EUROPEAN HEMATOLOGY ASSOCIATION

EHA-TSH Hematology Tutorial

Clinical Case – Session 4 [Treatment approachs in R/R PTCL]

Speaker: Dr. Meral ULUKOYLU MENGUC

Ankara, Türkiye
June 30, 2024

Disclosure

- Turkish Society of Hematology (Transport ,Accomodation)

Clinical history

- 62 y ,female
- May 2021➔ Left cervical painful lumps.

- No response to antibiotherapy
- June 2021 ➔Pruritis emerged.
  Progressing cervical lumps
- She had B symptoms (fever and night sweats)
- History: Herpes zoster infection (a few months ago)
- Active smoker : 30 package / year

Physical examination

- ECOG performance score : 1
- Temperature: **38.8 ºC**
- Bilateral cervical 1 cm , axillary 0.5 cm sized lymphadenopathy
- Pulmonary sounds are reduced
- No palpable organomegaly

Laboratory

WBC	6.4 x 10^9/L (4-10)
Neutrophils	4.1 x 10^9/L (2-7)
Lymphocytes	0.9 x 10^9/L (0.9 – 4)
Hemoglobin	125 g/L (12-16)
Hematocrit	37 % (37-54)
Platelets	196 x 10^9/L (100 - 400)

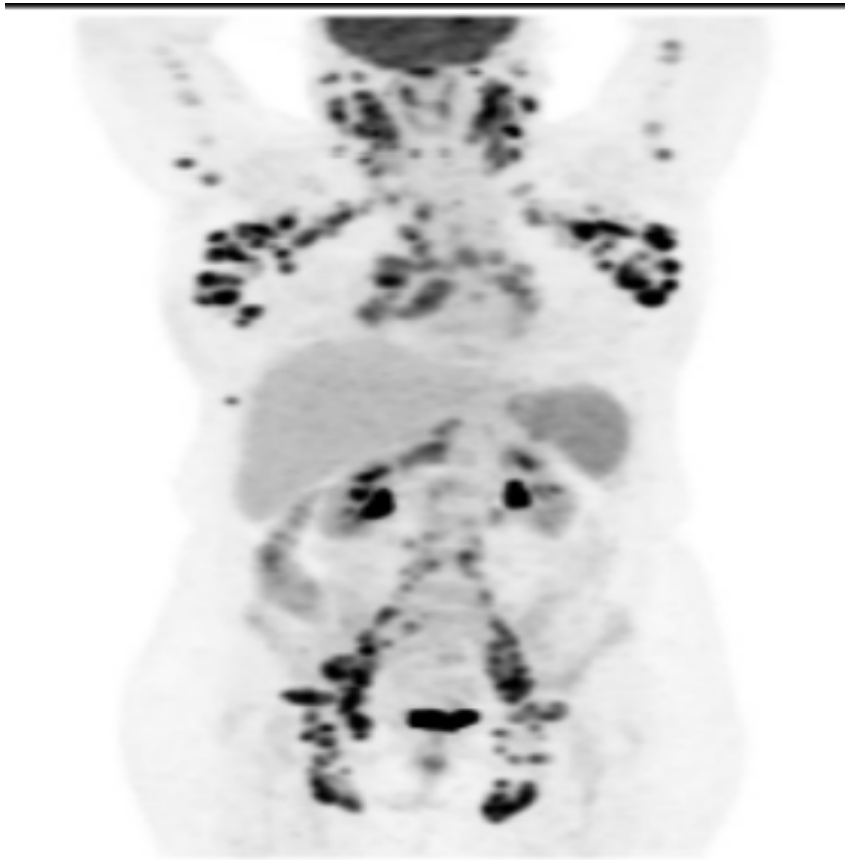
Peripheral smear	Normochromic normocytic erythrocytes, normal platelets , leukocytes showed mature neutrophile dominancy (72 %)

Blood ure nitrogen	10 mg / dl (6-23)
Creatinine	0.67 mg /dL (0-1.2)
AST	21 U / l (10-37)
ALT	13 U / l (10-40)
LDH	282 U / l (0-248)
Albumin	40 g / L (35-52)
Calcium	8.7 mg / dL (8.5 - 10.5)
Erythrocyte sedimentation rate (ESR)	8 mm / h (<10)

B12	200 ng/ L (200-600 pg/mL)
Folic acid	3.5mcg / L (> 3.9 mcg / L)
Transferrin saturation	19 %
Ferritin	34 mcg / L (12-150)

PET /CT (June 2021)

- Multiple lymph nodes largest diameter 24 x 19 mm (SUVmax 13.3) in the supra / infradiaphragmatic lymphatic stations ,
- 8 mm sized hypermetabolic soft tissue density lesion on the lateral side of the right 9th rib (SUV max 7.3) ,
- The liver/spleen metabolic activity ratio increased in favour of the spleen.
- Bilateral pleural effusion of 11 mm size with non-FDG uptake



Lymph node biopsy (June 2021)

- Small, medium and large-sized T lymphoid cells constitute 45-50% of the total population.
- T lymphoid cells are CD3 + , CD5 + , CD7 + BCL-6 + and the CD4 / CD8 ratio is 2 - 3 / 1 .
- CD30 staining was observed in 2-3% of the total population.
- Ki67 proliferation index is high in germinal centers. In other areas, it is up to 30-35%.

DIAGNOSIS: ATYPICAL T LYMPHOID PROLIFERATION,

PERIPHERAL T CELL LYMPHOMA ; NOS

Clinical history

- 06.08.21 Bone marrow biopsy : no infiltration
- ECHOCARDIOGRAPHY : Normal

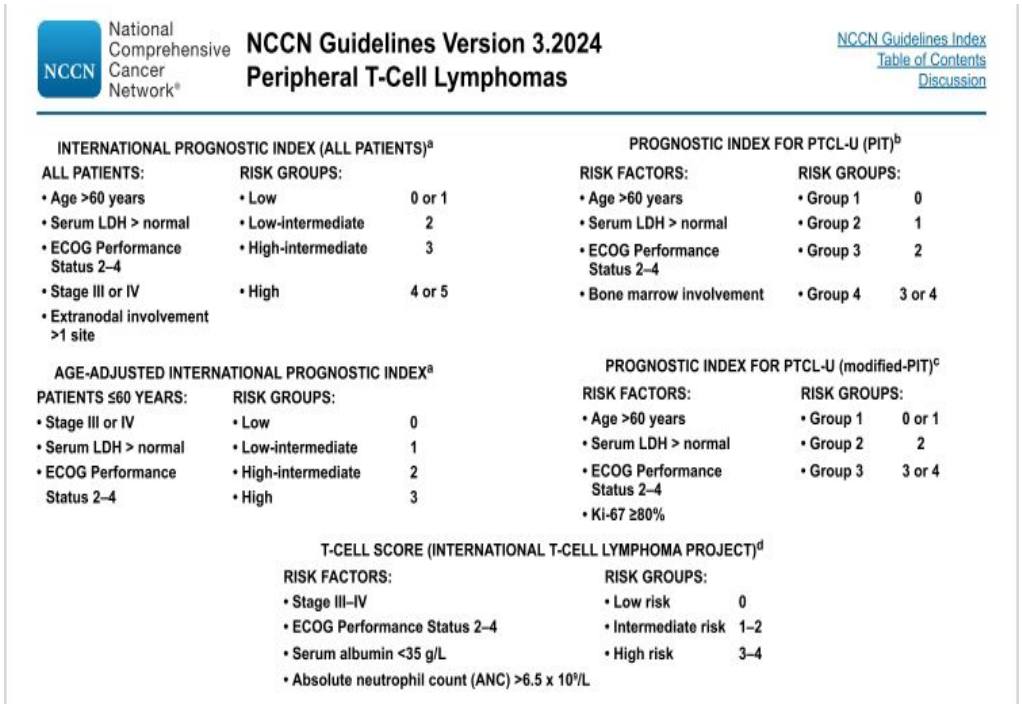
ANN-ARBOR STAGE III

IPI : 3 (HIGH – INTERMEDIATE)

