Ifosfamide and etoposide in advanced-stage, relapsed or refractory primary cutaneous T-cell lymphomas

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Context

Only **allogeneic hematopoietic stem cell transplantation (HSCT)** holds a potential **for cure** in advanced CTCL

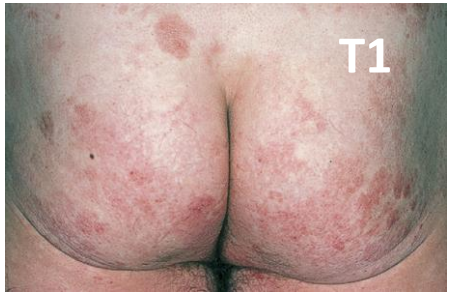
A **very good partial response** is needed for allogeneic HSCT success

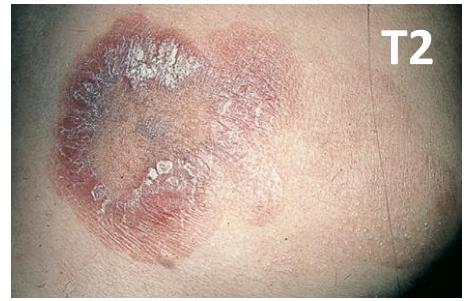
This is **difficult to achieve in advanced, especially transformed disease**

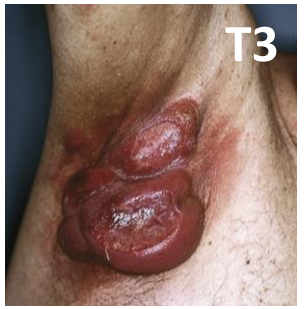
Monoclonal antibodies (alemtuzumab, mogamulizumab, lacutamab) are poorly effective in transformed disease

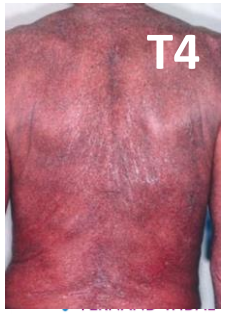
Objective

To evaluate **efficacy and tolerance** of the association of **etoposide (VP16) and ifosfamide** in relapsed and refractory CTCL

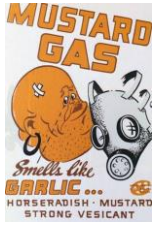






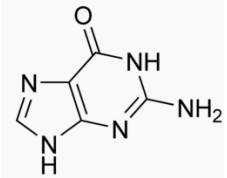


Ifosfamide



- Alkylating agent, nitrogen mustard
- **Toxicity**
  - Specific: hemorrhagic cystitis, encephalopathy
  - Common to chemotherapies: cytopenias, alopecia, nausea
- **Modalities:** IV 1000-1500mg/m^2/day over 3 consecutive days, every 3 weeks
- **Used in:** sarcoma, lymphoma

Etoposide/VP16



- Podophyllotoxin derivative, natural component of *Podophyllum peltatum* (perennial)
- Topoisomerase II inhibitor
- **Toxicity**
  - Common to chemotherapies
  - Bone marrow: cytopenias, secondary AML
- **Modalities:** IV 100 -150mg/m^2/day over 3 days
- **Used in:** MF (1975), lymphoma, lung cancer

=> Ifosfamide +Etoposide (I+E) has been used in Hodgkin lymphoma and PTCL

Material and methods

- Retrospective, monocentric study, Dermatology department at St Louis Hospital in Paris
- Inclusion criteria
  - MF or SS according to ISCL/EORTC criteria
  - Stage ≥ IIB and/or refractory to at least one line of systemic treatment
  - Having received at least one cycle of ifosfamide and etoposide between 01/2001 and 01/2020
- **Protocol:**
  - Full dose: ifosfamide 1500mg/m²/day + etoposide 100mg/m²/day x3 days, every 3 weeks

  - Low dose: ifosfamide 1500mg/m²/day + etoposide 300mg/m²/day x1 day, every 2 to 3 weeks

  + uromitexan, G-CSF in the full dose regimen

  Low dose used in older and/or heavily pretreated patients
- Endpoints: Overall response rate (ORR), ORR>4 months ($ORR_{4)}$, Time To Next Treatment (TTNT), Time to Progression (TTP), AE according to international criteria

