospective, single-arm, multi-centre, phase II trial enrolled adults (≥18 years), ECOG 0-1, with relapsed/refractory stage IB-IVB CTCL MF or SS after ≥1 systemic therapy. Eligibility required central clinicopathological confirmation of CTCL and either a total modified Severity Weighted Assessment Tool (mSWAT) score ≥10 or ≥2 measurable lesions of any size. Exclusion criteria included inadequate organ function, recent chemotherapy/targeted therapy (<4 weeks), or monoclonal antibody therapy (<15 weeks, <12 weeks for alemtuzumab). Response assessments and endpoints followed ISCL and EORTC international consensus as described by Olsen et al. [31].

Treatment protocol

Patients received pembrolizumab 200mg IV every 3 weeks for up to 2 years, discontinued for post-RT disease progression or unacceptable toxicity. No dose reductions were permitted but infusions could be delayed for ≤12 weeks for immune-related adverse events (irAEs).

RT to the skin (12 Gy in 3 daily fractions, recommended field 50-400cm^2) was given at the 5th pembrolizumab infusion or at progression if earlier. Unless in CR at infusion 5, patients retained measurable CTCL outside the RT field to assess abscopal effect.

Assessments

Baseline staging (TNMB) and biopsy (archival ≤6 months permitted) were required within 4 weeks of entry. Global response was assessed before RT, at infusion 9 (+/- 7 days), infusion 13 (+/- 7 days) and end of treatment (+/- 7 days), incorporating radiology plus skin, blood and viscera. Clinical photographs were obtained at baseline and every global response assessment. mSWAT was recorded at each treatment visit, with irradiated and non-irradiated areas scored separately from RT to infusion 9. Quality of life (QoL) (Skindex 29, EORTC QLQ-C30) was assessed at baseline, before RT, infusion 9, infusion 13 and end of treatment. Adverse events (from first dose to 5 months post-treatment) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Endpoints

The primary endpoint was global response rate (CR + PR) at infusion 9. Patients not achieving ≥PR, or who discontinued before infusion 9 due to toxicity, progression, or death, were considered as non-responders. Secondary endpoints included best response, duration of response, abscopal response, TTNT, PFS, OS, compliance and toxicity.

Sample size and statistical analysis

Using an A'Hern single stage design (10% one-sided significance , 80% power), 46 patients were required to detect a 40% response rate, ruling out 25%. The primary endpoint was met if ≥16 achieved CR/PR at infusion 9.

Duration of response was measured from first CR/PR until post-RT progression or death. TTNT, PFS, and OS were measured from registration, censored at last follow-up if no event. QoL changes from baseline to infusion 9 were assessed with paired t-tests, with significance set at $p<0.01$ to account for multiple testing.

Patients were considered to have shown evidence of an abscopal effect if the change in mSWAT from baseline to RT was smaller than the change in mSWAT in non-irradiated skin from RT to infusion 9. This analysis included all RT-treated patients but excluded those who withdrew before infusion 9 for reasons other than progression or death.

A post-hoc analysis assessed outcomes in IB-IIB MF patients.

Results

Patients

Between April 3rd 2019 and December 21st 2022, 46 patients were recruited to the study from 9 UK sites. Median age was 63 (range 24-83, IQR 53-75), 17 (37%) were female and 29 (63%) had a WHO performance status of 0. There were 41 (89%) patients with MF compared to 5 (11%) with SS, and a median time since diagnosis of 7 years (range 1-24). A substantial proportion of patients had stage IV disease at the point of study entry (11/46, 24%) (Table 1). The median follow-up was 24.8 months (IQR 14.9-37.6).

Treatment compliance

The median number of pembrolizumab infusions received was 8 (range 1-36, IQR 3-18). 11 (24%) remained on treatment for over 12 months whilst 26 (57%) received <9 infusions, including all those with stage IV disease or SS. The most common reasons for stopping treatment were disease progression (18/46, 39%) followed by toxicity (7/46, 15%) (Figure 1). The majority of patients (30/46, 65%) had at least one infusion delayed, with adverse events being the most common cause for delay (30 out of a total of 81 treatment delays, 37%). 35 (76%) patients proceeded to radiotherapy, with 6 receiving it prior to infusion 5. Radiotherapy was administered as per protocol to all those that received it.

Efficacy

The primary endpoint for the trial was not met with 9 patients achieving a PR at infusion 9, giving an overall response rate (ORR) of 20% (80% CI 12-29). The best ORR across all assessments was slightly higher at 26% (95% CI 14-41). Patients that did respond experienced enduring remissions with 1 and 2-year duration of response rates of 75% (95% CI 41-91) and 57% (95% CI 25-80), respectively.

