

BREAST IMPLANT ASSOCIATED LYMPHOMA



A PERFECT STORM?

H. Miles Prince

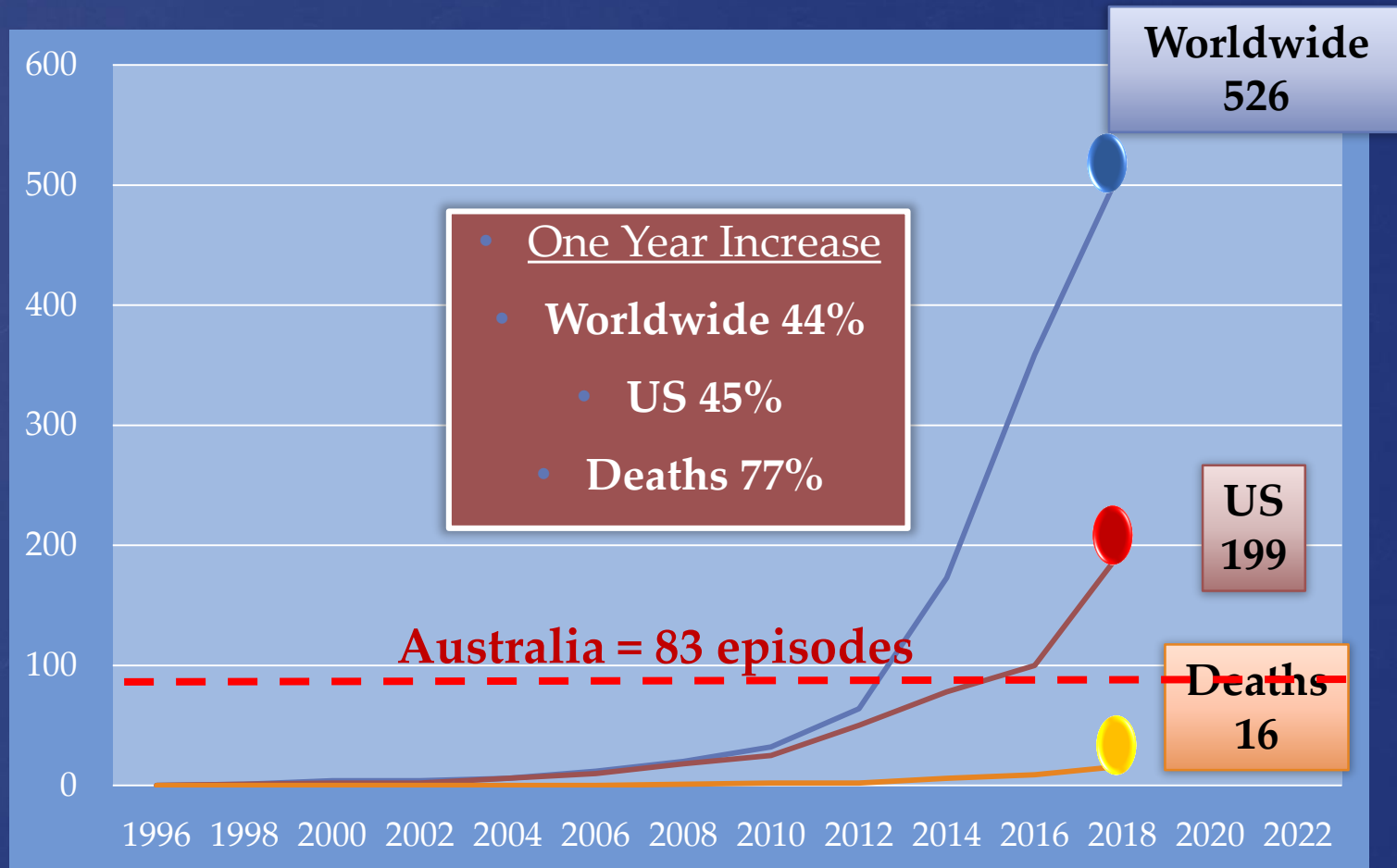
*Peter MacCallum Cancer Centre
Melbourne, Australia*

Disclosure

Allergan: Advisor and Research Funding

Takeda/Millennium: Advisory Board

BIA-ALCL at 21 years



BACKGROUND

Breast Lymphomas

- 90% B cell: If localized = DLBCL, Burkitts, MZL
- 10% T cell
 - PTCL (NOS)
 - ALCL
 - Systemic – ALCL Alk pos
 - Systemic – ALCL Alk neg
 - Primary Cutaneous ALCL [Alk neg]
 - **Implant associated ALCL [Alk neg]**

