innate pharma

TEACH IN CTCL

PR MARTINE BAGOT

HOP. ST LOUIS, PARIS

PARIS,
2 DECEMBRE 2015

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MANAGEMENT TEAM

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Novo Nordisk A/S

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ARIAD, Pfizer, Novartis, Aventis

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Movetis, Zeltia, Morgan Stanley

Yannis Morel
PhD,
Chief Business Officer

Innate Pharma

INNATE PHARMA AT A GLANCE

Leading scientific edge
in innate immunity pharmacology

Primary focus
in immuno-oncology

innate pharma

Portfolio of first-in-class
checkpoint inhibitors

Partnerships with leaders in IO
BMS and AZN

A LONG TERM STRATEGY
CREATE AND RETAIN MAXIMAL VALUE

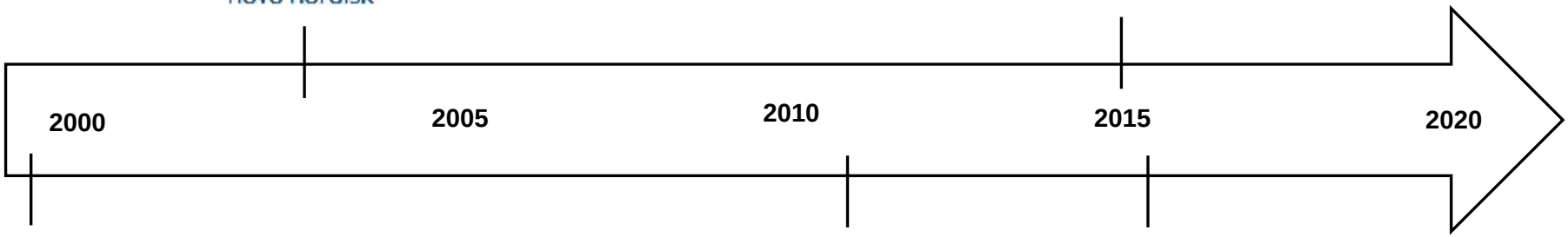
NK Cell
R&D collaboration
2003 - 2009

novo nordisk

IPH2201 (PII)

- Global co-development and commercialization (2015)
- Initial payment: **$250 million**
- Further milestone payments: **up to $925 million**
- Double digit royalties on sales
- **Right to co-promote** in Europe (50% profit share)

AstraZeneca
MedImmune



Inception

Lirilumab (PII)

Bristol-Myers Squibb

- License (2011)
- Upfront payment: **$35 million**
- Milestone payments: **up to $430 million**
- Double-digit royalties on sales

IPH4102
In house development

IPH4102, A CANDIDATE FOR AN IN-HOUSE DEVELOPMENT

- IgG1 - cytotoxic antibody - aiming at depleting KIR3DL2^{+} cells
- Defined, targeted patient population
- Potential associated biomarker
- Patients treated in a small number of specialized hospitals

- **Straightforward path to market**
- **Effort commensurate with Innate's size and means**
- **Strategy is to keep full rights**

MARTINE BAGOT, MD, PROFESSOR,
HEAD OF THE DERMATOLOGY DEPARTMENT AT THE SAINT-LOUIS HOSPITAL, PARIS

Mrs Martine Bagot is Professor and Chairperson in the Dermatology Department at Saint Louis Hospital in Paris, Paris 7 University and INSERM Unit U976 “Dermatology, Immunology and Oncology”.

Pr M. Bagot co-authored 439 publications. Her bibliography includes many clinical trial experience reports in dermato-oncology, as well as reference guidelines for the diagnosis, classification and clinical management of cutaneous lymphomas, a therapeutic area where she is recognized as a key international expert.

She has served as Board member of the International Society for Cutaneous Lymphoma (2002-2007), Board member of the European Society for Dermatological Research (2001-2005), President of the European Dermatology Forum (2012-2013) and President (2008-2011) of the EORTC Cutaneous Lymphoma Task Force, among many others, illustrating her leading position in the field.

FIRST-IN-HUMAN TRIAL OF ANTI-KIR3DL2 IPH4102 IN CTCL

DECEMBER 2015

CONFLICTS OF INTERESTS

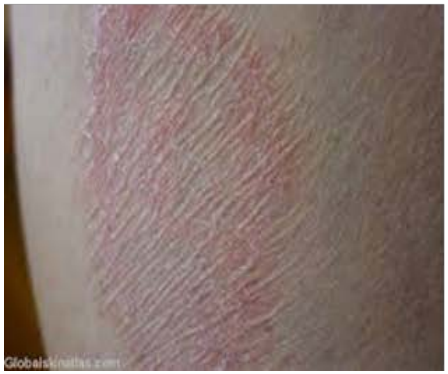
- Trial participation: Millenium, Kyowa, Innate
- ***No financial compensation or honorarium from Innate***

CTCL

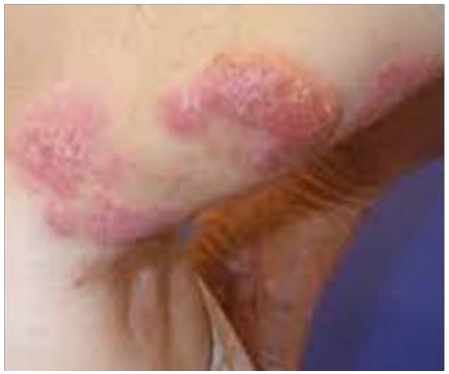
A RARE DISEASE WITH HIGH UNMET MEDICAL NEED

CUTANEOUS T-CELL LYMPHOMA

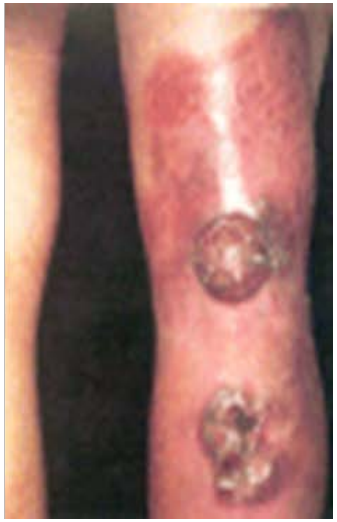
- CTCL is a heterogeneous group of non Hodgkin lymphomas which arise primarily in the skin and are characterized by the presence of malignant clonal mature T cells
- CTCL exhibit diverse clinical, histological and molecular presentations



Patch



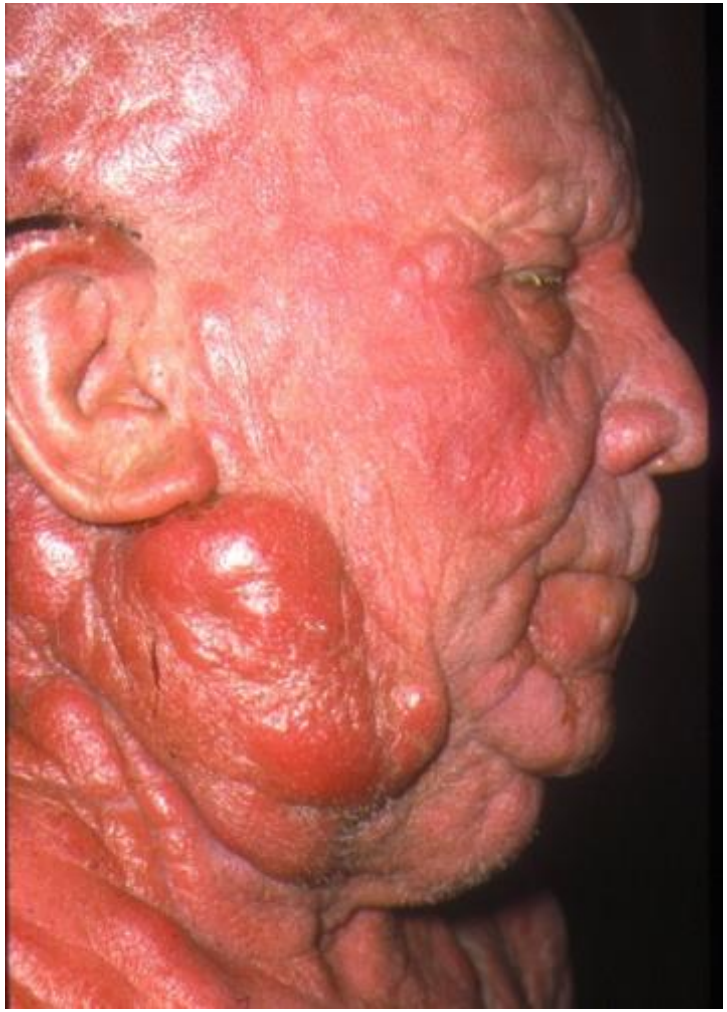
Plaque

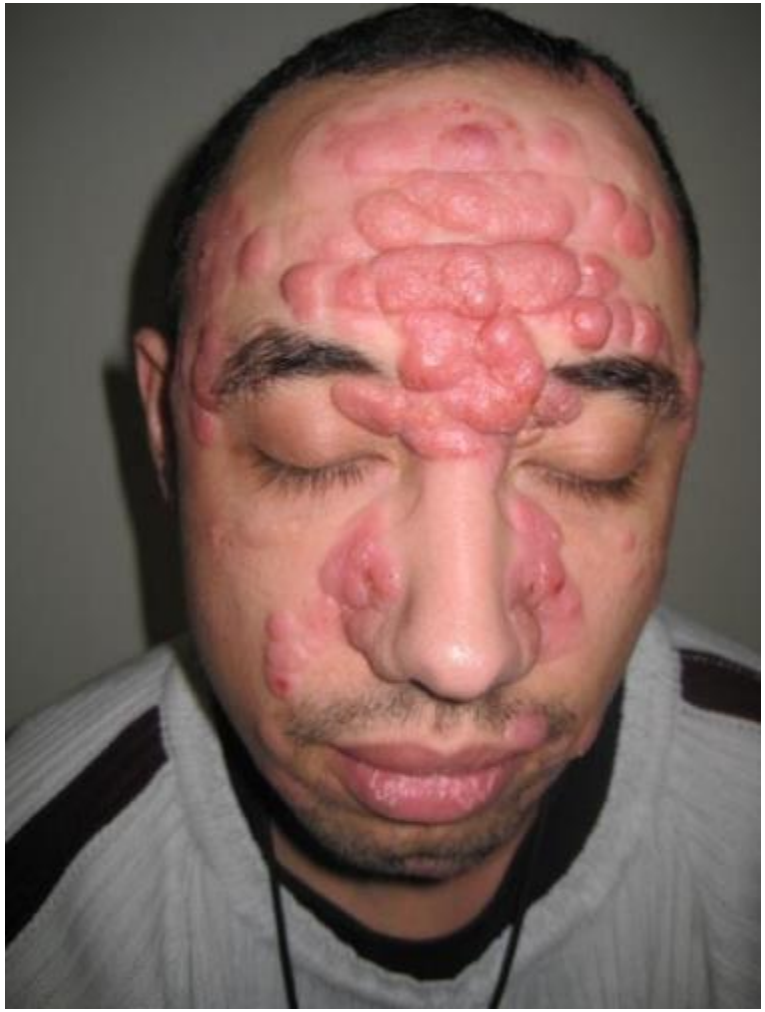


Tumor

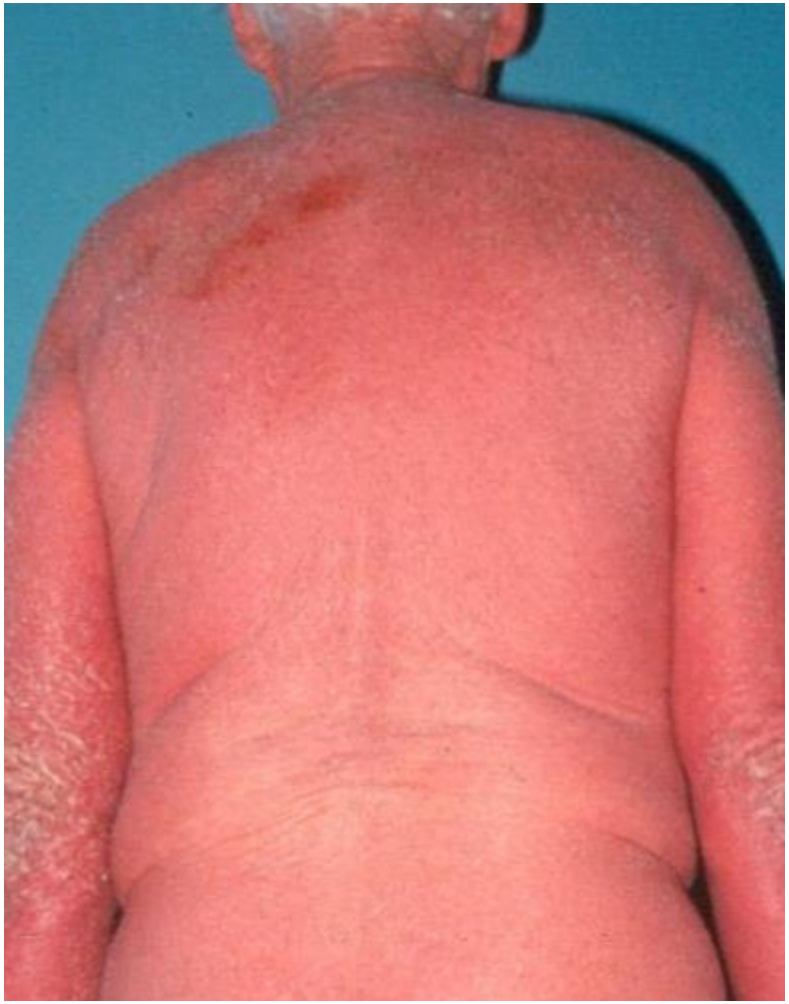
- In advanced disease, malignant cells can spread to extra cutaneous sites, such as blood, lymph nodes or viscera