PIT : 2 (Group 3))

Modified- PIT : 3 (Group 3)

T cell score : 2 (Intermediate risk)



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Peripheral T-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

INTERNATIONAL PROGNOSTIC INDEX (ALL PATIENTS)[a]

ALL PATIENTS:	RISK GROUPS:	
• Age >60 years	• Low	0 or 1
• Serum LDH > normal	• Low-intermediate	2
• ECOG Performance Status 2–4	• High-intermediate	3
• Stage III or IV	• High	4 or 5
• Extranodal involvement >1 site		

PROGNOSTIC INDEX FOR PTCL-U (PIT)[b]

RISK FACTORS:	RISK GROUPS:	
• Age >60 years	• Group 1	0
• Serum LDH > normal	• Group 2	1
• ECOG Performance Status 2–4	• Group 3	2
• Bone marrow involvement	• Group 4	3 or 4

AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX[a]

PATIENTS ≤60 YEARS:	RISK GROUPS:	
• Stage III or IV	• Low	0
• Serum LDH > normal	• Low-intermediate	1
• ECOG Performance Status 2–4	• High-intermediate	2
	• High	3

PROGNOSTIC INDEX FOR PTCL-U (modified-PIT)[c]

RISK FACTORS:	RISK GROUPS:	
• Age >60 years	• Group 1	0 or 1
• Serum LDH > normal	• Group 2	2
• ECOG Performance Status 2–4	• Group 3	3 or 4
• Ki-67 ≥80%		

T-CELL SCORE (INTERNATIONAL T-CELL LYMPHOMA PROJECT)[d]

RISK FACTORS:	RISK GROUPS:	
• Stage III–IV	• Low risk	0
• ECOG Performance Status 2–4	• Intermediate risk	1–2
• Serum albumin <35 g/L	• High risk	3–4
• Absolute neutrophil count (ANC) >6.5 x 10^9/L		

IPI= international prognostic index
PIT= prognostic index T cell lymphoma

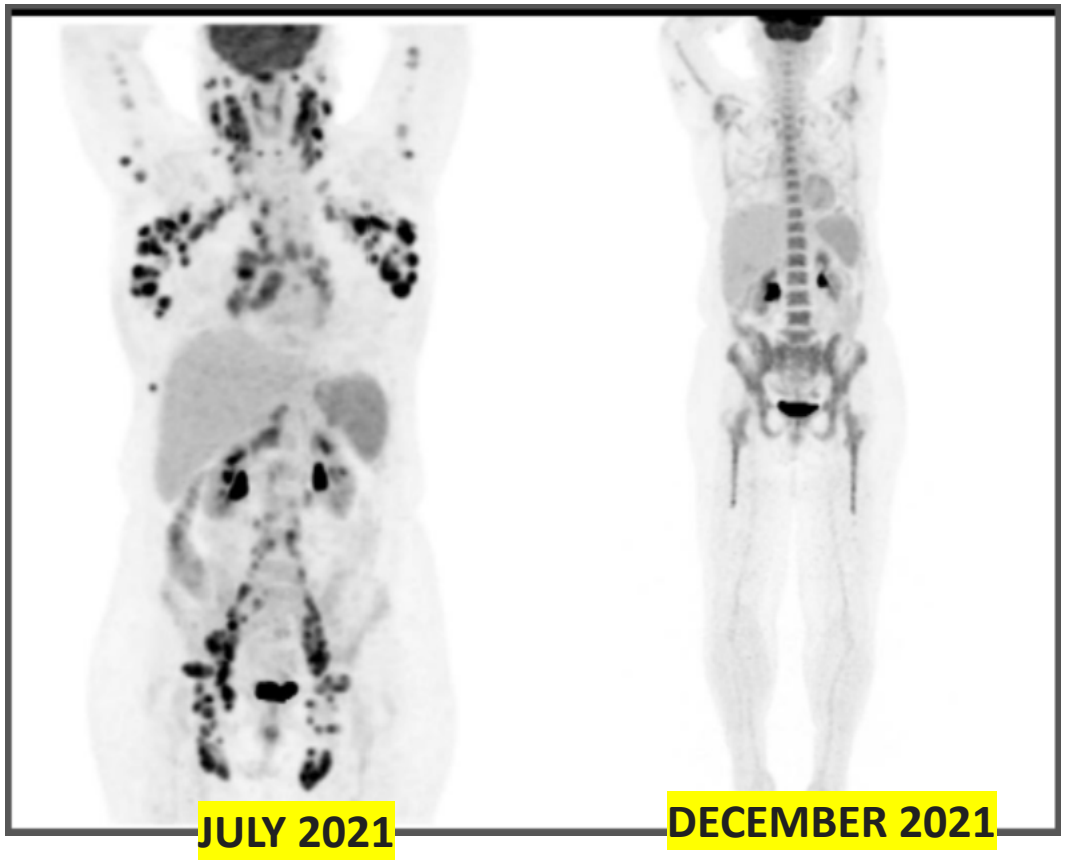
Jacobsen, E.D. (2013). Pharmacotherapy of peripheral T-cell lymphoma: review of the latest clinical data. *Clinical investigation, 3*, 665-679.

CHOP ± ASCT planned

- 10.08.2021 – CHOP (Cyclophosphamide 750 mg/m^2, doxorubicine 50 mg /m^2, vincristin 1.4 mg / m^2, methyl prednisolone 60 mg / m^2)

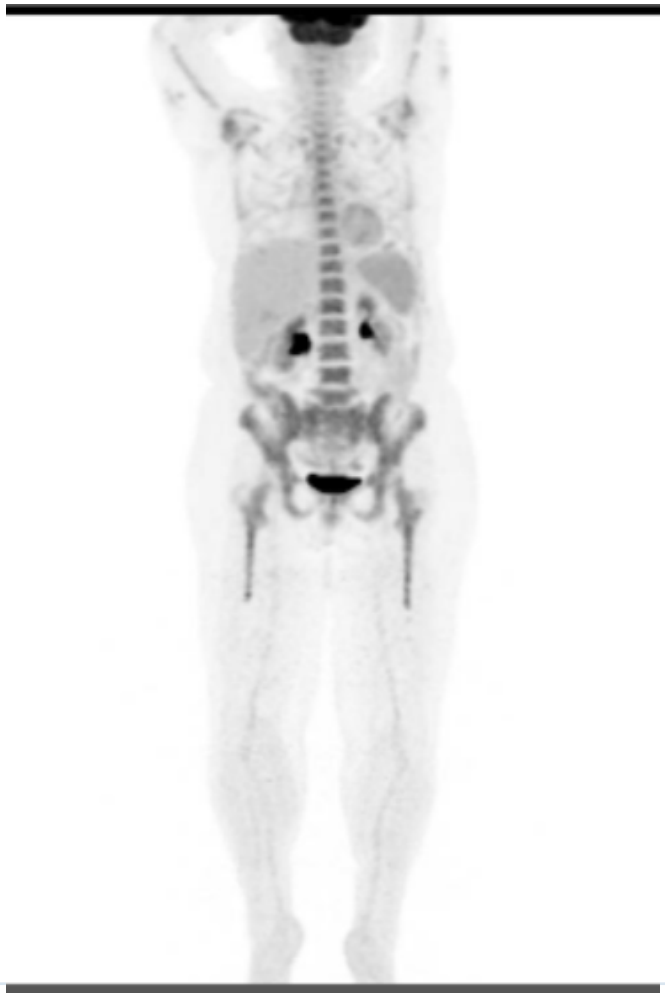
- Febrile neutropeni , pulmonary embolism
- Interim PET/ CT : CR
- 25.10. 21- Fever (No focus defined , moxifloxacin)