Olsen EA, J Clin Oncol 2011; CTCAE version 5.0

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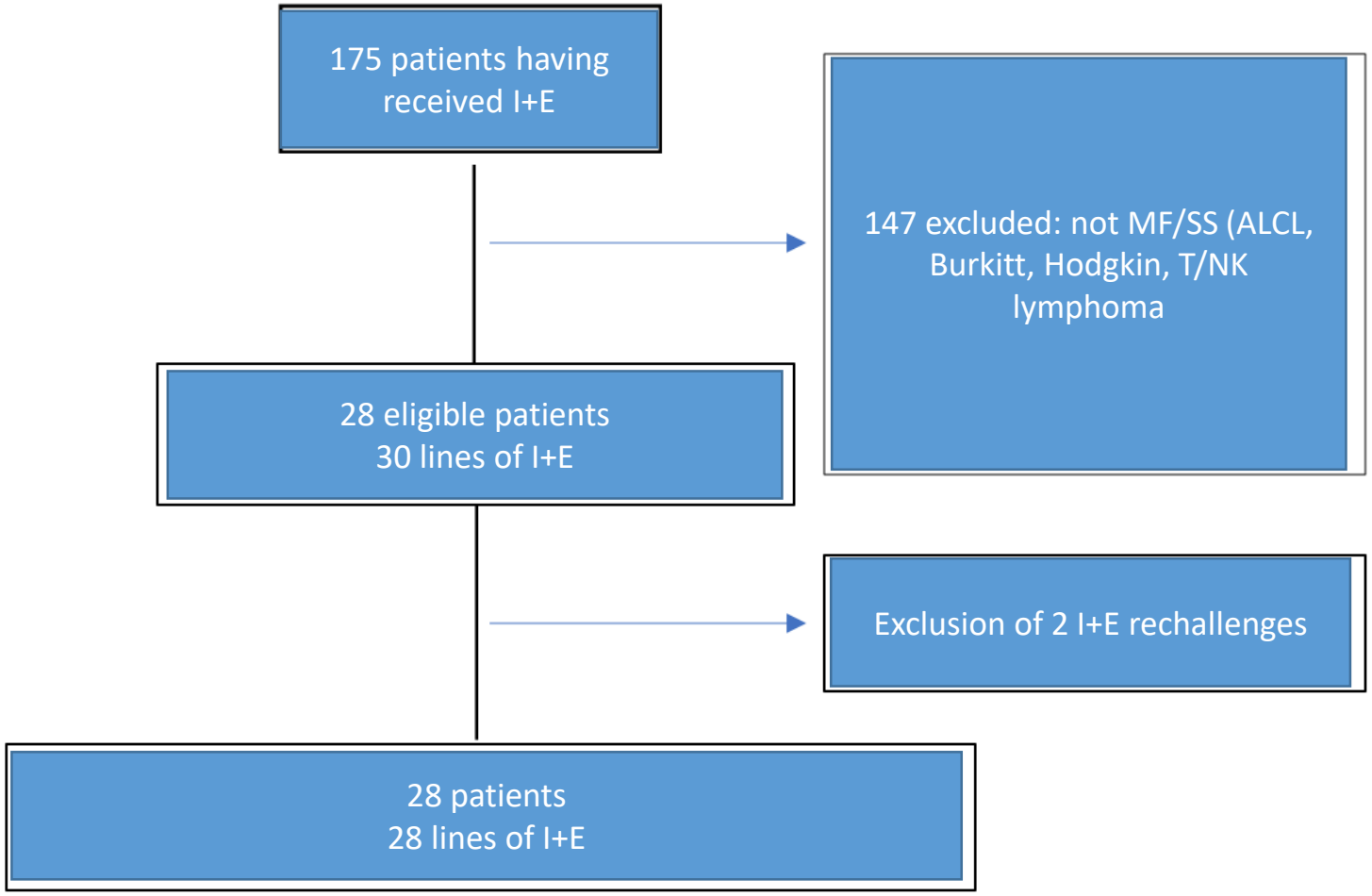
Flow chart



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Patients characteristics at I+E start (n=28)

Sex, n (%)	
Male	17 (61)
Age (years), median (range)	66 (23-88)
Diagnosis, n (%)	
Mycosis fungoides (MF)	15 (54)
- Classical MF	10 (36)
- Folliculotropic MF	5 (18)
Sézary syndrome (SS)	13 (48)
Large-cell transformation, n (%)	19 (68)
- Transformed MF	13 (46)
- Transformed SS	6 (21)
Number of systemic treatment lines before I+E, median (range)	6 (1-13)

Patients characteristics at I+E start (n=28)

Time from diagnosis to I+E treatment in years, median (range)	2.1 (0.4-14,2)
ISCL/ EORTC Stage, n (%)	
IB	1 (4)
IIB	8 (29)
IIIA	1 (4)
IVA1	9 (32)
IVA2	4 (14)
IVB	5 (18)
I+E treatment protocol, n (%) *	
Full dose Ifosfamide 1500mg/m^2 and Etoposide 100mg/m^2 3 days every 3 weeks	13 (46)
Low dose Ifosfamide 1500mg/m^2 and Etoposide 300mg/m^2 1 day every 2/3 weeks	15 (54)

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Systemic treatments before I+E, n (%)	
Bexarotene per os	25 (89)
Methotrexate	15 (54)
Interferon- α	5 (18)
Extraorporeal photopheresis	8 (29)
Gemcitabine	22 (79)
Pegylated liposomal doxorubicin	21 (75)
CHOP	5 (18)
HDAC inhibitors	6 (21)
Lacutamab (anti-KIR3DL2)	4 (14)
Mogamulizumab (anti-CCR4)	3 (11)
Brentuximab vedotin (anti-CD30-MMAE)	8 (29)

⇒ **100%** of patients (n=28) had received one line of chemo before I+E

⇒ **54%** of patients had received monoclonal antibodies

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Results

Primary endpoint

ORR (MF + SS) = **43%** (11 PR, 1 CR)

Secondary endpoints

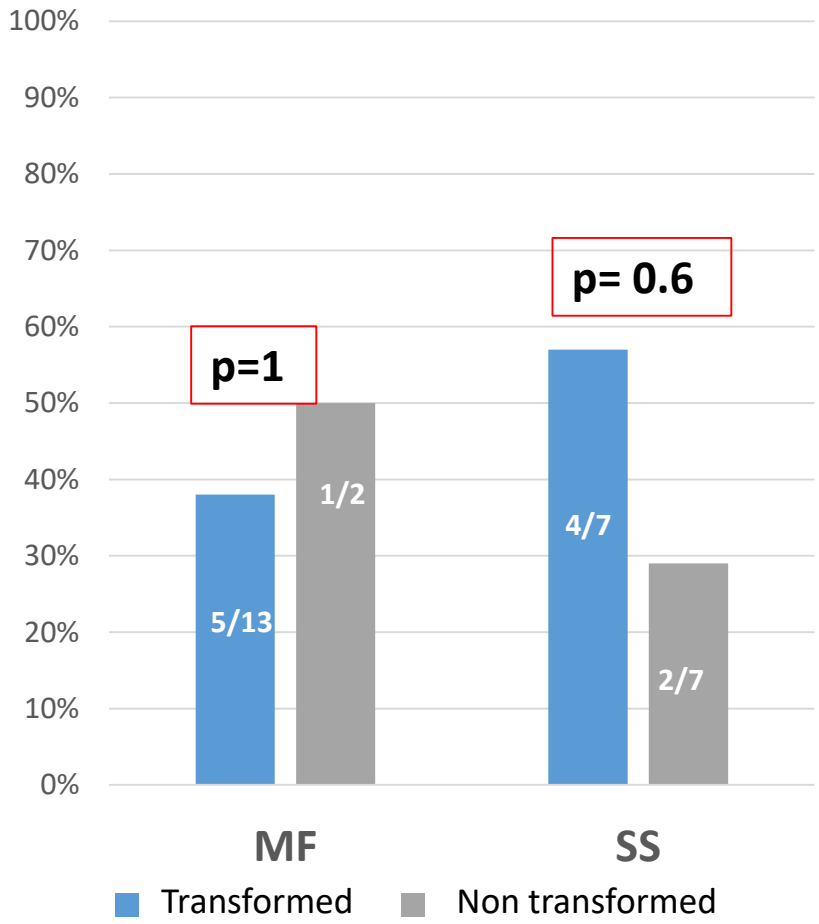
-Duration of response in responders: **8.7 months** (range 1-69+)

