Sequential Intranodal ImmunTherapy (SIIT) in Malignant Lymphoma

- A cancer vaccine created in the patient

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KG JEBSEN CENTER
for Cancer Immunotherapy

Why is FL a very interesting cancer for immunotherapy and cancer vaccines?

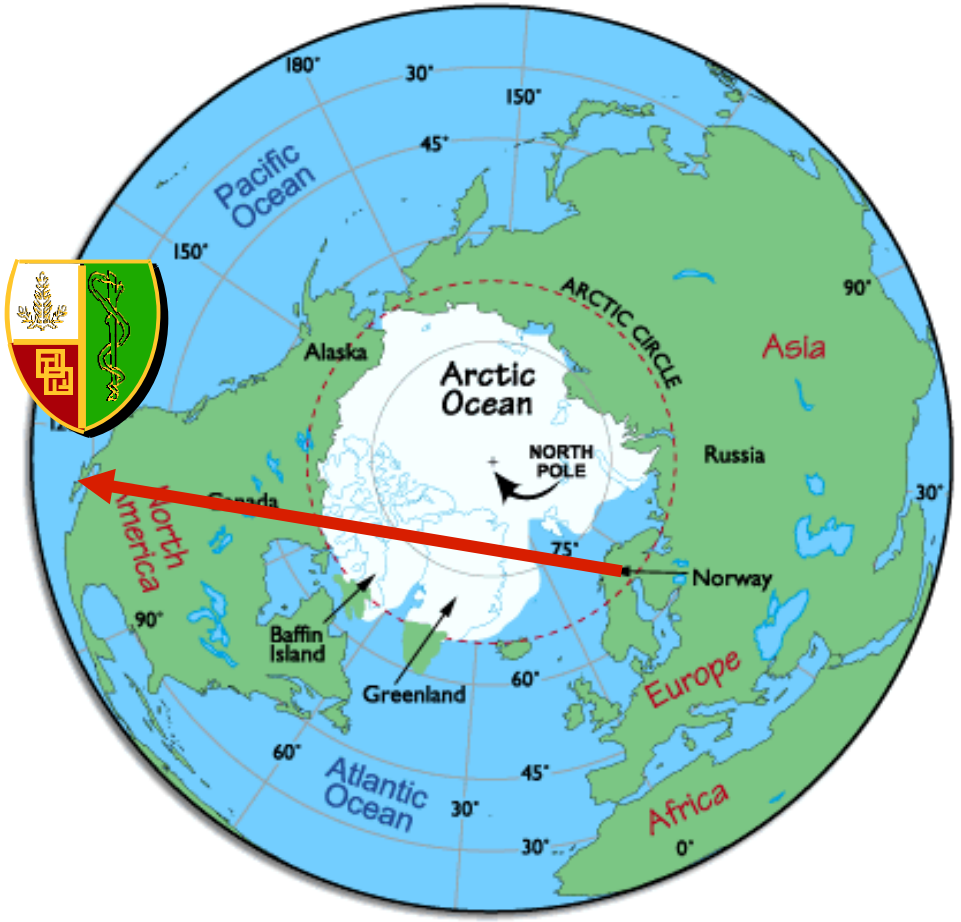
- **The most common type of indolent non-Hodgkin`s lymphoma**
- **Incurable lymphoma**
- **Patients can live with disease for > 10 years**
- **Watch and wait strategy is acceptable**
- **Immunogenic tumor, FL responds to immunotherapy**

- **At present; no effective cancer vaccines have been developed in malignant lymphoma (or any other cancer)**

From Oslo to Stanford…….

Visiting professor at Stanford University, California

2006-2007



New concept of cancer vaccines

- **Vaccines are generally given to prevent disease**
- **In cancer patients the disease is allready present – makes it more difficult – therapeutic vaccines**

- **Vaccines are generally made in the laboratory and then administered to the patient**
- **We create an «*in situ vaccine*» in the cancer lymph nodes**

Sequential Intranodal ImmunoTherapy (SIIT) in follicular lymphoma – Lymvac-1

Participating center

Oslo University Hospital, Radiumhospitalet

Inclusion criteria

Age 18 years and older

Histologically confirmed (by WHO classification) untreated or relapsed follicular lymphoma grade I-IIIA.

