innate pharma

CTCL LUNCHEON

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PROF. OF DERMATOLOGY, STANFORD CANCER INSTITUTE & SCHOOL OF MEDICINE

NEW YORK,
OCTOBER 2, 2015

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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

2000 **2005** **2010** **2015** **2020**

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

INNATE PHARMA PIPELINE

PROGRAM	TARGET	INDICATIONS AND SETTING	ONGOING STUDIES
Lirilumab (IPH2102/BMS-986015) licensed to Bristol-Myers Squibb	KIR2DL1,2,3	AML, single agent	• Randomized Phase II
		Solid & heme tumors Multiple combinations	• 6 Phase I and II trials
IPH2201 co-development with AstraZeneca	NKG2A	Solid & heme tumors Multiple combinations	• Phase II
IPH4102	KIR3DL2	Cutaneous T-cell lymphomas	• Phase I to start in 2015
IPH33	TLR3	Inflammation / Autoimmunity	• Preclinical
IPH43	MICA	Cancer	• Preclinical
Other / Discovery	Undisclosed	Cancer / Inflammation	• Preclinical

YOUN KIM, MD, PROFESSOR OF DERMATOLOGY, STANFORD MEDICAL SCHOOL

Youn H. Kim, M.D., is an internationally renowned expert in cutaneous lymphomas.

She serves as Director of the Multi-disciplinary Cutaneous Lymphoma Program, Director of the Residency Program in the Department of Dermatology, and Medical Director of the Photopheresis Unit at Stanford Medical Center. Dr. Kim is also Co-Director of the Lymphoma Research Program at the Stanford Cancer Institute and the first recipient of Stanford University's Joanne and Peter Haas Jr. Professorship for Cutaneous Lymphoma Research. She is a member of the National Comprehensive Cancer Network Non-Hodgkin's Lymphoma Panel.

Dr. Kim received her medical degree and completed her residency at Stanford University School of Medicine. She is Board Certified in Dermatology.

TARGETING KIR3DL2 WITH IPH4102 IN CTCL

Youn H Kim, MD

Department of Dermatology
Director, Multidisciplinary Cutaneous Lymphoma Group
Stanford Cancer Institute & School of Medicine

DISCLOSURE STATEMENT

Youn Kim, MD

- Steering Committee
  - > Eisai, Kyowa Hakko Kirin, Takeda/Millennium
- Consultant or Advisory Board
  - > Actelion, Celgene, Galderma, Soligenix, Neumedicine, Seattle Genetics, MiRagen, Horizon
- Investigator
  - > Kyowa Hakko Kirin, Merck, Takeda/Millennium, Seattle Genetics, Actelion, Eisai, Genentech, Tetralogic, Innate

- *No financial compensation or honorarium from Innate*

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

SEPTEMBRE 2015

CTCL

A RARE DISEASE WITH HIGH UNMET MEDICAL NEED

Cutaneous T-cell Lymphomas (CTCL)

CTCL is heterogeneous group of NHL presenting primarily in the skin, of malignant clonal T cells

New WHO-EORTC Classification
Mycosis fungoides and variants/subtypes
Sézary syndrome
PC CD30+ lymphoproliferative disorders
Subcutaneous panniculitis-like T-cell lymphoma
Cutaneous γ/δ T-cell lymphoma
Adult T-cell leukemia/lymphoma
PC peripheral T-cell lymphoma, unspecified • Aggressive epidermotropic CD8+ T-cell lymphoma • CD4+ sm/med-sized pleomorphic T-cell LPD • PTCL, other

Blood 2005;105: 3768-85

WHO monogram, 4th Ed, 2008

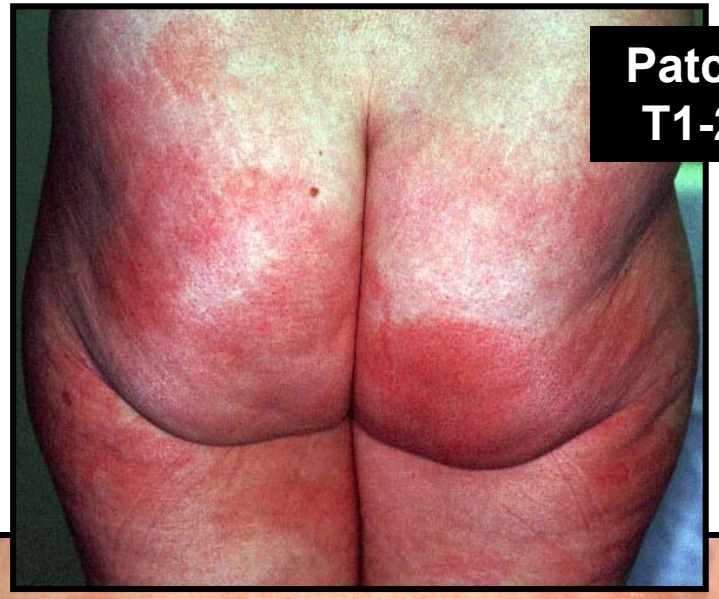
MYCOSIS FUNGOIDES & SÉZARY SYNDROME

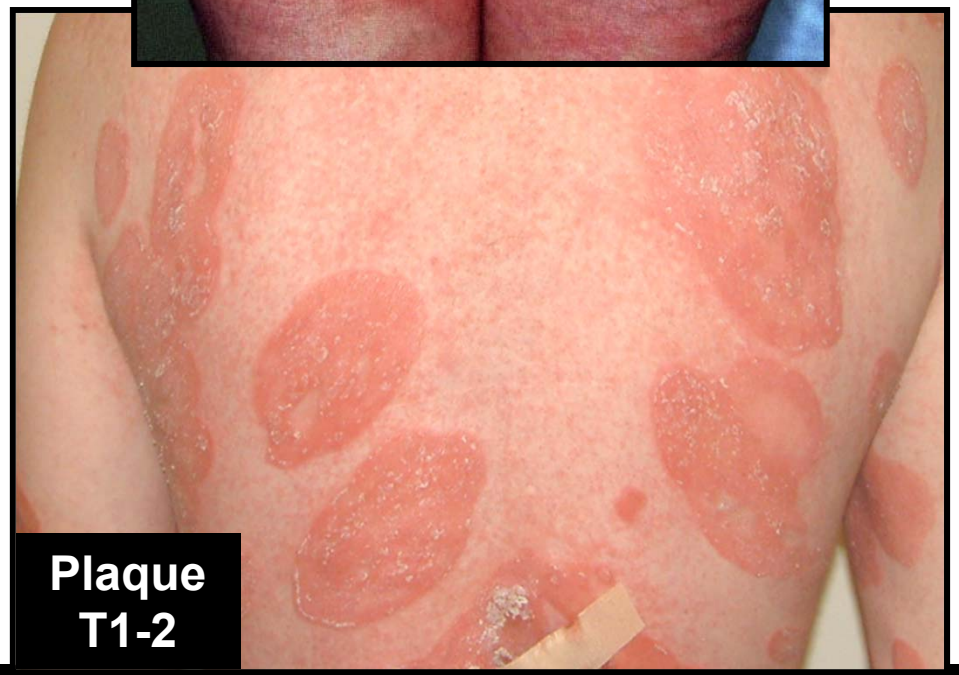
Most common of the cutaneous T-cell lymphomas

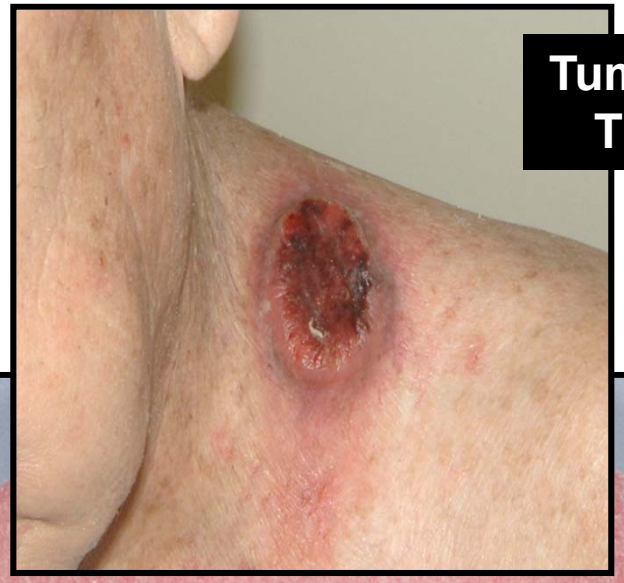
- Continued rising annual incidence in US (SEER)[1]
  - > 0.96 per 100,000
    - 3,000 new cases
  - > ↑ by 2.9 per million per decade
  - > 4% of NHLs
- Median age at diagnosis is 55-65 yrs
  - > Two-thirds present with early stage disease (IB-IIA)
- Factors predictive of disease progression or survival[2,3]
  - > 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)