-Overall response rate >4 months: 11 patients = **38%** (ORR_4)

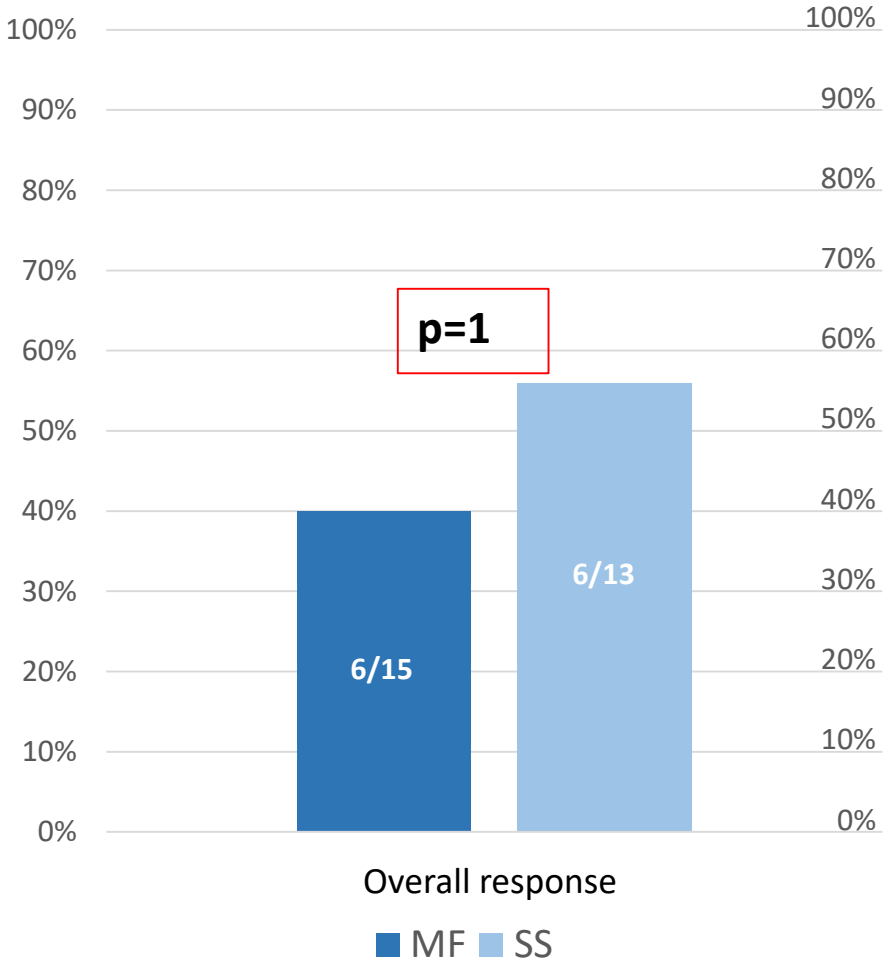
-Median time to response in responders: **34 days** (range, 15-56)