Stage III/IV, non-symptomatic, incurable follicular lymphoma

Sample size

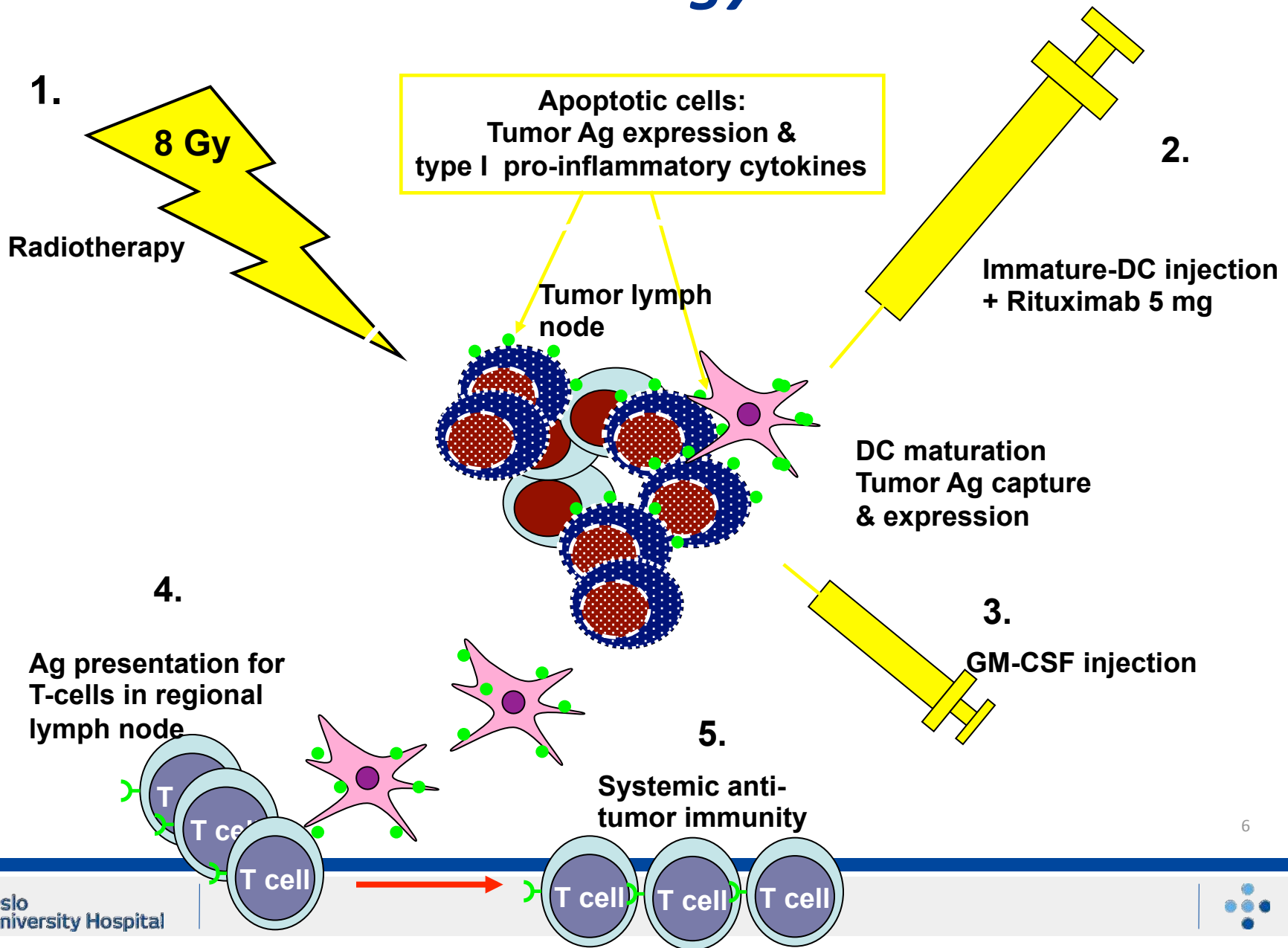
14 evaluable patients

Primary aims

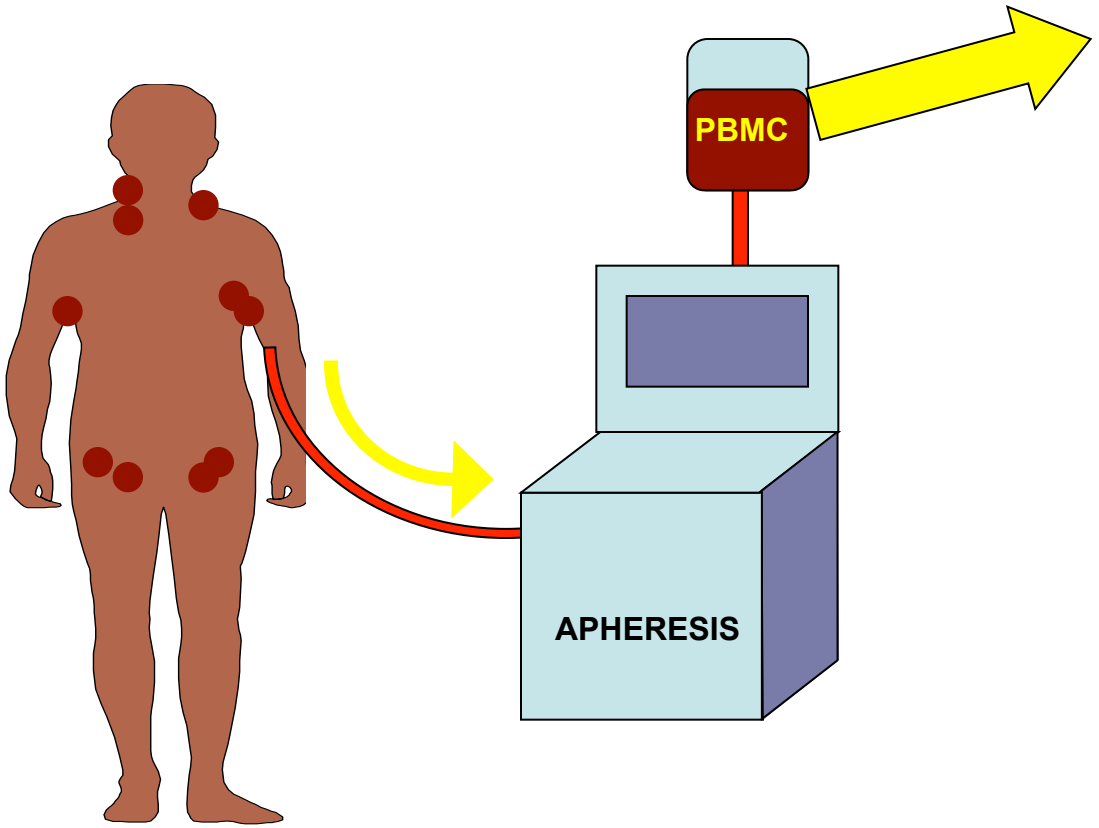
To induce **systemic clinical responses**