The median PFS for all patients was 12.6 months (95% CI 5.5-21.7), with 54% (95% CI 37-68) and 34% (95% CI 20-49) alive and progression-free at 1 year and 2 years, respectively. TTNT was similarly impressive with a median of 12.8 months (95% CI 6.9-26.2). 21 patients died during follow-up (11 CTCL, 3 Covid-19, 1 sepsis due to treatment, 1 other and 5 unknown). Median OS was 33.5 months (95% CI 12.8-47.4) with a 2-year rate of 62% (95% CI 45-75) (Figure 2).

The subgroup of patients with stage IB-IIB MF had superior outcomes. Among this population (N=31), the best ORR was 35% (95% CI 19-55) and the median TTNT was 22.0 months (95% CI 9.7-N/A).

Evidence of abscopal effect

11 patients withdrew from the study prior to RT and 4 withdrew for reasons other than progression or death before infusion 9 (figure 1). Of the remaining 31 patients, 6 (19%) showed evidence of a possible abscopal effect or 6/20 (30%) of those who reached infusion 9 (Figures 3 and 4 and supplementary table S1).

Safety

Just over half the patients on the study (25/46; 54%) experienced a grade 3 or above adverse event, with the most common being infections (8/46; 17%), followed by gastrointestinal disorders (6/46; 13%) (Table 2).

Quality of life

QoL subscales were mostly stable across all timepoints, with average QLQ-C30 global health status scores remaining around an average score of 60. When comparing infusion 9 scores to baseline, patients scored significantly worse on emotional functioning (mean change from baseline -10.8, 95% CI -19.2 to -2.4, p=0.01) and fatigue (+13.9, 95% CI +5.0 to +22.8, p<0.01). There were no significant changes in any of the Skindex-29 domains.

Discussion

The PORT trial was designed to investigate the efficacy of the ICI, pembrolizumab in CTCL and whether the addition of RT could further enhance the anti-tumour immune responses to improve clinical responses. Although the best ORR across all assessments was 26% the responding patients experienced enduring remissions with 1 and 2-year response rates of 75% and 57%, respectively. The median PFS for all patients was 12.6 months with 54% and 34% alive and progression-free at 1 year and 2 years, respectively. TTNT may be a better measure of therapeutic benefit in this patient cohort and was impressive in this study; with a median TTNT of 12.8 months. The median OS was 33.5 months with a 2-year rate of 62% (Figure 2). The subgroup of patients with stage IB-IIB MF had superior outcomes and amongst this population (N=31), the best ORR was 35% and the median TTNT was 22.0 months. Interestingly we observed evidence of an abscopal effect in 6/31 (19%) assessable patients and in 6/20 (30%) of those who reached infusion 9 (Figure 3). Future strategies to incorporate RT earlier than this requires further investigation as to whether this may improve outcomes further.

Increased expression of PD-1 and PD-L1 is seen across a broad spectrum of lymphoma sub-types, suggesting the PD1-/PD-L1 axis may play a pivotal role in tumour evasion across both NHL and Hodgkin Lymphoma (HL). The use of ICI targeting PD1/PD-L1 has revolutionised the treatment of Hodgkin lymphoma initially in the relapsed and refractory setting [19] and more recently in front line treatment [32]. However, responses in most NHL have largely been disappointing and have failed to change clinical practice in the most common NHL types [33, 34]. In keeping with these disappointing results in B cell lymphomas, a phase II study of the PD-L1 blocker atezolizumab included 26 MF/SS patients and reported an ORR of 15.4% with one complete response observed after 1 year. Median PFS was just 3 months and median TTNT was 6.2 months [35]. Pembrolizumab has previously been investigated in a Phase 2 single arm study in MF and SS. The ORR was 38% in 24 evaluable patients, median time to response was 11 weeks. Some responses were durable with 85% of responses ongoing at a median of 32 weeks duration. In this small sample group, there was no correlation found with CD8 T cell, PD-1, PD-L1 or PD-L2 expression levels in the skin or blood compartments with clinical responses. Immune related skin flare reaction was noted in 6 patients (two grade 2 and four grade 3), all of which had

Sézary syndrome [25]. The median PFS for all patients in the PORT study was encouraging at 12.6 months, with 54% and 34% alive and progression-free at 1-year and 2-years respectively and compares favourably with standard of care therapies including the more recently approved drugs including the anti-CCR4 mAb mogamulizumab with an ORR of 28% and PFS of 7.7 months [13] and a PFS of 16.7 months for brentuximab vedotin [12]. The median TTNT for PORT was similarly impressive at 12.8 months compared to 14.2 months in the brentuximab vedotin arm of the ALCANZA trial versus just 5.6 months for physicians' choice. Hyper progression of cutaneous T cell lymphoma after anti-PD1 treatment has been reported in ATLL [36] and more recently PD-1 has been found to act as a tumour suppressor for malignant T cells with oncogenic TCR activation in a single case of CTCL [37].