Better recognition?
Better reporting
True increase

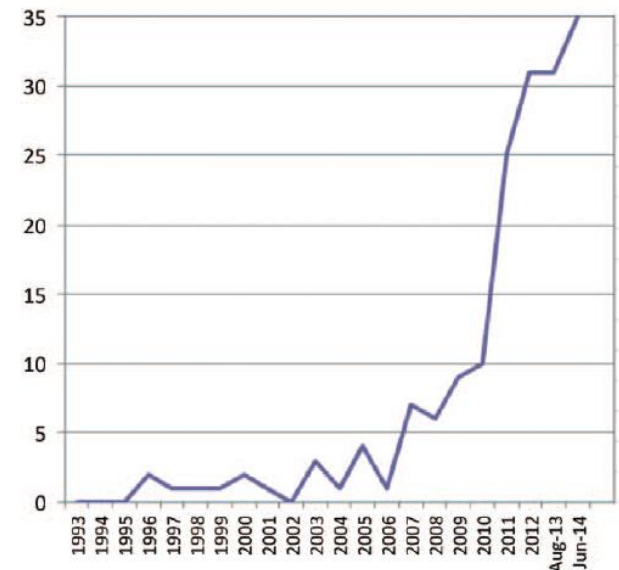
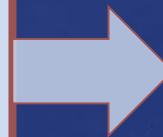


Fig. 3. Number of newly diagnosed patients per year (where date is known) through June 1, 2014.

Types of implant-associated ALCL

Mass-associated (often with effusion)

= infiltrative

Non-Mass-associated

= seroma-associated

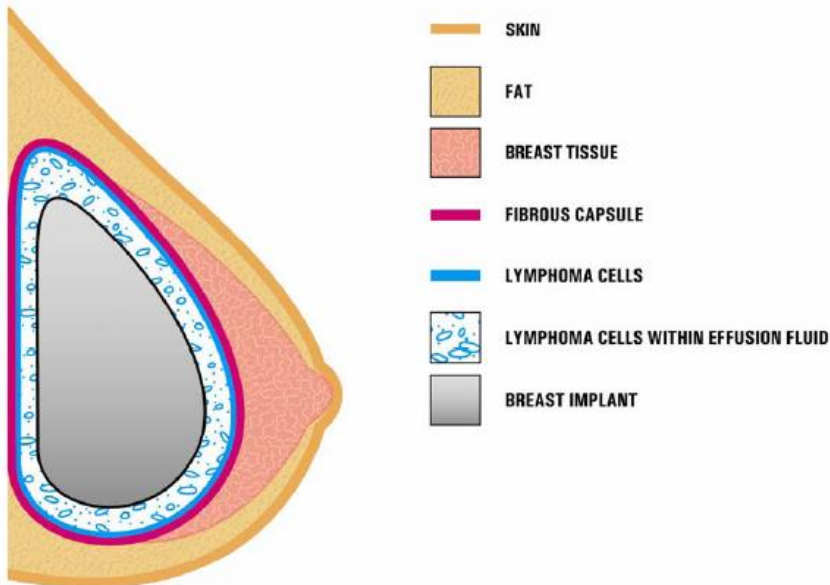
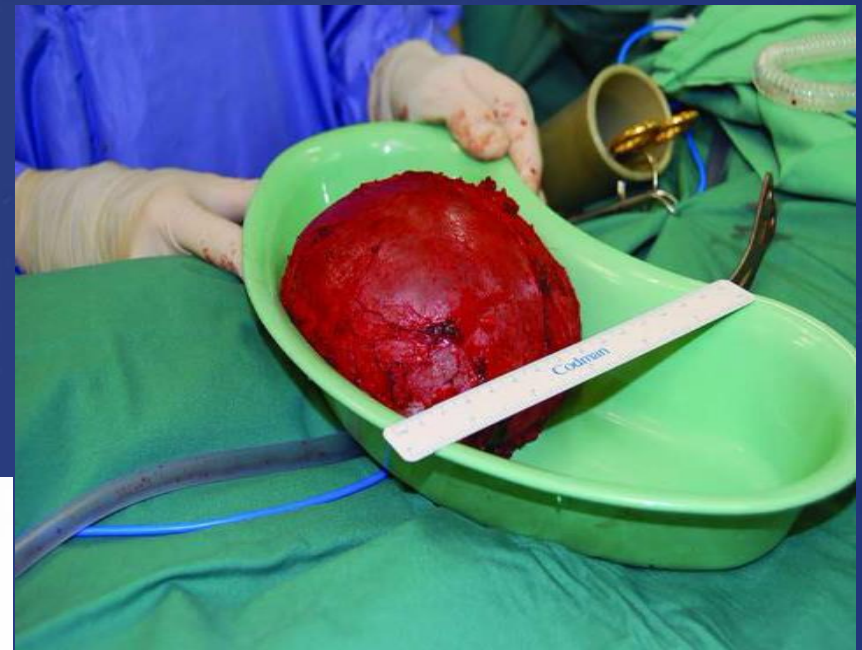
= effusion-associated