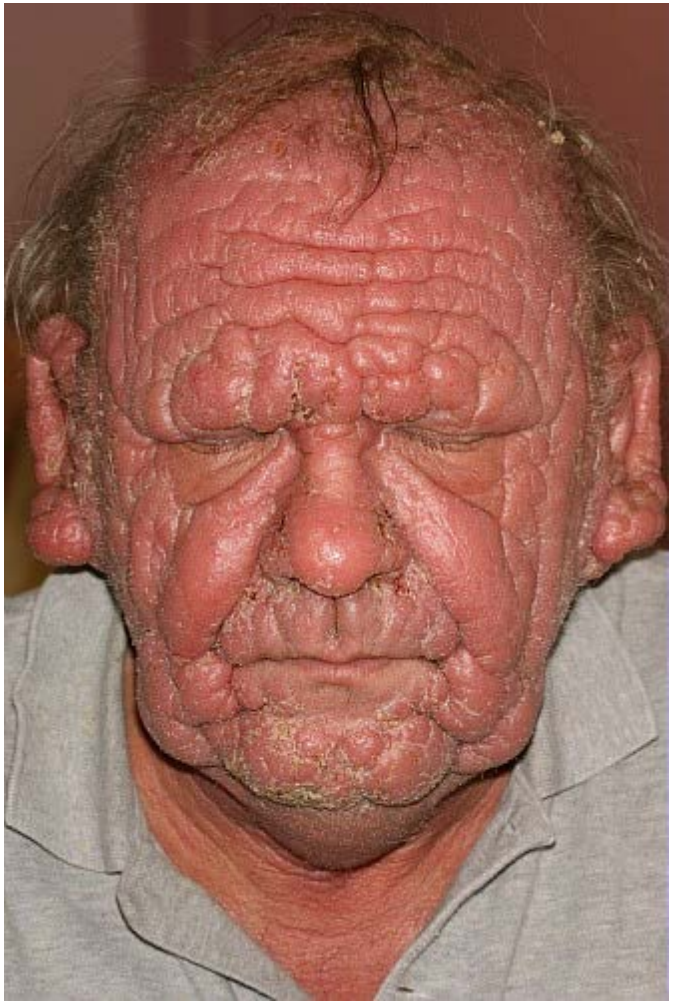
ADVANCED MYCOSIS FUNGOIDES





SÉZARY SYNDROME





CUTANEOUS T-CELL LYMPHOMA EPIDEMIOLOGY

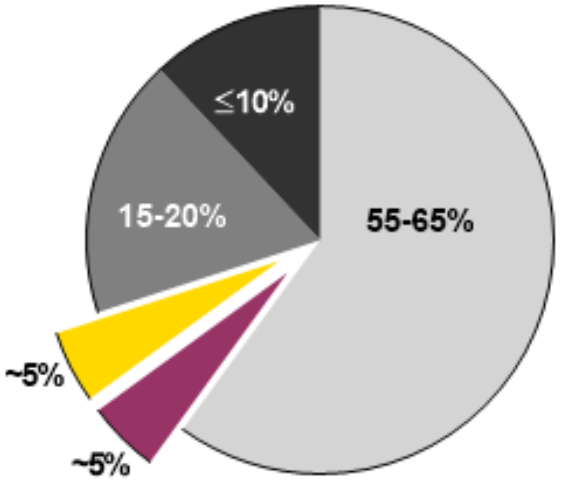
- CTCL account for ~4% of all NHL cases
- Age-adjusted annual incidence of CTCL is estimated around 4.1 to 6.4 cases per million
- Median age at diagnosis is 55-65 yrs
  - > Two-thirds present with early stage disease (IB-IIA)
- Factors predictive of disease progression or survival[1,2]
  - > Advanced skin involvement (greater BSA, tumors/erythroderma)
  - > Involvement of sites other than skin
  - > Older age, male gender, blacks
  - > Folliculotropism (hair follicle involvement- deeper)
  - > Large cell transformation (change to larger cells, rapid growth)
  - > Increased LDH (blood marker of lots of disease, more than skin)

[1]Arch Dermatol 2003;139:857-866
[2]JNCCN 2008;6:436-441

CTCL LANDSCAPE

SURVIVAL PER WHO-EORTC SUBTYPE

Relative frequency of CTCL subtypes per WHO-EORTC classification



	5-year Overall Survival
Mycosis Fungoïdes (MF)	20 to 95%*
transformed MF	≤ 15%
CD30$^+$LPD (ALCL subtype)	76 to 96%
Sézary Syndrome	~10%
Others (ATL, NK/T, γδ,…)	≤ 20%

* Depending on TNMB stage

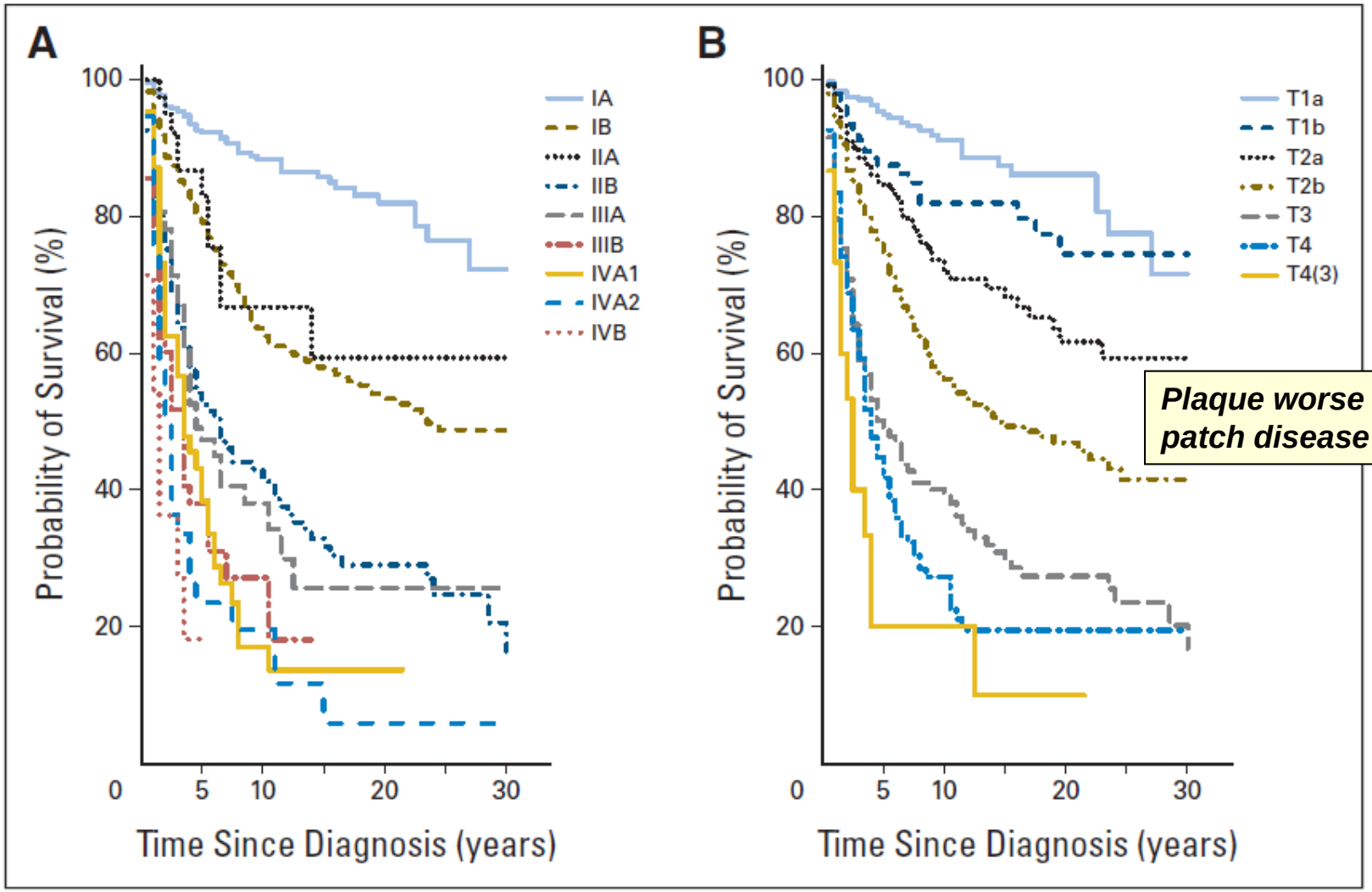
Mycosis fungoides (MF) and Sézary syndrome (SS), its leukemic variant, are the most common CTCL subtypes.

Overall survival depends in part on disease subtype.

Agar et al, JCO 2010; Kempf et al, Blood 2011;
Willemze, Blood 1997; Willemze et al, Annals Oncol 2011; Kim et al, Arch Dermatol 2003

