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Extracorporeal photopheresis vs. systemic immunosuppression for immune-related adverse events: Interim analysis of a prospective two-arm study

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ABSTRACT

Background: Checkpoint inhibitor-induced steroid-refractory (sr) and steroid-dependent (sd) immune-related adverse events (irAE) account for about 11 % of irAE. Although these patients face worse outcomes due to irAE mortality and/or sustained immunosuppression, which impairs anti-tumor response, there is no established second-line treatment based on prospective trial data.
Methods: This prospective comparative study investigates outcomes of extracorporeal photopheresis (ECP), an immunomodulating therapy, versus second-line immunosuppressants (SLI) in sr/sd-irAE. The primary endpoint was longitudinal change in immunophenotype; secondary endpoints were outcome of irAE and tumor response. Patient demographics, quality of life (EORTC QLQ-C30; global health status (GHS/QoL)) and longitudinal blood samples were analyzed at baseline; in weeks 1, 4, 8, and 12.
Results: At interim analysis, 21 patients (11 ECP, 10 SLI) with 7 different sr/sd-irAE were included. Compared with the SLI group, the ECP group demonstrated a higher clinical response rate of irAE (93 % vs. 80 %; 95 % CI 0.83–1.92; $P = 0.54$) and a better GHS/QoL score throughout all follow-up visits. ECP patients showed a numerically higher overall survival (23 vs. 12 months; 95 % CI 0.02–3.02; $P = 0.27$) and lower cancer progression rates (33 % vs. 67 %; 95 % CI 0.09–1.60; $P = 0.52$). Immunophenotyping revealed changes in immune cell populations and the regulation of immune checkpoints. There were no significant safety issues in either treatment group.
Conclusion: This prospective comparative study supports the clinical efficacy of ECP in the treatment of sr/sd-irAE in comparison to the SLI cohort. Thus, ECP represents a potential treatment option for this indication, given its good safety profile while maintaining anti-tumor response.
Trial Registration: ClinicalTrials.gov, NCT05700565, https://classic.clinicaltrials.gov/ct2/show/NCT05700565.

1. Background

Immune checkpoint inhibitor (ICIs)-induced steroid-refractory (sr) or steroid-dependent (sd) immune-related adverse events (irAE) occur in around 11 % of all irAE [1–3] and can be fatal [4]. There is no evidence on the best second-line therapy of sr/sd-irAE [5–7]. Side effect registries like SERIO (www.serio-registry.org) can help to gather data [8,9], but prospective data, ideally comparing different therapy options, is needed.

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Corticosteroid administration induces side effects with detrimental effects on anti-tumor response like reduced progression-free survival (PFS; HR 1.69) or overall survival (OS; HR 1.97) in melanoma patients [10,11]. Treatment recommendations for sr/sd-irAE differ considerably [3,5–7,12], with infliximab and mycophenolate mofetil (MMF) being among the most commonly used second-line immunosuppressants (SLI) [1], though they carry an increased risk of infections and tumor progression [13–16].

Extracorporeal photopheresis (ECP) represents an established therapy for cutaneous T-cell lymphoma [17–19], graft-vs.-host disease (GvHD) and rejection in solid organ transplants [20]. The procedure comprises leukapheresis, photoactivation with 8-methoxypsoralen (8-MOP) and UVA, and reinfusion of leukocytes [21]. It is safe with very few reported side effects, like fatigue or transient hypotension (5 %) [19,22–24]. The immunomodulatory mechanisms of ECP include changes in the cytokine profile, activation of T cell subsets, and modulation of dendritic cells (DCs) [24,25]. Since ECP is not known to negatively influence anti-tumor response [26–28] and has been successfully used in the treatment of irAE [2,23,28–31], we performed a prospective study comparing irAE outcome, global health status (GHS) and quality of life (QoL), longitudinal changes in immunophenotype, and tumor outcome in patients with sr/sd-irAE within a two-arm study comparing ECP to SLI.

2. Methods

2.1. Study design

This study (NCT05700565) enrolled tumor patients with at least one sr-irAE (defined as failure to improve symptoms within 72 h with high dose corticosteroids) or sd-irAE (defined as inability to taper steroids to $\leq$ 5 mg per day without recurrence of symptoms) induced by any approved ICI therapy (neoadjuvant, adjuvant, or metastatic setting). The open trial with an instrumental variable independent of the outcome was conducted in accordance with the Declaration of Helsinki after obtaining ethics approval from the institutional review board (Project-Nr. 21-0874) and written informed consent of each patient (Fig. 1A).

Patients with known sensitivity to psoralen compounds such as 8-MOP, comorbidities that may result in photosensitivity, aphakia, pregnancy, underweight, history of heparin-induced thrombocytopenia, unsatisfactory cardio-circulatory function, or low hematocrit were excluded. Treatment allocation was made collaboratively with each patient based on travel distance to the clinic. Patients were treated with ECP, using the Therakos™ Cellex®, on 2 consecutive days every 2 weeks (Arm A) or another second-line therapy (Arm B) according to investigator's choice, e.g., infliximab, tocilizumab, JAK inhibitors, rituximab, vedolizumab or MMF with standard dosing [3,5–7]. During the 12-week follow-up period, patients underwent ECP treatment every 2 weeks as described in the study protocol. After an average of 10 cycles of ECP, or 20 weeks of treatment, respectively, the intervals were extended individually by 1 week at a time, upon significant improvement of the patients' symptoms.