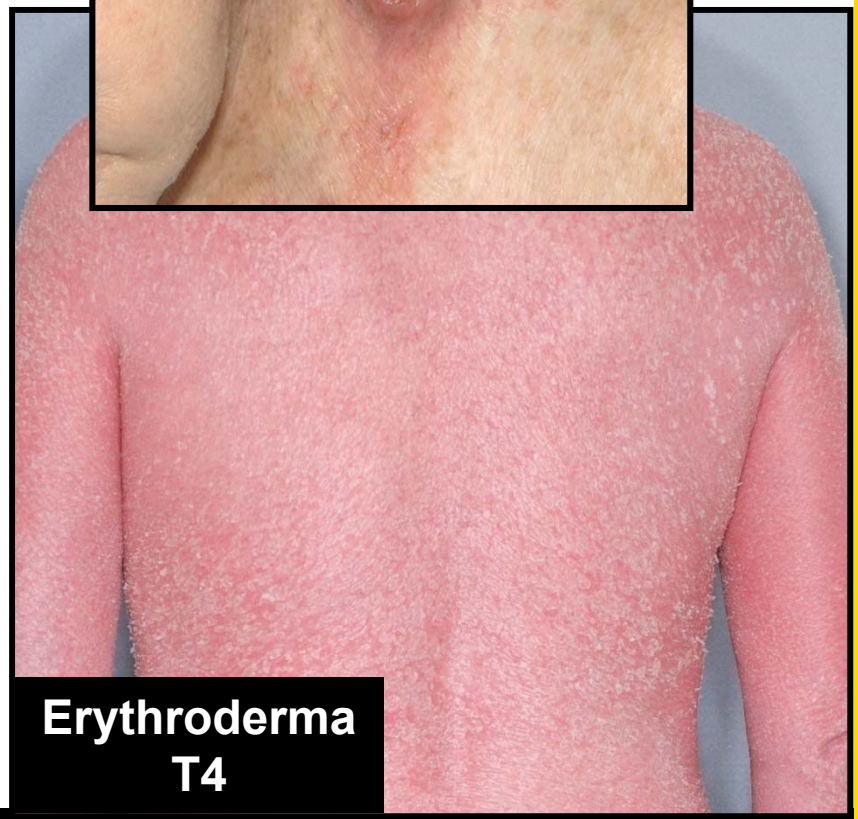
[1] Arch Dermatol 2007;143:184-189; [2]Arch Dermatol 2003;139:857-866; [3]JNCCN 2008;6:436-441