SURVIVAL DECREASED WITH ADVANCING T CLASS AND CLINICAL STAGE

DSS UTILIZING REVISED STAGING SYSTEM

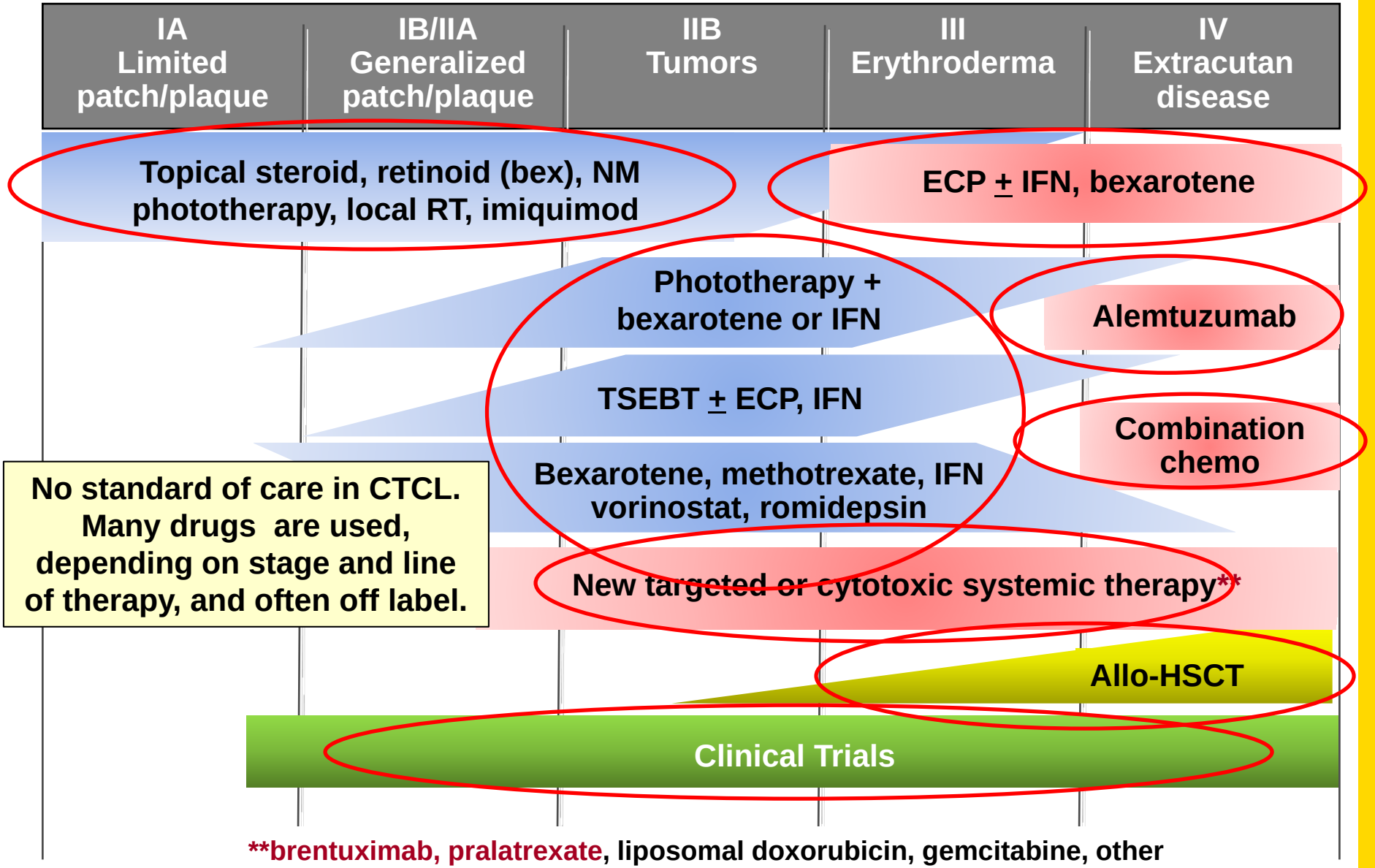


Plaque worse than patch disease

Agar et al. J Clin Oncol 2010;28:4730

CURRENT CLINICAL MANAGEMENT OF CTCL, 2015

WWW.NCCN.ORG => NHL => MF/SS



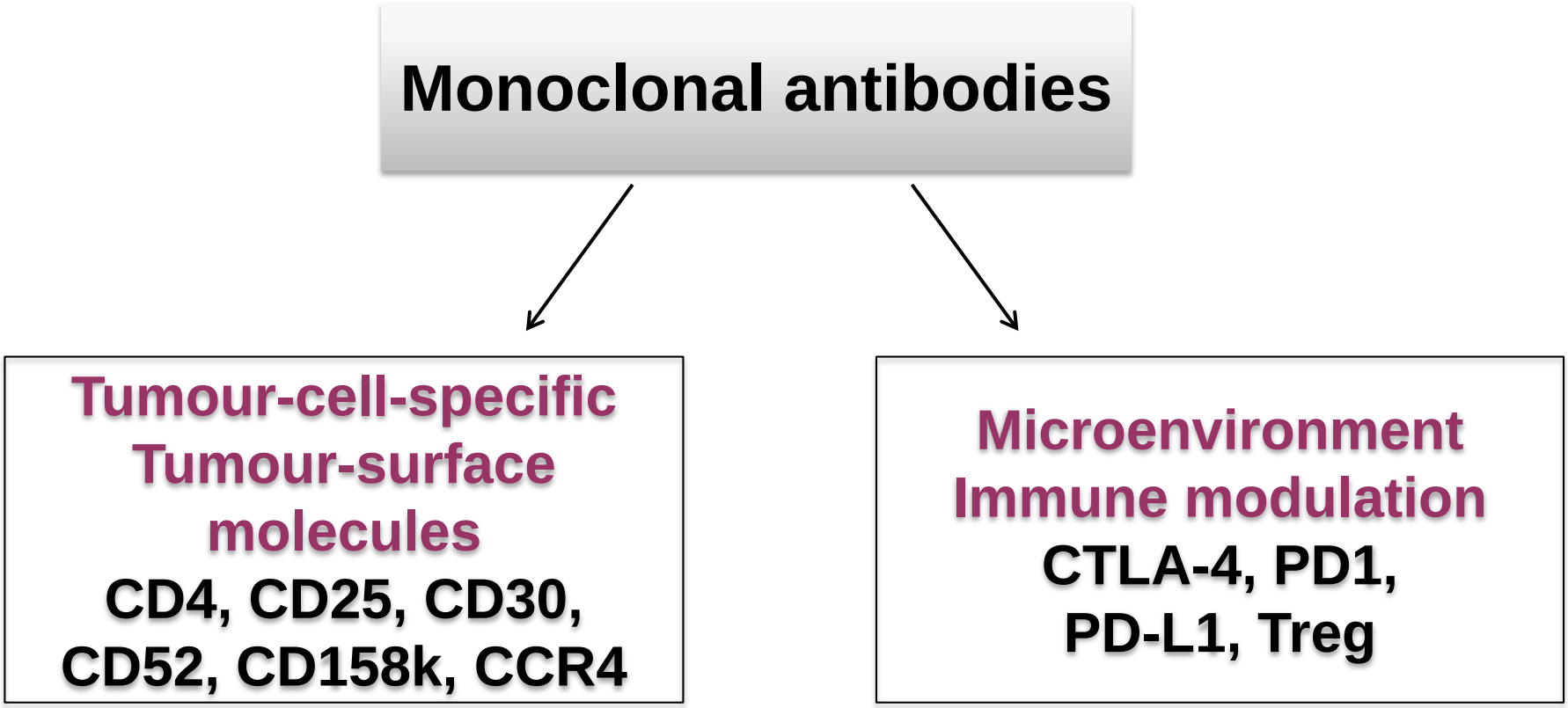
**brentuximab, pralatrexate, liposomal doxorubicin, gemcitabine, other

EFFICACY OF SYSTEMIC AGENTS IN CTCL

ONLY 4 AGENTS WITH FDA APPROVAL, 1 WITH EU APPROVAL

	Efficacy data for FDA approval					
Agent (Class)	Indication	Year	Study	N	ORR	DOR
Romidepsin (HDAC inhibitor, not approved in EU)	CTCL with prior systemic therapy	2009	Pivotal	96	34%	15 mo
			Supportive	71	35%	11 mo
Vorinostat (HDAC inhibitor, not approved in EU)	Cutaneous manifestations	2006	Pivotal	74	30%	6+ mo
			Supportive	33	24%	4 mo
Denileukin diftitox (Fusion protein, not approved in EU)	Tumors that express CD25	1999, 2008	Pivotal	71	30%	4 mo
Bexarotene (RXR activator)	Cutaneous manifestations	1999	Pivotal	62	32%	5+ mo

TARGETS FOR IMMUNOTHERAPY WITH MONOCLONAL ANTIBODIES IN CTCL



CCR4, C-C chemokine receptor type 4; CTCL, cutaneous T-cell lymphoma; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD1, programmed cell death protein 1; PD-L1, programmed death ligand 1; Treg, regulatory T cell.

LANDSCAPE OF MONOCLONAL ANTIBODIES IN CTCL

- Anti-CD52 mAb *(alemtuzumab)*
- Anti-CD30 mAb *(brentuximab vedotin)*
- Anti-CCR4 mAb *(mogamulizumab/KW-0761)*
- *Anti-PD1 mAb (nivolumab)*
- Anti-CD158k mAb *(IPH4102)*

mAb, monoclonal antibody.

ALEMTUZUMAB (ANTI-CD52)

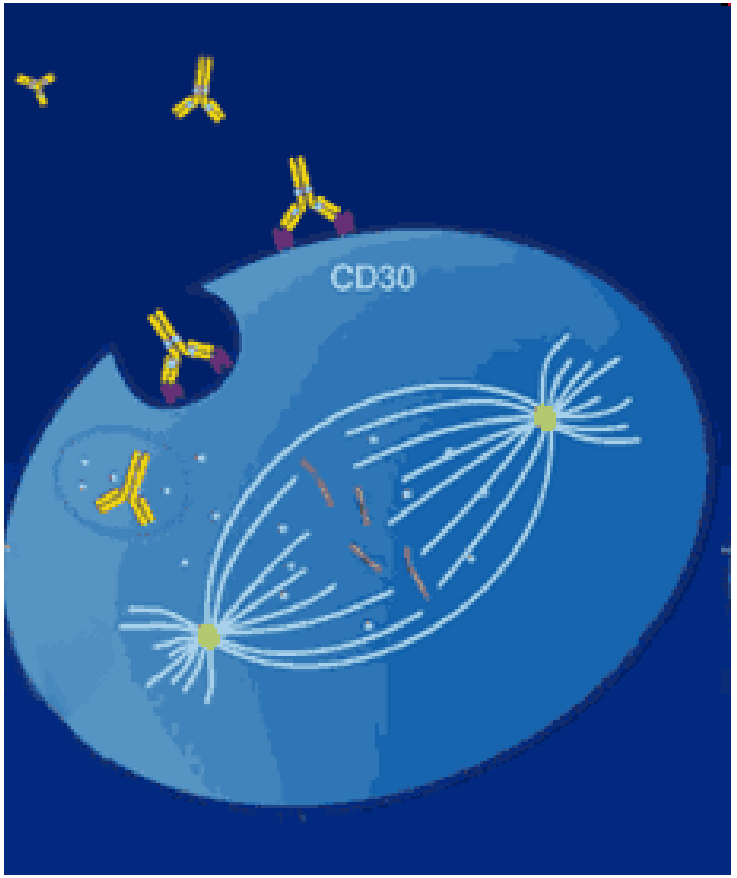
- CD52 antigen, expressed by most T and B lymphocytes
- In retrospective studies:
  - > RR range: 38 to 86%
  - > Median time to progression: 3 – 12 months
- Good efficacy in Sézary syndrome at high dose
- Lead to severe immune depletion and opportunistic infections
- Lack of long duration of response
- Approval withdrawn for the treatment of hematological malignancies
- Protocols of lower-dose administration in order to minimize immune suppression and infections

Bernengo MG, et al. Haematologica. 2007;92:784-94.
Lundin J, et al. Blood. 2003;101:4267-72.
Kennedy GA ,et al. Eur J Haematol. 2003;71:250-6.
Querfeld C, et al. Leuk Lymphoma. 2009;50:1969-76.
Bernengo MG, et al. Haematologica. 2007;92:784-94.
de Masson A, et al. Br J Dermatol. 2014;170:720-4.

DRUGS IN DEVELOPMENT IN CTCL

BRENTUXIMAB VEDOTIN (ANTI-CD30 DRUG CONJUGATE)

- CD30: is expressed on activated B, T and NK cells, and activated monocytes in hematopoietic tissues.
- Brentuximab vedotin (SGN-35) is a chimeric anti-CD30 mAb conjugated to monomethyl auristatin E (MMAE), a cytotoxic anti-tubulin agent
- Infusions every 3 weeks
- In recurrent sALCL: ORR:86%, CR: 59%



Bartlett NL, et al. J Clin Oncol. 2010;28 Suppl 15:abstract 8062.
Pro B, et al. J Clin Oncol. 2012;30:2190-6.
NCI Cancer Bulletin. 2010;7:24.

sALCL, systemic anaplastic large-cell lymphoma.

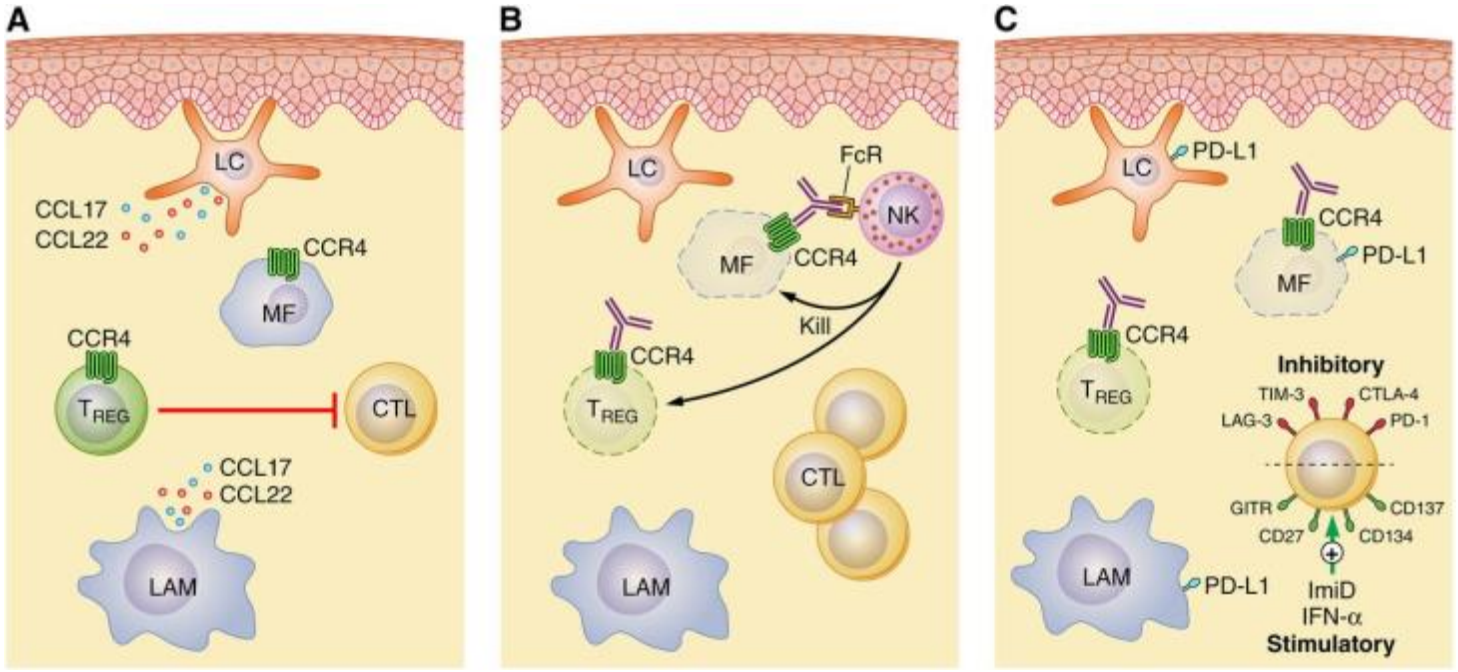
DRUGS IN DEVELOPMENT IN CTCL
BRENTUXIMAB VEDOTIN (ANTI-CD30 DRUG CONJUGATE)