At all visits (baseline, weeks 1, 4, 8 and 12), medical and laboratory assessments (including peripheral blood mononuclear cell (PBMC) analyses) were conducted, along with an evaluation of patients' history, treatment of side effects and patients' health-related quality of life (QoL) using the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire Core (QLQ-C30) (Fig. 1B).

The primary objective was to assess longitudinal changes in immunophenotype; secondary objectives included response of irAE to second-line treatment, steroid treatment prior and during the study, time to response and resolution of sr/sd-irAE according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) grading.

Tumor response, defined as the initial response of cutaneous metastatic melanoma patients (stage IV, AJCC 2017) at the first staging following the start of second-line therapy (1–3 months) was analyzed. PFS and OS were defined as the time from initiation of second-line therapy until disease progression and until death from any cause, or date of censorship, respectively.

2.2. Immunophenotyping

PBMC [32] for FACS analysis were permeabilized and fixated with eBioscience™ Foxp3/Transcription Factor Staining Buffer Set (Invitrogen), followed by intracellular staining with antibodies diluted 1:100 (Suppl. File 1). Measurements were conducted on CytoFLEX LX (Beckman Coulter) with antibody panels for T-cell phenotype including naïve T cell, stem-like memory T cell (T_{SCM}), central memory T cell (T_{CM}), effector memory T cell (T_{EM}), effector activated T cell (T_{EFF}), and regulatory T cell (Treg cell), T-cell activation markers (cluster of differentiation (CD) 27, inducible co-stimulatory molecule (ICOS), CD44, CD107a, CD28), and exhaustion markers (T-cell immunoglobulin and mucin domain-3 (TIM-3), T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT), cytotoxic T-lymphocyte–associated antigen 4 (CTLA4), lymphocyte activation gene (LAG3)), B-lymphocytes, macrophages and dendritic cells. Longitudinal changes of immunophenotypes within each group were analyzed and compared between groups.

2.3. Statistical analysis

Statistical evaluation and graph generation were performed using GraphPad Prism Version 9.3.1, the Microsoft Office Suite, and the swim plot package in R. Immunophenotype analyses were conducted with FlowJo 10.8.1 (BioSciences). Comparisons between groups were made using the Mann-Whitney U test, unpaired Student's t-test, Wilcoxon test and Fisher's test. Continuous data are presented as median (interquartile range [IQR]) or mean (standard deviation [SD]), while categorical data shown as percentages. Survival probabilities were estimated using the Kaplan-Meier method. A p-value < 0.05 was considered significant.

3. Results

3.1. Therapy of steroid-refractory and steroid-dependent irAE

For interim analysis of this prospective two-arm study, 21 patients (11 ECP, 10 SLI) with different tumor entities and irAE types were analyzed (Table 1; Fig. 2A). Altogether 25 sr/sd-irAE occurred (15 irAE in ECP group, 10 irAE in SLI group), since 4 out of 21 patients developed two concurrent sr/sd-irAE (Table 1). At the initiation of second-line therapy, the median severity of reported sr/sd-irAE was grade 3 CTCAE [IQR 2.5–3]. At the 12-week follow-up, complete resolution of side effects was achieved in 60 % (9/15) of cases under ECP therapy (median CTCAE grade 0 [IQR 0–1]; $p < 0.0001$, ****), compared to 40 % (4/10) with SLI (median CTCAE grade 1 [IQR 0–2.4]; $P = 0.0034$, **) (Fig. 2B).

The overall response rate (RR) for sr/sd-irAE under ECP therapy was 93 % (73 % resolution, 13 % improvement, 7 % resolution with sequelae), with symptoms showing improvement within 1–4 weeks (median 1 week [IQR 1–4]; Fig. 2C). Complete resolution of symptoms and normalization of laboratory results were observed between week 1 and 30 (median 12 weeks [IQR 8–13.5]). Ongoing symptoms were reported in 7 % of cases (1/15). In the SLI group, 50 % of cases resolved, 20 % improved, 10 % resolved with sequelae, and 20 % were still ongoing, resulting in an overall RR of 80 % (Fig. 2C).

At a 12-week follow-up, the proportion of patients in whom steroid dose could be significantly reduced was 88 % for ECP vs. 80 % for SLI (Fig. 2D/E). The ECP group had a longer median duration of pretreatment with steroids (97 vs. 21 days [IQR 30.5–231 vs. 9.5–32]; $P = 0.0057$, **) and fewer median steroid tapering attempts since the initiation of irAE treatment (1.5 vs. 2.5 [IQR 1–2.5 vs. 1–3]; $P = 0.41$, *ns*), with a similar median time to irAE improvement (1 week; [IQR 1–4 for both]; Table 1).