EOT PET/ CT:(December 2021)
Progression



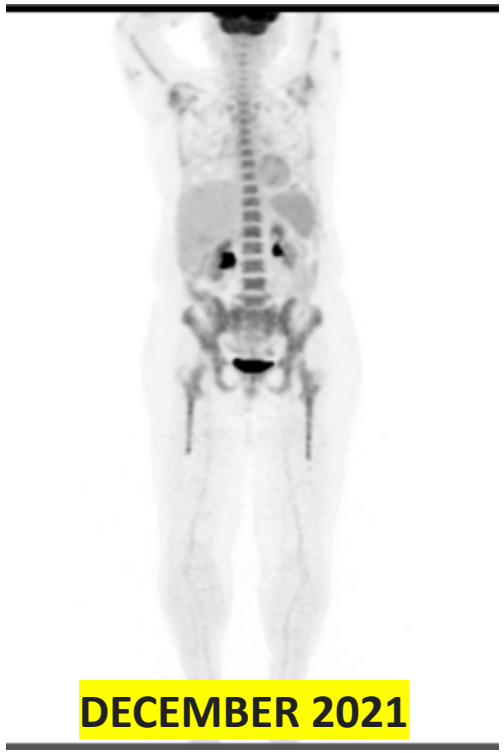
End of treatment PET /CT (December 2021)

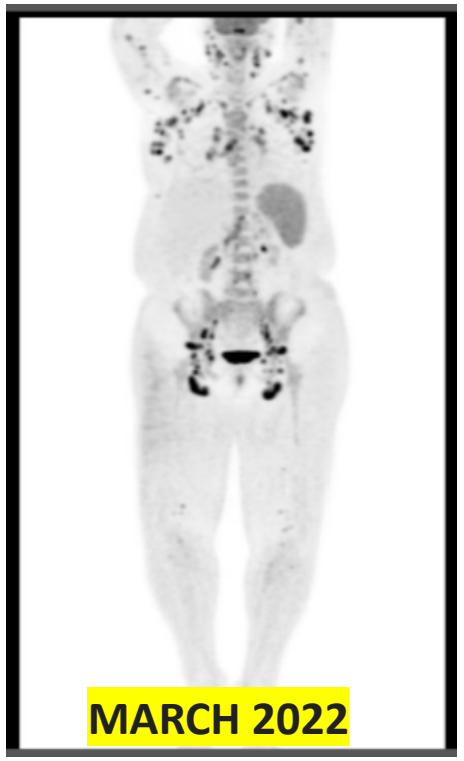
- Newly developed thickening area in the nasopharynx (SUVmax: 9.22)
- Increased metabolic activity of lymph nodes in lymphatic station 7 in the mediastinum and bilateral hilar/peribronchial area
- Increase in the size and metabolic activity (SUVmax 4.52) of the lymph nodes in the peripancreatic and interaortocaval area
- Hypermetabolic (SUVmax 2.32) nodular density areas observed in the subcutaneous fatty planes on the lateral sections of both arms and the anterior abdominal wall



Clinical history

- Nasopharynx bx: PTCL , NOS
- Skin bx: PTCL , NOS
- 03.02. 2022- ICE (Ifosfamid , carboplatin , etoposide),
- Available donor search ? autoSCT? DLCO: 52 %- Ineligible for SCT
- 19. 03. 2022- Hospitalisation due to pneumonia
- After 2 cycles ICE →30. 03. 2022 PET –**Progression**

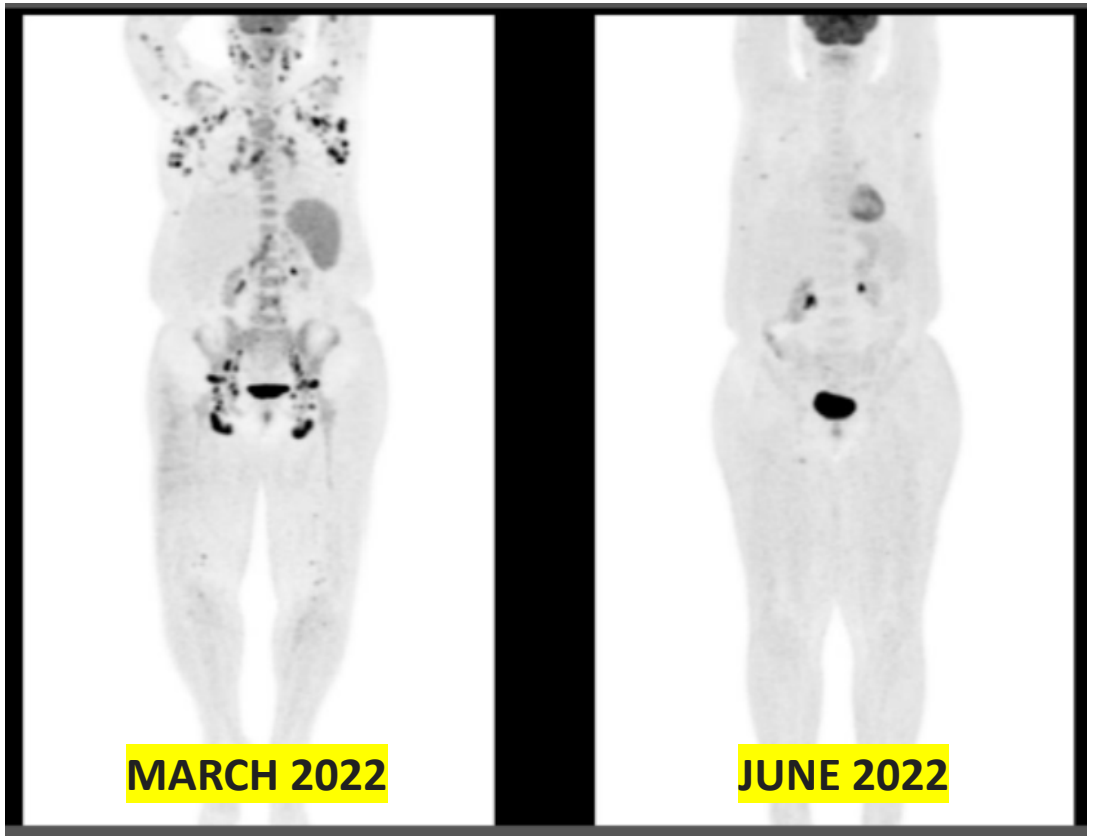




Clinical history

- 20. 04. 2022-Brentuximab (Bv)
- Hypercalcemia: 12.5 mg/dl-→ hospitalization

- PET/ CT (2 X Bv) June 2022: Regression
- No available sibling donor , MUD search continued
- New skin lesion; punch biopsy