To induce tumor-specific **systemic immune responses**

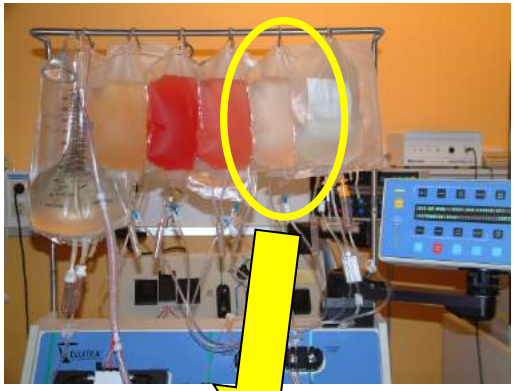
Treatment strategy - cartoon



Autologous dendritic cells cultured from patients with follicular lymphoma



PBMC ELUTRIATION



MONOCYTES

Ex vivo culture and generation of immature DCs

Lymvac-1 study protocol

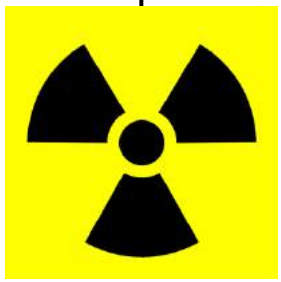
Low dose 5mg

Low dose 5mg

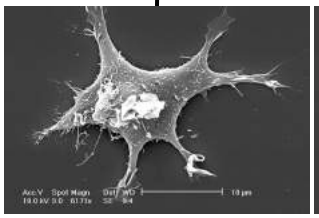
GM-CSF 50ug s.c.

GM-CSF 50ug s.c.

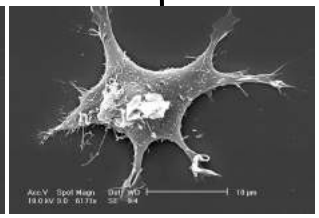
Day 1 → Day 2 → Day 3 → Day 4 → Day 5



Single dose (8 Gy)