= *in situ*

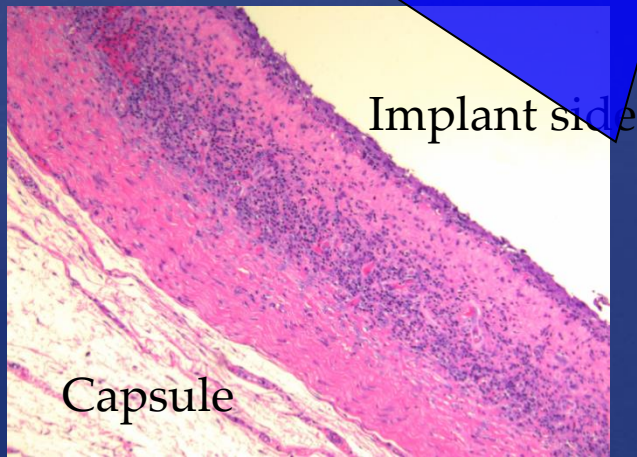
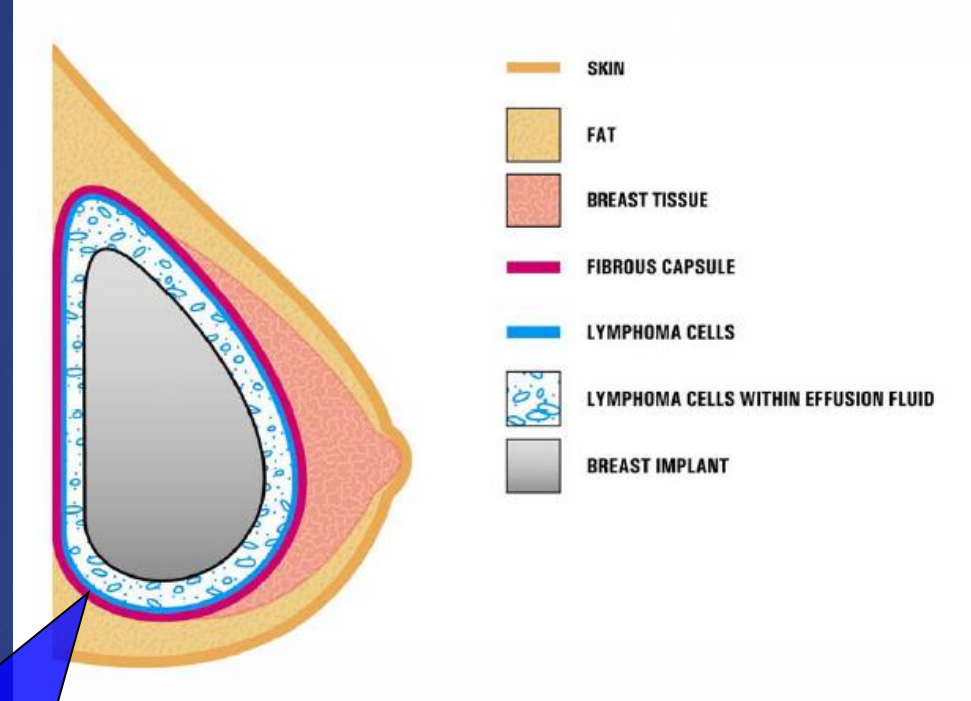
Without tumor mass and effusion-associated



Without tumor mass and effusion- associated



Effusion-associated



Breast implant related Anaplastic Large Cell Lymphoma presenting as late onset peri-implant effusion