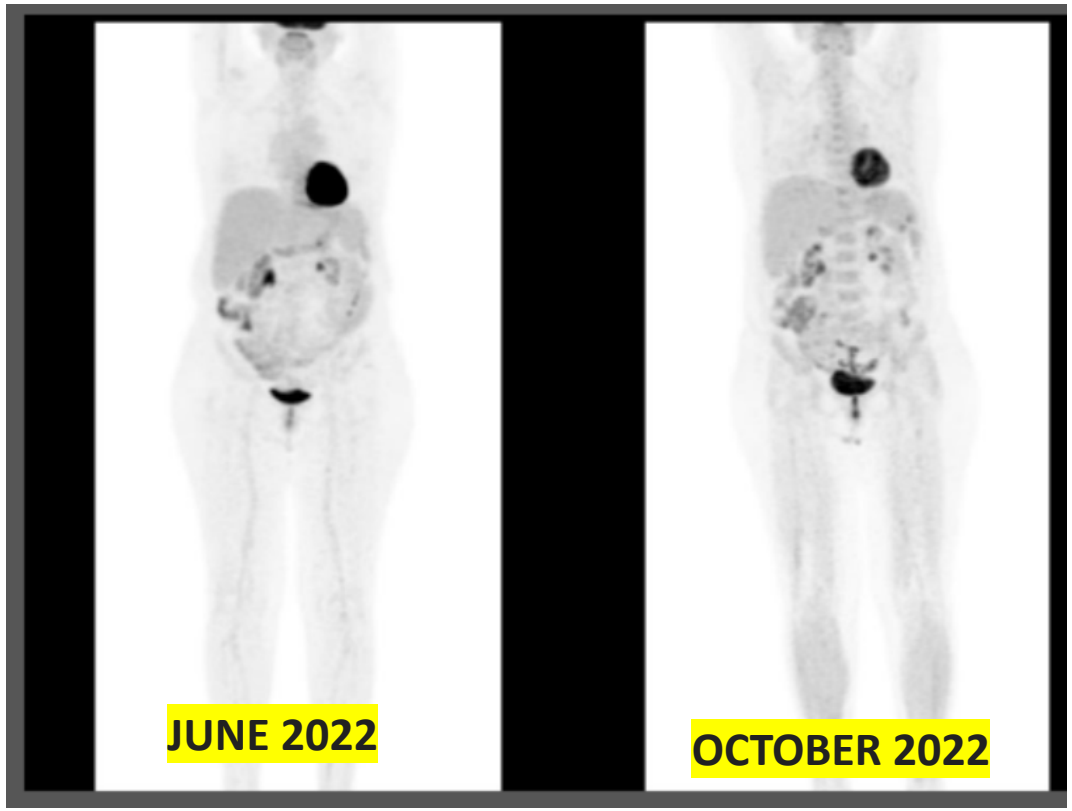


SKIN BIOPSY (13.07.22)

- CD2 weak + , CD3 + ,CD5 weak + , CD7 + ,CD4 + , CD8 - , CD20 –
- DIAGNOSE: PTCL , NOS

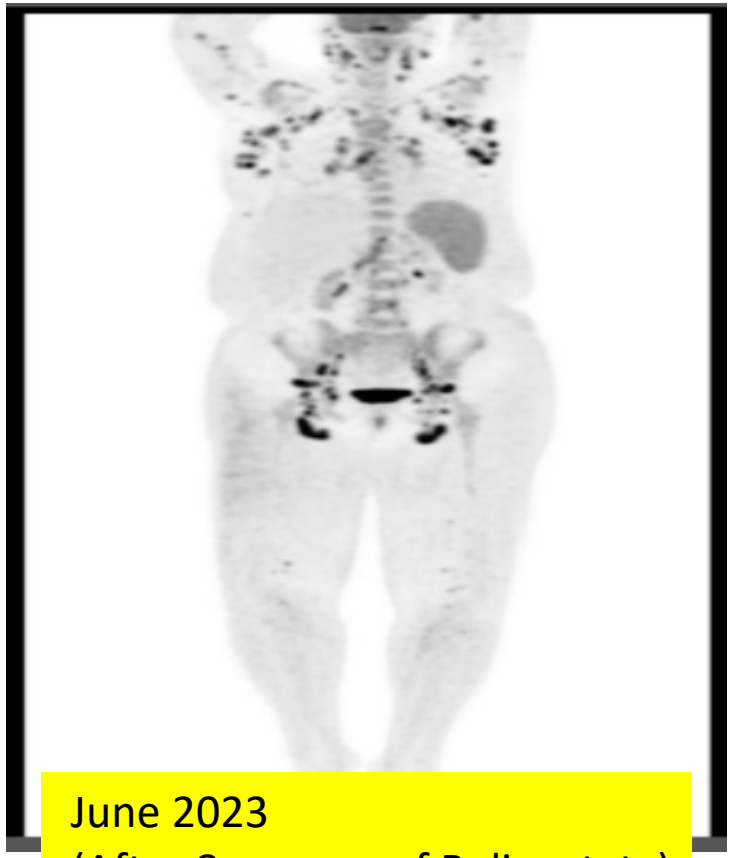
Clinical history

- 23.08.22- Belinostat
- End of 2nd course PET/ CT (05.10.22) – Regression skin lesions improved
- After 3th course ; Covid infection
- No available donor for allo-tx



Clinical History

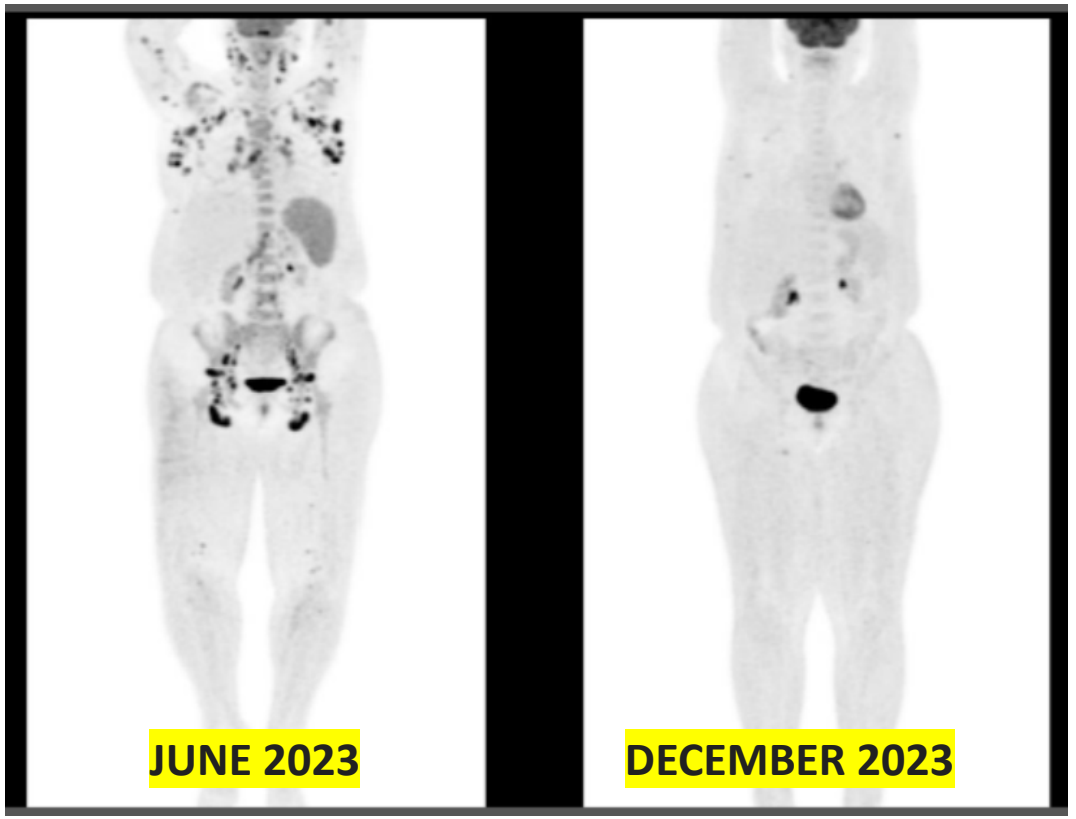
- 24.02.23 Itchy rash all over the body, swelling of the feet
- PHYSICAL EXAMINATION: maculopapular rash on both arms; derma consult – skin biopsy
- 27.03.23 - 8th course Belinostat
- 24.02.23 - Skin punch biopsy result: Atypical T lymphoid proliferation (Findings support T-cell lymphoid malignancy).
- PET-CT : Progression