iDCs 50-100M

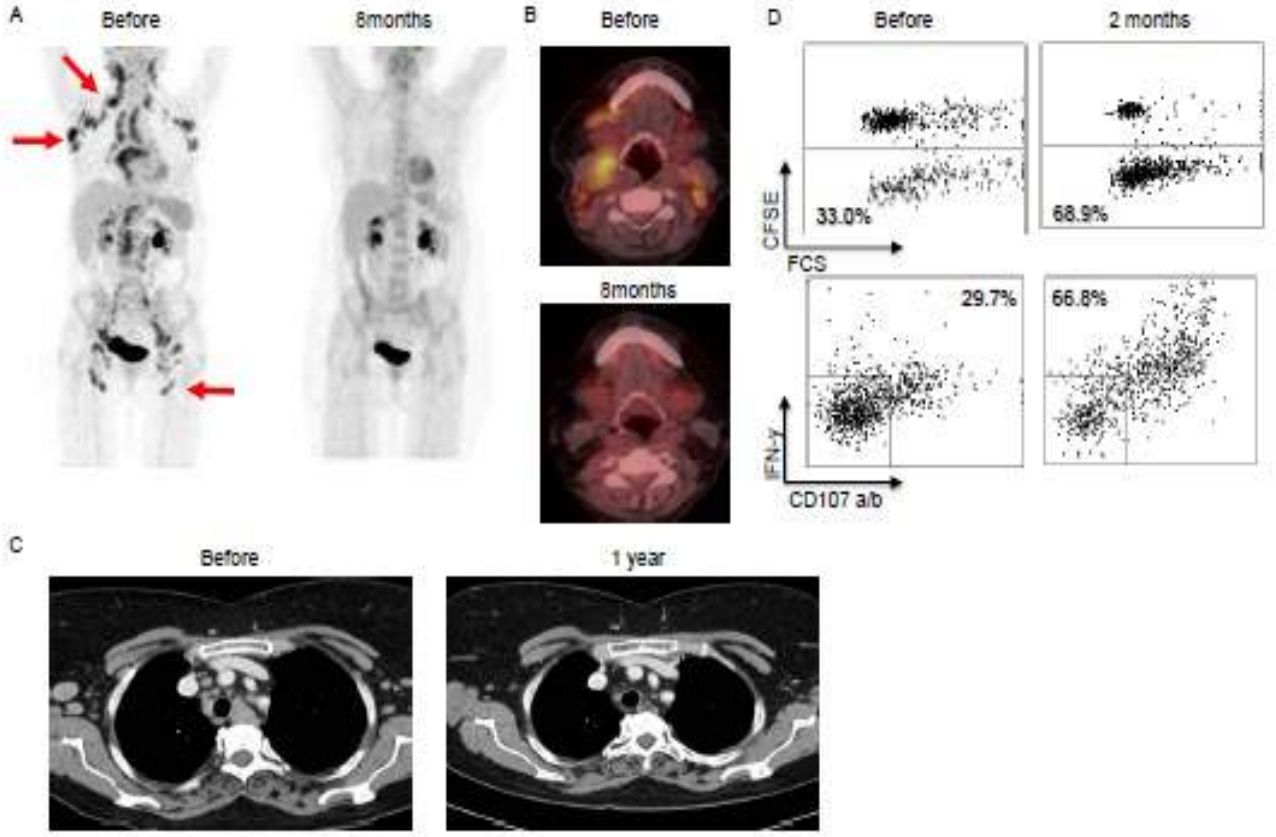


iDCs 50-100M

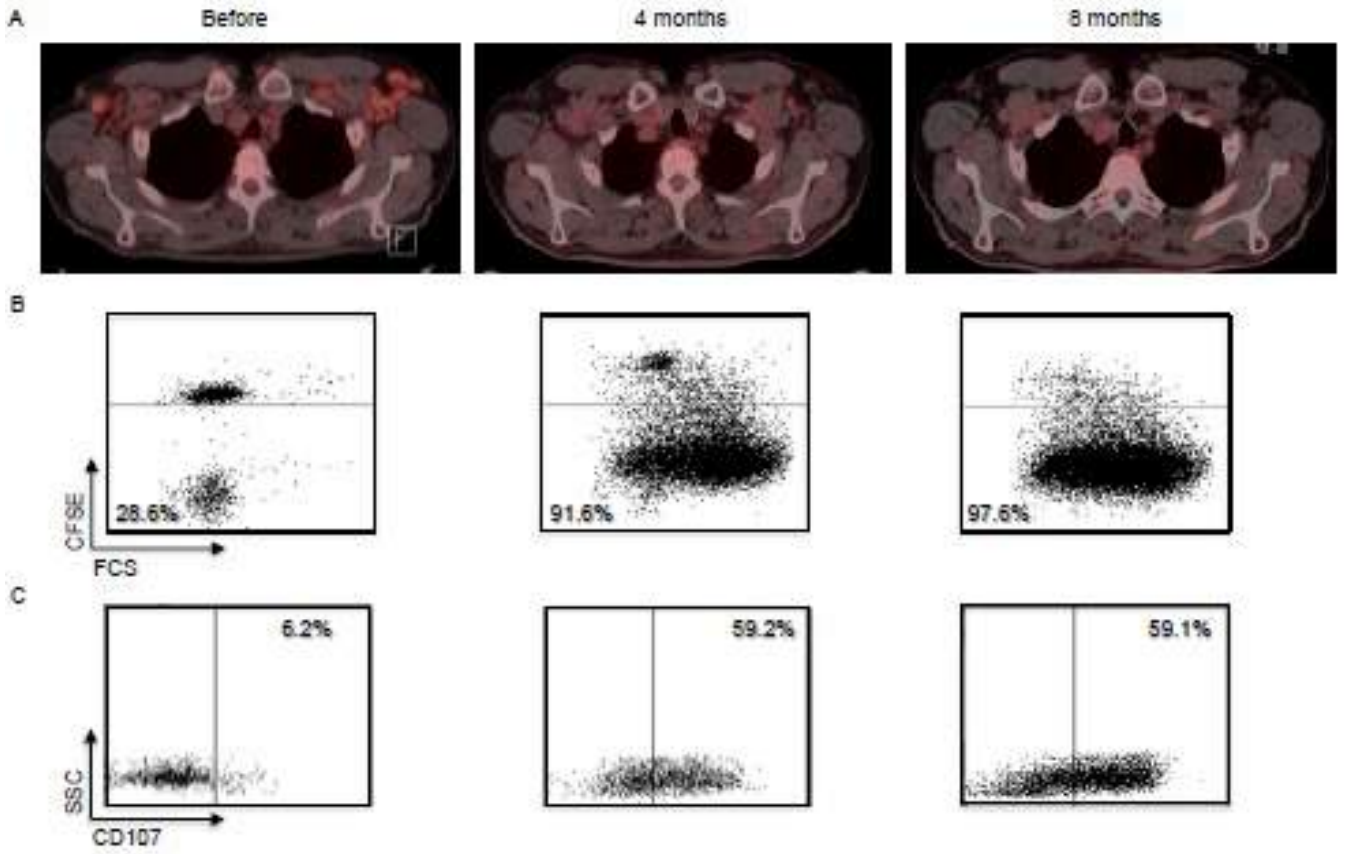
x3

Kolstad et al., Blood, 2015

Patient no 2. Complete remission after 6 years



Patient no 5. In complete remission for 2 years



Patient no 8. Partial remission at 8 months

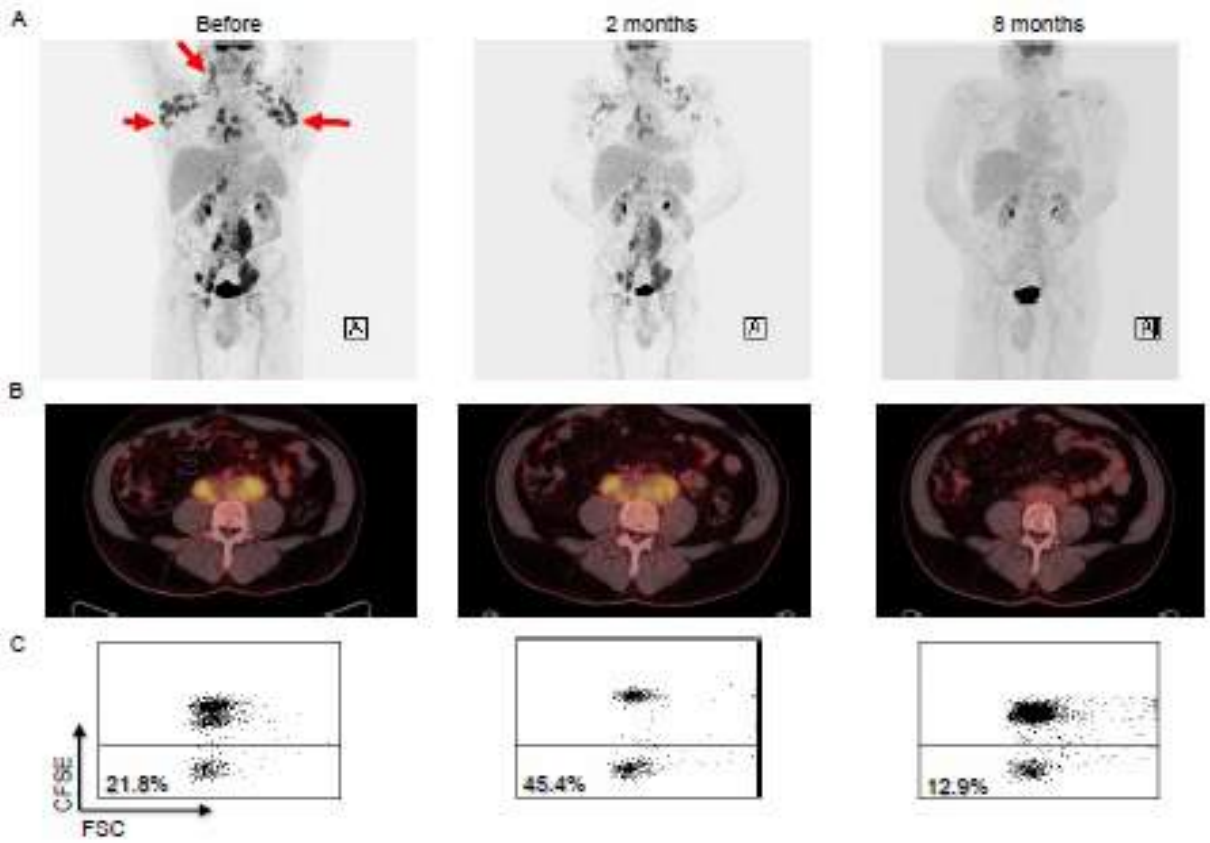


Table 1. Patients' characteristics and systemic response to local immunotherapy

Pt	Age	Disease Grade	Stage	FLIPI†	Previous treatment	Months since diagnosis or treatment	Response IWG 1999[24]	Response IWG 2007[25]
1	59	FL* II	IVA	2	None	13	PD	PD
2	66	FL II	IVA	4	None	5	CR	CR
3	43	FL I	IVA	2	None	3	SD	SD
4	55	FLII	IVA	2	None	6	SD	SD
5	72	FL I	IVA	2	None	6	CR	PR
6	54	FL II	IIIA	2	None	6	SD	SD
7	62	FL II	IVA	4	Zevalin	35	SD	SD
8	62	FL II	IVA	3	Radiotherapy	37	PR	PR
9	40	FL IIIA	IVA	1	Rituximab	33	PR‡	PR‡
10	81	FL I	IVA	3	None	3	SD	SD
11	53	FL II	IVA	2	None	9	PD	PD
12	58	FL II	IVA	2	None	2	SD	SD
13	66	FL I	IVA	3	None	12	SD	SD
14	33	FL I	IVA	2	None	13	PR	PR

* FL = follicular lymphoma
† FLIPI = follicular lymphoma prognostic index
‡ Cutaneous lymphoma not evaluable by IWG 1999 or 2007