MYCOSIS FUNGOIDES
TREATMENT OF VARYING SKIN MANIFESTATIONS

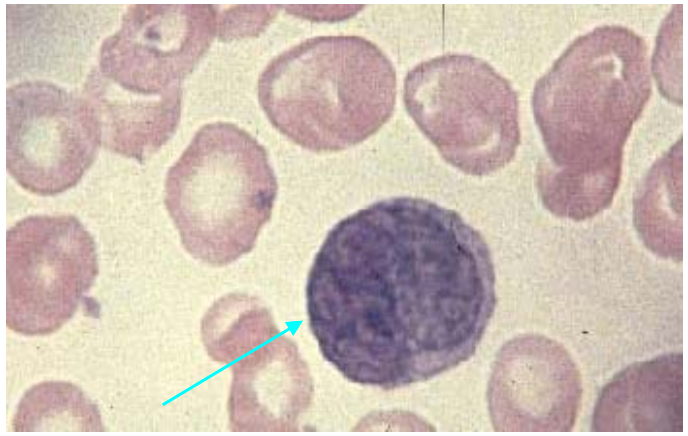






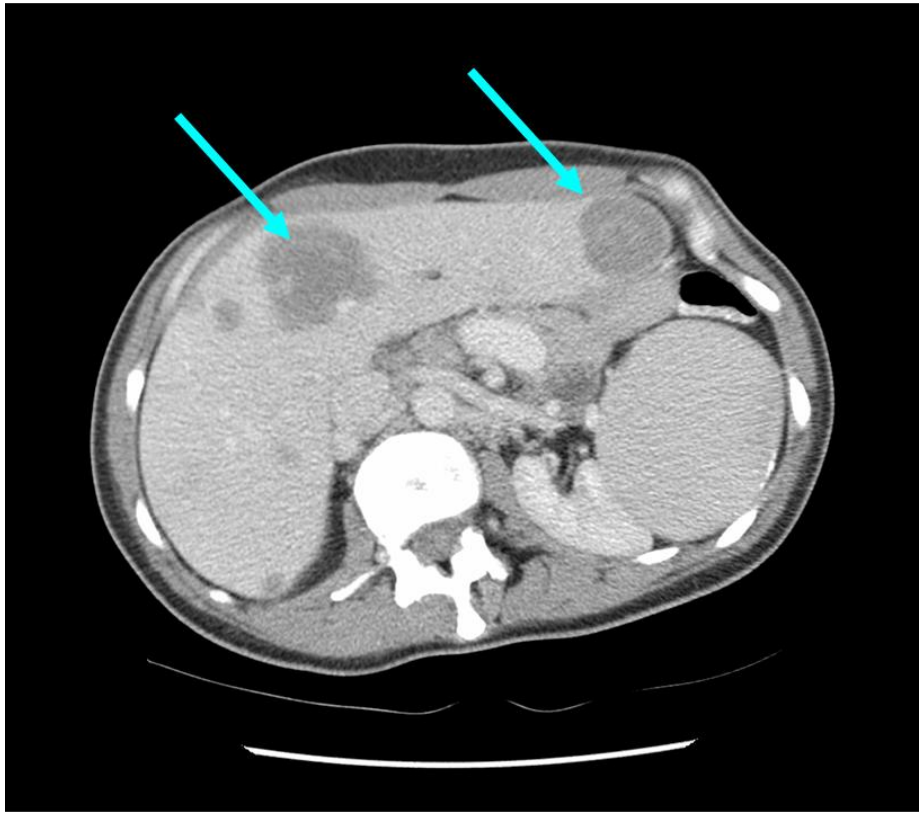


MANAGEMENT OF EXTRACUTANEOUS DISEASE

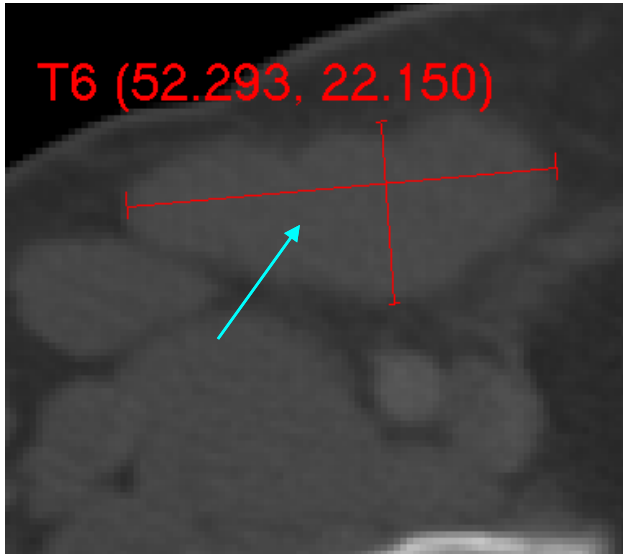


Blood

Viscera

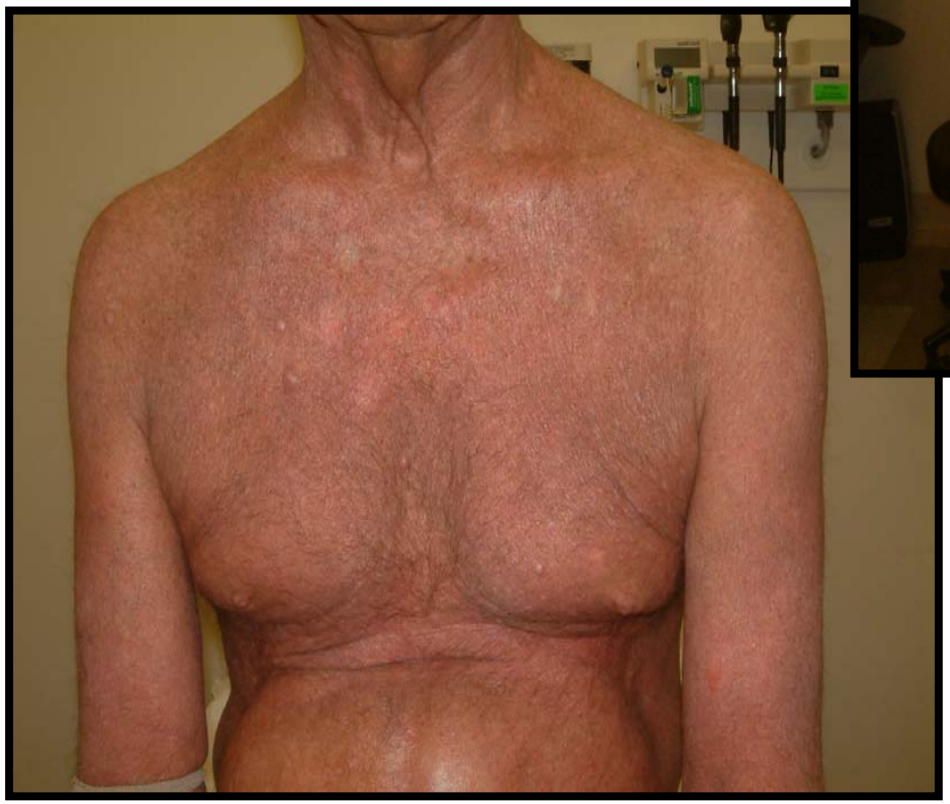


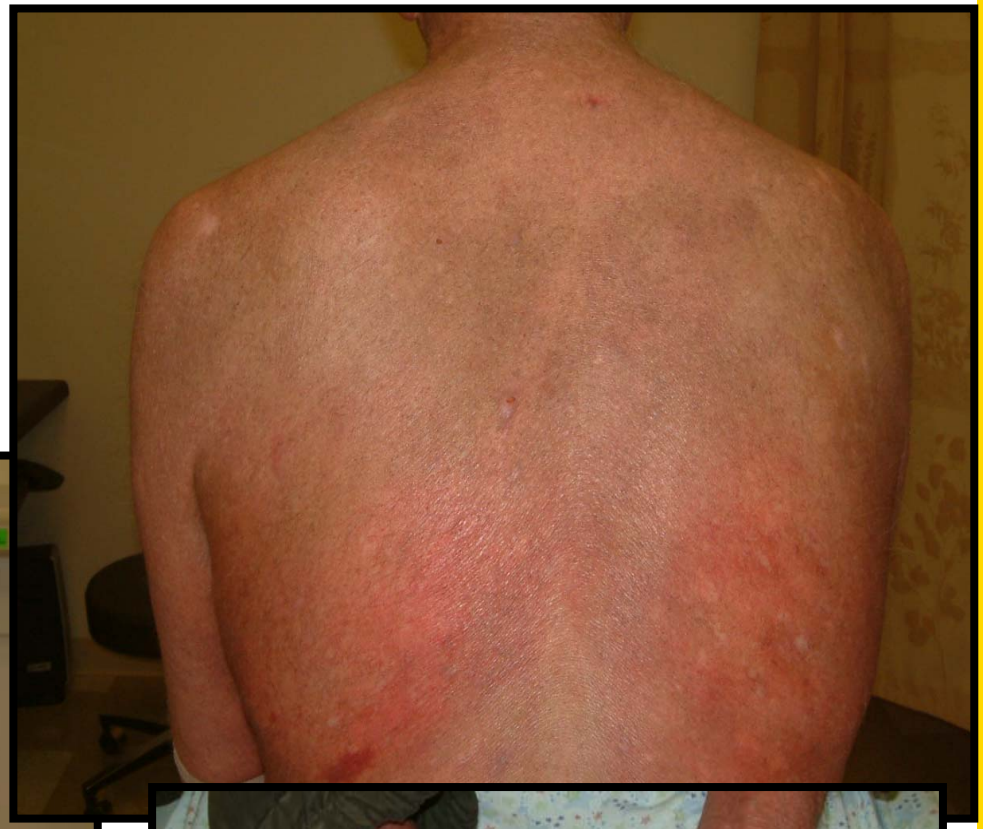
Lymph node

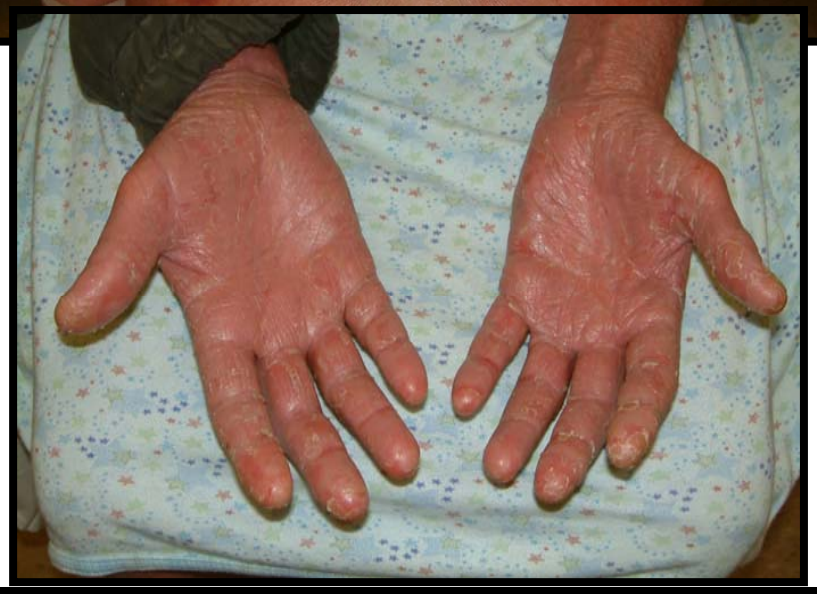


Sézary syndrome-

generalized erythroderma, keratoderma, severe itching; freq staph aureus infection