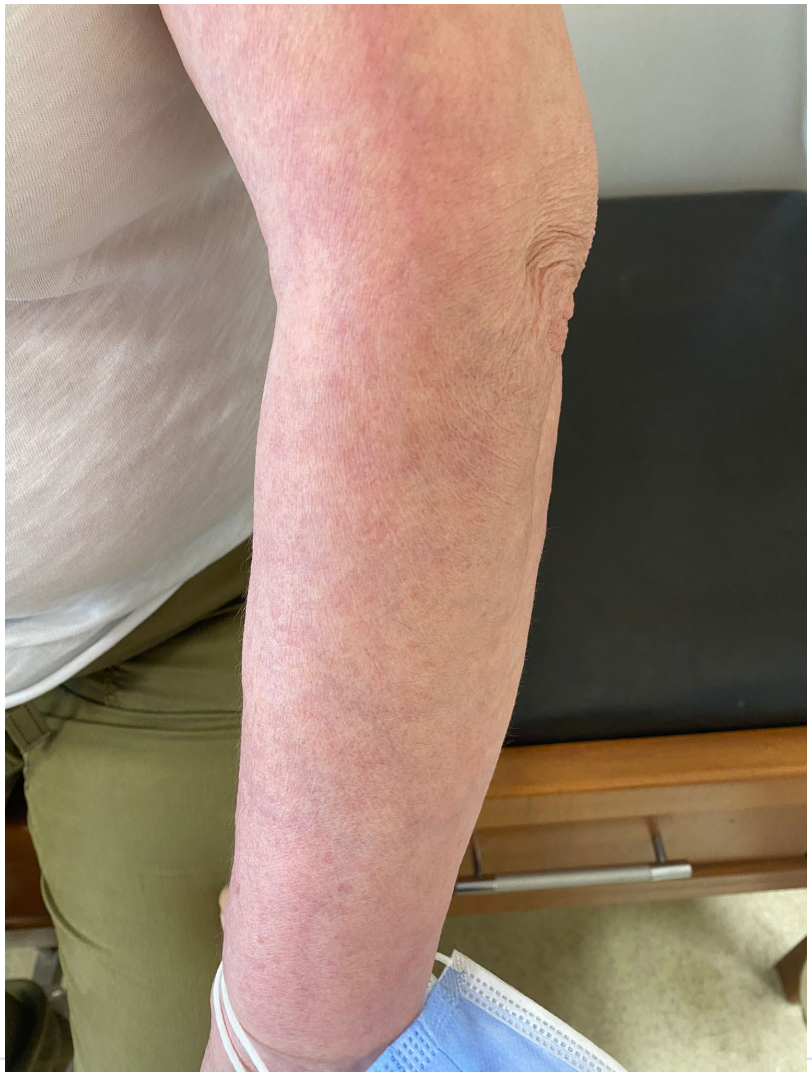
June 2023
(After 8 courses of Belinostat)

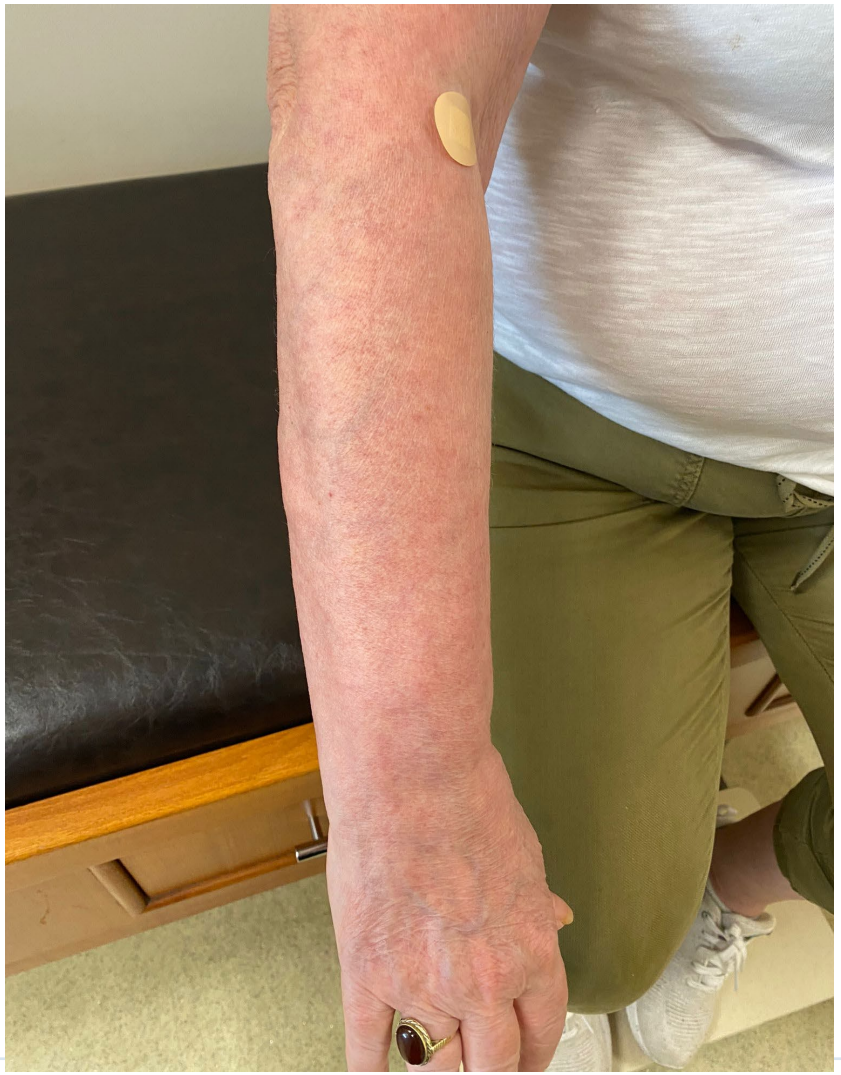
Clinical history

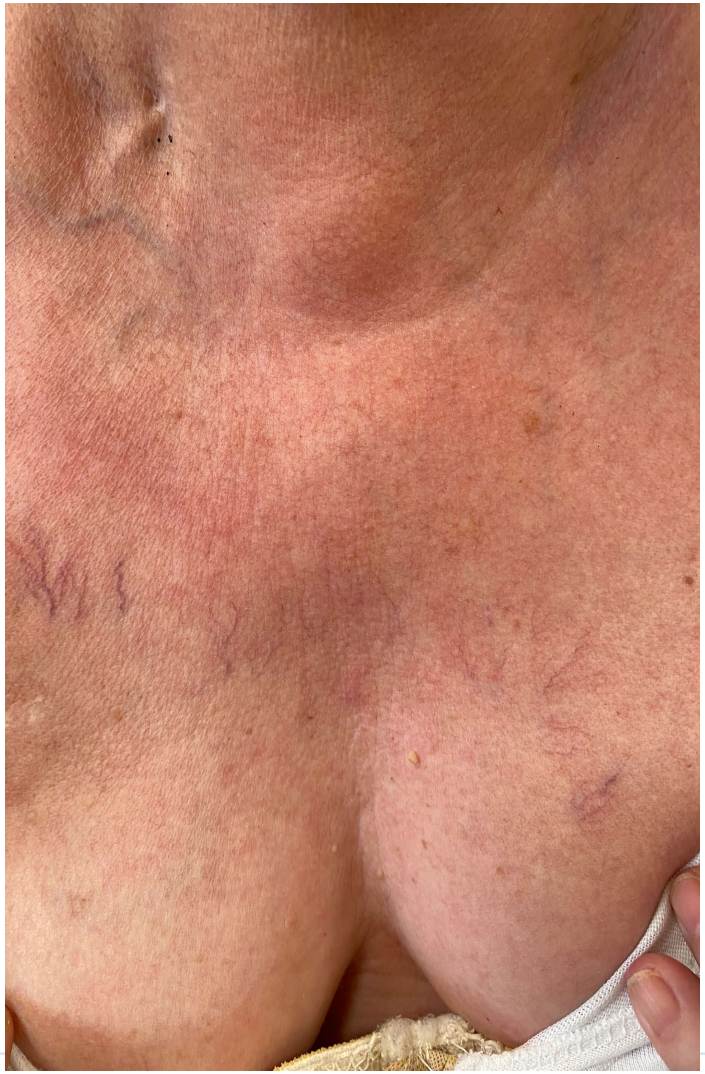
- 15.06.23 –Gemcitabine-oxaliplatin (Gem-ox) commenced
- 14.08.23 – 2nd course Gem-ox
- 06.09.23- PET : Partial response
- 16.11.23 –Gem-ox 4th cycle
- 15.12.23 PET /CT partial response , failure of stem cell mobilisation
- Follow up without therapy-patient's preference
- 27.06.24 – Last visit ; asymptomatic with macular rash on upper extremities