- Preliminary results:
  - > 2 Phase II studies (48 pts with CD30+ MF/SS and LPD; 30 pts with MF/SS with various degree of CD30 expression)
  - > ORR ~ 70%; CR rate 35 and 3% respectively
  - > Median duration of response ~ 32+ weeks
  - > Peripheral neuropathy reported in ~ 2/3 of the patients with a median time to improvement of 42-49 weeks
- Ongoing developments
  - > Randomized Ph III against bexarotene or methotrexate (NCT01578499)
  - > Relapsed/refractory CD30-positive CTCL, ***excluding*** **Sézary syndrome**

Kim et al, JCO 2015; Duvic et al, JCO 2015

DRUGS IN DEVELOPMENT IN CTCL

MOGAMULIZUMAB (ANTI-CCR4)



CCR4: trafficking receptor for systemic memory Th2 and regulatory T cells to skin and lung

Wilcox RA, 2015

DRUGS IN DEVELOPMENT IN CTCL
MOGAMULIZUMAB (ANTI-CCR4)

- Preliminary results:
  - > Phase I/II study in MF + SS patients (38 evaluable pts):
    - ORR = 36.8% (28.6% in 21 MF patients and 47.1% in 17 SS patients)
    - Median PFS = 11.4 months
    - Median DOR = 10.4 months
    - Mogamulizumab well tolerated
- Approved in Japan
- Ongoing clinical development
  - > Randomized Phase III against vorinostat (NCT01728805)
  - > Relapsed/refractory stage ≥ IB CTCL, ***excluding transformed MF***

Duvic et al, Blood 2015

DRUGS IN DEVELOPMENT IN CTCL

PD-1 INHIBITOR NIVOLUMAB

- PD-1 expression was evidenced in CTCL
- Preliminary results:
  - > Phase I study of nivolumab in pts with relapsed or refractory lymphoid malignancies: 105 patients including 13 with mycosis fongoides
  - > ORR in MF: 2/13 (15%), no complete response

	Objective Response Rate, n (%)	Complete Responses, n (%)
B-Cell Lymphoma* (n=29)	8 (28)	2 (7)
Follicular Lymphoma (n=10)	4 (40)	1 (10)
Diffuse Large B-Cell Lymphoma (n=11)	4 (36)	1 (9)
T-Cell Lymphoma† (n=23)	4 (17)	0 (0)
Mycosis Fungoides (n=13)	2 (15)	0 (0)
Peripheral T-Cell Lymphoma (n=5)	2 (40)	0 (0)
Multiple Myeloma (n=27)	0 (0)	0 (0)
Primary Mediastinal B-Cell Lymphoma (n=2)	0 (0)	0 (0)

Lesokhin et al, ASH2014

FROM KIR3DL2 TO IPH4102, A NEW TARGETED THERAPY FOR CTCL

KIR3DL2

A SPECIFIC MARKER OF CTCL CELLS

HOW CAN WE FIND NEW EFFICIENT TREATMENTS FOR CTCL PATIENTS ?

- Genomic studies to identify mutations and relevant targets within various signaling pathways
- Non specific immunotherapy: unleashing the immune system by releasing its negative regulatory checkpoints
- Specific immunotherapy: identifying tumor specific antigens to develop monoclonal antibodies specific for tumor antigens

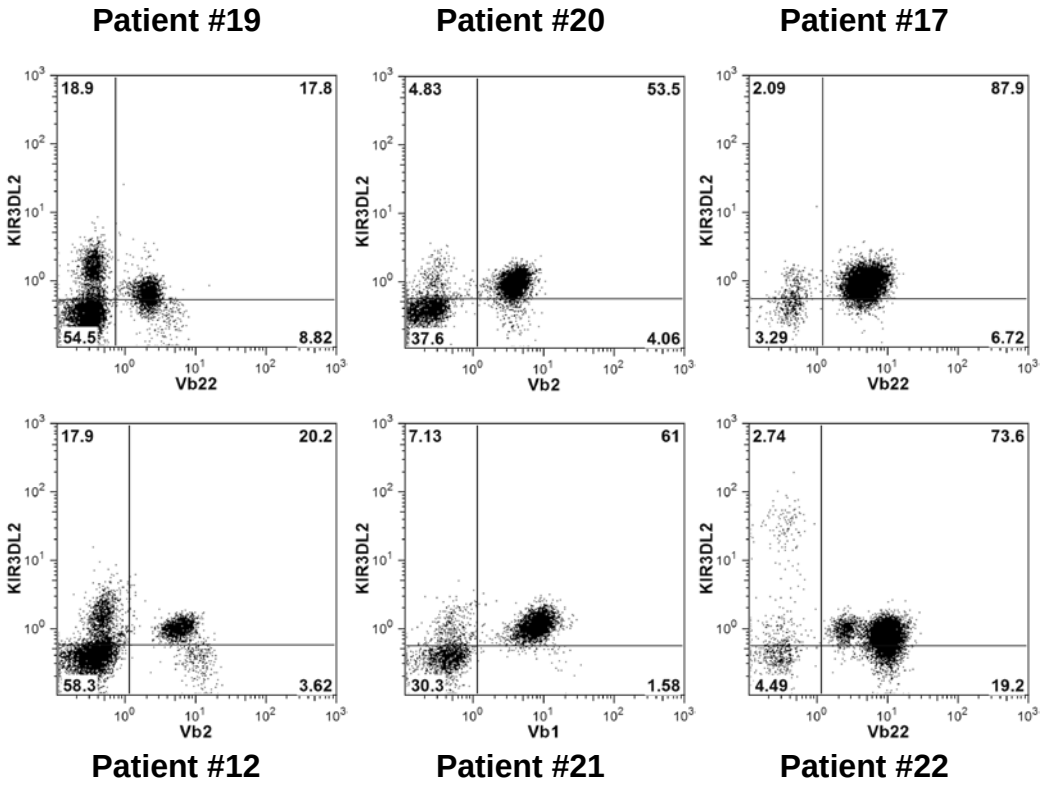
T CELL CLONES ISOLATED FROM CTCL MAY ARISE FROM TUMOR T LYMPHOCYTES BUT ALSO FROM REACTIVE T LYMPHOCYTES

Significance of circulating T-cell clones in Sézary syndrome

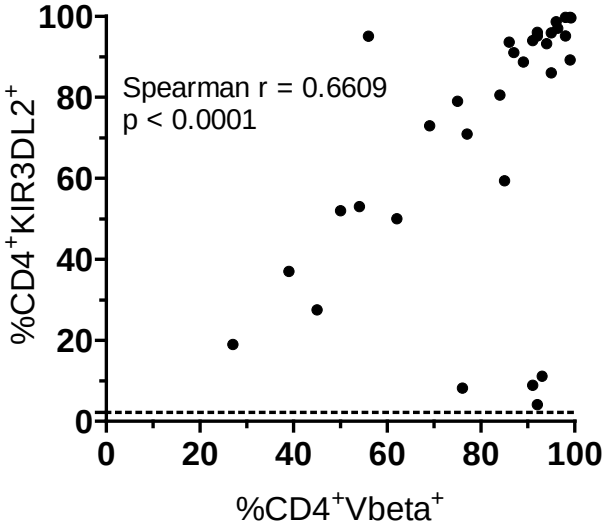
Nicolas Ortonne, Delphine Huet, Caroline Gaudez, Anne Marie-Cardine, Valérie Schiavon, Martine Bagot, Philippe Musette, and Armand Bensussan

Identification of malignant Sézary cells by T-cell receptor (TCR) clonality studies is routinely used for the diagnosis of Sézary syndrome, but T-cell clones expressed in a single patient have never been accurately characterized. We previously reported that CD158k expression delineates Sézary syndrome malignant cells, and, more recently, we identified vimentin at the surface membranes of Sézary cells and normal activated lymphocytes. In the present study, T-cell clones from 13 patients with Sézary syndrome were identified by immunoscopy and further characterized in the blood according to their TCR Vβ, CD158k, and vimentin cell-surface expression. We found in most patients a unique malignant T-cell clone that coexpressed CD158k and vimentin and that, when patients were tested, was also present in the skin. However, in some patients we detected the presence of a nonmalignant circulating clone expressing high amounts of vimentin and lacking CD158k. These results indicate that clonal expansion may originate from circulating malignant and nonmalignant CD4$^+$ T cell populations in patients with Sézary syndrome. Identification of the malignant cells in Sézary syndrome cannot be achieved by T-cell clonality studies or by TCR Vβ monoclonal antibody (mAb) analysis alone; it also relies on CD158k phenotyping. (Blood. 2006;107:4030-4038)

KIR3DL2 IS A PHENOTYPIC MARKER FOR SEZARY CELLS



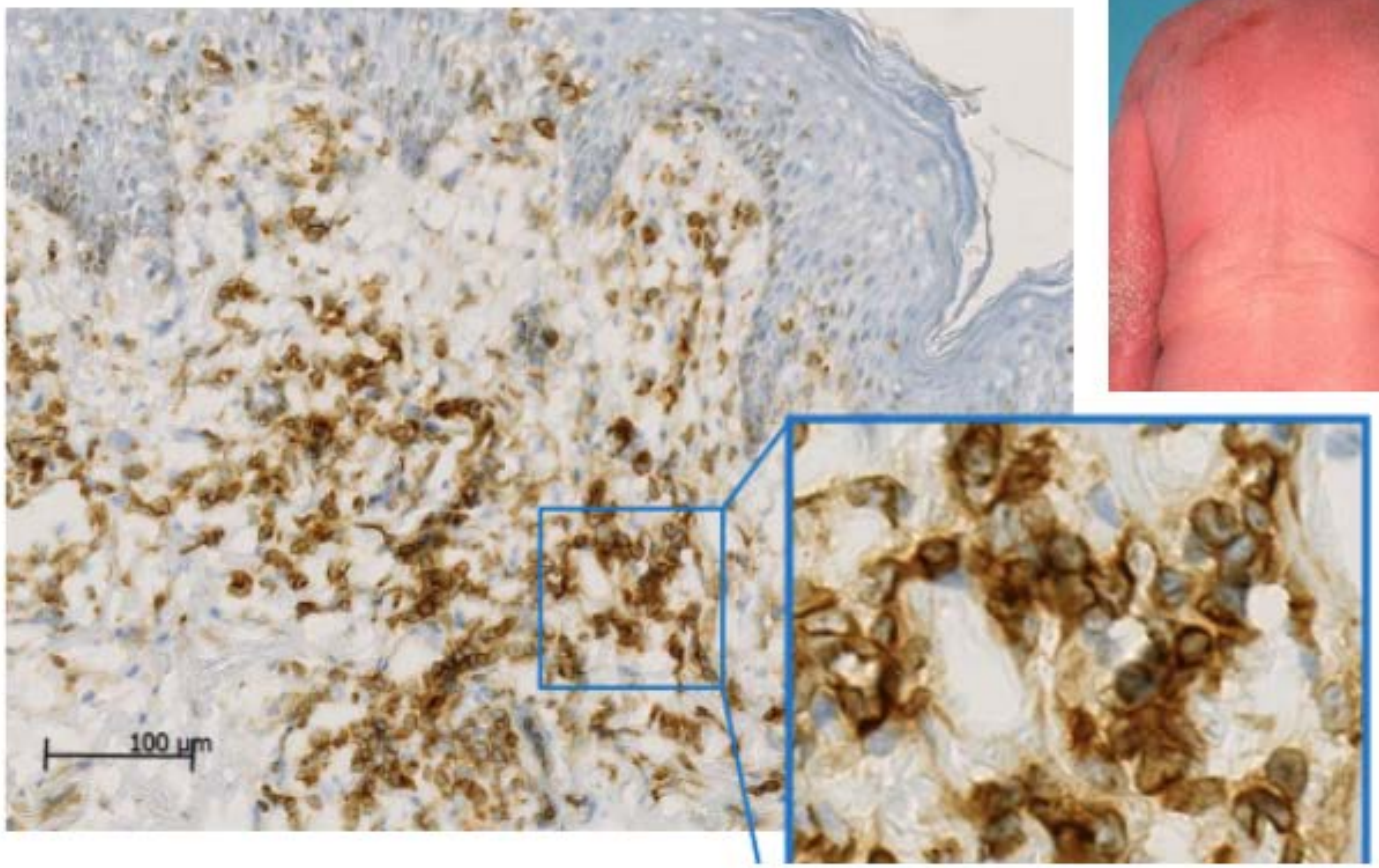
Clonal leukemic Sézary cells, defined by a single Vβ chain expression, are KIR3DL2⁺ in patient blood.