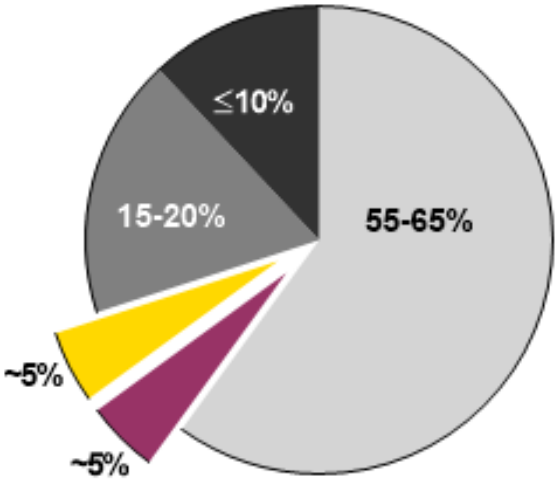






CTCL LANDSCAPE
SURVIVAL PER WHO-EORTC SUBTYPE

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%

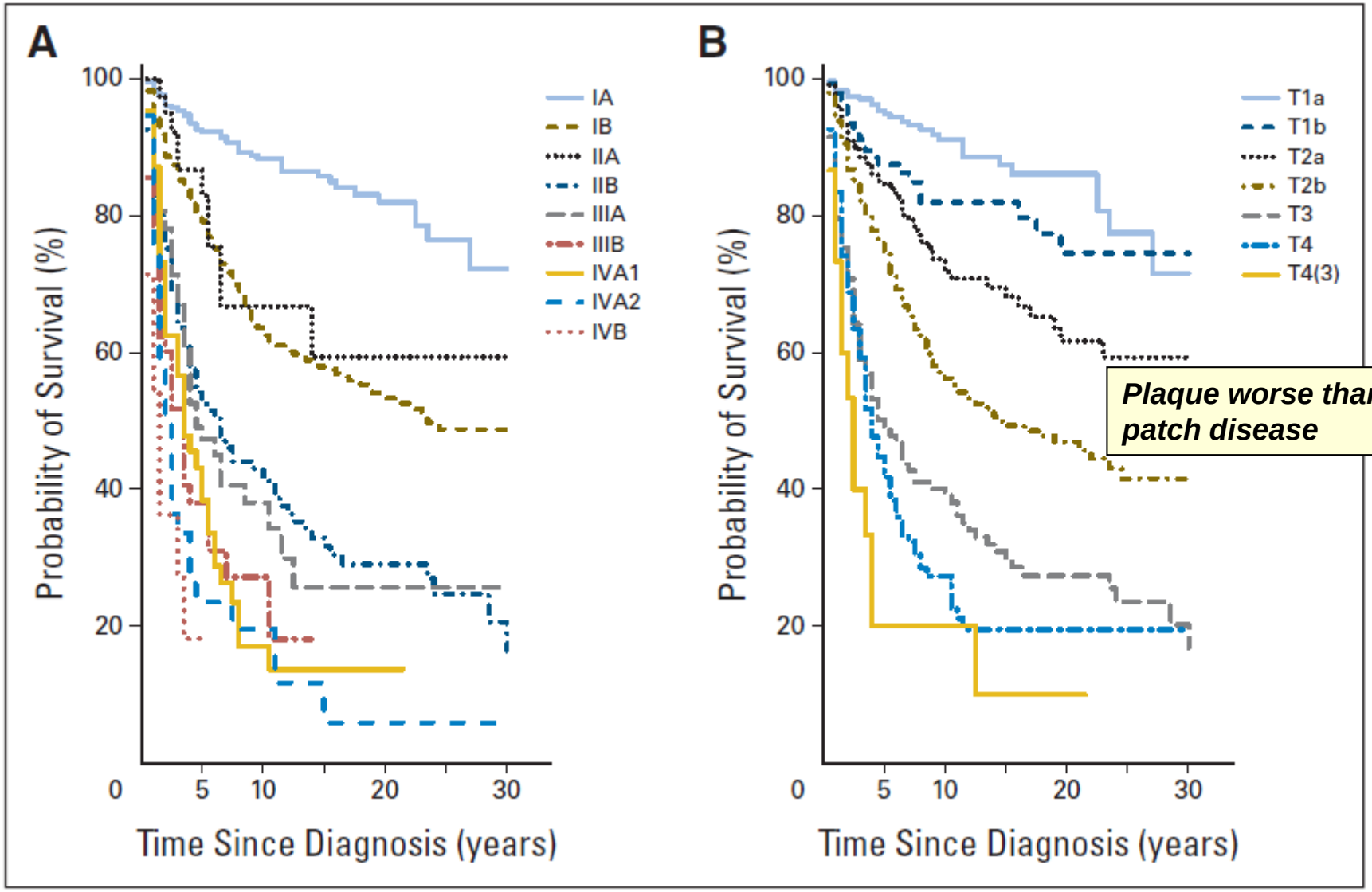
* Depending on TNMB stage

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

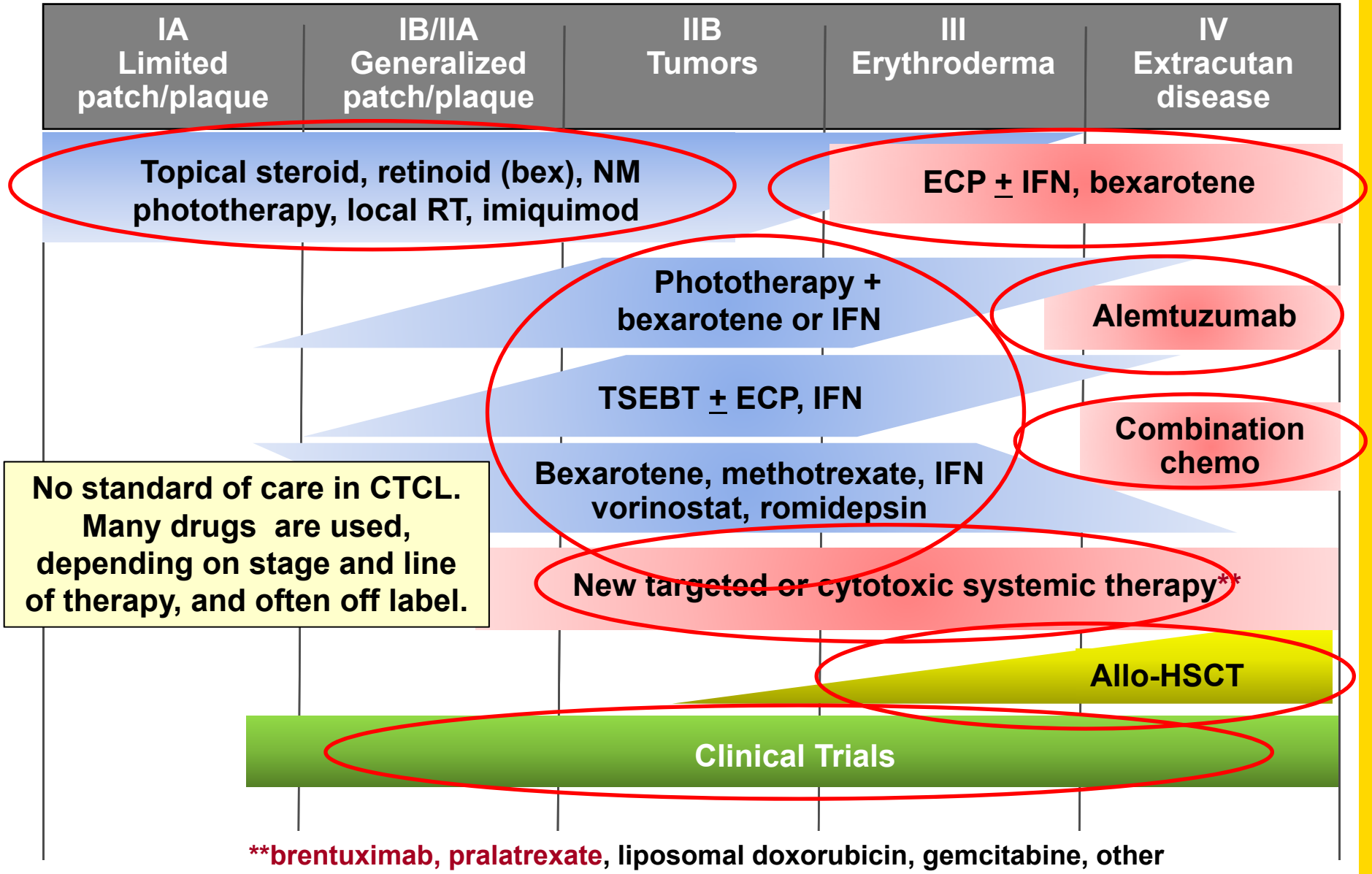


Plaque worse than patch disease

Agar et al. J Clin Oncol 2010;28:4730 Page 17

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

Efficacy data for FDA approval

Agent (Class)	Indication	Year	Study	N	ORR	DOR
Romidepsin (HDAC inhibitor)	CTCL with prior systemic therapy	2009	Pivotal	96	34%	15 mo
			Supportive	71	35%	11 mo
Denileukin diftitox (Fusi	Tumors that	1999,	Pivotal	71	30%	4 mo
Bexar (RXR						5+ mo
Vorin (HDA						6+ mo 4 mo