Results: ORR

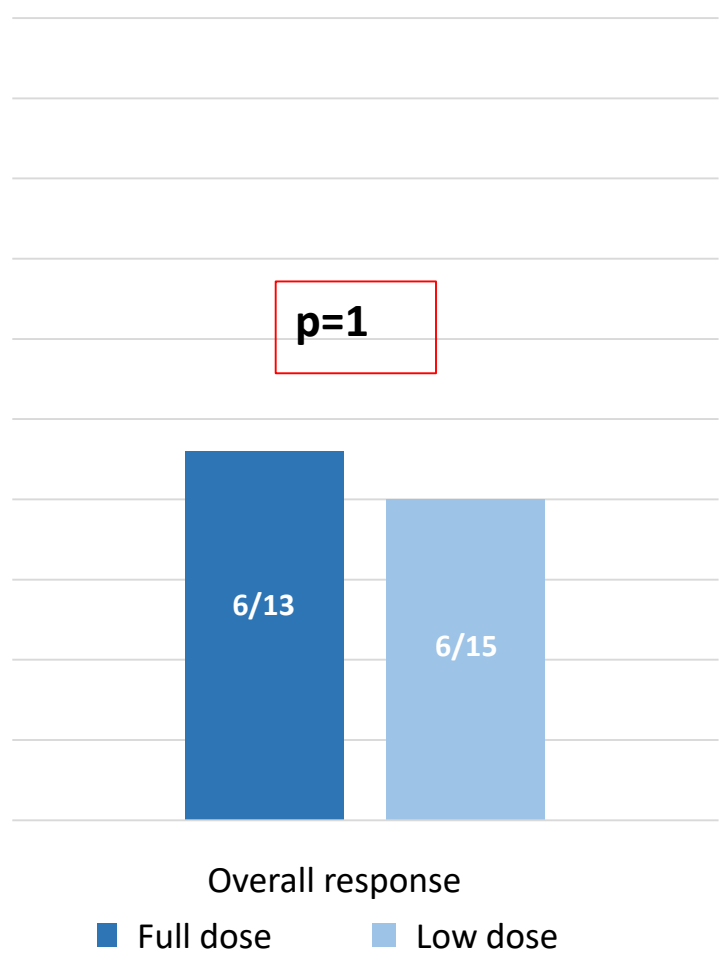
Transformed / non transformed



MF / SS



Full versus low dose



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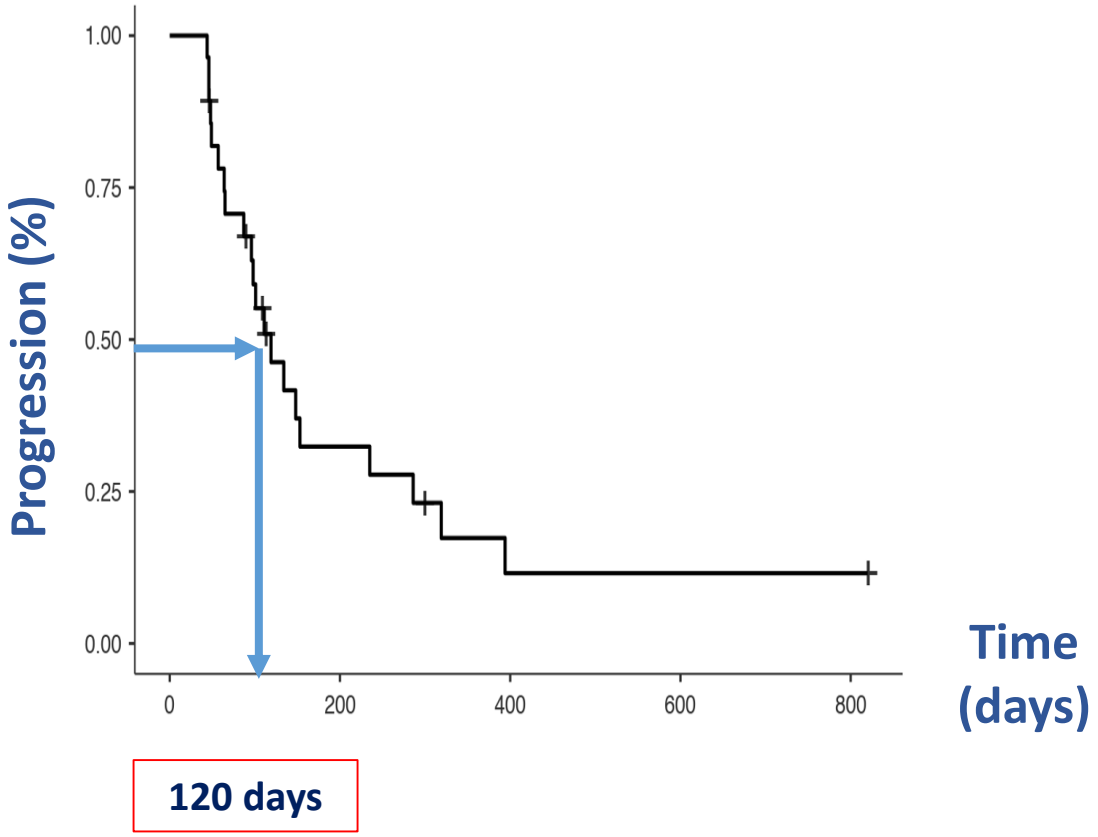
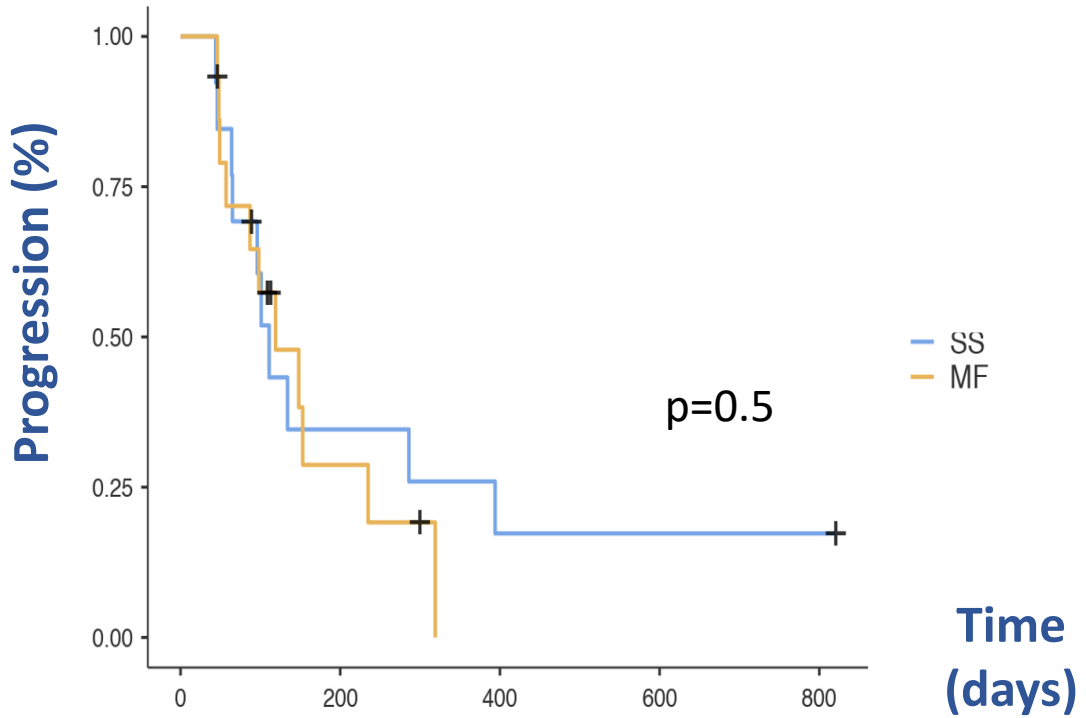
Median time to progression