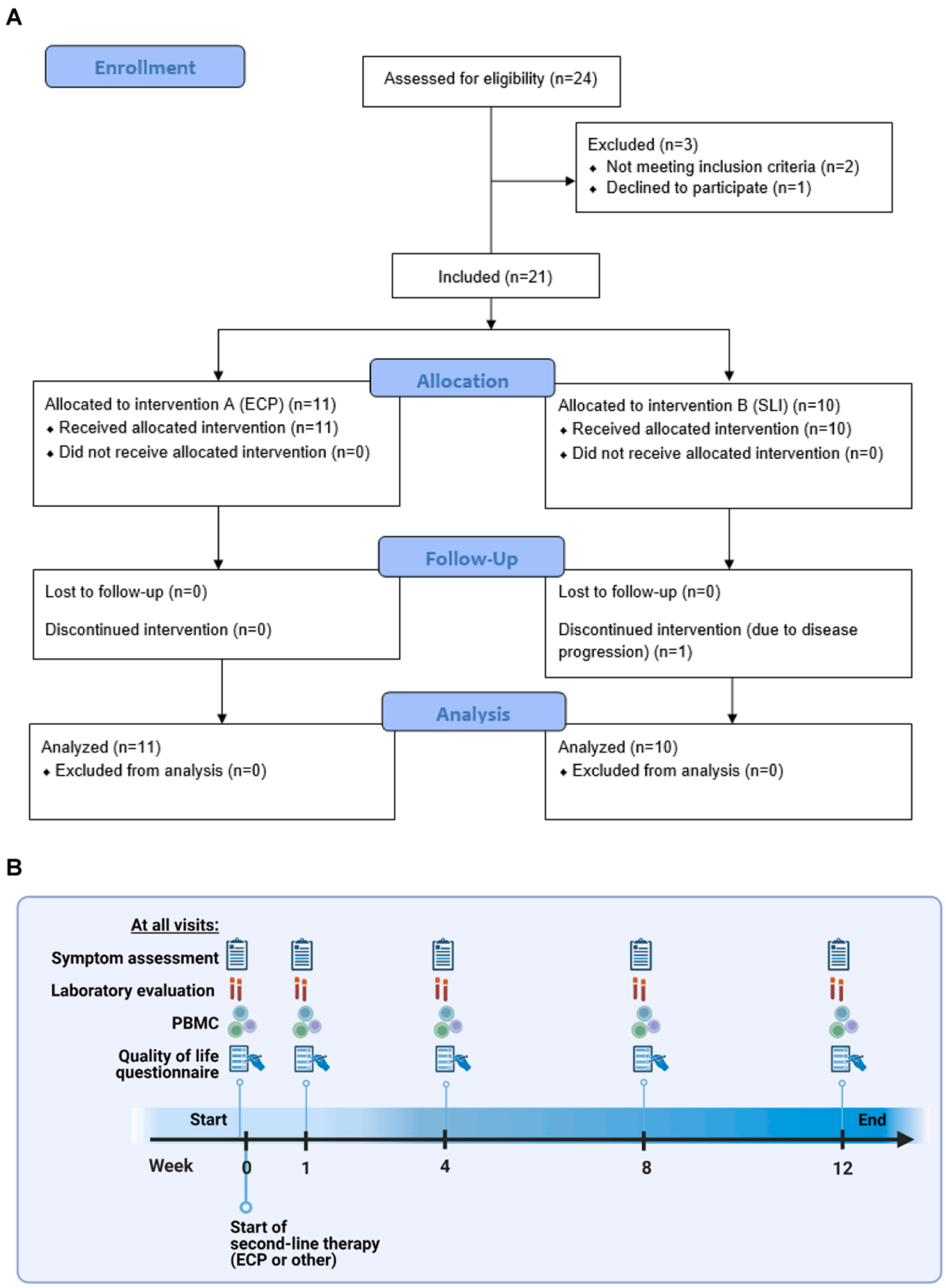

Fig. 1. Study design of the prospective two-arm quality improvement study. (A) CONSORT 2010 flow diagram of the Cohort Selection. (B) Study design of the open label two-arm study treating steroid-refractory or steroid-dependent irAE with ECP or second-line immunosuppression. ECP = Extracorporeal Photopheresis; PBMC = Peripheral Blood Mononuclear Cell; SLI = Second-line immunosuppression.

Table 1
Baseline characteristics of study cohort treated with immune checkpoint inhibitors. Percentages may not sum up to 100 due to rounding. Age: median displayed with range in brackets. Primary AJCC 2017 stage and immune-related adverse event (irAE) displayed. IrAE are graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, published: November 27, 2017.