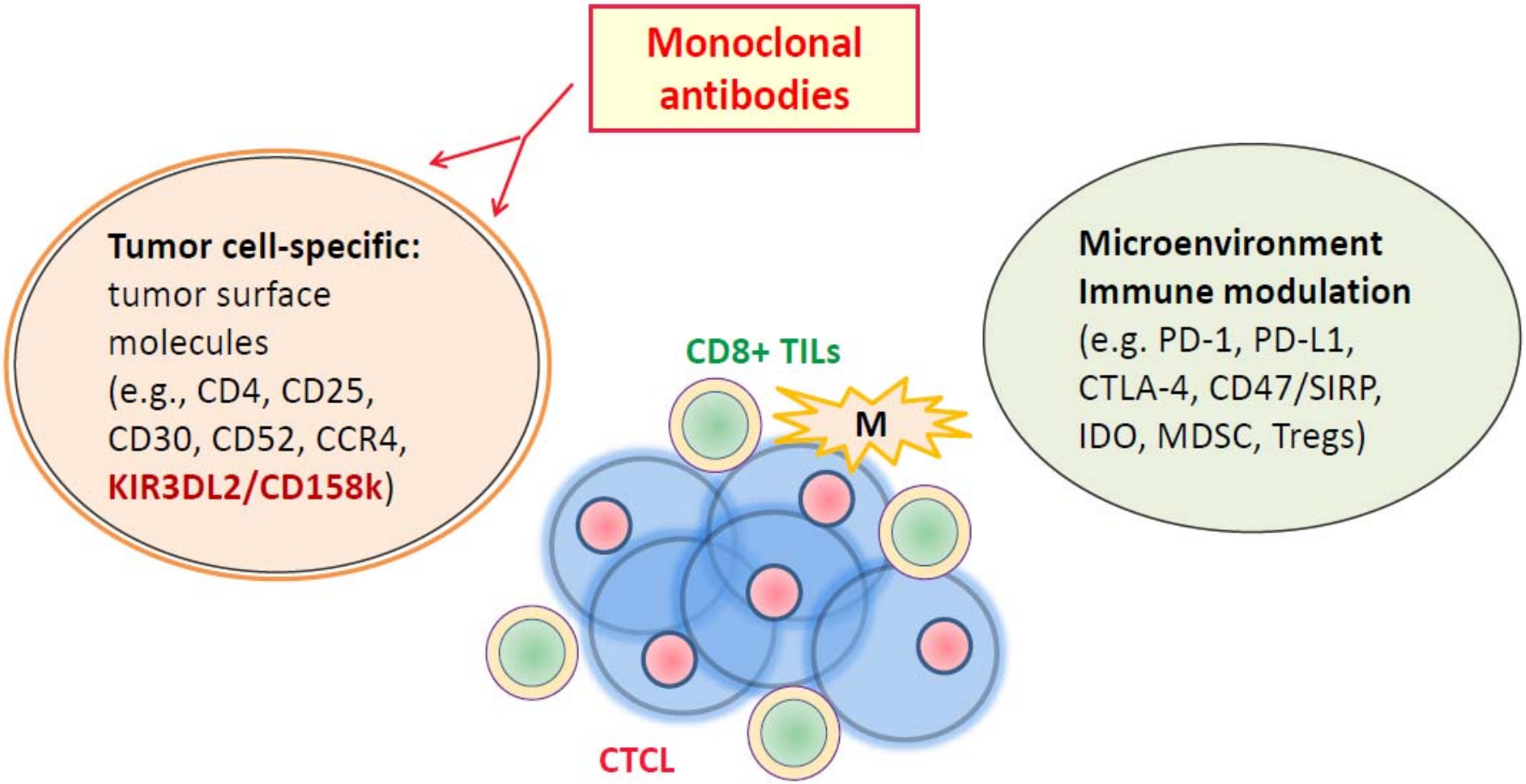
Need better therapies, more options:

Brentuximab vedotin (anti-CD30 ADC)

Mogamulizumab (anti-CCR4 mab)

Both in phase 3 trials

IMMUNE MODULATION WITH MABS IN CTCL



DRUGS IN DEVELOPMENT IN CTCL
MOGAMULIZUMAB (ANTI-CCR4)

- CCR4: trafficking receptor for systemic memory Th2 and regulatory T cells to skin and lung.
- 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
- Ongoing clinical development
  - > randomized Phase III against vorinostat (NCT01728805)
  - > Relapsed/refractory stage ≥ IB CTCL, ***excluding transformed MF***

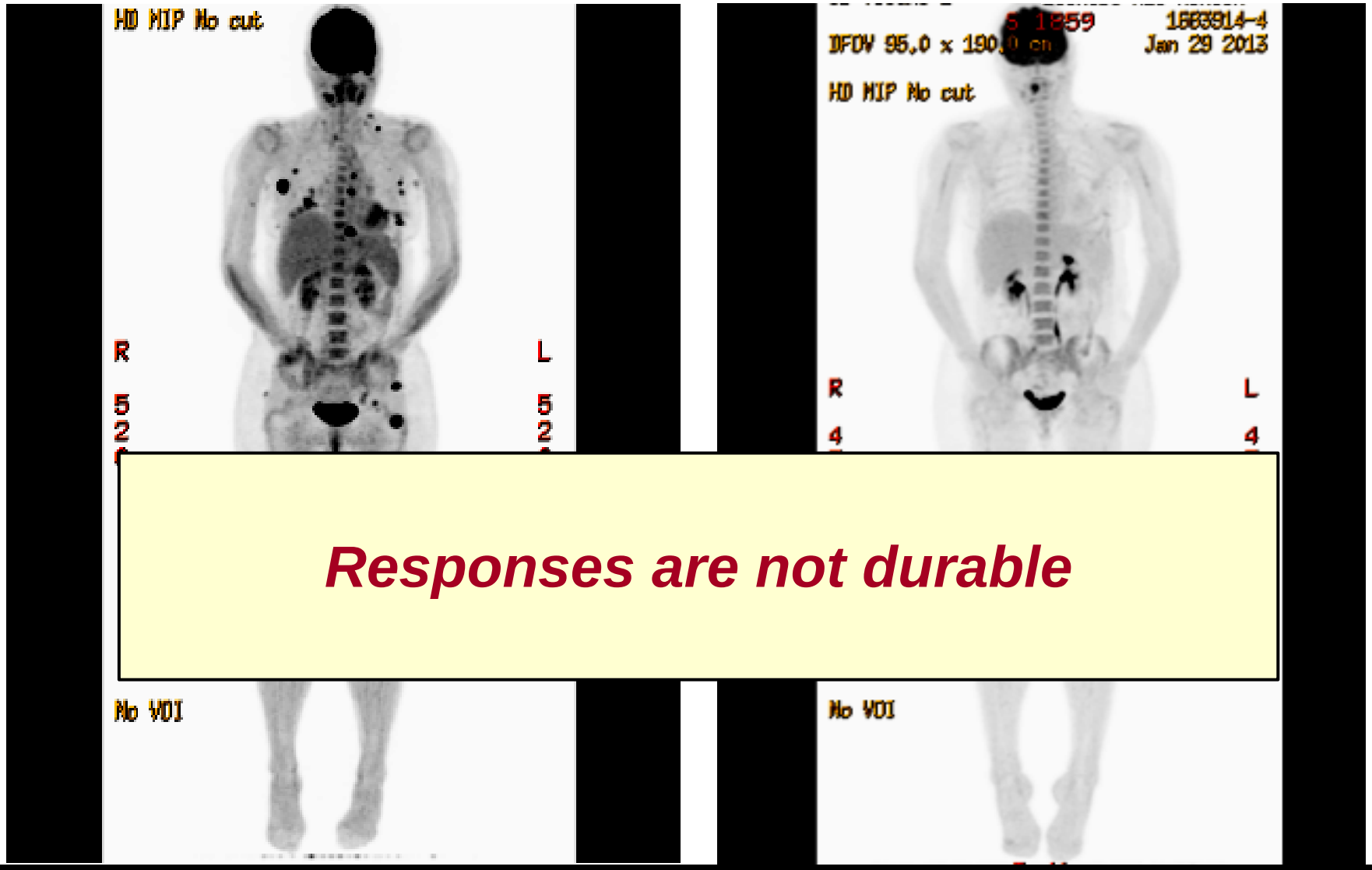
DRUGS IN DEVELOPMENT IN CTCL
BRENTUXIMAB VEDOTIN (ANTI-CD30 DRUG CONJUGATE)

- CD30: is expressed on activated B, T and NK cells, and activated monocytes in hematopoietic tissues.
- Targeted delivery of potent tubulin disrupting drug (MMAE)
- 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

51 yo F stage IVA2 MF with LCT in skin/LNs: response to brentuximab vedotin

Pre-treatment 12/20/2012 **Post 2 cycles 1/29/2013**



Responses are not durable

Preliminary Results of a Phase I Study of Nivolumab in Patients with Relapsed or Refractory Lymphoid Malignancies