120 days



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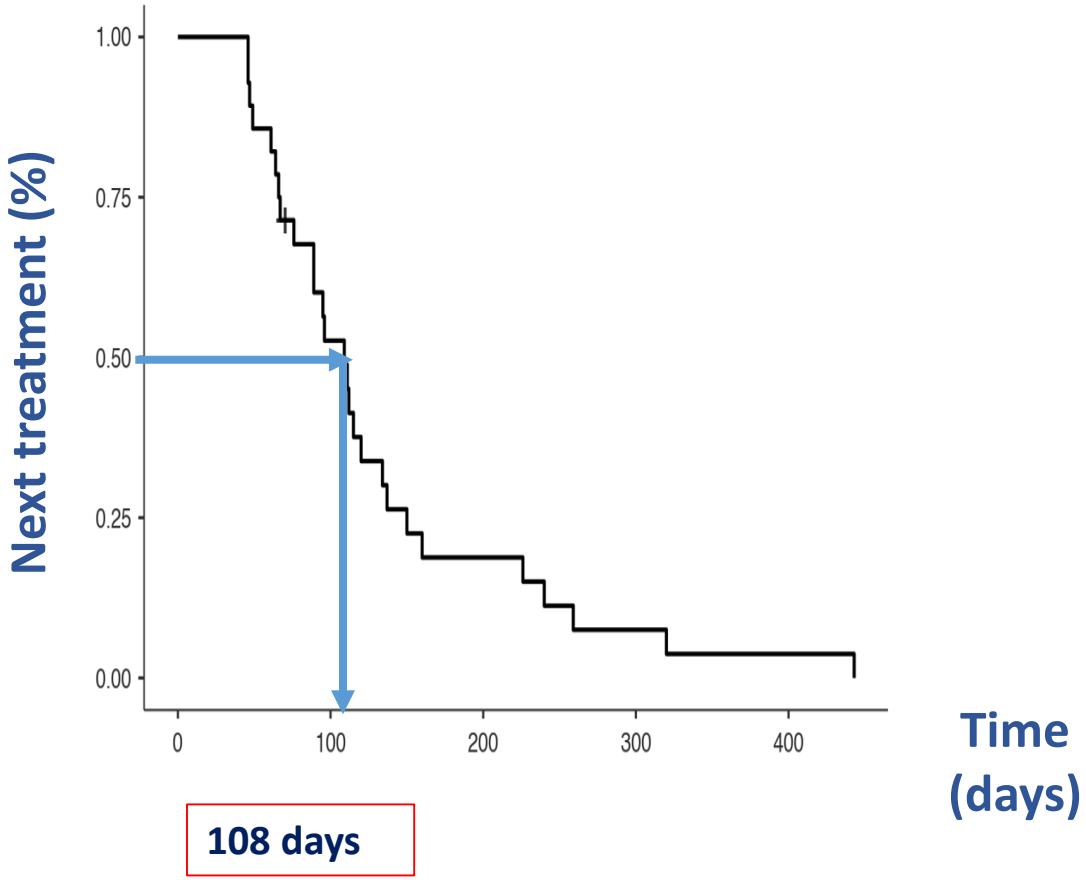
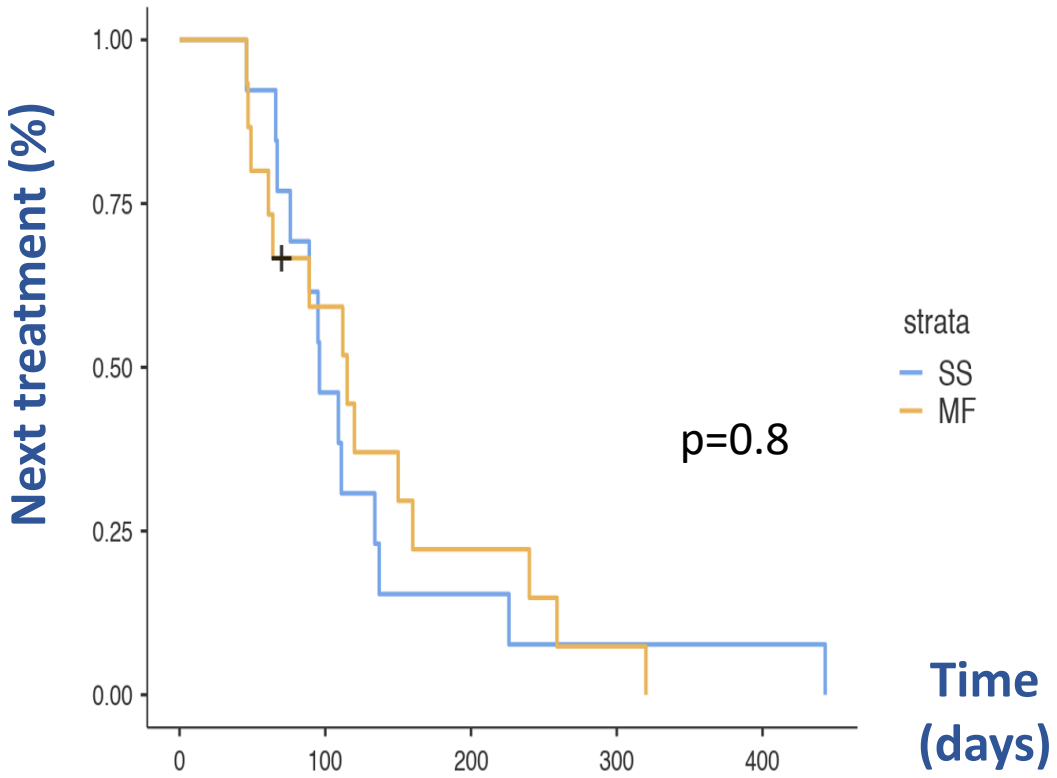
Median time to next treatment