Patients' characteristics	ECP cohort	SLI cohort	Total cohort
Patients, n	11	10	21
irAE, n	15	10	25
Age (years), median [IQR]	56 [43-63.5]	62 [58–73.5]	58 [45–68]
Sex: female - male: n (%)	8 - 3 (73%-27%)	5 - 5 (50–50 %)	13 - 8 (62–38 %)
Melanoma			
Primary AJCC (2017) stage, n (%)			
I	1 (9%)	0 (0 %)	1 (5 %)
II	0 (0%)	0 (0 %)	0 (0 %)
IIIA	2 (18%)	0 (0 %)	2 (10 %)
IIIB/C	2 (18%)	0 (0 %)	2 (10 %)
IV[a]	3 (27%)	10 (100 %)	13 (62 %)
Adrenocortical carcinoma	1 (9%)	0 (0 %)	1 (5 %)
Hepatocellular carcinoma	1 (9%)	0 (0 %)	1 (5 %)
Lung cancer	1 (9%)	0 (0 %)	1 (5 %)
Treatment setting, n (%)			
Adjuvant	4 (36%)	0 (0 %)	4 (19 %)
Metastatic	7 (64%)	10 (100 %)	17 (81 %)
Therapy regimen ICI, n (%)			
Atezolizumab/Bevacizumab	1 (9%)	0 (0 %)	1 (5 %)
Nivolumab	2 (18%)	1 (10 %)	3 (14 %)
Ipilimumab + Nivolumab	2 (18%)	9 (90 %)	11 (52 %)
Pembrolizumab	6 (55%)	0 (0 %)	6 (29 %)
ICI treatment, n (%)			
Stopped	7 (78%)	7 (70 %)	14 (74 %)
Rechallenge	2 (22%)	3 (30 %)	5 (26 %)
irAE, n (%)			
Capillary Leak Syndrome	3 (20%)	0 (0 %)	3 (12 %)
Colitis	3 (20%)	8 (80 %)	11 (44 %)
Hepatitis	0 (0%)	1 (10 %)	1 (4 %)
Lichenoid reaction	2 (13%)	0 (0 %)	2 (8 %)
Pancreatitis	3 (20%)	1 (10 %)	4 (16 %)
Pneumonitis	1 (7%)	0 (0 %)	1 (4 %)
Serositis	3 (20%)	0 (0 %)	3 (12 %)
Second-line therapy for irAE, n (%)			
ECP	15 (100%)	0 (0 %)	15 (60 %)
Infliximab	0 (0%)	8 (80 %)	8 (32 %)
IVIG	0 (0%)	1 (10 %)	1 (4 %)
MMF + Tacrolimus	0 (0%)	1 (10 %)	1 (4 %)
irAE, CTCAE grade n (%) – baseline			
1–2	4 (27%)	2 (20 %)	6 (24 %)
3–4	11 (73%)	8 (80 %)	19 (76 %)
irAE, CTCAE grade n (%) – after treatment			
< 1–2	15 (100%)	7 (70 %)	22 (88 %)
3–4	0 (0%)	3 (30 %)	3 12 %)
Number of steroid tapering attempts, median [IQR]	1.5 [1-2.5]	2.5 [1–3]	2 [1–3]
Pretreatment with steroids, median [IQR] days	97 [30.5–231]	20.5 [9.5–32]	35 [18–105]
Cause of death, n (%)			
Tumor disease	2 (100%)	3 (100 %)	5 (100 %)
Other	0 (0%)	0 (0 %)	0 (0 %)

ECP = Extracorporeal photopheresis, ICI = Immune checkpoint inhibitor, irAE = immune-related adverse event, IQR = Interquartile range, IVIG = Intravenous immunoglobulin, MMF = Mycophenolate mofetil, SLI = Second-line immunosuppression.
[a] Includes two patients with uveal melanoma.

Tumor response in the subgroup of patients with metastatic cutaneous melanoma was assessed during ECP and SLI therapy. Complete response was reported in 33 % vs. 0 %, partial response in 0 % vs. 0 %, stable disease in 33 % vs. 33 %, and progressive disease according to RECIST 1.1 occurred in 33 % vs. 67 % of patients receiving ECP *(n = 3)* vs. SLI *(n = 9)*), respectively (Fig. 2F). Cutaneous melanoma patients treated with ECP therapy showed a trend towards longer median PFS (6 vs. 3 months [IQR 6–14.5 vs. 1–12]; [95 % CI 0.08–1.88]; *P = 0.24, ns*) and median OS (23 vs. 12 months [IQR 14.5–23.5 vs. 7–14]; [95 % CI 0.02–3.02]; *P = 0.27, ns*) compared to those who received SLI (Fig. 2G). These results can only be interpreted once the full cohort of the study is evaluated. Importantly, no deaths occurred due to irAE or irAE-related therapies. In the ECP group, 36 % (4/11) of patients were treated in an adjuvant setting with recurrence-free survival between 18 and 41 months (median 24.5 months [IQR 21–30.5]).

In our study, 2 out of 11 ECP patients and 3 out of 10 SLI patients received an ICI-rechallenge with recurrence rates of 50.0 % (1/2) for the same irAE (irPancreatitis) in ECP vs. 33 % (1/3; irColitis) in SLI. Interestingly, irAE recurrence after ECP therapy (irPancreatitis) was manageable with steroids and easier to resolve than recurrence after SLI (irColitis) which again did not respond to steroids and thus again required second-line treatment for resolution.

ECP therapy showed an excellent safety profile, with fatigue being the only reported adverse event in 27 % (3/11) of treated patients. Until last follow-up, no infections related to immunosuppressants occurred in the SLI group.

3.2. Global health status and quality of life in patients with sr/sd-irAE

Global health status and QoL (GHS/QoL) improved in all patients during second-line therapy (Fig. 2H). Patients treated with ECP consistently demonstrated higher GHS/QoL scores than patients treated with SLI (mean 61 % (ECP) vs. 52 % (SLI) [SD 5.839]; *p = 0.03*).

3.3. Distinctly regulated immunophenotype in ECP- vs. SLI-treated patients

Immunophenotyping showed differential changes between the two groups with lower expression of LAG3 on CD4 + T cells at week 1 (Fig. 3A), reduced frequencies of activated CD8+ T cells by week 4, and higher frequencies of BDCA-classic dendritic cells (cDCs) and B cells by week 4 in the ECP group (Fig. 3B). CD8+ T_{SCM} were decreased by week 8 (Fig. 3C), and activated CD4+ T cell showed a decrease by week 12 (Fig. 3D). These changes could not be observed in SLI treated patients when compared to baseline.

In contrast, the SLI group exhibited significantly decreased expression of ICOS and CTLA4 on CD4+ T cells in week 1 compared to baseline (Fig. 3E), and downregulated TIM-3 on CD4+ T cells and CTLA4 on CD8+ T cells by week 4 (Fig. 3F). CD28 and TIM-3 on CD8+ T cells were decreased by week 8 (Fig. 3G). By week 12, there was significantly reduced expression of LAG3 and CTLA4 on CD4+ T cells, along with elevated CD86 expression on monocytes (Fig. 3H).