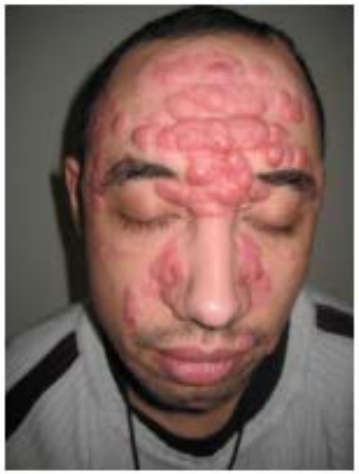
Marie-Cardine A. et al, Cancer Research 2014

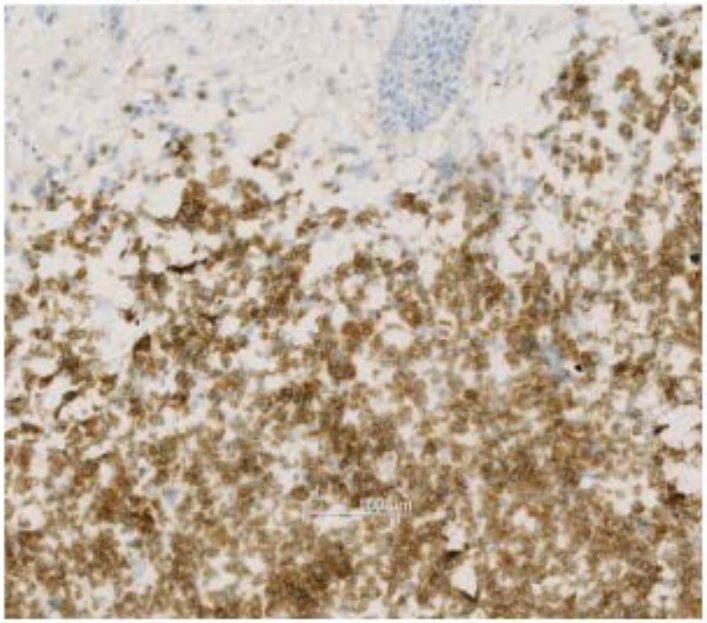
SÉZARY SYNDROME

KIR3DL2 STAINING

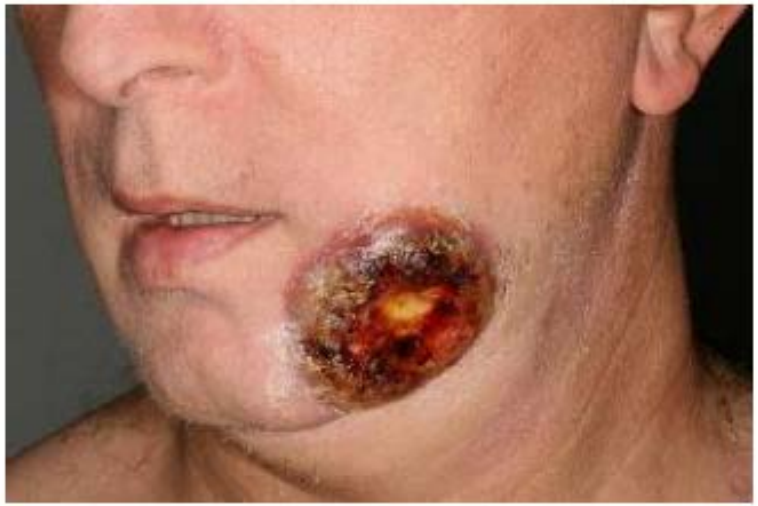


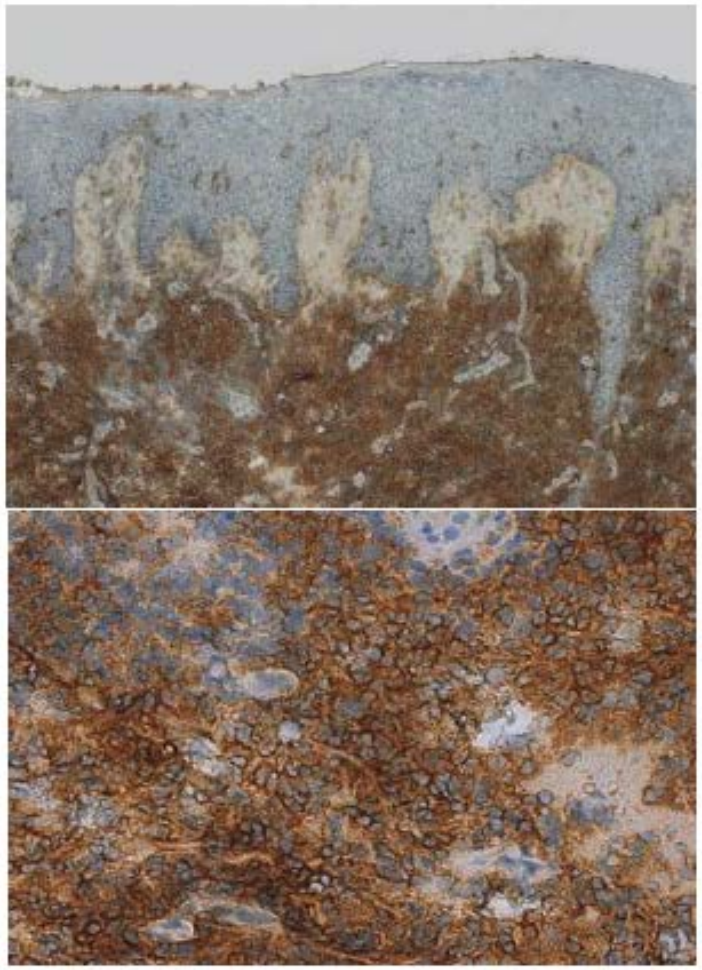
TRANSFORMED MYCOSIS FUNGOIDES
KIR3DL2 STAINING



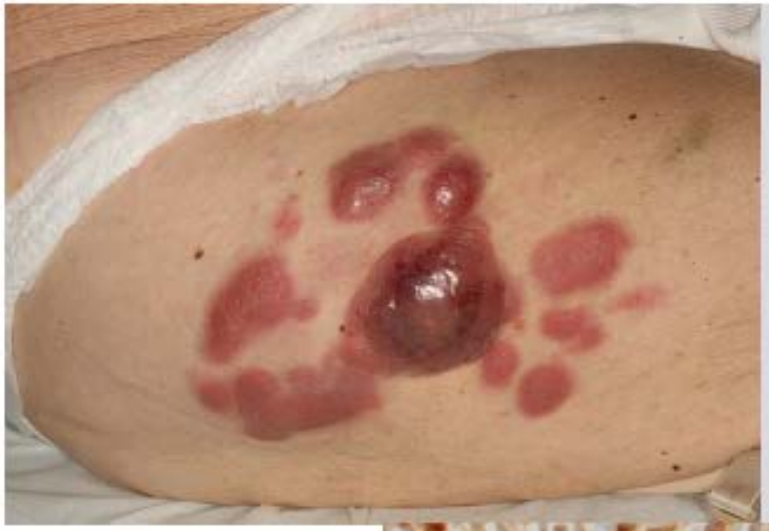


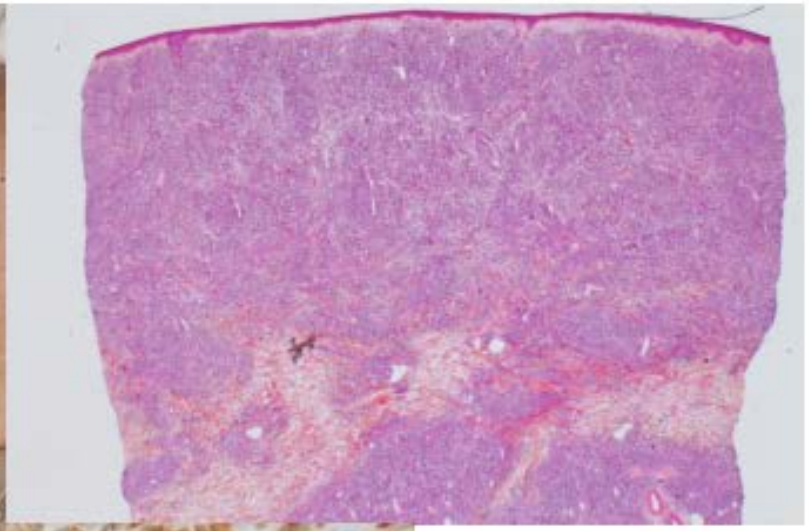
PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA
KIR3DL2 STAINING

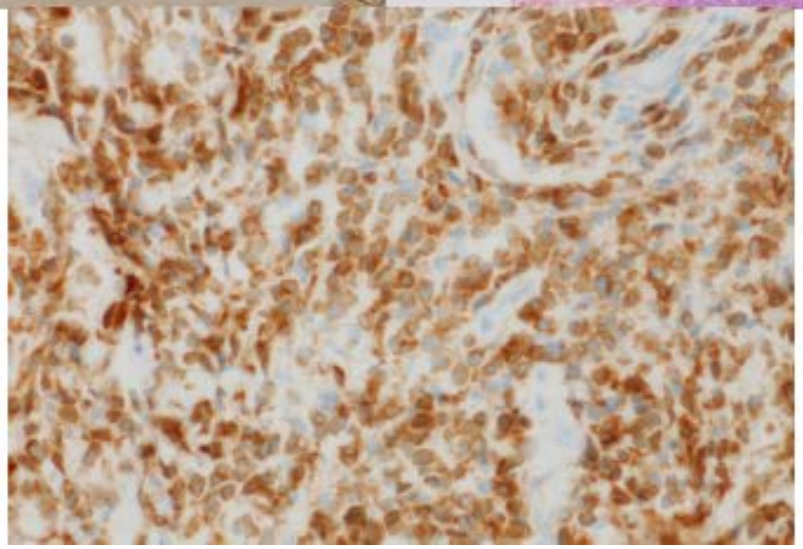




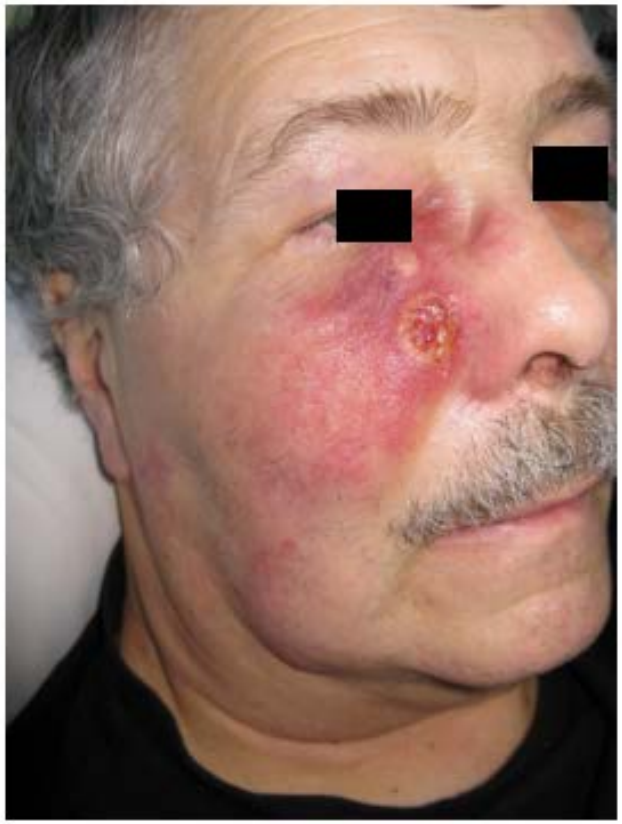
CUTANEOUS γ/δ T-CELL LYMPHOMA
KIR3DL2 STAINING