Last visit 27.06.24







Pictures are provided with the patient's consent

REFERENCES

- Stuver R, Moskowitz AJ. Therapeutic Advances in Relapsed and Refractory Peripheral T-Cell Lymphoma. Cancers (Basel). 2023 Jan 18;15(3):589. doi: 10.3390/cancers15030589. PMID: 36765544; PMCID: PMC9913081.
- Ngu HS, Savage KJ. Past, present and future therapeutic approaches in nodal peripheral T-cell lymphomas. haematol [Internet]. 2023Dec.1 [cited 2024May8];108(12):3211-26.
- Luan, Y., Li, X., Luan, Y. et al. Therapeutic challenges in peripheral T-cell lymphoma. Mol Cancer 23, 2 (2024). https://doi.org/10.1186/s12943-023-01904-w

DISCUSSION

- R/R PTCL ; Median PFS and OS is too short (3.7 months , 5.6 months)
- Primary refractory disease has poor outcomes compared to relapsed disease. (3 years PFS of 21 %)
- In the R / R setting best outcomes are measured in patients who had relapsed > 12 months and received SCT .

Monica Bellei et al.The outcome of peripheral T-cell lymphoma patients failing first-line therapy: a report from the prospective, International T-Cell Project. Haematologica 2018;103(7):1191-1197

Mak V, Hamm J, Chhanabhai M, et al. Survival of Patients With Peripheral T-Cell Lymphoma After First Relapse or Progression: Spectrum of Disease and Rare Long-Term Survivors. J Clin Oncol.

2013;31(16):1970-1976.

Biasoli I, Cesaretti M, Bellei M, et al. Dismal outcome of T-cell lymphoma patients failing first-line treatment: results of a population-based study from the Modena Cancer Registry. Hematol Oncol. 2015;33(3):147-151.

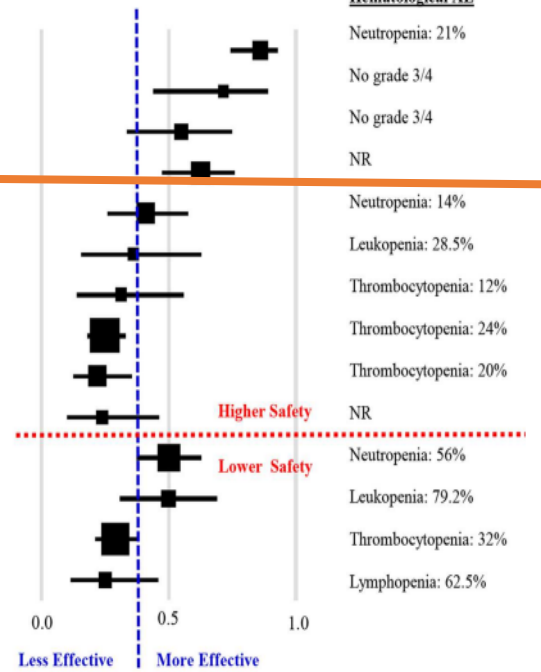
Management of R / R PTCL ,NOS

Chemotherapy	ORR (%)	CR (%)	mPFS (months)
GDP	69	19	4
Bendamustin	50	28	DOR 3.5
ICE	70	35	6
ESHAP	32	18	2.5

Mak et al. Clin Oncol. 2013; 31:1970–1976

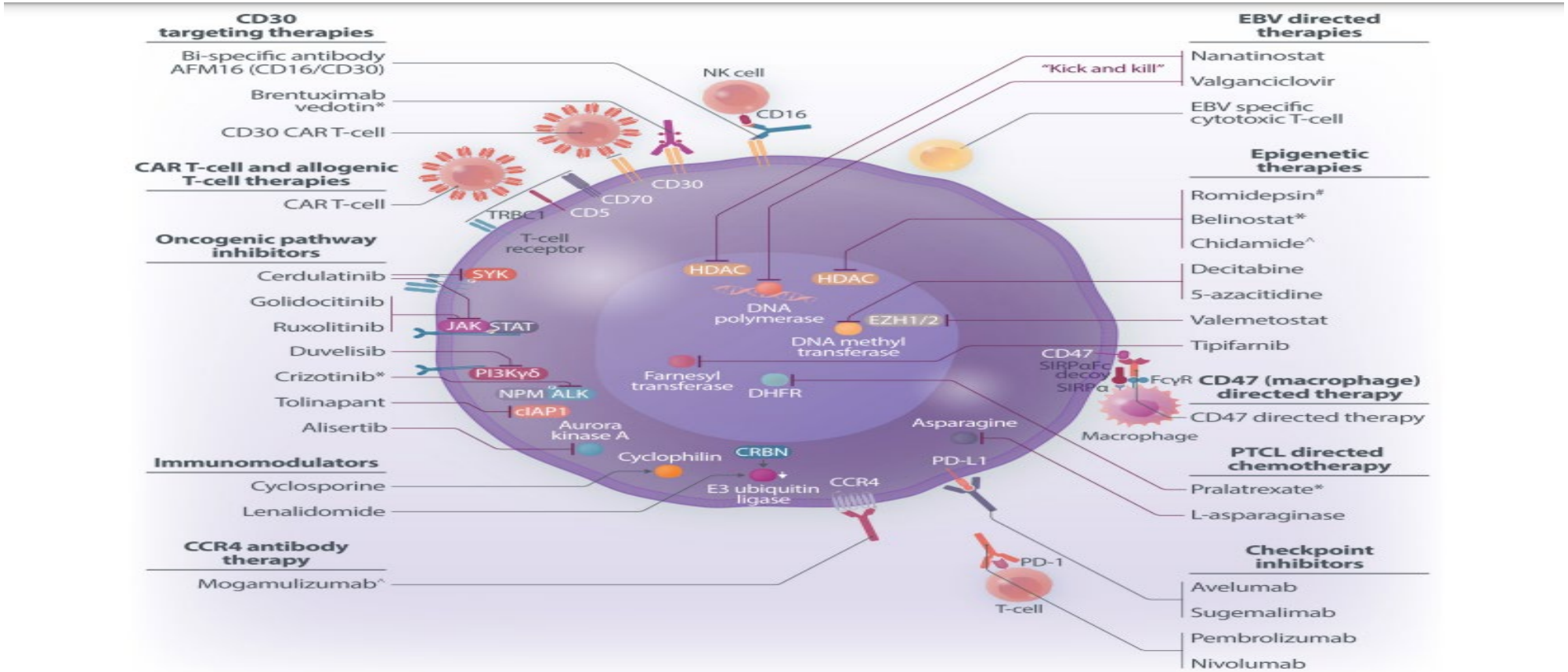
Salvage Therapy for Relapsed/Refractory PTCL