Alexander M. Lesokhin[1], Stephen M. Ansell[2], Philippe Armand[3], Emma C. Scott[4], Ahmad Halwani[5], Martin Gutierrez[6], Michael M. Millenson[7], Adam Cohen[8], Stephen J. Schuster[8], Daniel Lebovic[9], Madhav Dhodapkar[10], David Avigan[11], Bjoern Chapuy[3], Azra H. Ligon[12], Scott J. Rodig[12], Deepika Cattry[1], Lili Zhu[13], Joseph F. Grosso[13], Su-Young Kim[13], Margaret A. Shipp[3], Ivan Borrello[14], John M. Timmerman[15]

[1]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; [2]Mayo Clinic, Rochester, MN; [3]Dana-Farber Cancer Institute, Boston, MA; [4] Oregon Health and Science University and the Knight Cancer Institute, Portland, OR; [5]University of Utah Huntsman Cancer Institute, Salt Lake City, UT; [6]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; [7]Fox Chase Cancer Center, Philadelphia, PA; [8]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [9]University of Michigan Hematology, Ann Arbor, MI; [10]Yale Cancer Center, New Haven, CT; [11]Beth Israel Deaconess Medical Center, Boston, MA; [12]Brigham and Women's Hospital Clinical Cytogenetics Laboratory, Boston, MA; [13]Bristol-Myers Squibb, Princeton, NJ; [14]Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [15]Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA

56TH ANNUAL ASH MEETING
DECEMBER 2014
SAN FRANCISCO, CA

Study Design

Relapsed or Refractory HM (N=105)

- No autoimmune disease
- No prior organ or stem cell allografting
- No prior checkpoint blockade

Dose Escalation

Nivolumab
1mg/kg→3mg/kg
Wks 1,4 then q2w

(N=13)
- **B-Cell Lymphoma (n=8)**
- **CML (n=1)**
- **Multiple Myeloma (n=4)**

Dose Expansion (3mg/kg)

Hodgkin Lymphoma (n=23)

(N=69)
- **B-Cell Lymphoma (n=23)**
- **T-Cell Lymphoma (n=23)**
- **Multiple Myeloma (n=23)**

Endpoints

Primary
- Safety and Tolerability

Secondary
- Best Overall Response
  - Investigator assessed
- Objective Response
- Duration of Response
- PFS
- Biomarker studies

Best Overall Response

	Objective Response Rate, n (%)	Complete Responses, n (%)	Partial Responses, n (%)	Stable Disease n (%)
B-Cell Lymphoma* (n=29)	8 (28)	2 (7)	6 (21)	14 (48)
Follicular Lymphoma (n=10)	4 (40)	1 (10)	3 (30)	6 (60)
Diffuse Large B-Cell Lymphoma (n=11)	4 (36)	1 (9)	3 (27)	3 (27)
T-Cell Lymphoma† (n=23)	4 (17)	0 (0)	4 (17)	10 (43)
Mycosis Fungoides (n=13)	2 (15)	0 (0)	2 (15)	9 (69)
Peripheral T-Cell Lymphoma (n=5)	2 (40)	0 (0)	2 (40)	0 (0)
Multiple Myeloma (n=27)	0 (0)	0 (0)	0 (0)	18 (67)
Primary Mediastinal B-Cell Lymphoma (n=2)	0 (0)	0 (0)	0 (0)	2 (100)

*includes other B-cell lymphoma (n=8)
†includes other cutaneous T-cell lymphoma (n=3) and other non-cutaneous T-cell lymphoma (n=2)

KIR3DL2 & IPH4102 IN CTCL

INTRODUCTION

KIR3DL2, UNIQUE THERAPEUTIC TARGET IN CTCL

- Inhibitory receptor, member of the Killer Immunoglobulin-like Receptor (KIR) family
- 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)
- KIR3DL2 is expressed by up to 95% CTCL cells irrespectively of disease stage and CTCL subtype (IHC study, N = 107 CTCL patients)
- Skin-resident CD4+ T cells express KIR3DL2 and may be the normal counterparts of CTCL (Sako et al, CytomA 2014)

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

CTCL LANDSCAPE

KIR3DL2 EXPRESSION BY WHO-EORTC SUBTYPE

CTCL subtypes per WHO-EORTC classification

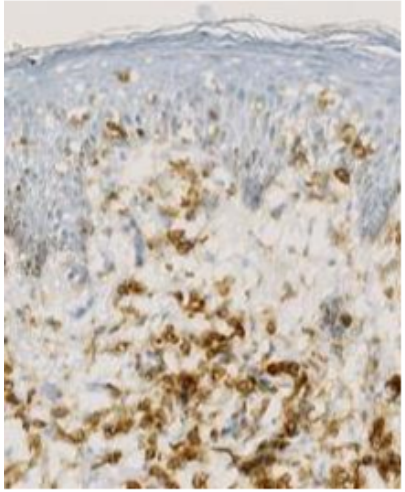
	%KIR3DL2$^+$ skin biopsies (n = 107 CTCL patients)
Mycosis Fungoïdes (MF)	~45%
transformed MF	>80%
CD30$^+$LPD (ALCL subtype)	100%
Sézary Syndrome	>85%
Others (ATL, NK/T, γδ,…)	~35% to 100%

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).

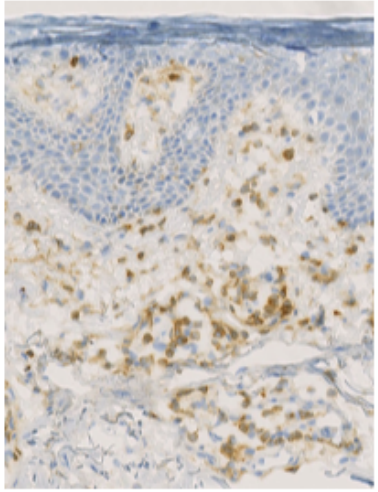
KIR3DL2 EXPRESSION IN CTCL

CUTANEOUS LESIONS

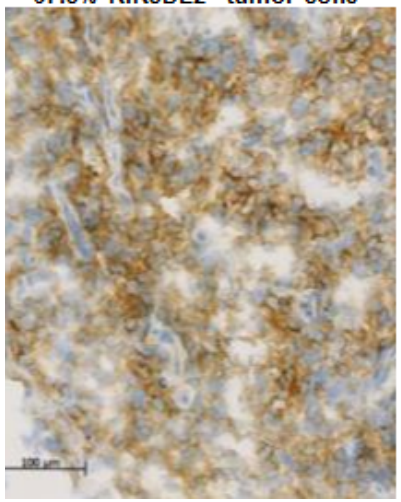
SS pt #1
86.5% KIR3DL2⁺ tumor cells



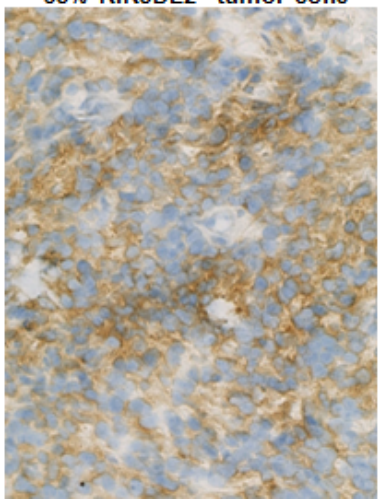
SS pt #2
75.5% KIR3DL2⁺ tumor cells



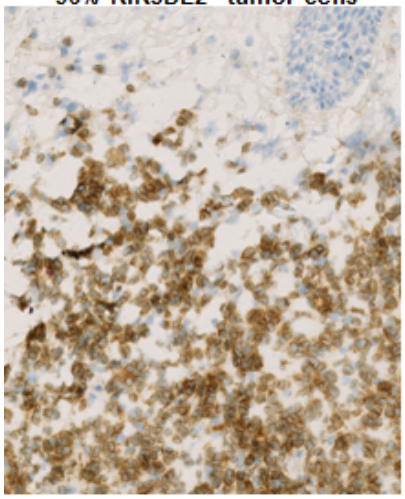
CD30⁺ LPD pt #1
67.5% KIR3DL2⁺ tumor cells