Trevor J. Smith^a, Reena Ramsaroop^{b,*}

^aThe Breast Centre Ltd, Suite 2, Ascot Integrated Hospital, 90 Greenlane Rd, Remuera, Auckland, New Zealand

^bDiagnostic Medical Laboratory, 10 Harrison Road, Ellerslie, Auckland, New Zealand

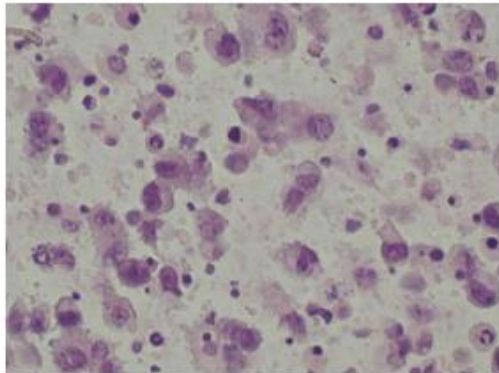


Fig. 1. H&E $\times 400$. Cell block preparation showing dis cohesive, pleomorphic lymphoid

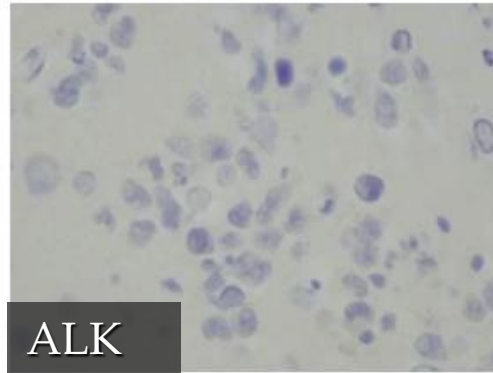
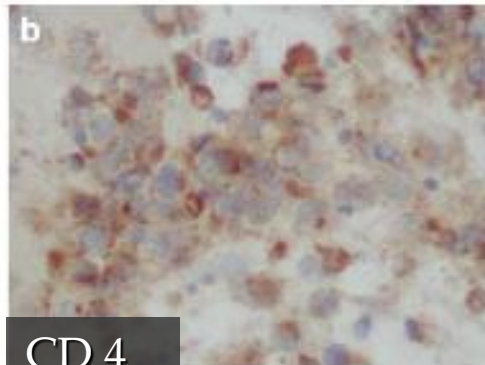
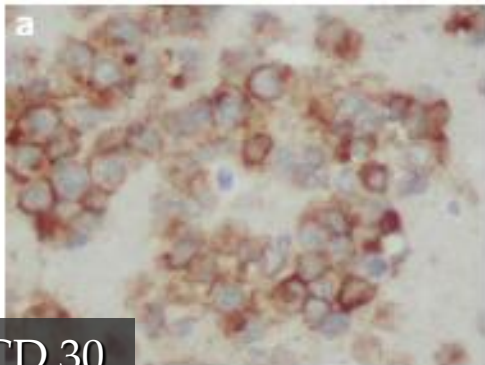


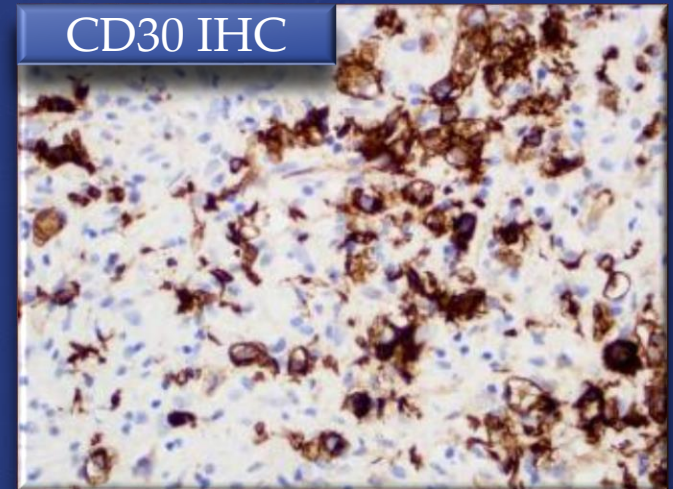
Fig. 3. IHC $\times 400$. ALK1 – malignant lymphoid cells – negative.