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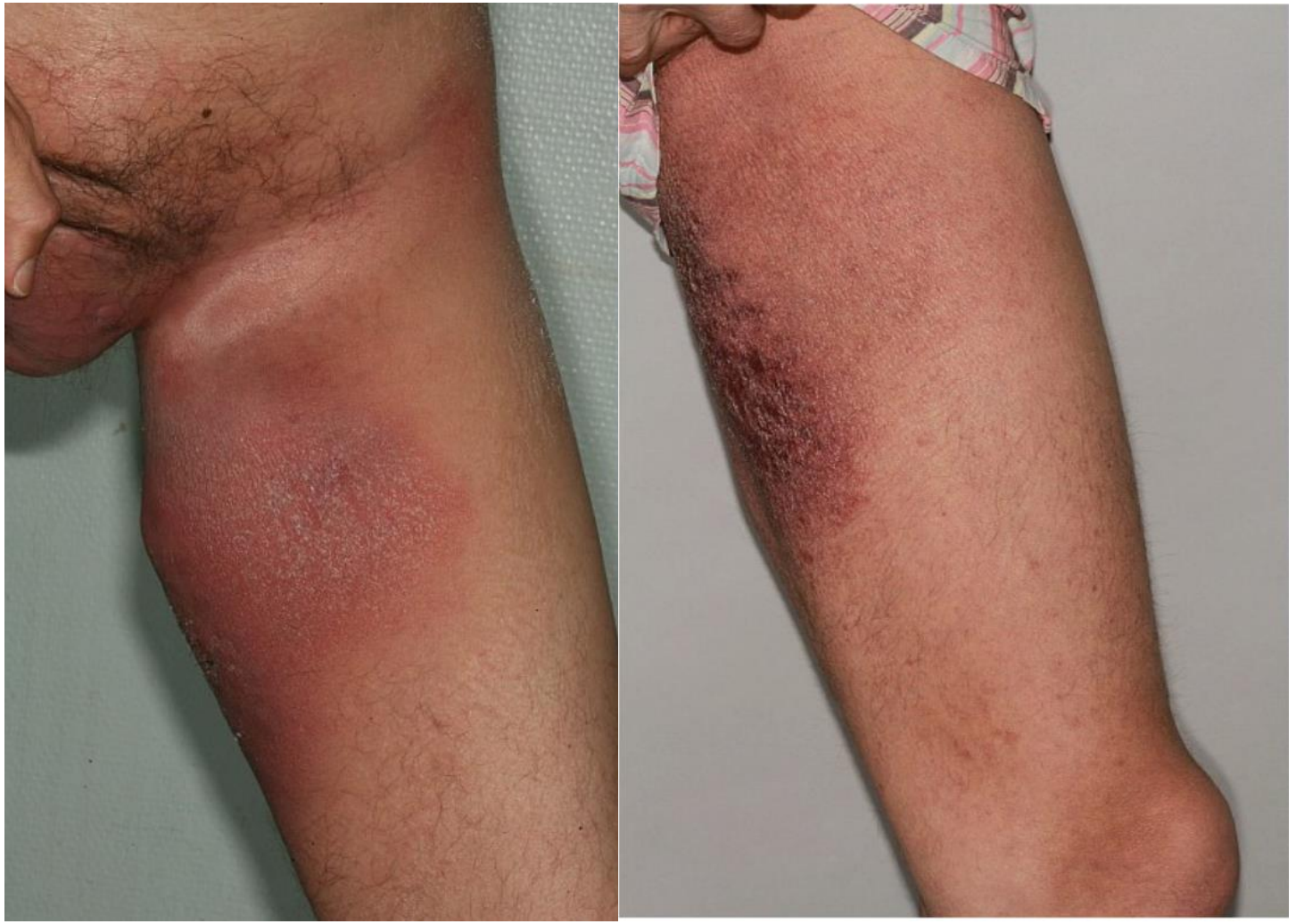
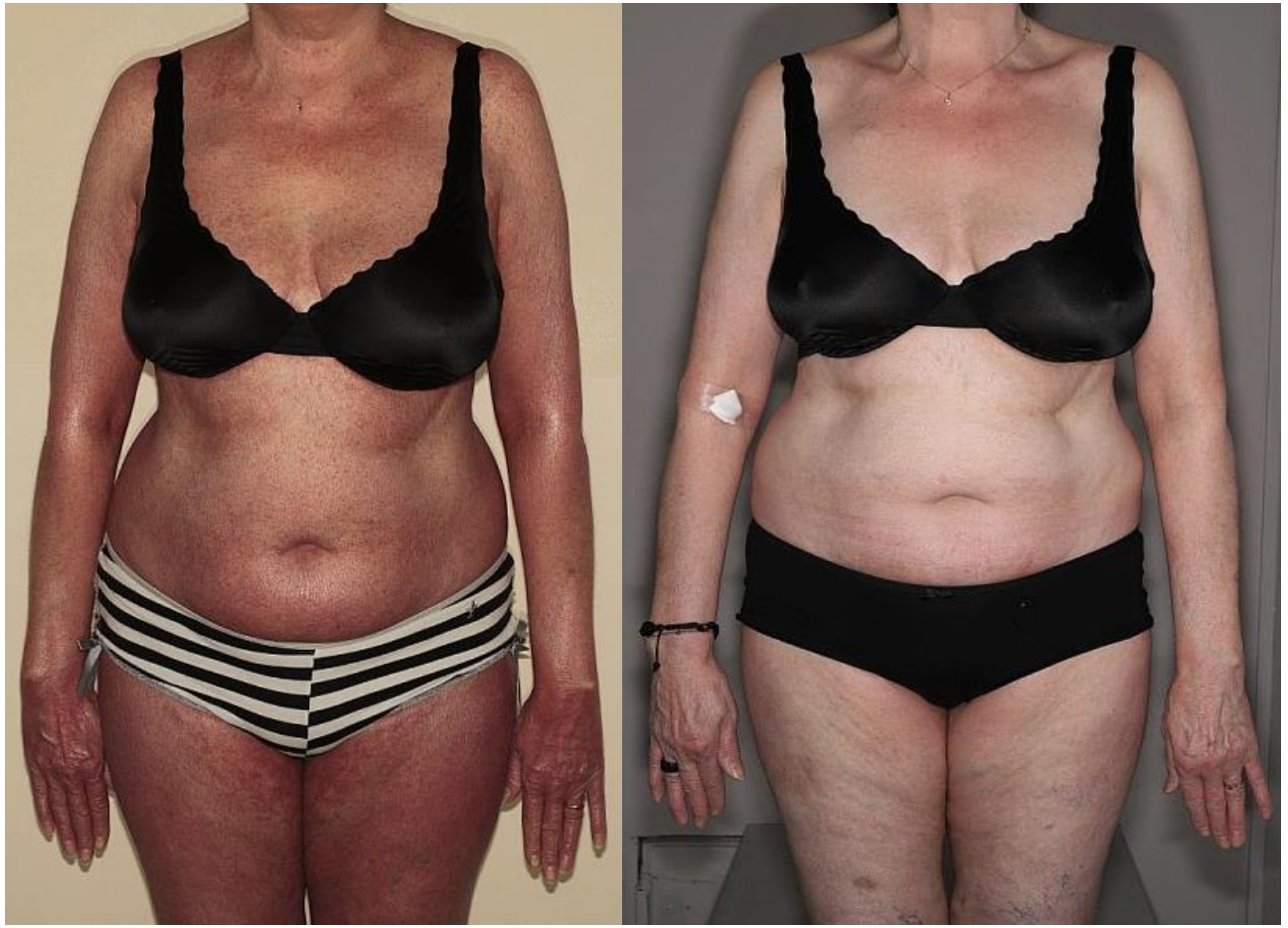
Causes of treatment interruption