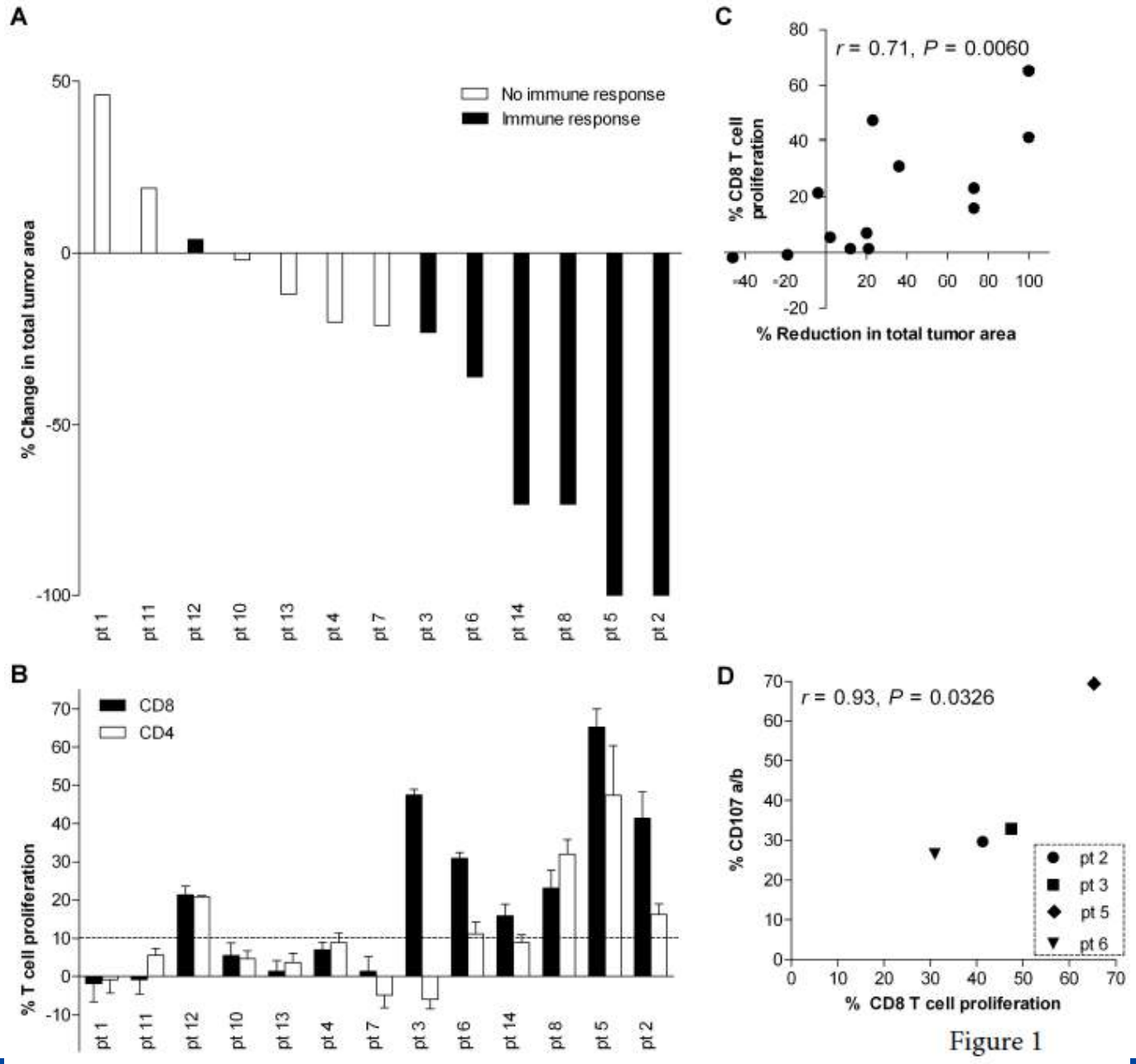
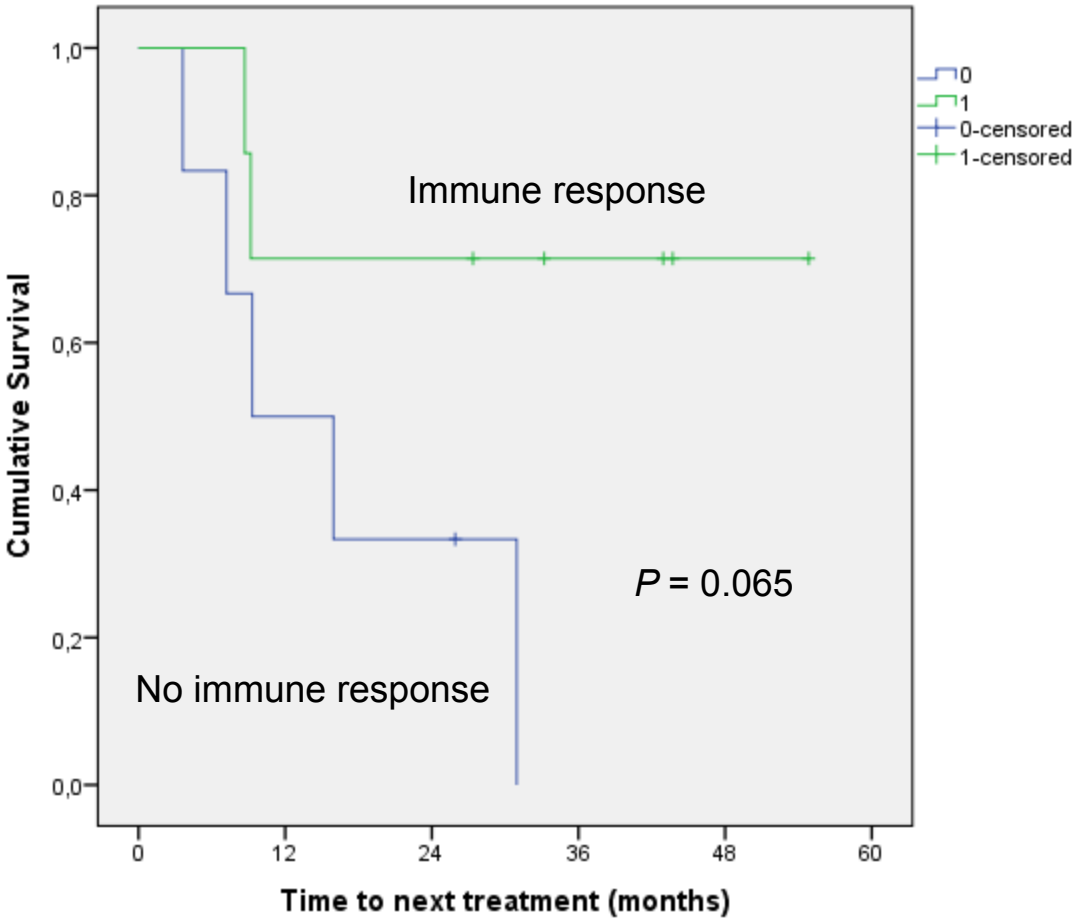

A
No immune response
Immune response
% Change in total tumor area
50
0
-50
-100
pt 1
pt 11
pt 12
pt 10
pt 13
pt 4
pt 7
pt 3
pt 6
pt 14
pt 8
pt 5
pt 2
C
r = 0.71, P = 0.0060
% CD8 T cell proliferation
80
60
40
20
-20
-40
-20
20
40
60
80
100
% Reduction in total tumor area
B
CD8
CD4
% T cell proliferation
70
60
50
40
30
20
10
0
-10
pt 1
pt 11
pt 12
pt 10
pt 13
pt 4
pt 7
pt 3
pt 6
pt 14
pt 8
pt 5
pt 2
D
r = 0.93, P = 0.0326
% CD107 a/b
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
% CD8 T cell proliferation
pt 2
pt 3
pt 5
pt 6

Figure 1

Prolonged time to next treatment for immune responders



Conclusion

- This sequential intra-nodal immunotherapy approach induced anti-tumor T-cell responses and corresponding clinical responses in patients with incurable stage III/IV follicular lymphoma.