Important:
The malignant cells may be only on the effusion

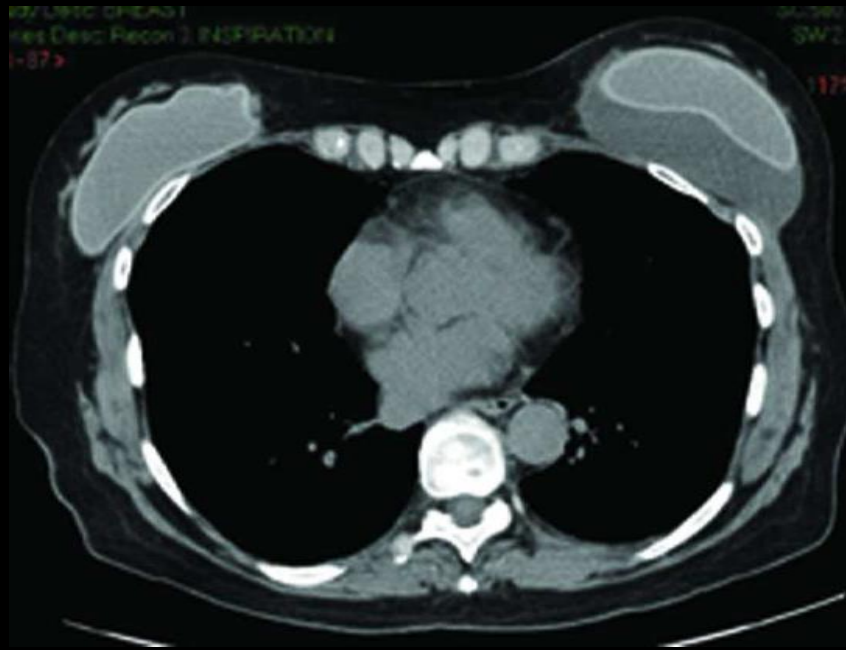
IMMUNOHISTOCHEMISTRY/FLOW

- ◆ CD30+ in all (n=64) cases,
- ◆ ALK and EBER negative in all (n=56 and 25 respectively) tested cases.
- ◆ CD3+ 15 of 62 (24%) cases
- ◆ CD4+ 43 of 61 (70%),
- ◆ CD8+ 6 of 57 (11%),
- ◆ CD43+ 37 of 46 (80%),
- ◆ CD45+ 29 of 49 (59%),
- ◆ EMA+ 25 of 42 (60%)
- ◆ TIA-1+ 28 of 46 (61%)
- ◆ Granzyme-B+ 28 of 47 (60%)
- ◆ TCR $\alpha\beta$ + 5 of 24 (21%)
- ◆ TCR $\gamma\delta$ + 1 of 23 (4%)