Overall, the ECP group exhibited a trend towards a reduction in immune cell populations including activated CD8 + T cells, CD8+ T_{SCM}, and activated CD4+ T cells. In contrast, the SLI group showed trends towards downregulation of immune checkpoints such as ICOS, CTLA4, TIM-3, CD28, TIM-3, and LAG3 (Fig. 3I).

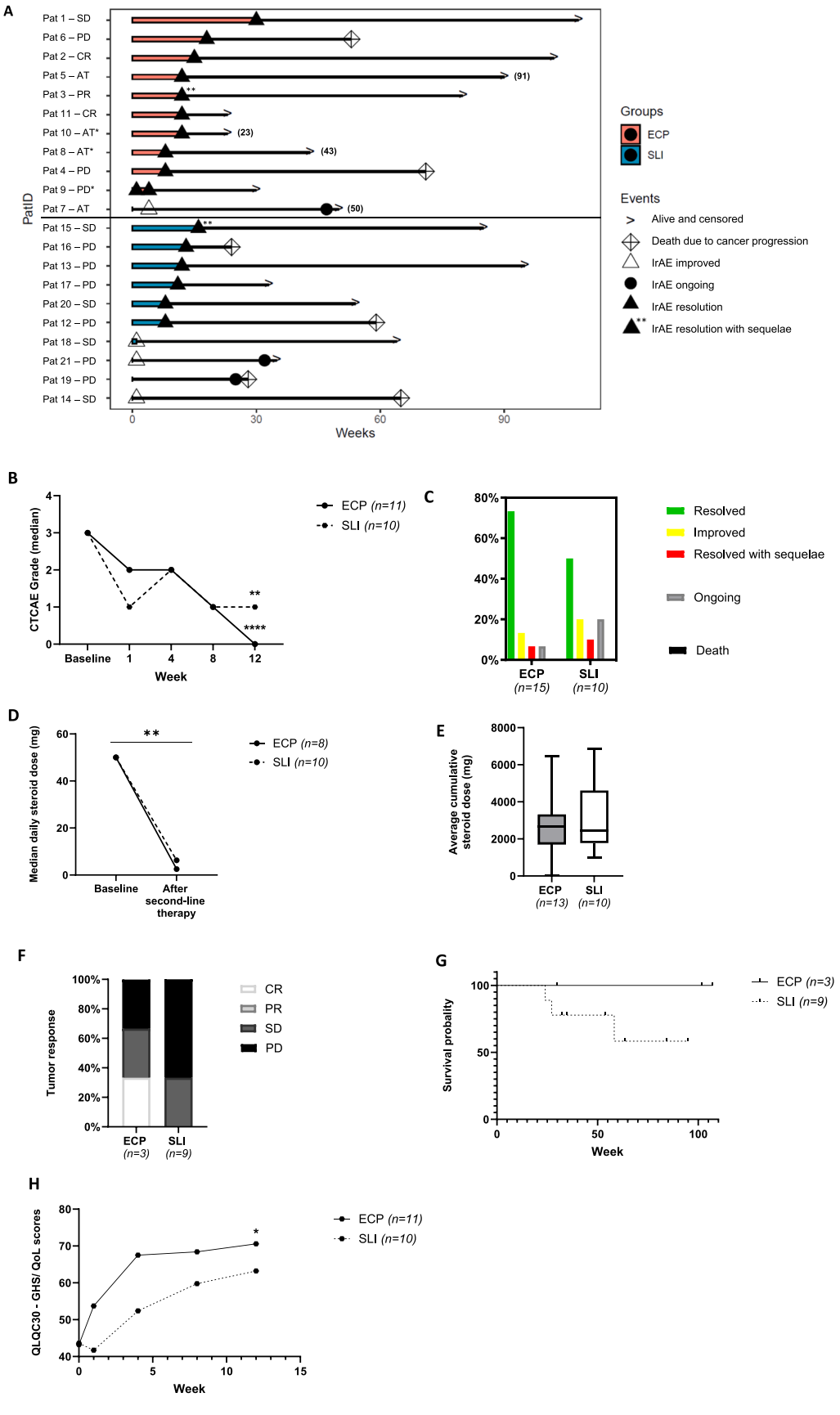

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Fig. 2. Overview of second-line therapy management and outcome. (A) Swimmer plot showing individual patient characteristics since initiation of second-line therapy including treatment type, time to irAE resolution and irAE outcome, as well as tumor outcome during second-line therapy, date of death or censorship. Each bar represents one patient in the study (n = 21). The recurrence-free survival (weeks) since the initiation of second-line therapy is indicated following each respective patient receiving adjuvant therapy. *Patient presented with two steroid-refractory (sr) or steroid-dependent (sd) immune-related adverse events (irAE). **sr/sd-irAE resolved with sequelae. (B) Severity of sr/sd-irAE (grade 1–5 CTCAE) (n = 25). Compared to baseline CTCAE grade, there was a significant reduction in CTCAE grade in ECP group *($p < 0.0001$, ****)* vs. SLI group *($P = 0.0034$, **)* after 12 weeks. (C) Outcome of sr/sd-irAE (n = 25). (D) Median prednisolone dose reduction during follow-up after initiation of second-line therapy in patients who were still receiving cortisone treatment at the start of second-line therapy (ECP: delta 48 mg/d (95 %), *$P = 0.0099$*, ** vs. SLI: delta 44 mg/d (88 %), *$P = 0.0014$*, **). (E) Average cumulative prednisolone dose for irAE treatment over time (ECP: 2638 mg vs. SLI: 3169 mg; calculation of estimated dosage according to steroid tapering schedule). Data was available for 92.0 % (23/25) of cases. (F) Tumor response in patients with metastatic cutaneous melanoma (AJCC stage IV) after initiation of second-line therapy (n = 12). (G) Survival of patients with metastatic cutaneous melanoma (AJCC stage IV) after initiation of second-line therapy. (H) Global health status and quality of life in patients with sr/sd-irAE as assessed by QLQ-C30. Compared to baseline, there was a significant improvement of GHS/QoL score in the ECP cohort *($P = 0.04$, *)*. CTCAE = Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0; ECP = Extracorporeal Photopheresis; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS = Global health status; irAE = immune-related adverse event; mg = milligram; QoL = Quality of life; sd = steroid-dependent; SLI = Second-line immunosuppression; sr = steroid-refractory.