- The best responses were slow, took 8-12 months before peak

- The treatment was very well tolerated

- No autoimmune side-effects

- ***First effective cancer vaccine in lymphoma with documented T cell responses detectable in blood after vaccination***

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blood

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Sequential intranodal immunotherapy induces anti-tumor immunity and correlated regression of disseminated follicular lymphoma

Arne Kolstad, Shraddha Kumari, Mateusz Walczak, Ulf Madsbu, Trond Hagtvedt, Trond Velde Bogsrud, Gunnar Kvalheim, Harald Holte, Ellen Aurlien, Jan Delabie, Anne Tierens and Johanna Olweus

Editorial commentary in the same issue of Blood

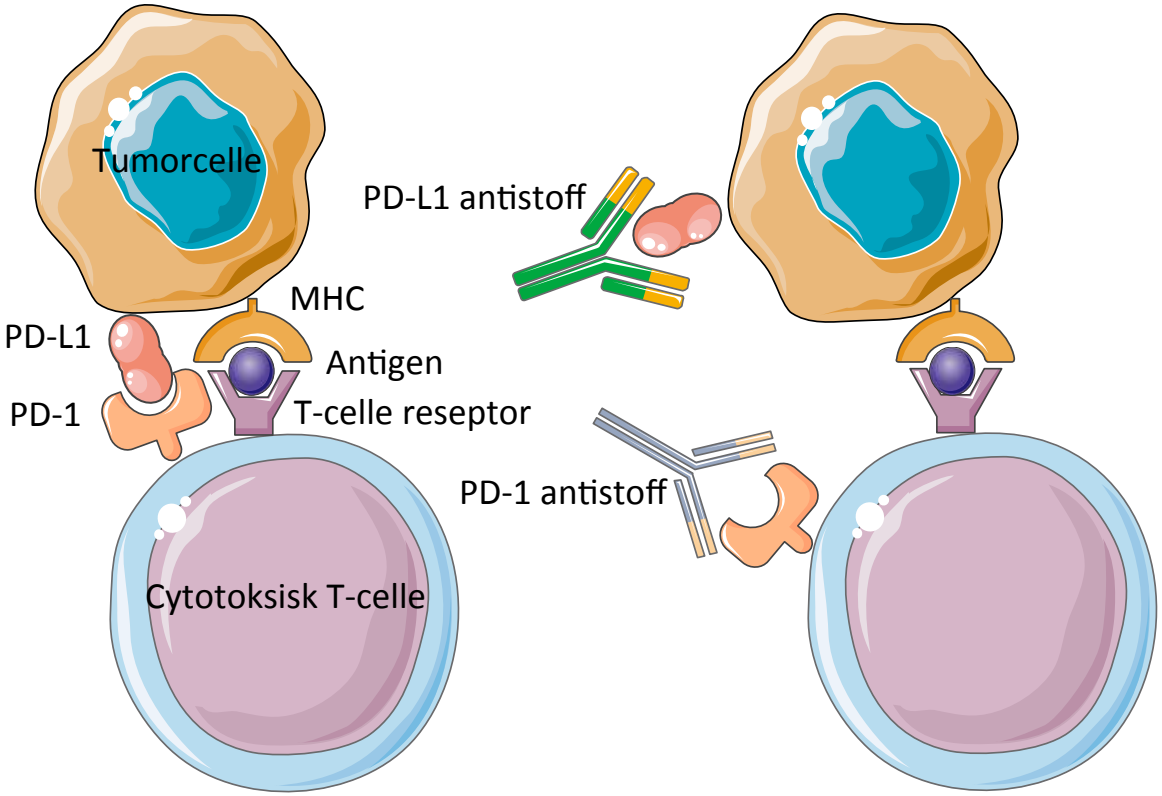
Next step: A new study has started

- **SPONSOR: Oslo University Hospital Radiumhospitalet**

- **TITLE: Sequential Intranodal Immunotherapy (SIIT) Combined with Anti-PD1 (Pembrolizumab) in Patients with Stage III/IV Untreated and Relapsed Follicular Lymphoma**

Lymvac-2 Study

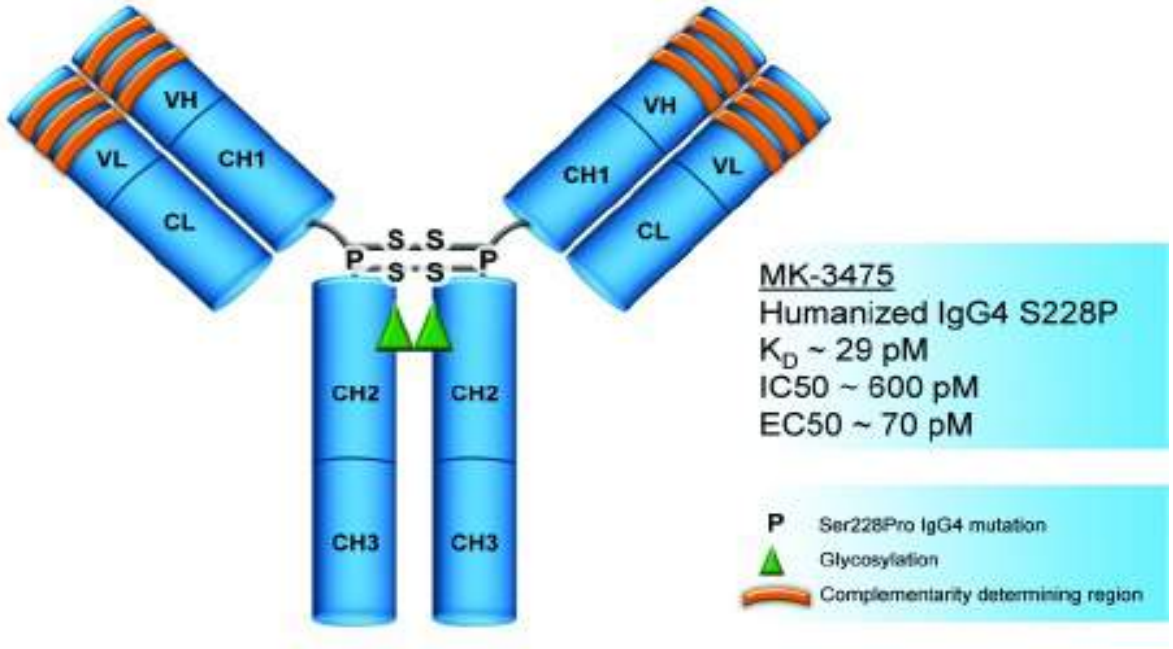
Check-point inhibition by blokkage of the co-inhibitory receptor PD-1 on T cells