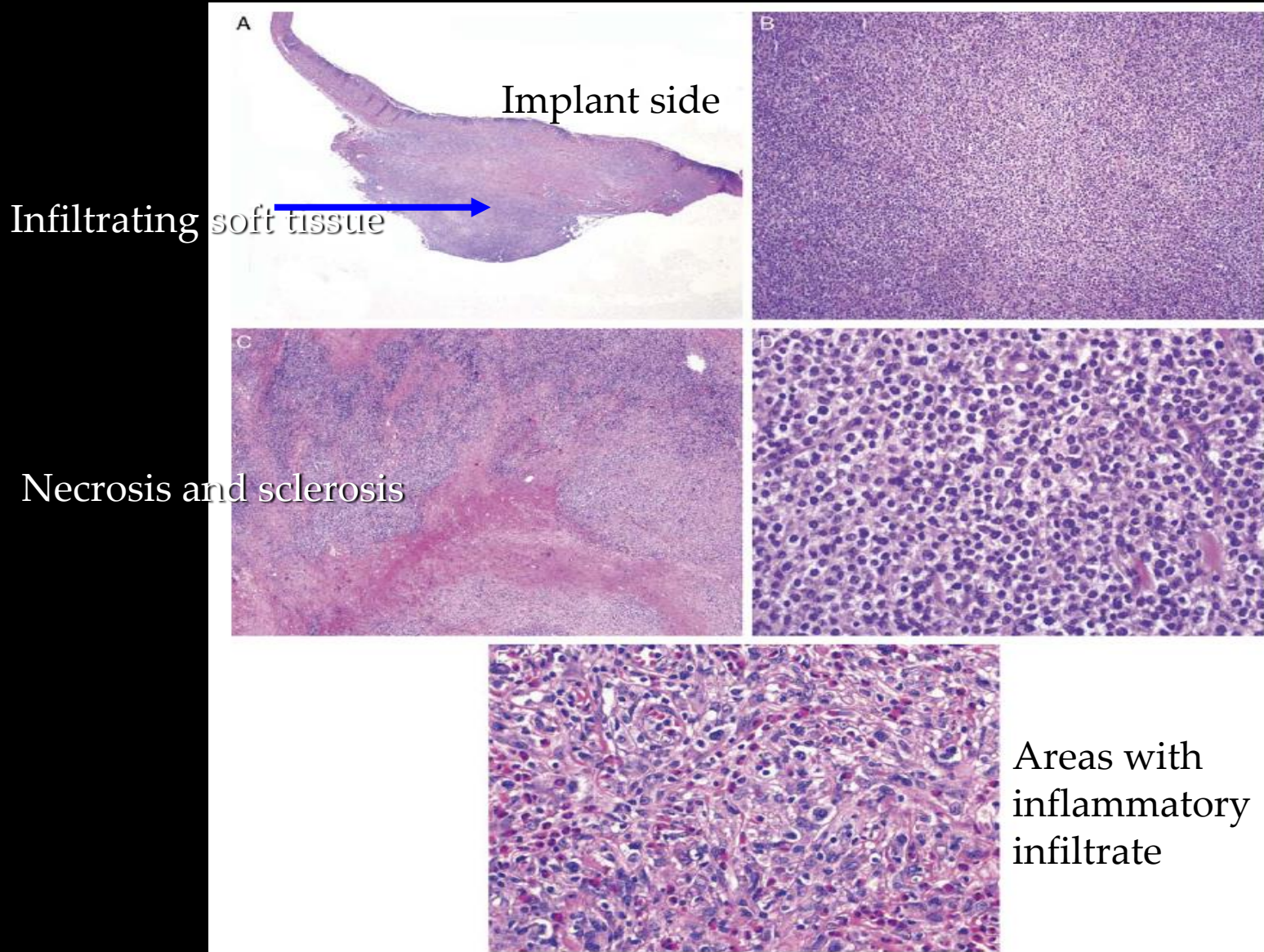
TCR deep sequencing – present
but ?? Not functioning (ie. sALCL)