A possible abscopal effect was observed in 6/20 (30%) of those who reached infusion 9 (Figure 3) and is of particular interest, albeit that a delayed response to pembrolizumab, although less likely, cannot be completely excluded as another possible explanation for this effect. It is also worth noting that some patients showed only a small reduction in mSWAT, which may reflect the variable nature of abscopal responses. RT is documented to be able to induce systemic immunostimulatory effects, often termed "abscopal" effects first defined as an "action at a distance from the irradiated volume but within the same organism," which may rarely lead to tumour control in metastatic sites [38]. However, the generation of anti-tumour systemic immune responses are rarely observed in the clinic following RT [39]. The major breakthrough of ICI and the emerging data demonstrating the potential of RT to induce immunomodulatory changes has led to growing interest in combining RT with immune ICIs to enhance tumour control. Preclinical studies demonstrated immune-mediated inhibition of metastasis following local RT and CTLA-4 blockade in a breast cancer mouse model [40], and further preclinical studies examining the combination of RT and ICIs, demonstrated successful anti-tumour effects [29, 30].

However, translating these promising preclinical results with RT and ICIs translational into clinical practice has presented significant challenges with the exception of successes using ICI as an adjuvant after Chemo-RT in The PACIFIC trial, a phase III clinical study in Stage III non-small cell lung cancer (NSCLC) which demonstrated improved survival outcomes for patients receiving durvalumab (anti-PD-L1) [41] . A recently reported Phase 1 trial investigated the combination of durvalumab with lenalidomide in relapsed/refractory cutaneous T-cell lymphoma. Although there were only 12 evaluable patients the overall global response rate was 58% (95% confidence interval, 27.7-84.8). 7 patients achieved partial response (PR), 4 patients had stable disease (SD), and 1 patient developed PD and developed multiple skin tumours with blood and nodal involvement. The median time to response was 3.2 months, and the median duration of response was 25.5 months, and notably long-lasting responses (12 months or longer) were seen in a subset of patients (n = 4). Translational investigation of the immune cell profiles in the TME niche revealed profiles associated with immune activation and surveillance in responders and included increased effector $CD8^+$ T cells and NK-cell activation, increased M0 macrophages, with decreased immature dendritic cells (resting) and Treg levels.[42]

Lenalidomide has also been investigated in combination with brentuximab vedotin (BV) in peripheral T cell lymphoma (PTCL) and CTCL in a phase II trial which enrolled 26 patients using reduced dose Lenalidomide (10 mg) due to tolerability. In this heavily pretreated population (median of 4.5 prior lines of therapy), 13 with MF (50%) , 8 with PTCL (31%), 3 with SS (12%), 5 patients achieved complete response (2 CTCL, 3 PTCL), four achieved PR (3 CTCL, 1 PTCL), and 10 had stable disease (all CTCL) leading to an ORR of 27.8% (5/18) for CTCL. 19 patients experienced grade 3 or higher adverse events, the most common of which were neutropenia (19.2%), lymphopenia, rash, fatigue, and abdominal pain (11.5%

each). Patients came off treatment most commonly for progression (54%) and adverse events (23%). [43]

In keeping with the durable responses seen with durvalumab and lenalidomide our results also suggest that a subgroup of patients have durable remissions and further understanding the underlying immunological mechanisms will inform future clinical trial design. We hypothesise that RT may enhance immunostimulatory effect and further increase anti-tumour immune responses seen with pembrolizumab. Serial skin biopsies and blood samples taken in these PORT trial patients and translational research is ongoing to provide further potential immunological mechanistic insights and potentially confirm the nature of these anti-tumour immune responses, which we hope to report separately. The combination of an anti-PD-1/ anti-PD-L1 in combination with lenalidomide provides an opportunity to further enhance clinical efficacy. Given that a proportion of patients progressed before receiving RT, we speculate that a more effective strategy might be to use RT to cytoreduce the largest lesions initially in all patients and then consolidate with an ICI and lenalidomide combination. Future clinical trial design will also be influenced by the ongoing clinical studies which are aimed at assessing the safety and efficacy of combining RT with immunotherapy e.g. A phase 2 trial of mogamulizumab (anti-CCR4 Ab) with low-dose TSEBT (ClinicalTrials.gov ID: NCT04128072). [44]

The study was initially conducted during the COVID-19 pandemic, which substantially influenced the toxicity observed, including 3 of the 21 deaths secondary to COVID-19 as well as the number of advanced stage heavily pretreated relapsed and refractory patients, leading to 11 early deaths due to CTCL, 1 due to treatment-related sepsis, 1 other, and 5 unknown. All stage 4 patients progressed before infusion 9 of pembrolizumab. Just over half of the patients on the study (25/46; 54%) experienced a grade 3 or above adverse event with a toxicity profile consistent with other tumour sites e.g. gastrointestinal disorders (6/46; 13%). No patients experienced pneumonitis and only one patient colitis (Table 2) but with perhaps more infections (8/46; 17%), potentially reflecting the tendency for this population to experience skin infections [45, 46]. Grade 3-4 adverse events were reported in 41% of patients receiving BV in the randomized ALCANZA trial [12]. We observed a worsening in quality-of-life measures related to emotional functioning and fatigue at infusion 9 compared to baseline, possibly reflecting the burden of ongoing hospital visits, which may have been exacerbated by the COVID-19 pandemic.