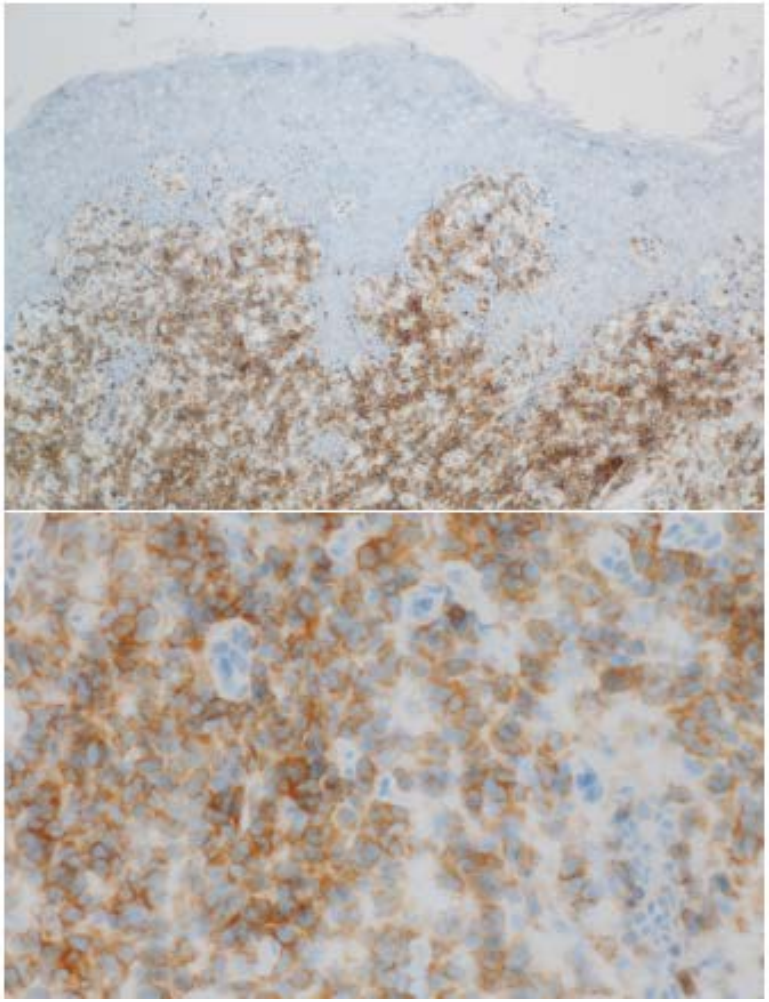






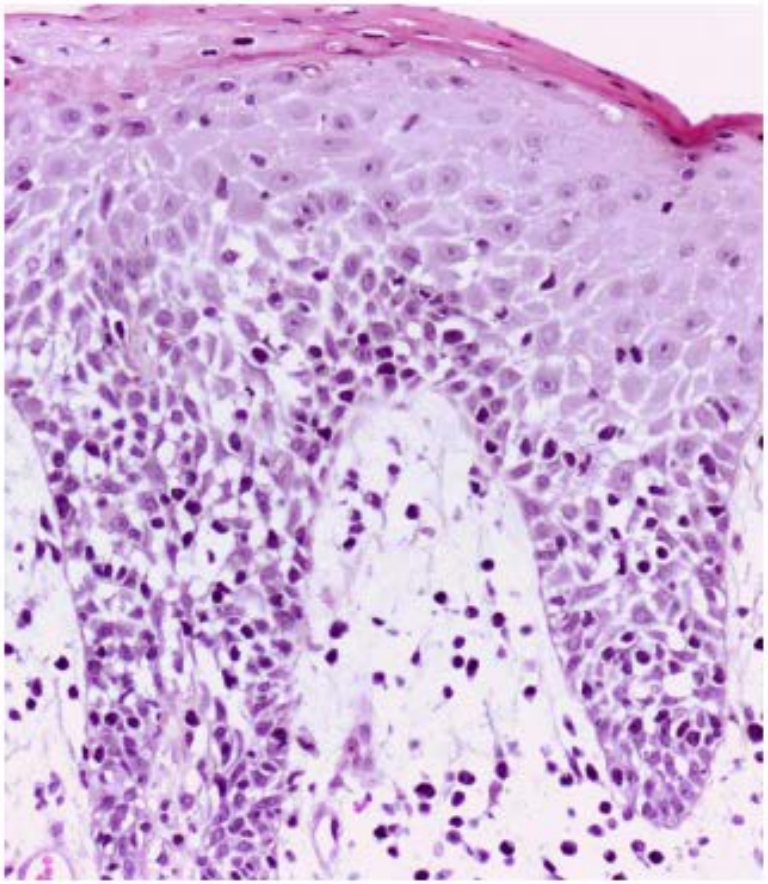
EXTRANODAL NK/T LYMPHOMA, NASAL TYPE
KIR3DL2 STAINING

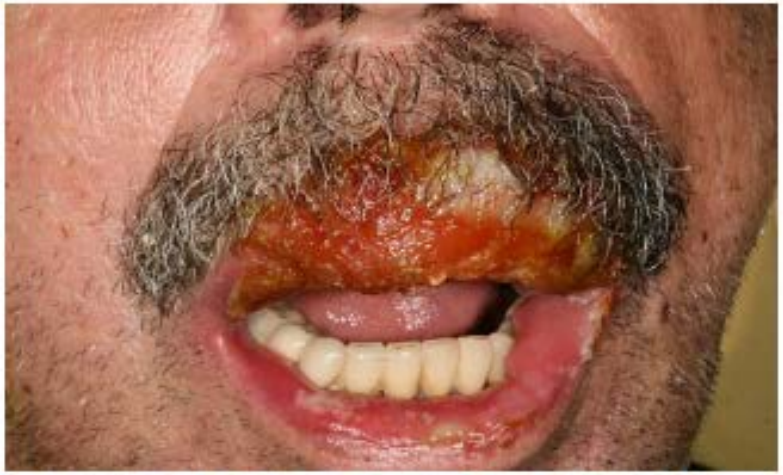


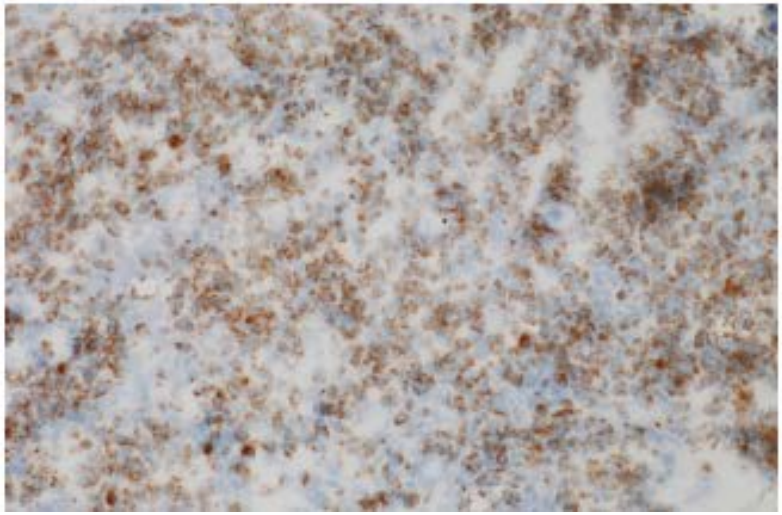


PRIMARY CUTANEOUS AGGRESSIVE EPIDERMOTROPIC CD8+ T-CELL LYMPHOMA

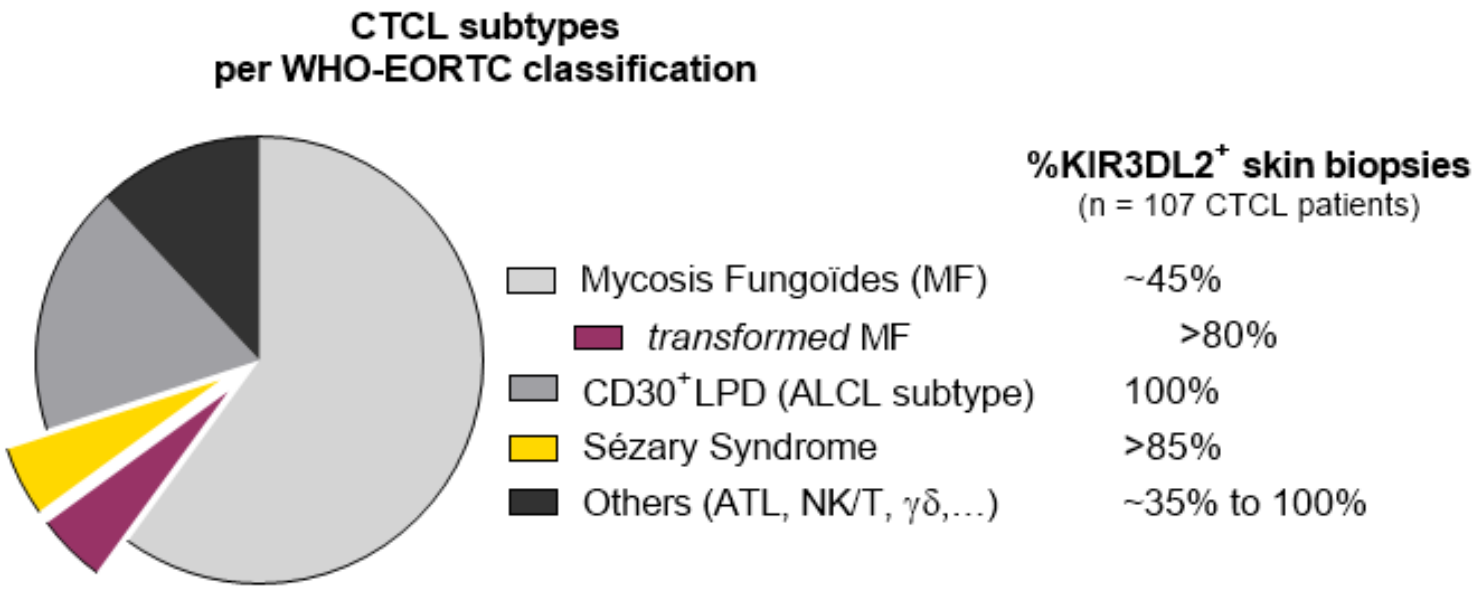
KIR3DL2 STAINING







CTCL LANDSCAPE
KIR3DL2 EXPRESSION BY WHO-EORTC SUBTYPE



KIR3DL2 is expressed in ~65% of all CTCL, irrespectively of disease subtype.

Expression is more prominent in Sézary syndrome, transformed mycosis fungoides and CD30+ LPD (ALCL subtype).

CTCL

RATIONALE FOR DEVELOPING AN ANTI-KIR3DL2 IMMUNOTHERAPY

NK CELLS OF SEZARY PATIENTS ARE FUNCTIONAL

Circulating Natural Killer Lymphocytes Are Potential Cytotoxic Effectors Against Autologous Malignant Cells in Sezary Syndrome Patients

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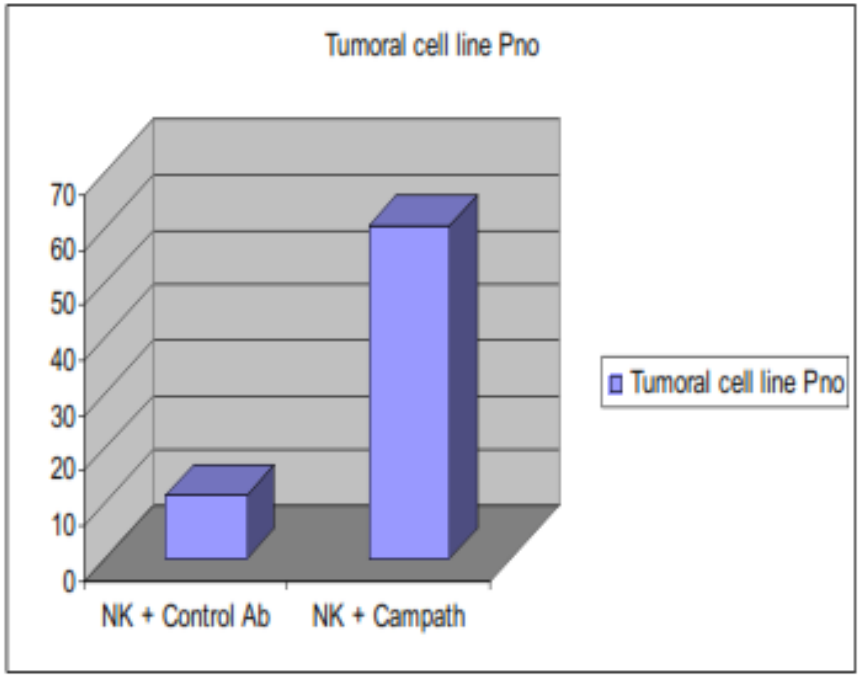
*INSERM 659, Faculté de Médecine de Créteil 8, rue de général Sarrail, Créteil, France

Patients with advanced cutaneous T cell lymphoma (CTCL) exhibit profound defects in cell-mediated immunity. Although it has been suggested that Sezary syndrome (SS) patients have a decreased natural killer (NK) lymphocyte activity, nothing has been reported concerning the sensitivity of Sezary cells to NK lymphocyte-mediated cytotoxicity. Peripheral blood NK cells from healthy donors were tested against Sezary tumoral cell lines as well as against freshly isolated Sezary cells. Further, we studied their ability to exhibit antibody -dependent cell-mediated cytotoxicity using either the murine anti-CD158k/KIR3DL2 monoclonal antibody (moAb) AZ158 that specifically recognizes Sezary cells, or the anti-CD52 monoclonal antibody alemtuzumab. The results show that Sezary cell lines are susceptible to NK lymphocyte lysis. More importantly, we found that freshly isolated malignant cells are killed either by IL-2 activated allogeneic NK lymphocytes or when the tumor lymphocyte targets are incubated with an anti-MHC class I F(ab)'2 antibody. Further, anti-KIR3DL2 and anti-CD52 moAb can enhance the NK lysis. Finally, we report that NK lymphocytes isolated from SS patients are potentially cytotoxic lymphocytes against autologous malignant Sezary cells. These findings indicate that antitumor-mediated NK lymphocyte cytotoxic activity can be triggered in patients with CTCL and raise the possibility of developing novel therapeutic strategies by stimulating their innate immunity.