With tumor mass

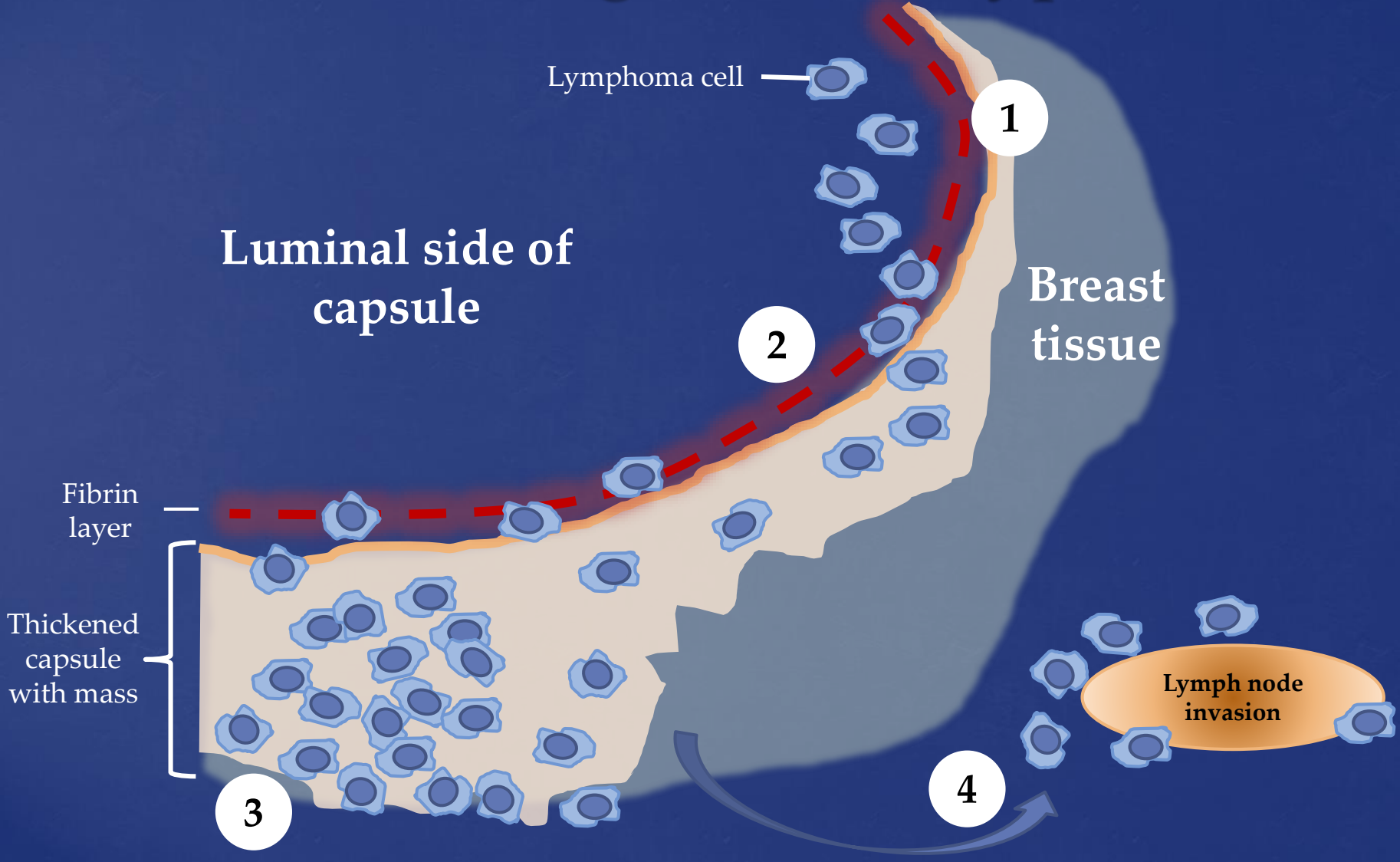


With tumor mass

Diffuse Growth Pattern



Solid Tumor Progression Hypothesis



BIA-ALCL behaves like a SOLID Tumor (like lung or breast cancer) and therefore treated surgically **(ALSO LIKE HODGKIN AND pcALCL)**

MDACC BIA-ALCL staging: Stage 1A¹

- **T1:** disease confined to effusion only or non-invasive layer luminal side
- **N0 M0**

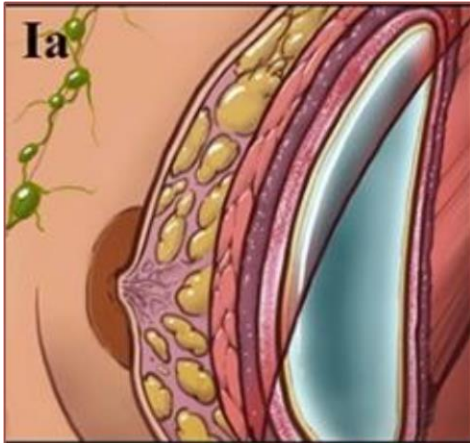
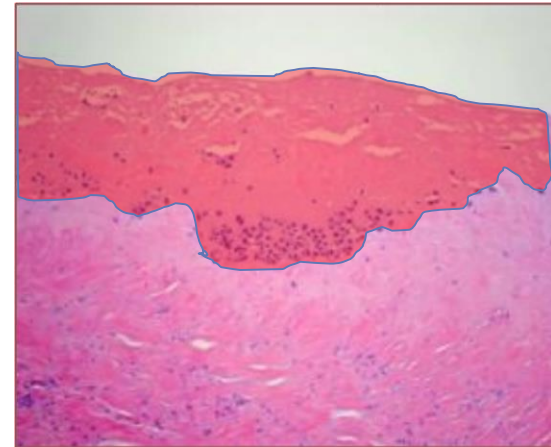
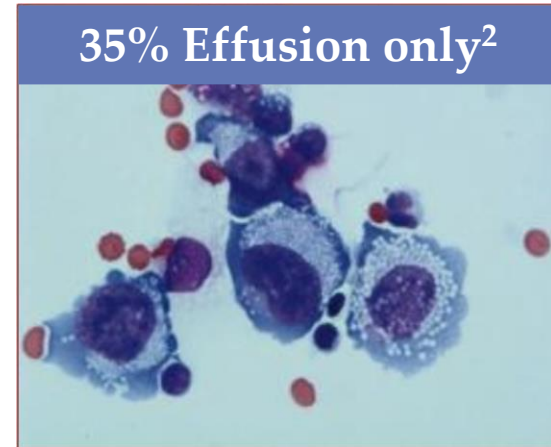