In conclusion, pembrolizumab in combination with RT did not meet the primary end point however the subset of patients with Stage IB-IIB disease appear to have benefited with durable clinical responses and encouraging evidence of a RT induced abscopal response. Whilst the ORR was only 26%, the best response rate in the MF stage IB-IIB group of patients was 35%, and in the 20/46 patients who received at least 9 infusions the ORR was 45%. Combined with durable remissions and TTNT exceeding 1 year these data suggests that pembrolizumab and ICI requires further investigation in CTCL with immune biomarker driven studies to further enhance patient selection.

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Table 1: Baseline characteristics

All patients	N=46
Age, median (range)	63 (24-83)
Sex	
Female	17 (37%)
Male	29 (63%)
Duration of CTCL (years), median (range)	7 (1-24)
CTCL stage at study entry	
IB	12 (26%)
IIA	6 (13%)
IIB	13 (28%)
IIIA	2 (4%)
IIIB	2 (4%)
IVA2	8 (17%)
IVB	3 (7%)
Disease type	
Mycosis Fungoides	41 (89%)
Sezary Syndrome	5 (11%)
WHO PS	
0	29 (63%)
1	17 (37%)
Disease status at registration	
Progressed	26 (57%)
Refractory	14 (30%)
Relapsed	6 (13%)
Previous skin directed therapy for	

CTCL	
No	10 (22%)
Yes	36 (78%)
Previous radiotherapy for CTCL	
No	8 (17%)
Yes	38 (83%)
Previous systemic therapies for CTCL	
Yes	46 (100%)
Total mSWAT score, median (range)	54.5 (7.8-139.0)
LDH	
Elevated	16 (35%)
Normal	30 (65%)

Table 2: Toxicities

Adverse events	Treated patients (N=46)	
	Grade 1-2	3+
Blood and lymphatic system disorders	7 (15%)	1 (2%)
Cardiac disorders	5 (11%)	1 (2%)
Ear and labyrinth disorders	2 (4%)	0
Endocrine disorders	4 (9%)	0
Hyperthyroidism	2 (4%)	0
Hypothyroidism	3 (7%)	0
Eye disorders	6 (13%)	0
Gastrointestinal disorders	13 (28%)	6 (13%)
Colitis	0	1 (2%)
Pancreatitis	0	1 (2%)
General disorders and administration site conditions	17 (37%)	4 (9%)
Hepatobiliary disorders	0	1 (2%)
Infections and infestations	20 (43%)	8 (17%)
Injury, poisoning and procedural complications	2 (4%)	1 (2%)
Investigations	11 (24%)	2 (4%)
Metabolism and nutrition disorders	2 (4%)	1 (2%)
Musculoskeletal and connective tissue disorders	9 (20%)	1 (2%)
Neoplasms benign, malignant and unspecified	0	1 (2%)
Nervous system disorders	14 (30%)	3 (7%)
Psychiatric disorders	4 (9%)	1 (2%)

Renal and urinary disorders	2 (4%)	1 (2%)
Respiratory, thoracic and mediastinal disorders	14 (30%)	1 (2%)
Pneumonitis	0	0
Skin and subcutaneous tissue disorders	18 (39%)	2 (4%)
Vascular disorders	5 (11%)	4 (9%)
Any toxicity (regardless of incidence)	**21 (46%)**	**25 (54%)**

Figure 1: CONSORT diagram

Footnote: Toxicity events leading to treatment withdrawals were colitis (N=1), headache (N=1), hypotension and arterial thromboembolism (N=1), infection (N=1), low platelets (N=1), pancreatitis (N=1), peripheral neuropathy (N=1).