Bouaziz et al, J Invest Dermatol, 2005

NK LYSIS OF TUMOR CELLS IS ENHANCED VIA AN ADCC MECHANISM

Alemtuzumab



Bouaziz et al, J Invest Dermatol, 2005

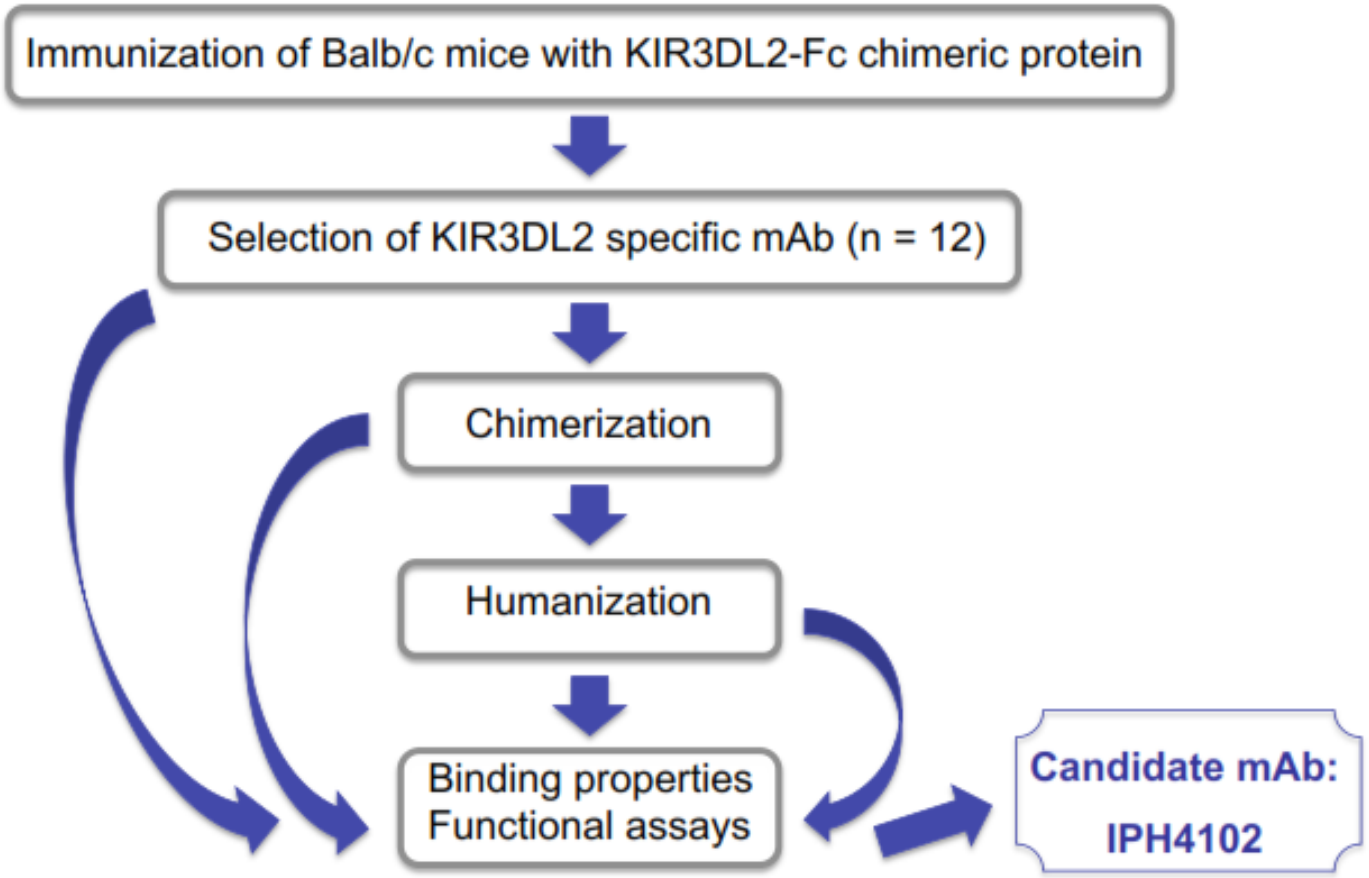
IS IT POSSIBLE TO DEVELOP A SPECIFIC ANTI-KIR3DL2 IMMUNOTHERAPY ?

- Inhibitory receptor, member of the Killer Immunoglobulin-like Receptor (KIR) family
- Specific expression of KIR3DL2 on the malignant CTCL clone, in skin or circulating in blood
  - > In healthy individuals, there is limited expression of KIR3DL2 by normal blood cells (~25% NK cells and <15% T cells)
  - > No KIR3DL2 expression on the FDA panel of human tissues (IHC)
- NK cells in CTCL patients are functional
- CTCL cells are sensitive to perforin/granzyme B lysis
- KIR3DL2 is expressed by up to 95% CTCL cells irrespectively of disease stage and CTCL subtype (IHC study, N = 107 CTCL patients)

➔ **KIR3DL2 is a very restricted and specific marker of CTCL**

➔ **Development of an anti-KIR3DL2 therapeutic monoclonal antibody (Innate Pharma)**

STRATEGY FOR THE GENERATION AND TESTING OF ANTI-KIR3DL2 THERAPEUTIC ANTIBODIES



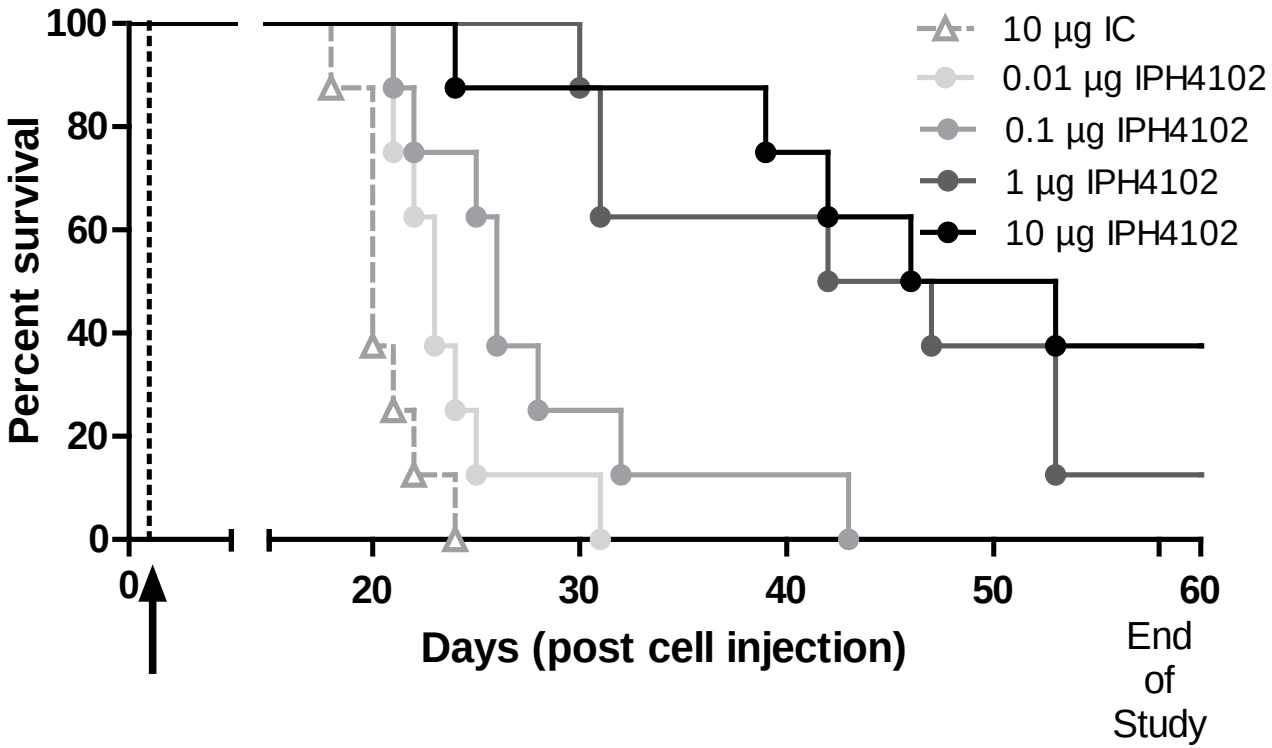
Marie-Cardine A, *et al.* Cancer Res. 2014;74:6060-70.

IPH4102 KEY FEATURES

- **Selective binding to human KIR3DL2 with high affinity**
  - > No cross-reaction to other human KIRs
- **Humanized IgG1 designed to deplete KIR3DL2-positive tumor cells**
- **Compelling efficacy in non clinical studies (large set of *in vitro*, *in vivo* and *ex vivo* models*)***
  - > Main MOA include ADCC and ADCP
  - > Reduces tumor growth and improves survival in murine xenograft models of KIR3DL2^{+} tumors
  - > Induces killing of primary CTCL tumors in the presence of patient autologous NK cells
- **Orphan Drug designation by the EU in 2014 for the treatment of CTCL**
- **Distinct anti-KIR3DL2 mAbs developed for biomarker purposes** (IHC and flow cytometry)

IPH4102 EFFICACY IN MOUSE IV MODELS

IPH4102 improves survival in a dose-dependent manner

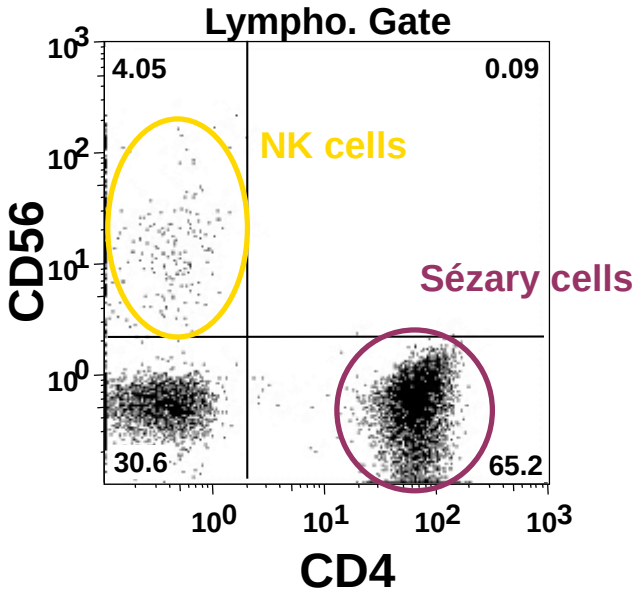


Mice: SCID (n = 8)
RAJI-KIR3DL2: 5 M IV at D0
IPH4102: single IV admin. at D1
Read-out: survival