Causes, n (%)	
Progression	10 (36)
Side effects	9 (32)
Progression and side effects	1 (4)
No complete response (needed for allogeneic HSCT)	3 (10)
Partial or complete response allowing maintenance treatment	4 (17)
Complete or near complete response allowing allogeneic HSCT	1 (4)

Clinical examples

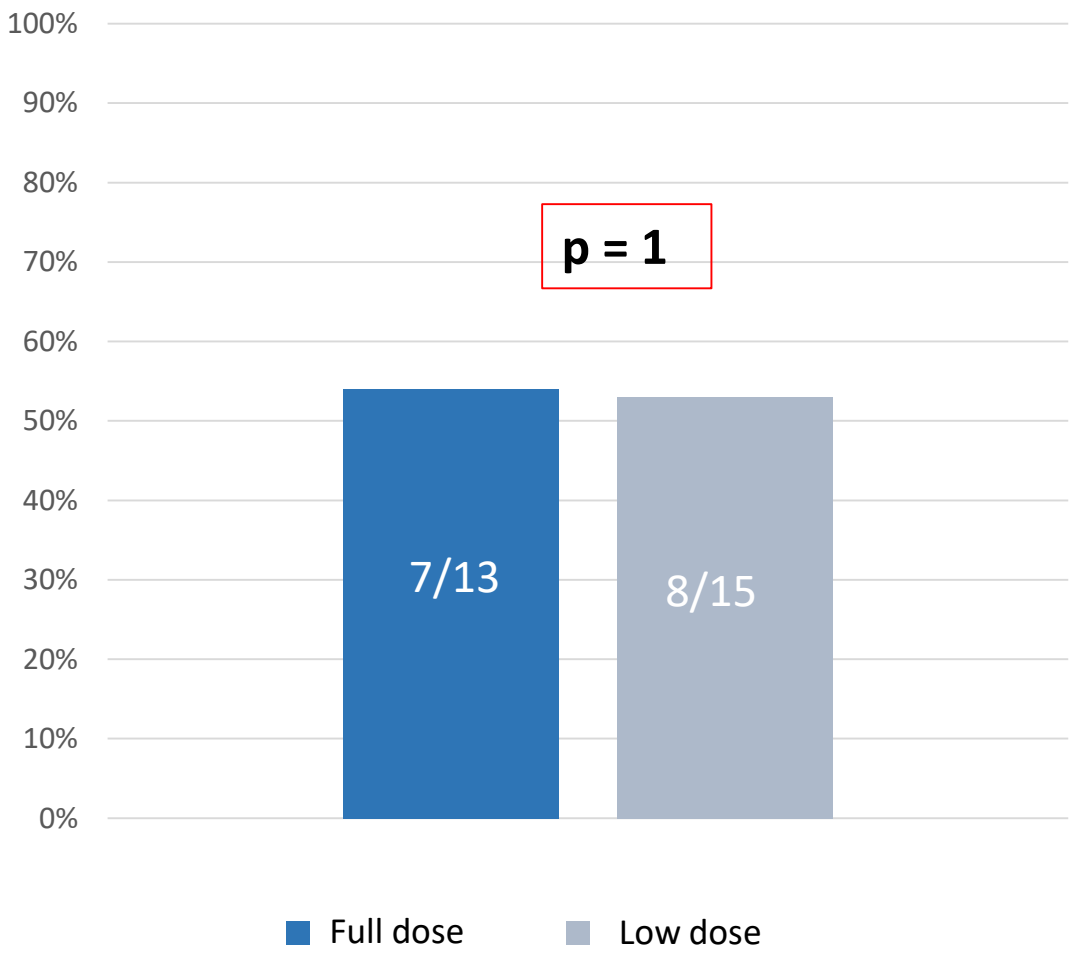


Clinical examples

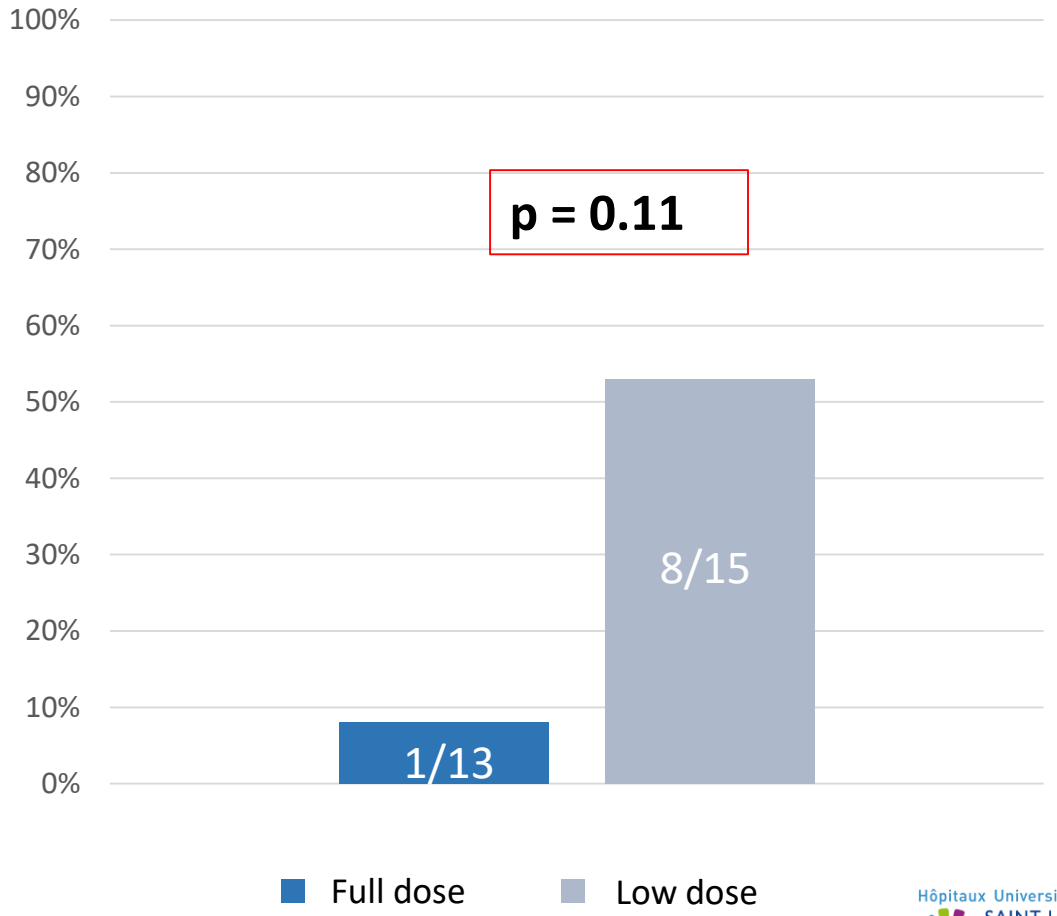


Toxicity according to the dose

Severe adverse events (CTCAE ≥ 3)



Treatment interruption due to SAE



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Toxicity

Most frequent adverse events	n (%)
Neutropenia (grade 2, n=2, grade 3, n=6, grade 4, n=1)	9 (32)
Pancytopenia (grade 3, n=3)	3 (11)
Infusion reaction*(grade 1, n=1, grade 2, n=1, grade 4, n=1)	3 (11)
Sepsis (grade 3, n=5, grade 4, n=1)	6 (21)
Nausea (grade 1, n=2, grade 2, n=3, grade 3, n=3)	8 (29)
Asthenia (grade 2, n=2)	2 (7)
Mucitis (grade 2, n=1, grade 3, n=1)	2 (7)
Cystitis (grade 2, n=1)	1 (4)

⇒15/28 (54%) severe adverse events (CTCAE≥3)

⇒Causing treatment stop: 9 patients

Discussion : comparison to other treatments of advanced CTCL

Ifosfamide and etoposide ORR 43%, ORR4 38%

Treatment	ORR	DOR	SAE
BRENTUXIMAB VEDOTIN	ORR_4= 56%	15 mo	41%
MOGAMULIZUMAB	28%	20 mo	41%
ALEMTUZUMAB	51%	4 mo	69%
LACUTAMAB	36%	13 mo	13%
GEMCITABINE	68%	4 mo	30%
DOXORUBICINE	40%	6 mo	30%