Figure 2: Kaplan-Meier curves

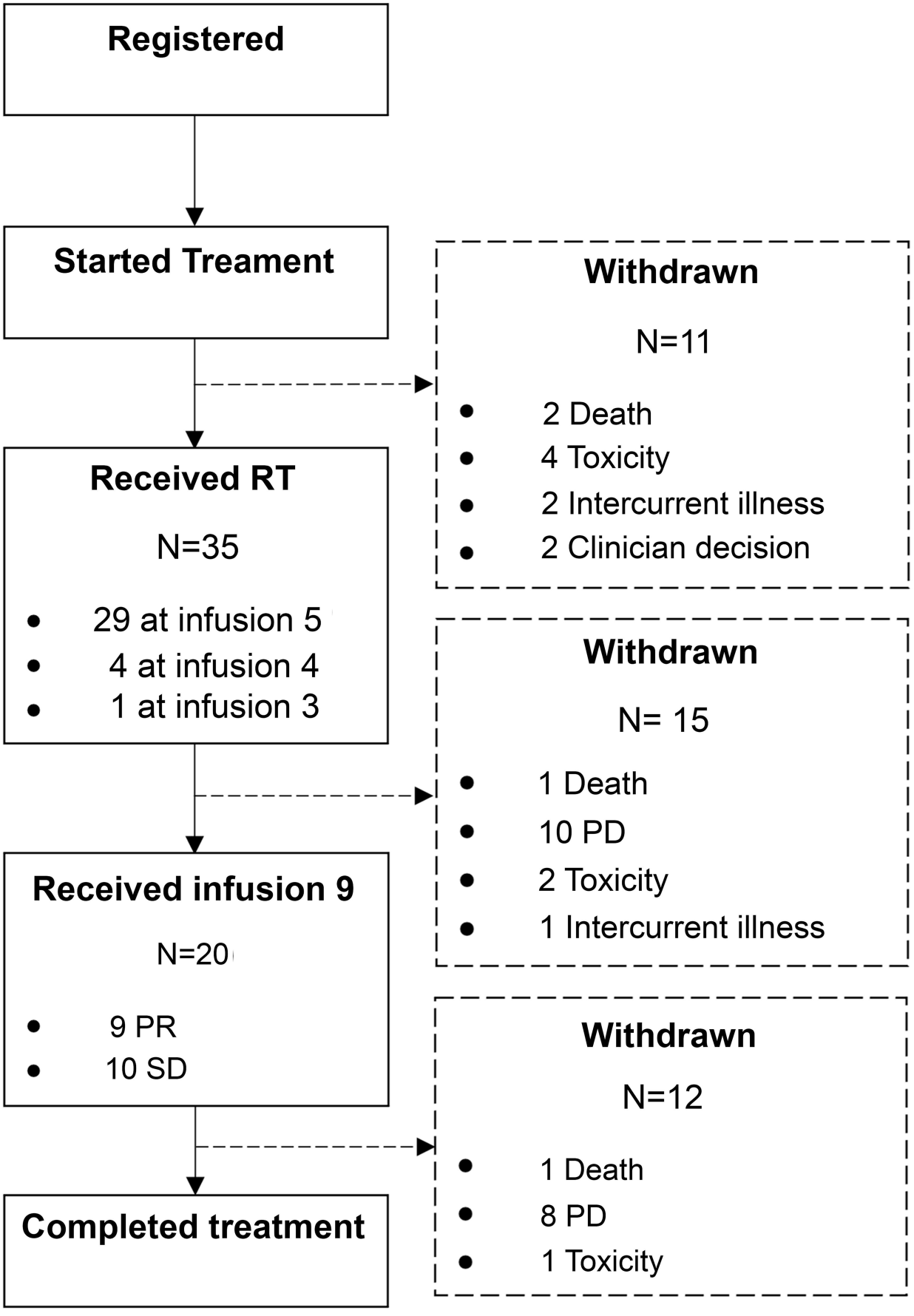
Footnote: Kaplan-Meier curves showing a) Progression-free survival (PFS), b) Overall survival (OS), c) Time to next treatment or death (TTNT) and d) Duration of response (DoR)