Removing the «brakes» from responding T cells

Anti-PD-1 antibody Pembrolizumab

Figure 1



Study design – Lymvac-2

- **Phase II single center trial**
- **20 patient with untreated or relapsed disseminated incurable follicular lymphoma**
- **Asymptomatic not in need of standard therapy**
- **PD1-inhibitor Pembrolizumab (Merck) will be added to the Lymvac-1 platform**

Primary end-points and aims

- **Response rates at time of best response**
  Anti-tumor CD8 and CD4 T-cell responses in peripheral blood after treatment

- **Improvement in clinical response rates compared to Lymvac-1**
- **Improvement in anti-tumor T-cell responses**
- **Show feasibility and safety**

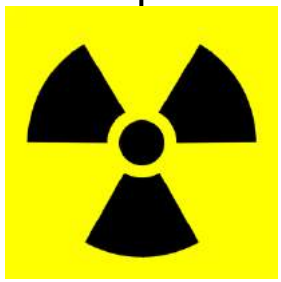
Lymvac-2 – Treatment schedule

Rituximab

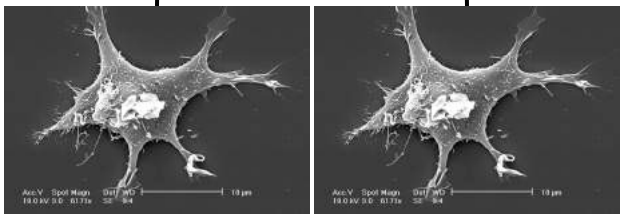
Rituximab

Anti-PD1 (Pembro)

Day 1 → Day 2 → Day 3 → Day 4 → Day 5



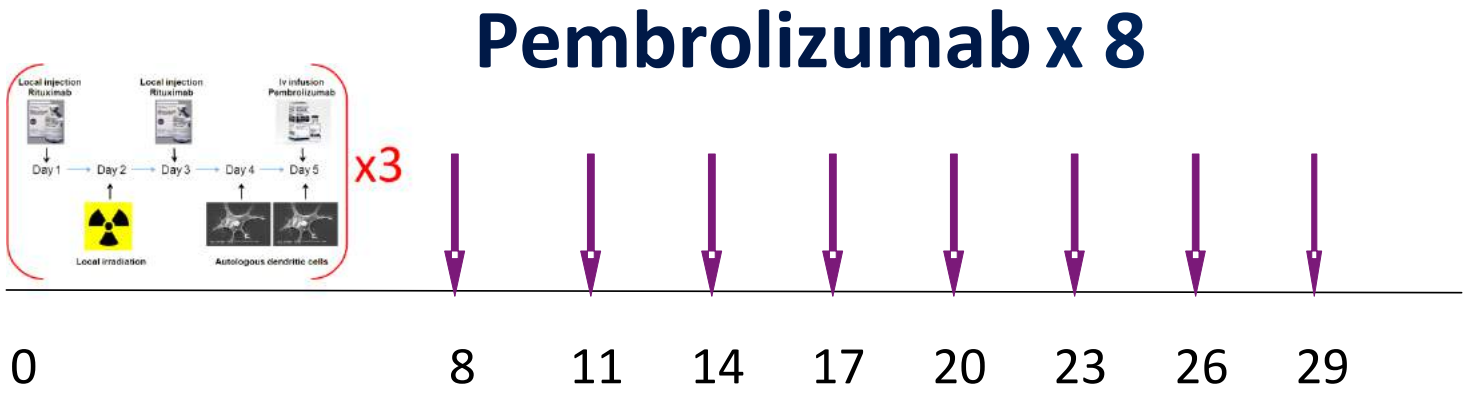
Radiotherapy



Immature DC Immature DC

x3

Lymvac-2 – Study: Treatment schedule



Clinical response evaluation by PET/CT, CT, BM-sampling

Immunomonitoring of anti-tumor T-cell responses by flow cytometry

Lymvac-2 study has started

- **Study protocol has been approved by IRB, Etics commitee, Norwegian Medicines Ageny**
- **Aggreement with Merck for delivery of Pembrolizumab free of charge for 20 patients**
- **Study has started, 2 patients are currently screened and expected to start treatment in May 2016**

The Norwegian Radium Hospital

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Cellular Therapy
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Ton Schumacher

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Thank you for listening!