BENDAMUSTINE	50%	3.5 mo	80%
PRALATREXATE	29%	10 mo	45%
BRENTUXIMAB + BENDAMUSTINE	7/9 (2 allogeneic CSH)		3/9

Discussion

+

1 Complete response

Efficacy in transformed disease

Allowed allo HSCT in one case

Long-term response in 2 patients (>1 y)
ORR_4 38%

Low dose may be useful in fragile patients

-

Short responses: TTNT 3.6 months
(Hughes et al 3.9 months for chemo)

SAE: 54%
Toxicity : nausea, neutropenia } G-CSF, ondansetron

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Discussion

- ORR 43% : 46% SS et 40% MF ≠ Mogamulizumab, Alemtuzumab
- ORR_4 38% ≠ < Brentuximab Vedotin ORR_4 56%; > MTX et Bexarotene (Alcanza) ORR_4 12%
- Efficacy in transformed disease ≠ Mogamulizumab, Lacutamab, Alemtuzumab
- I+E cheaper than Brentuximab or Romidepsine

- 1 Complete response, Long-term response in 2 patients (>1 y)
- Allowed allo HSCT in one case
- Low dose may be useful in fragile patients

Dangien A, Ram-Wolff C, Brice P, Battistella M, Roelens M, Moins-Teisserenc H, Peffault de Latour R, Mourah S, Bouaziz JD, Lebbé C, Bagot M, de Masson A. Ifosfamide and etoposide in advanced-stage, relapsed or refractory primary cutaneous T-cell lymphomas. ***Br J Dermatol****. 2020 Nov;183(5):961-962. doi: 10.1111/bjd.19220. Epub 2020 Jul 13. PMID: 32407544.*

Thank you !

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