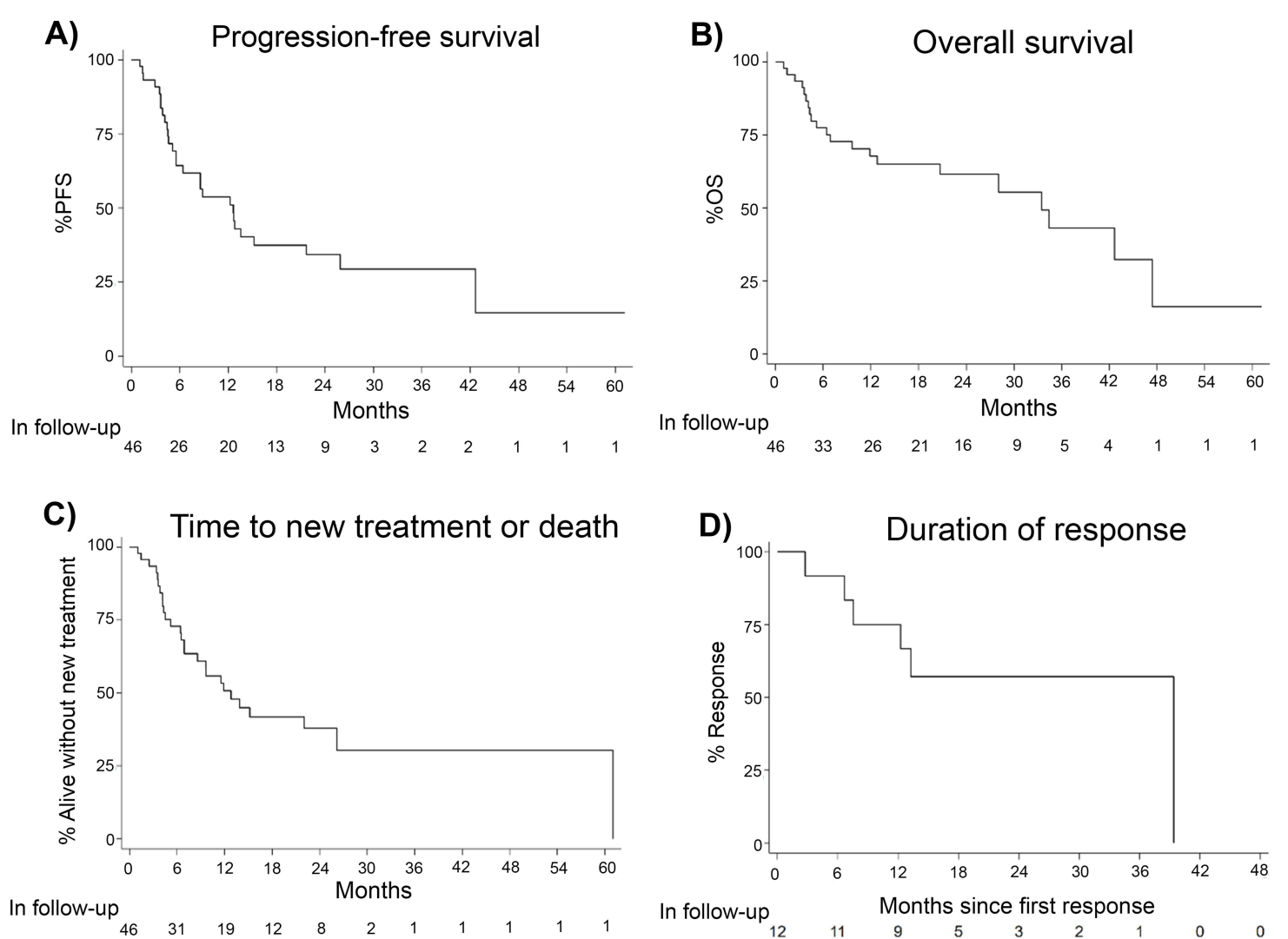
Figure 3: Evidence of abscopal effect

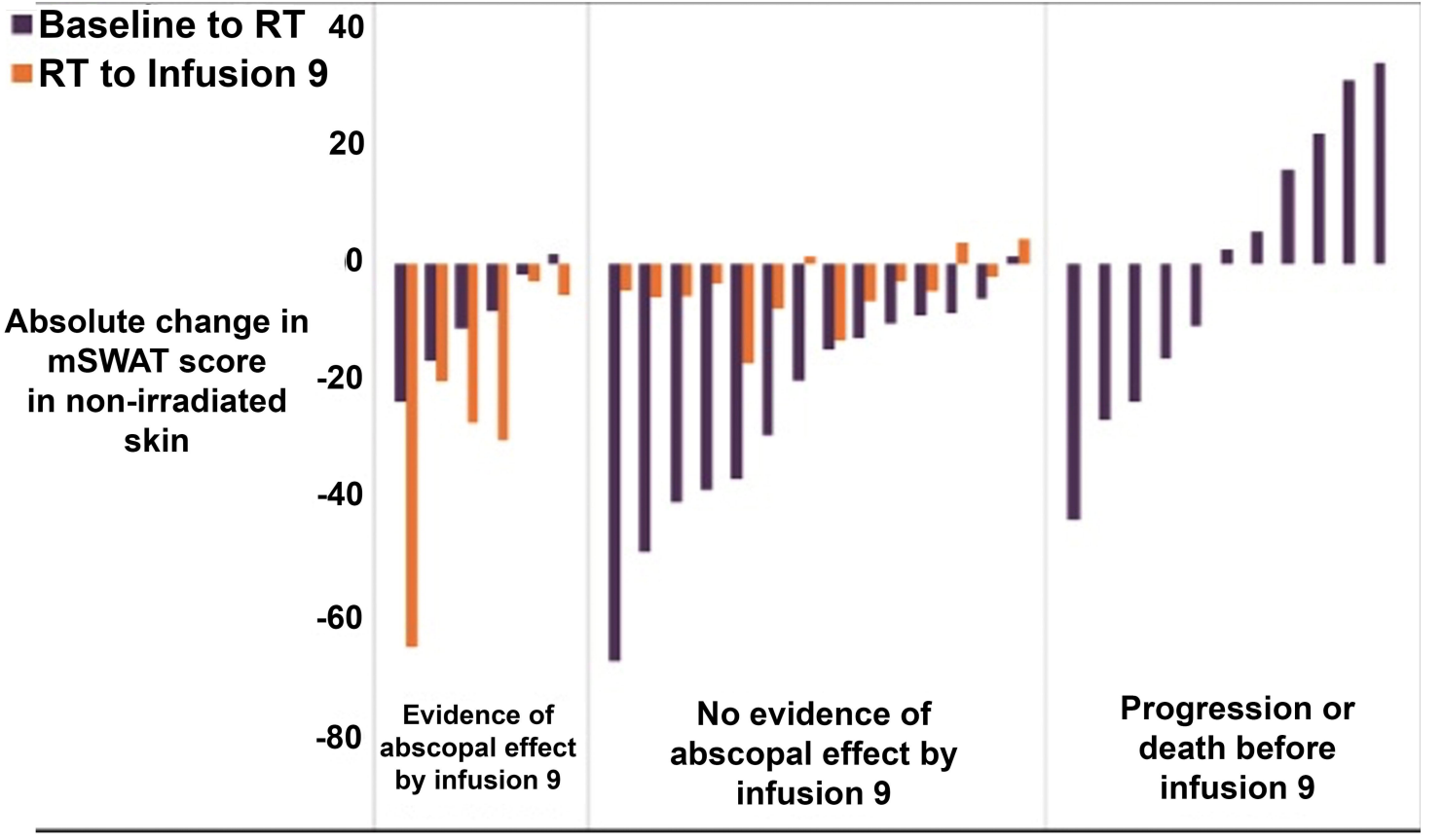
Footnote: 6/31 (19%) of patients with available data showed evidence of abscopal effect. 11 patients (21-31 on plot) progressed or died due to CTCL after radiotherapy and before infusion 9 and are assumed to have had no abscopal effect. 4 patients that received radiotherapy are not included in the denominator as they withdrew for reasons other than progressive disease before infusion 9 and so cannot determine possible abscopal effect.