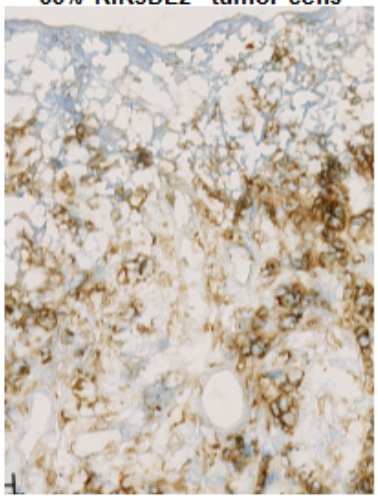
CD30⁺ LPD pt #2
53% KIR3DL2⁺ tumor cells



tMF pt #1
96% KIR3DL2⁺ tumor cells



tMF pt #2
88% KIR3DL2⁺ tumor cells

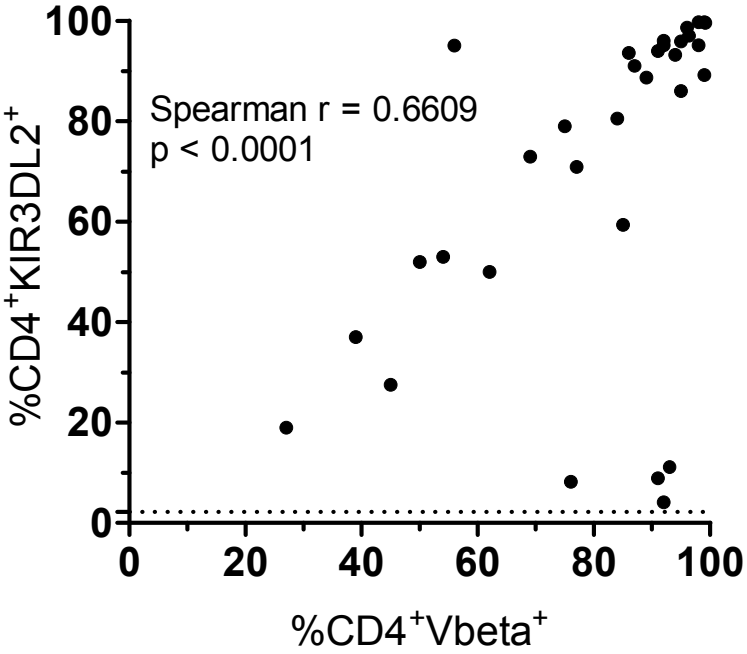


IHC staining of KIR3DL2 on skin biopsies of CTCL patients with Sézary syndrome, mycosis fungoides and CD30⁺ lymphoproliferative disorder (ALCL subtype)

KIR3DL2 EXPRESSION IN CTCL

LEUKEMIC FORMS

Correlation between KIR3DL2 and TCR-Vβ expression in flow cytometry on blood CTCL cells in Sézary syndrome patients (n = 32)



IPH4102 HAS THE POTENTIAL TO BE A HIGHLY TARGETED CTCL THERAPY

- KIR3DL2 exhibits homogeneous expression on tumor cells
- KIR3DL2 has very limited expression on normal cells subsets
- Altogether, targeting KIR3DL2 may lead to
  - > Improved targeting and better anti-tumoral effect
  - > Improved safety profile
  - > Higher exposure and longer treatment duration
  - > Greater opportunity for combinations

IPH4102 IN CTCL

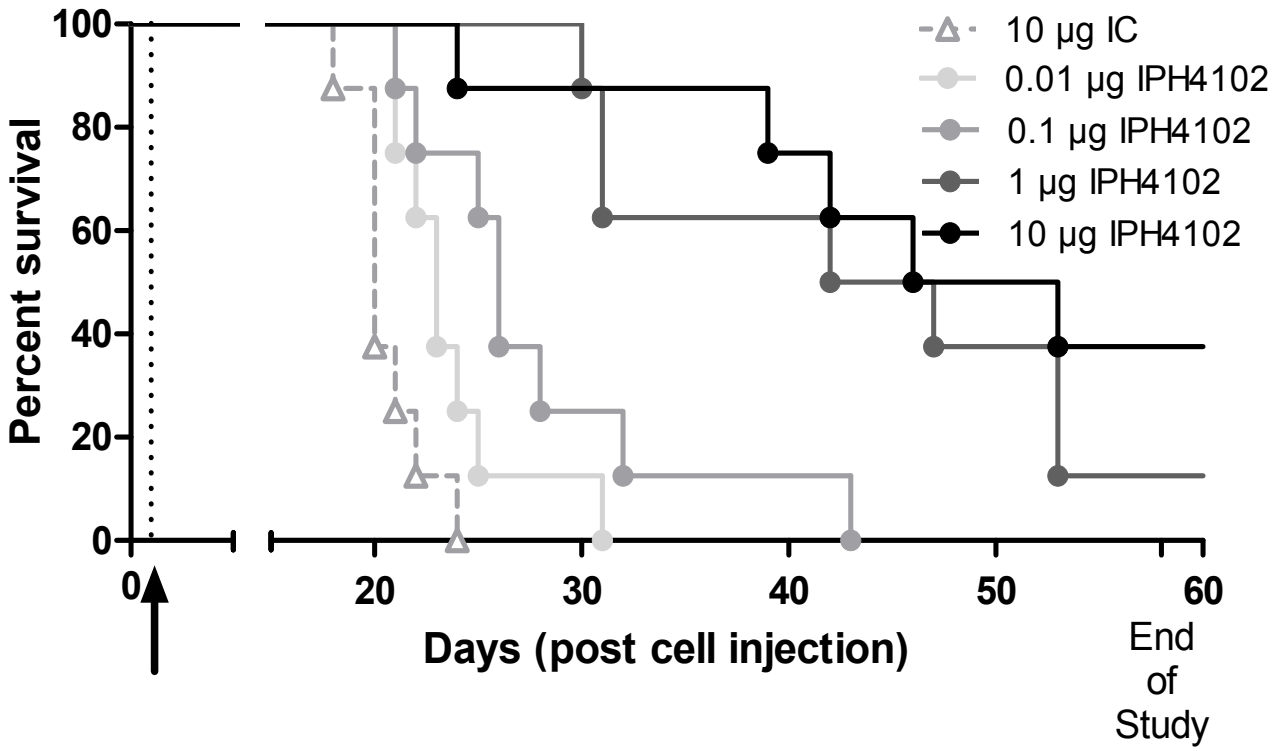
NON CLINICAL EFFICACY SUMMARY

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

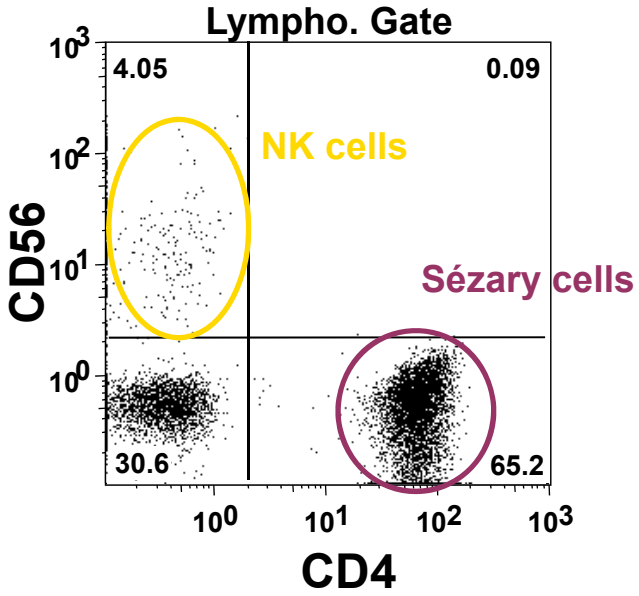


Mice: SCID (n = 8)
RAJI-KIR3DL2: 5 M IV at D0
IPH4102: single IV admin. at D1
Read-out: survival