Study	Drug regimens	Study Design	N	Median age	Major PTCL subtype	Median no. of prior therapy	ORR	Most frequent Grade 3/4 Hematological AE
Pro et al. (2012)	Brentuximab vedotin	Phase II trial	58	52	ALCL	2	86%	Neutropenia: 21%
Zinzani et al. (2000)	Gemcitabine	Prospective study	14	58	PTCL-NOS	3	72%	No grade 3/4
Zinzani et al. (2010)	Gemcitabine	Prospective study	20	54	PTCL-NOS	3	55%	No grade 3/4
Zelenetz et al. (2003)	ICE	Prospective study	43	46	PTCL-NOS	NR	63%	NR
Horwitz et al. (2014)	Brentuximab vedotin	Phase II trial	35	64	PTCL-NOS	2	41%	Neutropenia: 14%
Enblad et al. (2004)	Alemtuzumab	Phase II trial	14	61	PTCL-NOS	2	36%	Leukopenia: 28.5%
Huang et al. (2002)	13-cRA+interferon-α	Phase II trial	17	47	PTCL-NOS	1	31%	Thrombocytopenia: 12%
Coiffier et al. (2012)	Romidepsin	Phase II trial	130	61	PTCL-NOS	2	25%	Thrombocytopenia: 24%
Morschhauser et al. (2013)	Lenalidomide	Phase II trial	51	65	AITL	3	22%	Thrombocytopenia: 20%
d'Amore et al. (2010)	Zanolimumab	Phase II trial	21	69	AITL	2	24%	NR
Damaj et al. (2013)	Bendamustine	Phase II trial	58	66	AITL	1	50%	Neutropenia: 56%
Seok et al. (2012)	A-DHAP	Phase II trial	24	49	PTCL-NOS	NR	50%	Leukopenia: 79.2%
O'Connor et al. (2011)	Pralatrexate	Phase II trial	109	58	PTCL-NOS	3	29%	Thrombocytopenia: 32%
Foss et al. (2015)	Belinostat	Phase II trial	24	64	PTCL-NOS	NR	25%	Lymphopenia: 62.5%



Yang YT et al .Highly Diverse Efficacy of Salvage Treatment Regimens for Relapsed or Refractory Peripheral T-Cell Lymphoma: A Systematic Review. PLoS One. 2016 Oct 6;11(10):e0161811.

Treatment Options

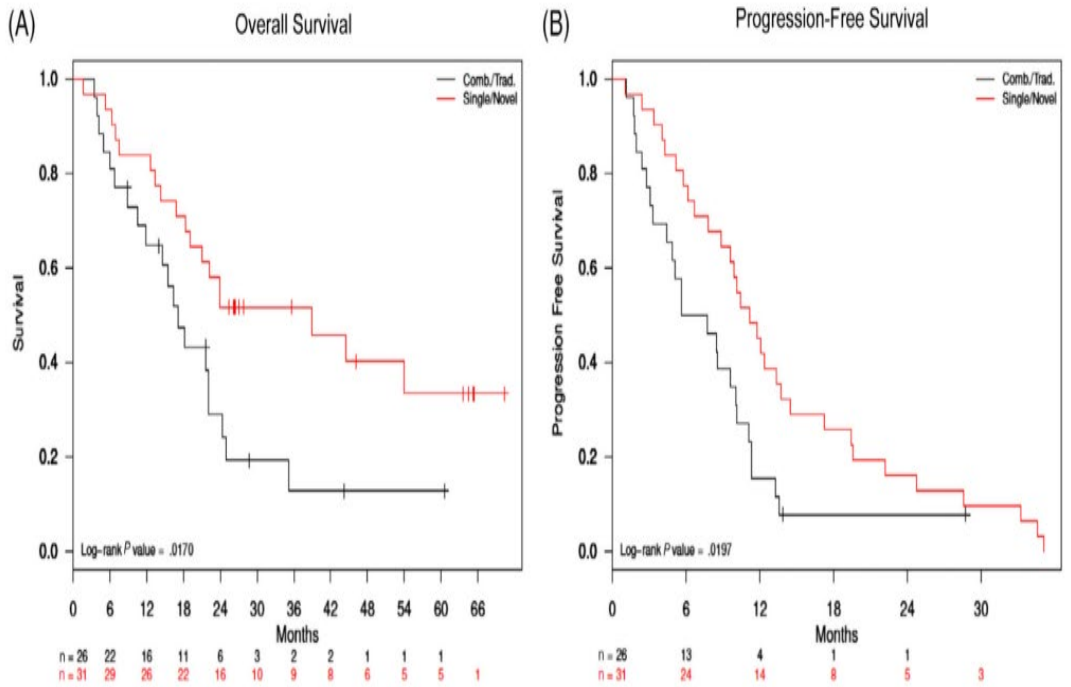


Savage KJ, De Leval L. Introduction to the peripheral T-cell lymphoma review series: advances in molecular characterization, classification refinement and treatment optimization. Haematologica. 2023 Dec 1;108(12):3204-3210.

Single agents improves survival compared to combination chemotherapy in R/R PTCL

Demographics performance status, and histopathological characteristics at

	Total (%)	Combination (26)	Single (31)	*P* value
Mean age (years) ± SD		50.8 ± 14.9	63.4 ± 13.1	.0014
Gender				
Female	19/57 (33.3)	6/26 (23.1)	13/31 (41.9)	.1325
Male	38/57 (66.7)	20/26 (76.9)	18/31 (58.1)	
ECOG performance status				
0–1	53/57 (93.0)	24/26 (92.3)	29/31 (93.5)	.8551
2	4/57 (7.0)	2/26 (7.7)	2/31(6.5)	
Number of extranodal sites				
<2	12/32 (37.5)	7/15 (46.7)	5/17(29.4)	.3144
2 or more align	20/32 (62.5)	8/15 (53.3)	12/17 (70.6)	
Serum LDH elevated IU/ml	24/57 (42.1)	10/26 (38.5)	14/31 (45.2)	.6099
IPI:				
0	3/57 (5.3)	2/26 (7.7)	1/31(3.2)	.3826
1	12/57 (21.1)	6/26 (23.1)	6/31(19.4)	
2	22/57 (38.6)	11/26 (42.3)	11/31 (35.5)	
3	16/57 (28.1)	7/26 (26.9)	9/31(29.0)	
4	4/57 (7.0)	0/26 (0.0)	4/31(12.9)	
PIT score				
Group 1	14/57 (24.6)	9/26 (34.6)	5/31(16.1)	.1728
Group 2	24/57 (42.1)	9/26 (34.6)	15/31 (48.4)	
Group 3	13/57 (22.8)	7/26 (26.9)	6/31(19.4)	
Group 4	6/57 (10.5)	1/26 (3.8)	5/31(16.1)	
Histo pathology				
ALCL-ALK−	7/57 (12.3)	0/26 (0.0)	7/31 (22.6)	.0600
ALCL-ALK+	3/57 (5.3)	3/26(11.5)	0/31 (0.0)	
AITL	11/57 (19.3)	6/26 (23.1)	5/31(16.1)	
EATL	3/57 (5.3)	1/26 (3.8)	2/31(6.5)	
HSTL	3/57 (5.3)	1/26 (3.8)	2/31(6.5)	
PTCL-NOS	22/57 (38.6)	10/26 (38.5)	13/31 (41.9)	



Stuver, R. N. et al. (2019). Single agents vs combination chemotherapy in relapsed and refractory peripheral T-cell lymphoma: Results from the comprehensive oncology measures for peripheral T-cell lymphoma treatment (COMPLETE) registry. *American journal of hematology*, *94*(6), 641–649.