IPH4102 EFFICACY EX VIVO: AUTOLOGOUS ADCC

EXPERIMENTAL CONDITIONS

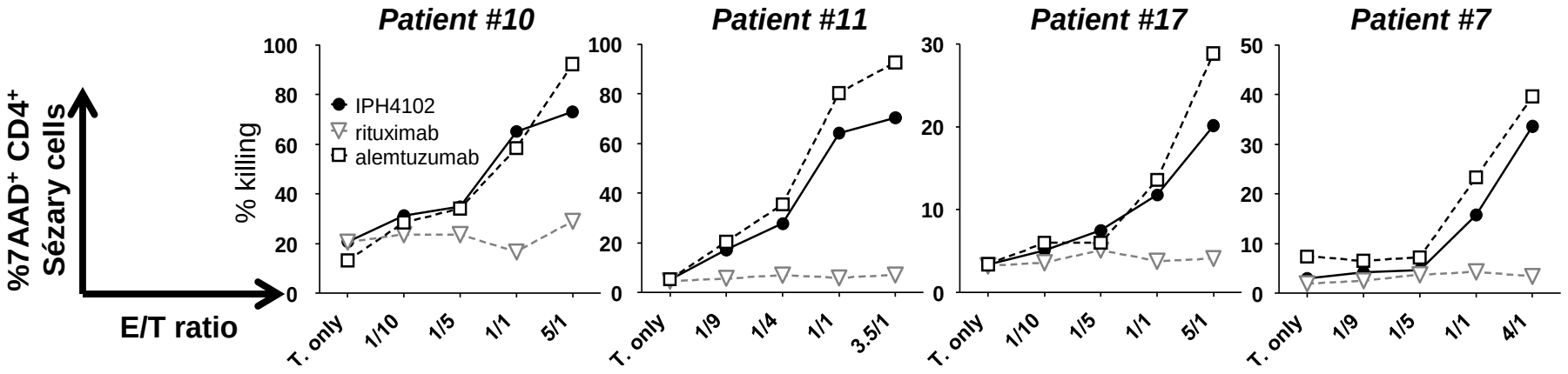
- Fresh blood taken from Sézary Syndrome patients
- CD4 and NK cells separately sorted from PBMC of the same patient (by negative selection)
- NK and CD4 mixed at various E/T ratios ± IPH4102 or alemtuzumab and rituximab as controls
- 4 to 6 hours incubation
- 7AAD incorporation used as marker of cell death
- Flow cytometry read-out



Marie-Cardine A. *et al*, Cancer Res. 2014

IPH4102 EFFICACY EX VIVO: AUTOLOGOUS ADCC

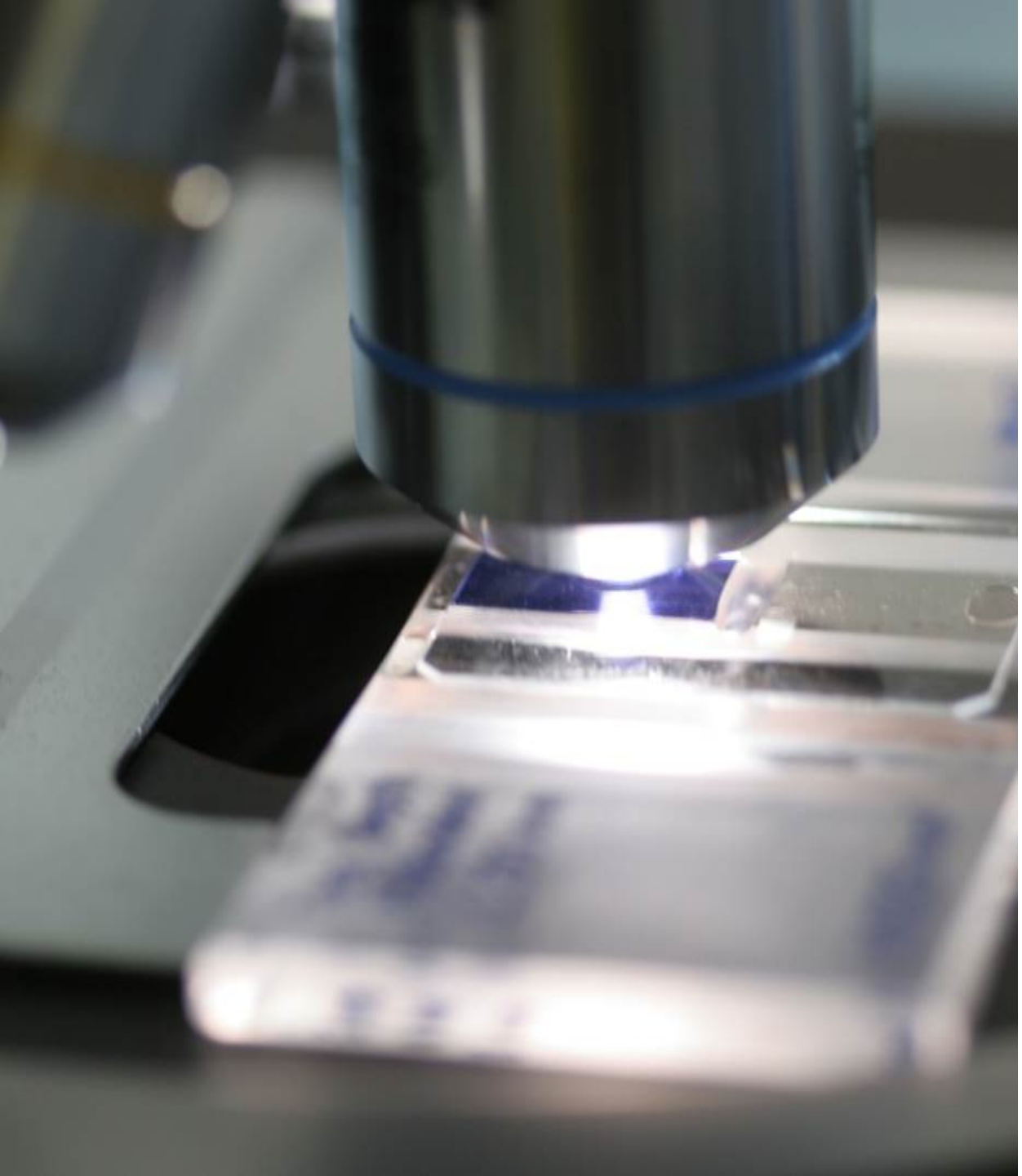
EFFICACY RESULTS



IPH4102 as potent as alemtuzumab in *ex vivo* autologous ADCC assays

mAb: 10 µg/mL
Incubation time: 4 – 6 hours
Read-out: 7AAD incorporation
KIR3DL2 sites per cell: 1,000 to 4,000
%KIR3DL2+ cells among CD4+ > 85%
Total n = 15 patients

Marie-Cardine A. *et al*, Cancer Res. 2014



IPH4102-101 FIH CLINICAL STUDY

OVERVIEW

IPH4102-101 FIRST-IN-HUMAN STUDY DESIGN

OVERVIEW

- **First-in-Human Phase I study of IPH4102**
- **Dose-escalation + cohort expansion study**
- **Dose-escalation part:**
  - > 10 dose levels of repeated administrations of IPH4102
  - > Modified 3+3 design with accelerated titration
  - > First patient expected to be treated 4Q15
  - > Will determine the recommended Phase II dose and schedule
- **Cohort expansion part:**
  - > Selected CTCL subtypes: SS and transformed MF
    - Highest unmet medical need, not fully addressed in the current Phase III trials
    - Most robust KIR3DL2 expression
  - > Start with n = 10 patients in each cohort, expandable according to signals of activity

IPH4102-101 FIRST-IN-HUMAN STUDY DESIGN
OVERVIEW

- **Patient population:**
  - > Relapsed/refractory (≥ 2 previous lines of systemic therapy) CTCL patients
    - All subtypes eligible
  - > For MF/SS patients: clinical stage ≥ IB
  - > KIR3DL2-positivity on skin biopsies is required for eligibility
    - Centrally assessed expression of KIR3DL2 on tumors
    - Allows more relevant assessment of IPH4102 safety profile
    - Allows detecting early signals of clinical activity

IPH4102-101 FIRST-IN-HUMAN STUDY DESIGN
OBJECTIVES

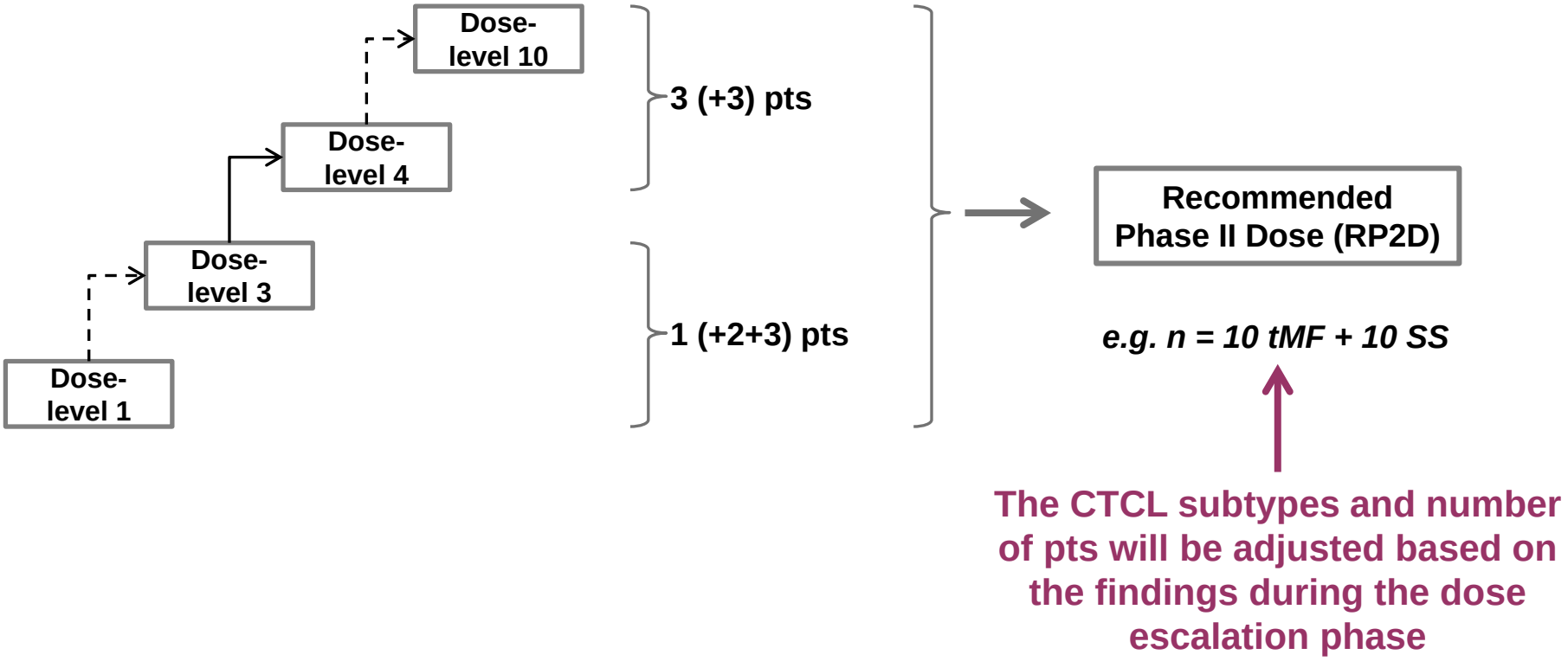
- **Primary objective: to assess safety & tolerability of increasing IV doses of single agent IPH4102 by:**
  - > Characterizing the dose-limiting toxicities (DLT) and (S)AEs
  - > Identifying the MTD or Recommended Ph 2 Dose (RP2D)
- **Secondary objectives:**
  - > To explore antitumor activity
  - > To assess pharmacokinetics (PK) and immunogenicity
- **Translational objectives, biomarker exploration:**
  - > To monitor the fate of KIR3DL2-expression cells in skin lesions, blood and lymph nodes (pharmacodynamics)
  - > To monitor immune cell activation in blood and explore NK cell and macrophage infiltration in skin lesions
  - > To assess Minimal Residual Disease (clonal Vβ chain)
  - > To assess cytokine release

IPH4102-101 FIRST-IN-HUMAN STUDY DESIGN

STUDY DESIGN

- **Dose-escalation Part:**
  accelerated 3+3 design
  pts with KIR3DL2+ tumors
  all CTCL subtypes eligible

- **Cohort expansion Part:**
  same dose for all: RP2D
  pts with KIR3DL2+ tumors
  pre-selected CTCL subtypes



IPH4102-101 FIRST-IN-HUMAN STUDY DESIGN
PARTICIPATING SITES

- **Two-continent Phase I study**
- **Clinical sites (dose-escalation part):**
  - St Louis Hospital, Paris France (M Bagot)
  - UMC Leiden, the Netherlands (M Vermeer)
  - Guy's and St Thomas' Hospital, London UK (S Whittaker)
  - Stanford U, Stanford CA, US (Y Kim)
  - MD Anderson, Houston TX, US (M Duvic)
  - OSU, Columbus OH, US (P Porcu)
- **Strong collaborative work between Innate Pharma and investigators**

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