Figure 4: Clinical photos of possible abscopal effect.

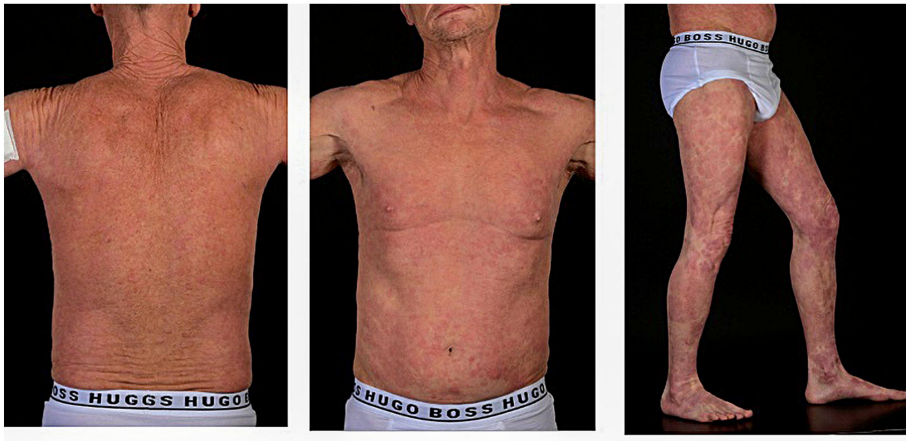
Footnote: a) baseline photos MSWAT 98.5, b) photos of areas treated with radiotherapy with mSWAT of 71.2 outside area treated with radiotherapy, c) Infusion 9 photos with mSWAT 2.7.


Registered
Started Treament
Withdrawn
N=11
2 Death
4 Toxicity
2 Intercurrent illness
2 Clinician decision
Received RT
N=35
29 at infusion 5
4 at infusion 4
1 at infusion 3
Withdrawn
N= 15
1 Death
10 PD
2 Toxicity
1 Intercurrent illness
Received infusion 9
N=20
9 PR
10 SD
Withdrawn
N=12
1 Death
8 PD
1 Toxicity
Completed treatment