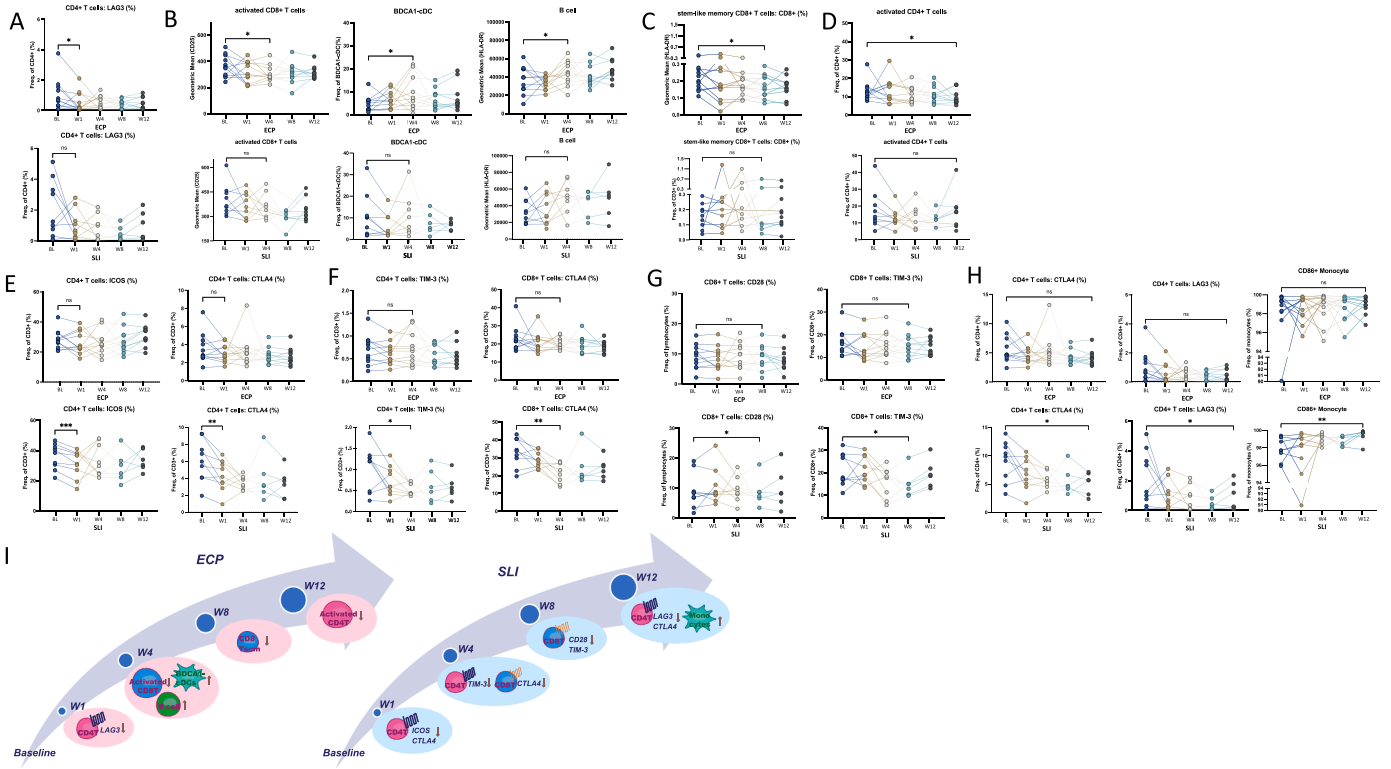

Fig. 3. PBMCs of patients treated with ECP (11 donors) or SLI (10 donors) were analyzed via flow cytometry. Frequencies of T cells, naïve T cells, T_{CM}, T_{SCM}, T_{EFF}, Treg cells in CD4+ and CD8+ T cells were investigated. The expression of activation markers (CD27, CD28, ICOS, CD107a, CD44) and exhaustion markers (CTLA4, TIM-3, TIGIT, LAG3), as well as the frequencies of BDCA1-cDC, MoDCs, B cells, NK cells, and monocytes were analyzed using FACS. (A) LAG3 expression on CD4+ T cells at specified time points is shown. Graph shows pooled data of 21 independent donors. (B) Line graphs showing the frequencies of BDCA1-cDC, the expression of CD25 on activated CD8+ T cells, and the expression of HLA-DR on B cells at the indicated time points across both treatment groups. (C) Line graph displaying the frequencies of T_{SCM} at the indicated time points across both treatment groups. (D) Line graph presenting the frequencies of activated CD4+ T cells at the indicated time points across both treatment groups. (E) Expression of ICOS and CTLA4 on CD4+ T cells is shown at the indicated time points across both treatment groups. (F) Expression of TIM-3 on CD4+ T cells, and CLTA4 on CD8+ T cell is presented at the indicated time points across both treatment groups. (G) Line graphs illustrating the expression of CD28 and TIM-3 on CD8+ T cells at the indicated time points across both treatment groups. (H) Line graphs showing the expression of CLTA4 and LAG3 on CD4+ T cells, and the frequencies of monocytes at the indicated time points across both treatment groups. (I) Overview of all the different immunophenotype regulation patterns derived by ECP and SLI. BDCA = Blood Dendritic Cell Antigen; CD = Cluster of Differentiation; cDC = classic dendritic cells; CTLA4 = cytotoxic T-lymphocyte–associated antigen 4; ECP = Extracorporeal Photopheresis; FACS = Fluorescence-activated Cell Sorting; ICOS=Inducible co-stimulatory molecule; LAG3 = Lymphocyte activation gene 3; MoDC = Monocyte-derived dendritic cell; NK cell = Natural killer cell; PBMC = Peripheral Blood Mononuclear Cell; SLI = Second-line immunosuppression; T_{CM} = central memory T cell; T_{EFF} = effector activated T cell; TIGIT = T cell immunoreceptor with immunoglobulin and ITIM domain; TIM-3 = T-cell immunoglobulin and mucin domain-3; T_{SCM} = stem-like memory T cell.

4. Discussion

The interim results of the first prospective two-arm study comparing ECP to SLI indicate that ECP is safe and has at least comparable efficacy to SLI in managing sr/sd-irAE. ECP favorably impacts QoL and is more effective in reducing the cumulative dose of steroids compared to SLI while maintaining tumor response. ECP thus emerges as a novel therapeutic approach for sr/sd-irAE.

Infliximab and vedolizumab [33] have been successfully applied for irColitis [23,29] but infliximab only showed a 30 % response rate in 13 patients with sr/sd-Colitis [34]. JAK inhibitors with effectiveness in GvHD (NCT03112603 [35]) also represent a potential treatment option