Single agents in R/R PTCL *

DRUG	Patients (n)	ORR / CR	mDOR (months)	PFS (months)	OS (months)
Brentuximab (Horwitz et al.)	n:35 (PTCL,NOS 22) 77 % primary refractory	33 % / 14 %	7.6	Median 1.6	No data
Pralatrexate (O'Connor et al.)	n: 111 (PTCL ,NOS 53)	29 % / 11 %	10.1	Median 3.5	Median 14.5
Romidepsin (Coiffier et al.) m3rd line	n: 130 (PTCL,NOS 69)	29 % / 14 %	17	Median 4	11.3
Belinostat (O'Connor et al.) ≥1 line	n: 120 (PTCL,NOS 77)	26 % / 11 %	13.6	Median 1.6	Median 7.9

*: Available in Turkey

AlloSCT is favoured in primary refractory PTCL

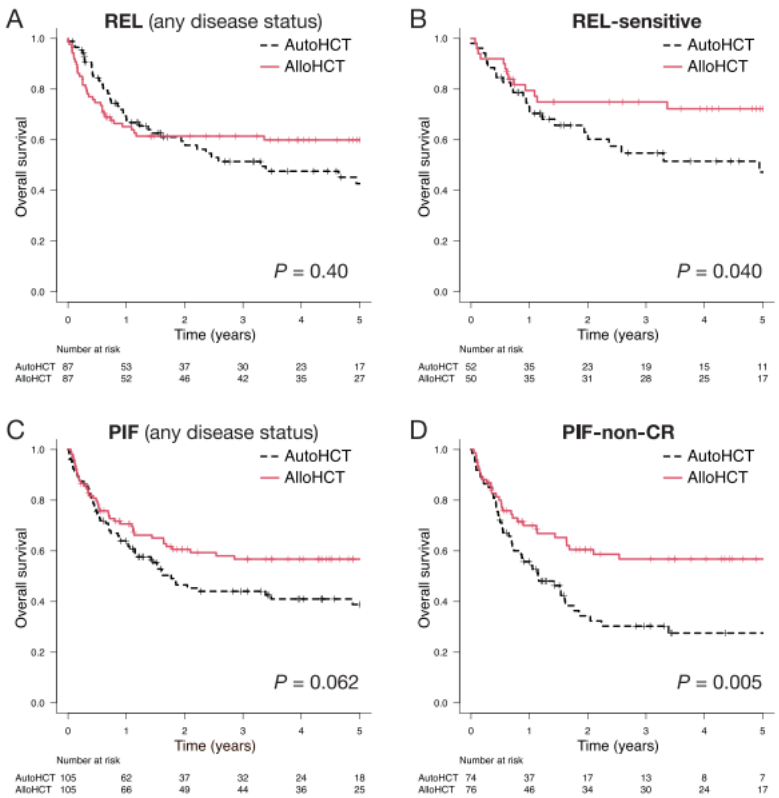


Fig. 4 Comparison of survival between auto- and alloHCT in the propensity-score-matched cohort. Overall survival in REL at any disease status (**A**), REL-sensitive (**B**), PIF at any disease status (**C**), and PIF-non-CR patients (**D**). HCT hematopoietic stem cell transplantation, autoHCT autologous HCT, alloHCT allogeneic HCT, REL relapsed after first complete remission, PIF primary induction failure, REL-sensitive complete, or partial remission at HCT in REL group, PIF-non-CR disease status other than complete remission at HCT in PIF group.

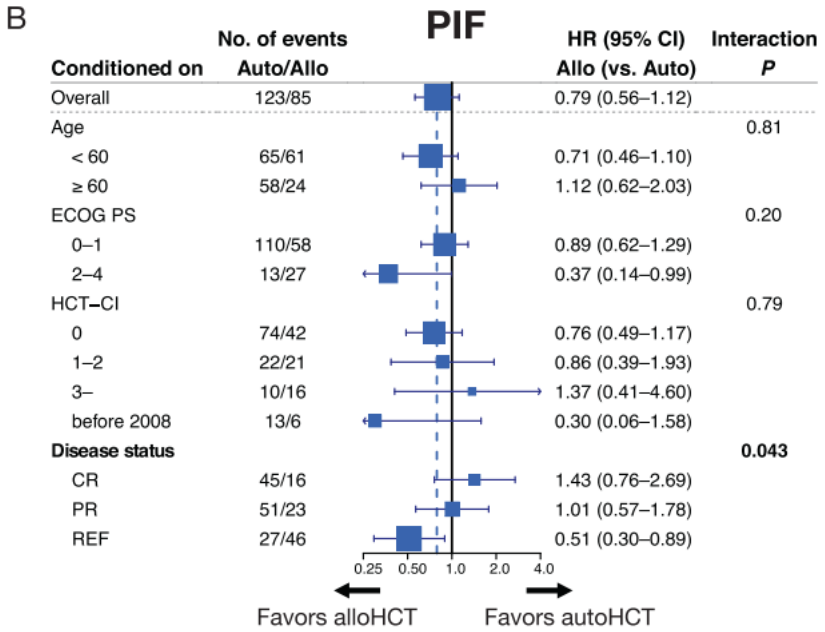


Fig. 3 Overall survival comparing alloHCT with autoHCT based on patients' characteristics in REL group (A) and PIF group (B). Vertical solid lines indicate HR 1.0, and dashed lines indicate HR in the overall cohort. HCT hematopoietic stem cell transplantation, autoHCT autologous HCT, alloHCT allogeneic HCT, REL relapsed after first complete remission, PIF primary induction failure, HR hazard ratio, 95% CI 95% confidence interval, ECOG PS Eastern Cooperative Oncology Group performance status, AITL angioimmunoblastic T-cell lymphoma, PTCL-NOS peripheral T-cell lymphoma not otherwise specified, CR complete remission, PR partial remission, REF refractory, HCT-CI HCT comorbidity index.

Kameda, K., Kako, S., Kim, SW. *et al.* Autologous or allogeneic hematopoietic cell transplantation for relapsed or refractory PTCL-NOS or AITL. *Leukemia* **36**, 1361–1370 (2022).

DISCUSSION

- In our patient CHOP followed by ASCT was planned as first line treatment
- She had progressive disease despite a CR in interim evaluation.
- Salvage with ICE chemotherapy which shows an ORR of 63% followed by allo-tx was selected due to refund regulations but she did not respond to ICE chemotherapy.
- Regarding her transplant ineligible condition due to decreased DLCO after pulmonary embolism , monotherapy of brentuximab ,belinostat , pralatrexate and romidepsin were all logical options at the second or further lines.
- Although she showed an initial response to brentuximab, in a short time she relapsed with a cutaneous involvement.

DISCUSSION

- Our patient received belinostat at the 4th line ; in that time point pralatrexate and romidepsin promised similar ORR. She had longest duration of response with Belinostat since her diagnosis but unfortunately progressed with cutaneous involvement as well as widespread lymphatic disease.
- Allogeneic transplant seems to be more efficient in the R/R setting with a higher toxicity profile compared to autotransplantation . Our patient was ineligible to both transplantation types due to lack of suitable donor and mobilisation failure of autologous stem cells.
- Regarding promising results of gemcitabine containing salvage data we preferred gemcitabin-oxaliplatin at the 5 th line due to limited access to novel agents.

Thanks…


Türk Hematoloji Derneği
56.Yıl
www.thd.org.tr
49. ULUSAL HEMATOLOJİ KONGRESİ
1-5 Kasım 2023 • Susesi Otel, ANTALYA
100
TÜRKİYE CUMHURİYETİ'NİN YÜZÜN