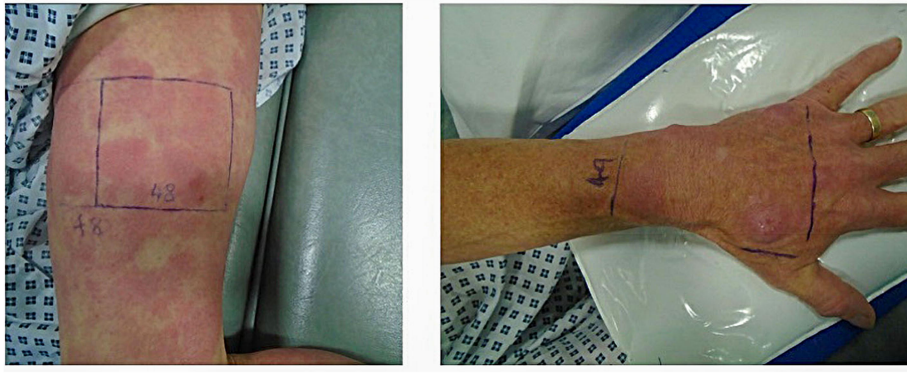

A)
Progression-free survival
%PFS
100
75
50
25
0
0 6 12 18 24 30 36 42 48 54 60
Months
In follow-up
46 26 20 13 9 3 2 2 1 1 1
B)
Overall survival
%OS
100
75
50
25
0
0 6 12 18 24 30 36 42 48 54 60
Months
In follow-up
46 33 26 21 16 9 5 4 1 1 1
C)
Time to new treatment or death
% Alive without new treatment
100
75
50
25
0
0 6 12 18 24 30 36 42 48 54 60
Months
In follow-up
46 31 19 12 8 2 1 1 1 1 1
D)
Duration of response
% Response
100
75
50
25
0
0 6 12 18 24 30 36 42 48
Months since first response
In follow-up
12 11 9 5 3 2 1 0 0


Baseline to RT
RT to Infusion 9
Absolute change in mSWAT score in non-irradiated skin
40
20
0
-20
-40
-60
-80
Evidence of abscopal effect by infusion 9
No evidence of abscopal effect by infusion 9
Progression or death before infusion 9

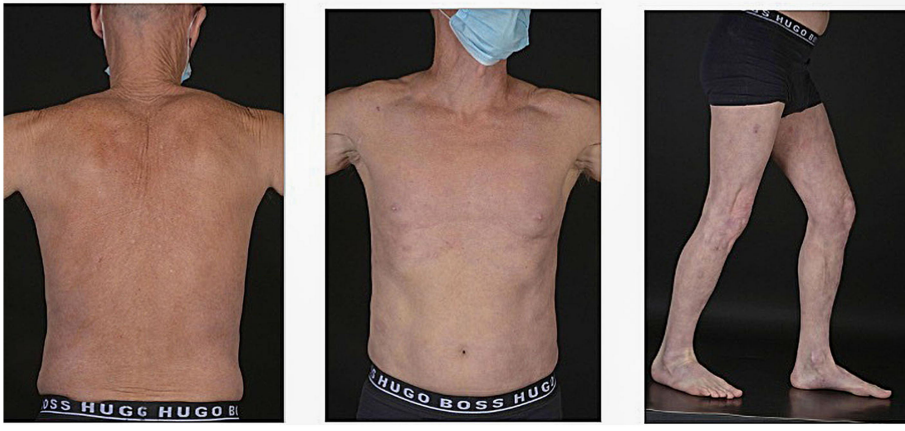
A



B



C



Supplementary material: Phase II trial of pembrolizumab and radiotherapy in cutaneous T-cell lymphoma (PORT)

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Table S1: Line listings of patients with evidence of abscopal effect (in same order as in figure 3)

	Abscopal 1	**Abscopal 2**	**Abscopal 3**	**Abscopal 4**	**Abscopal 5**	**Abscopal 6**
Baseline details						
Age	50 years	76 years	77 years	74 years	46 years	50 years
Sex	Male	Male	Male	Male	Female	Male
Duration of CTCL	14 years	13 years	24 years	10 years	6 years	11 years
Stage	IB	IIB	IIIA	IB	IIA	IB
TNMB	T2N0M0B0	T3N0M0B0	T4N0M0B0	T2N0M0B0	T2NxM0B0	T2N0M0B1
Disease type	Mycosis fungoides	Mycosis fungoides	Mycosis fungoides	Mycosis fungoides	Mycosis fungoides	Mycosis fungoides
WHO PS	0	1	0	0	0	0
Disease status	Progressed	Progressed	Progressed	Refractory	Refractory	Refractory
Previous skin-directed therapy for CTCL	Yes	Yes	Yes	Yes	No	Yes
Previous RT for CTCL	Yes	Yes	Yes	Yes	Yes	Yes
LDH	Normal	Normal	Elevated	Normal	Elevated	Elevated
Nodal sites	Borderline axillary & inguinal	None	None	None	Axillary & inguinal	None
mSWAT						
Baseline	94.5	54	100	94	19.75	27
Pre-RT (all)	71.2	37.5	89.2	86	17.9	28.5
Pre-RT (non-irradiated)	67.45	34.5	87.9	84	16.2	14
Infusion 9 (non-irradiated)	2.7	14.5	61	54.25	13.05	8.75
Outcomes						
Nodal disease post-RT	None	None	None	None	Axillary	None
Infusion 5 response	SD	SD	SD	SD	SD	SD
Infusion 9 response	PR	PR	SD	SD	SD	PR
Last FU	Alive without PD at 1.7 years	PD at 0.7 years, alive at 4.8 years	Alive without PD at 2.0 years	PD at 2.2 years, death at 4.0 years	Alive without PD at 4.1 years	PD at 1.1 years, alive at 2.5 years