for sr/sd-irAE [36]. However, immunosuppressants are associated with various side effects, including organ toxicities, severe infections, and impairment of anti-tumor response in melanoma, lung cancer, and genitourinary cancer [13,33].

We successfully treated sr/sd-irAE with ECP, with an irAE response rate of 93 % and a median time to resolution of 12 weeks as well as reduced corticosteroid need compared to SLI. This corresponds to an easier corticosteroid taper with ECP in 88 % of patients with a median reduction of 95 % of the initial steroid dose. ECP patients had fewer attempts in steroid tapering, despite the considerably longer duration of corticosteroid pretreatment before study inclusion. These findings are consistent with the favorable results in GvHD where ECP showed promising clinical responses and a steroid-sparing effect [26].

ECP can spare immunosuppressants used for irAE therapy, thereby potentially improving tumor outcomes as its immunomodulatory effects have been shown to preserve anti-tumor effects [27]. In our cohort, ECP-treated patients demonstrated a tendency towards a higher rate of complete cancer remission and a lower rate of cancer progression during second-line therapy with a trend towards a longer OS and PFS.

Moreover, the safety profile of ECP was excellent in our ECP group with no notable side effects like prospective ECP studies that have focused on the safety (NCT05414552, NCT06074874).

Persistent irAE significantly reduce the QoL of cancer patients [37]. Consistent with our findings, a retrospective study investigating the impact of ECP on QoL in patients with mycosis fungoides or GvHD found significant improvements in the dermatology life quality index (DLQI) ($P = 0.001$), particularly in feelings, daily/social activities ($P < 0.05$), and functionality ($P \leq 0.05$) [38]. A case report of a patient with therapy-resistant atopic dermatitis who documented his QoL for more than 15 years indicated long-term QoL improvement with ECP [39].

During ECP, leukocytes exposed to psoralen and UVA undergo apoptosis resulting in a reduced production of pro-inflammatory cytokines, including IL-6, and an increased secretion of anti-inflammatory cytokines [8]. ECP enhances Treg function and activated MDSCs, while maintaining both, the quantity and quality of anti-tumor cells [8,24,26]. Another phase I/II open-label clinical trial (NCT04940299), combining ipilimumab, nivolumab and the IL-6R blocker tocilizumab for the treatment of metastatic melanoma, showed that tocilizumab could reduce irAE while enhancing ICI-efficacy [40,41]. In our study, B cell subsets and DCs increased, while activated CD8+ and CD4+ T cells, as well as CD8+ T_{SCM} in the ECP group decreased. Altogether, these immunophenotypic changes in patients receiving ECP therapy may have contributed to the positive irAE response observed. Therefore, ICOS, CTLA4, TIM-3, CD28, and LAG3 could potentially serve as markers for a favorable irAE response.