IPH4102 EFFICACY *EX VIVO:* AUTOLOGOUS ADCC

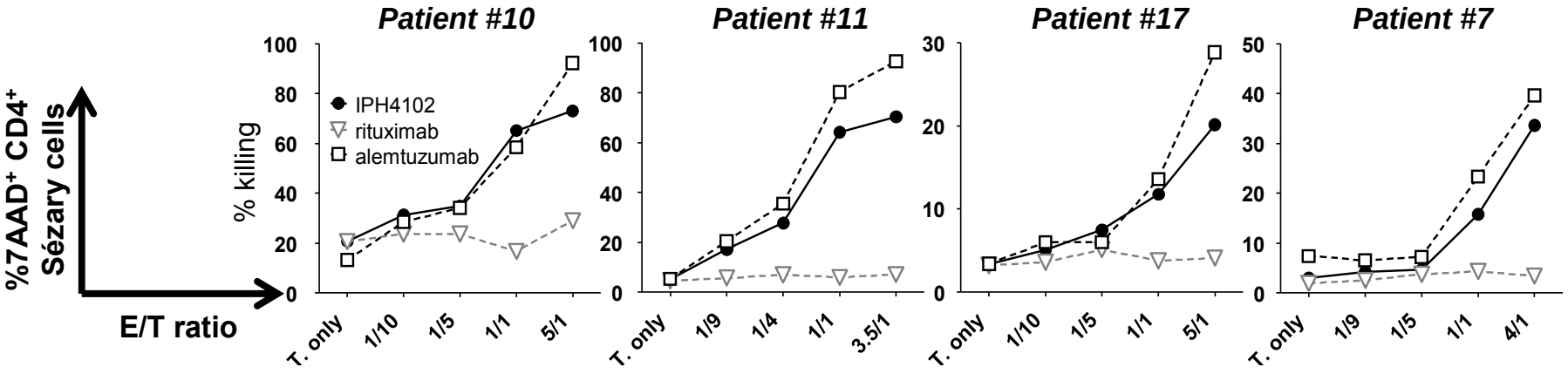
EXPERIMENTAL CONDITIONS

- 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



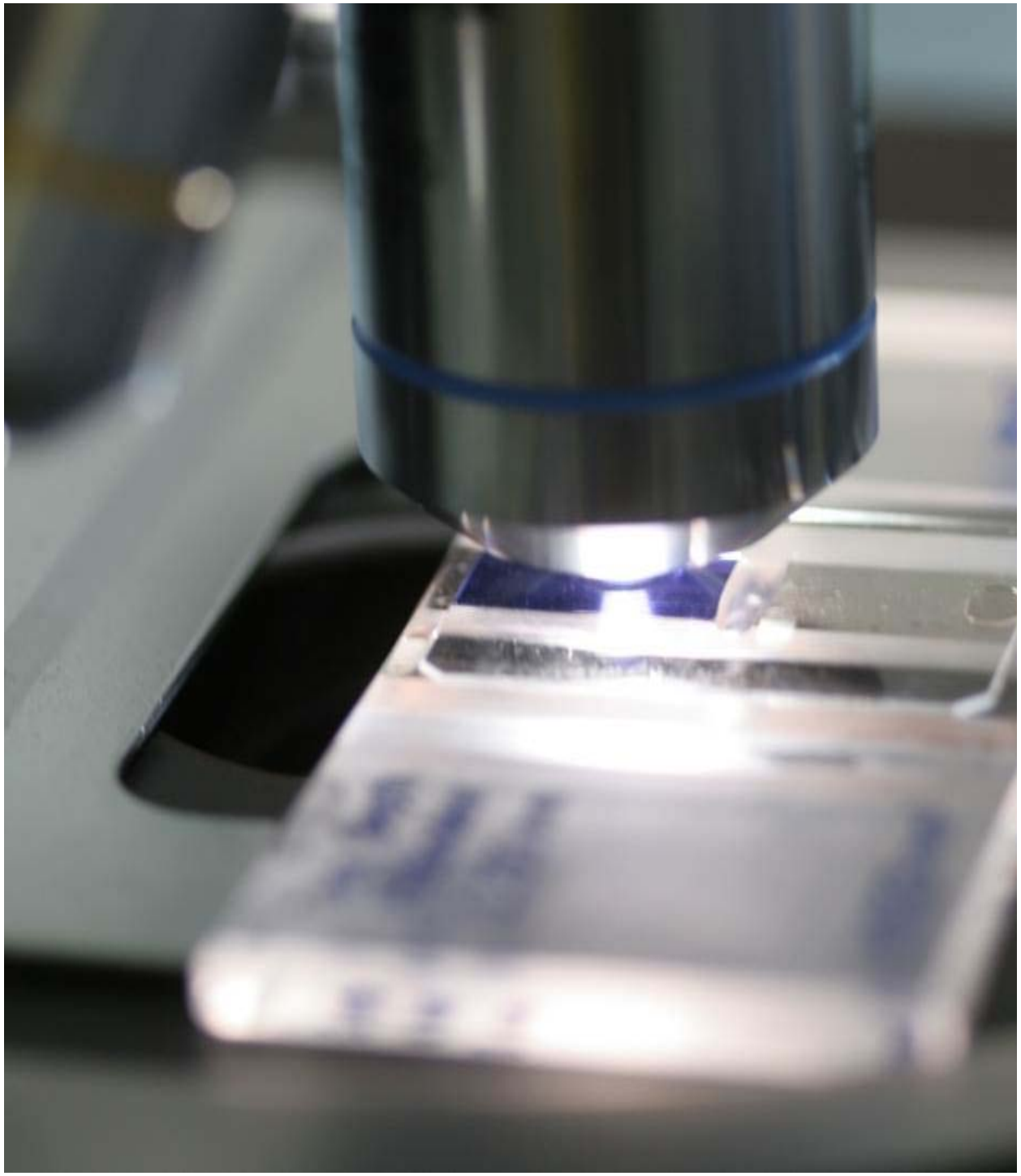
IPH4102 EFFICACY *EX VIVO:* AUTOLOGOUS ADCC

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



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

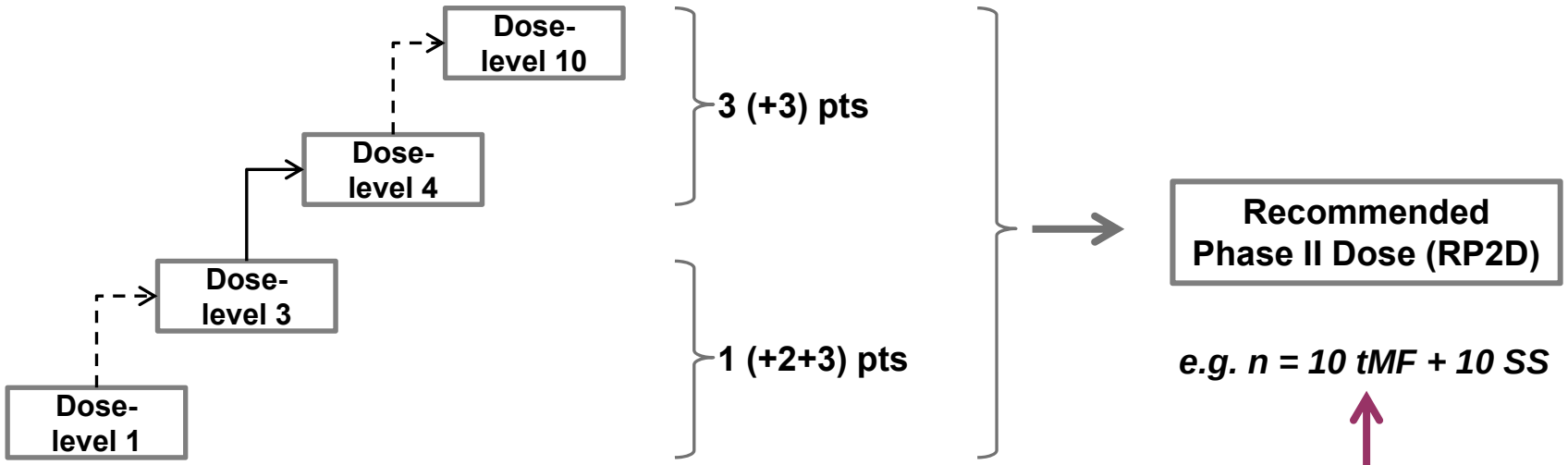
- **Primary objective: to assess safety & tolerability of increasing IV doses of single agent IPH4102 by:**
  - characterizing the dose-limiting toxicities (DLT) and (S)AEs
  - identifying the MTD or Recommended Ph 2 Dose (RP2D)
- **Secondary objectives:**
  - > To explore antitumor activity
  - > To 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



The CTCL subtypes and number of pts will be adjusted based on the findings during the dose escalation phase

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**
- **First patient expected to be treated in October 2015**
- **IPH4102 IND-enabling data and Phase I design presented in Turin EORTC CLTF meeting, September 2015, by Martine Bagot**

A NOVEL TARGETED IMMUNOTHERAPY FOR CTCL

- See Pr Martin Bagot presentation at EORTC cutaneous lymphoma task force meeting - Torino sept. 2015