Limitations of this study include the small cohort size, with ECP patients being more often in the adjuvant therapy setting. The study population was very heterogeneous, presenting with different organ toxicities and various tumor entities. The assignment to treatment based on the instrumental variable of location of the patients' residence may have impacted the results, but instrumental variables provide a valid and robust solution when the intervention is not randomly assigned [42], if the instrument is independent of the confounder and does not affect outcome. However, unfortunately in this case it did not lead to balanced cohorts with respect to tumor stages and with the ECP cohort showing higher pretreatment steroid doses while the SLI cohort had more advanced tumor stages. This could have influenced the differential treatment effect and thus have biased the results. Additionally, the open-label application of the therapy could have introduced a bias, since in ECP studies sham application is not feasible. In complex cases with several symptomatic therapies, it can be challenging to determine which intervention led to irAE resolution. We strongly recommend expanding the cohorts in order to achieve a more balanced distribution among the two groups, ensuring greater comparability and robustness in the study's findings.

Nonetheless, ECP could be especially helpful for complex irAE, such as irSerositis, which are characterized by multiple frustrating treatment attempts [43]. All 3 patients with irSerositis treated with ECP in combination with IVIGs responded positively, whereas a previous case series reported no case of resolution of irSerositis treated with other second-line therapies [43].

We believe that ECP therapy expands the options for sr/sd-irAE treatment. It is safe, effective, and increases QoL.

5. Conclusion

ECP represents a novel therapy option for complex and/or severe irAE without being detrimental for tumor control. This prospective study revealed that ECP therapy, compared to second-line immunosuppressive drugs, led to better response rates of sr/sd-irAE with better long-term outcome and differentially regulated immunophenotypes. Furthermore, ECP was associated with an excellent safety profile and overall improvement in patients' quality of life. We plan a multicenter study to further investigate the therapeutic potential of ECP as a second-line treatment for irAE.

CRediT authorship contribution statement

Enrico N. de Toni: Writing – review & editing, Validation. **Peter Bonczkowitz:** Writing – review & editing, Validation, Investigation. **Canan Kabakci:** Writing – review & editing, Validation, Investigation. **Xiomara Garza Vazquez:** Writing – review & editing, Validation, Data curation. **Theresa Ruf:** Writing – review & editing, Validation, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Jérôme Srour:** Writing – review & editing, Validation. **Carolin Ertl:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Richard David-Rus:** Writing – review & editing, Visualization, Validation. **Dirk Tomsitz:** Writing – review & editing, Validation. **Christina Schmitt:** Writing – review & editing, Validation, Data curation. **Ying Wang:** Writing – review & editing, Visualization, Formal analysis, Data curation. **Lucie Heinzerling:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ignazio Piseddu:** Writing – review & editing, Validation, Investigation, Data curation. **Lars E. French:** Writing – review & editing, Validation. **Linda Hammann:** Writing – review & editing, Validation, Investigation, Data curation.

Ethics approval

The study (ClinicalTrials.gov: NCT05700565) was conducted in accordance with the Declaration of Helsinki after obtaining ethics approval from the institutional review board of the medical faculty of the LMU Munich (Project-Nr. 21-0874) and written informed consent of each patient.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: LH received speaker and consultancy fees from BiomeDx, BMS, Kyowa Kirin, Merck, MSD, Myoncare, Novartis, Pierre-Fabre, Roche, Sanofi, SUN and Therakos. The LMU received research grants or clinical study grants from Agenus, AstraZeneca Inc., BMS, Hoffmann-La Roche AG, Huya Bioscience, Immunocore, IO Biotech, Merck, Merck Sharp & Dome GmbH, Miltenyi Biomedicine GmbH, Novartis, Pfizer, Pierre Fabre, Regeneron, Replimune, and Sanofi Aventis. CE reports on speaker fees from BristolMyers Squibb, GSK, Immunocore, Kyowa Kirin, MSD. DT reports consultancy, speaker fees or travel grants: BMS, Roche, Novartis, Sanofi, Recordati, Kyowa Kirin, Sun Pharma and Pierre Fabre. EDT reports consultations for AstraZeneca, Bayer, BMS, EISAI, Eli Lilly & Co, MSD, Mallinckrodt, Omega, Pfizer, IPSEN, Terumo, and Roche and employment at Boehringer-Ingelheim. He reports reimbursement of meeting attendance fees and travel expenses from Arqule, Astrazeneca, BMS, Bayer, Celsion and Roche, and lecture honoraria from BMS and Falk. He has received third-party funding for scientific research from Arqule, AstraZeneca, BMS, Bayer, Eli Lilly, and IPSEN and Roche. IP reports reimbursement of travel expenses from Roche and received third-party funding for scientific research from Novartis. JS reports consultancy, speaker fees or travel grants: Derma2Go, Abbvie, Almirall, Novartis, La Roche Posay, BMS, Leo, UCB, Beiersdorf, Boehringer Ingelheim. LEF has served as consultant for Janssen, Leo Pharma, Eli Lilly, Almirall, Union Therapeutics, Regeneron, Novartis, Amgen, Abbvie, UCB, Biotest, Boehringer Ingelheim, InflaRx and Alys Pharmaceuticals. TR declared speaker's honoraria and travel grants from Therakos and SUN. CK, CS, LH, PB, RDR, YW, XGV have declared no conflicts of interest.

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Data sharing agreement

The datasets supporting the conclusions of this article are included within the article and its Supplemental file. Further enquiries can be directed to the corresponding author upon reasonable request (via email: lucie.heinzerling@med.uni-muenchen.de).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115049.

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