Image from Clemens MW, et al. J Clin Oncol 2016



Images courtesy of Dr Mark Clemens

MDACC BIA-ALCL staging: Stage 1B¹

- T2: early invasion, mix of lymphocytes with ALCL within capsule
- N0 M0

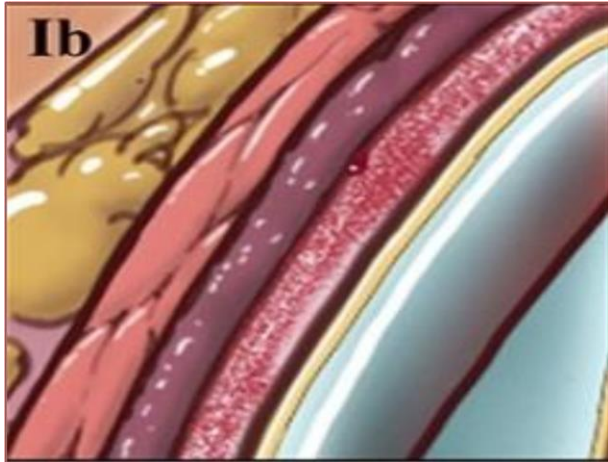


Image from Clemens MW, et al. J Clin Oncol 2016

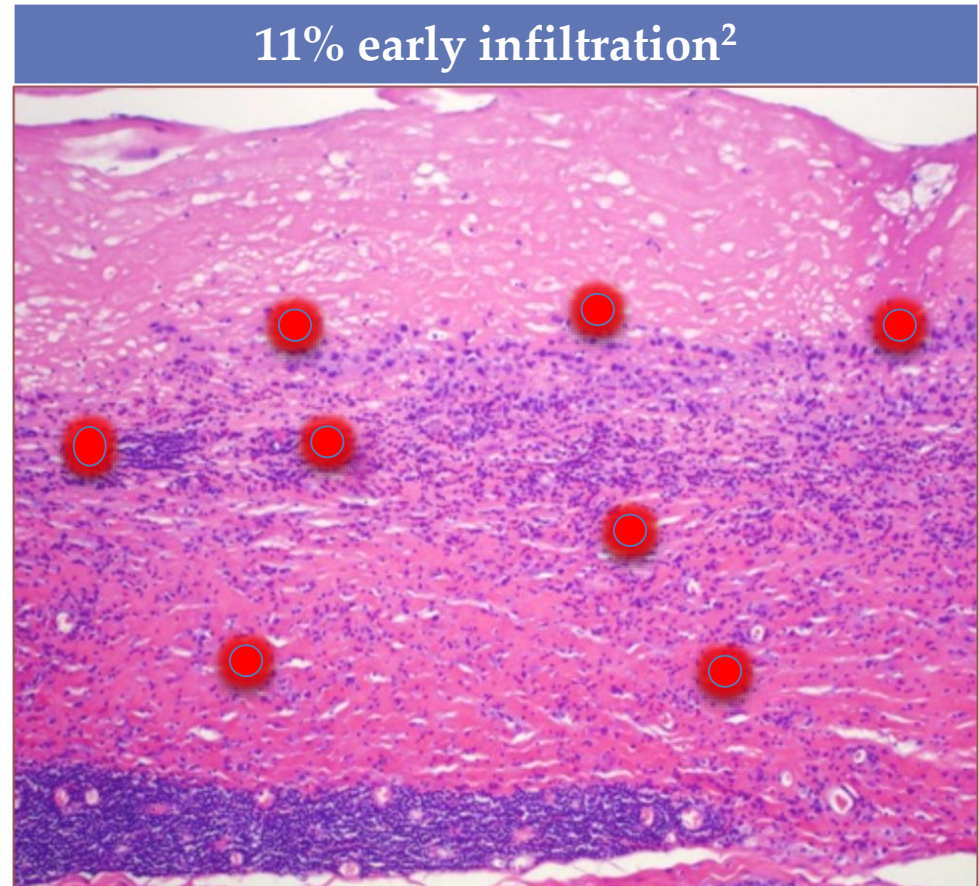


Image courtesy of Dr Mark Clemens

MDACC BIA-ALCL staging: Stage 1C¹

- T3: aggregate mass confined by the capsule
- N0, M0

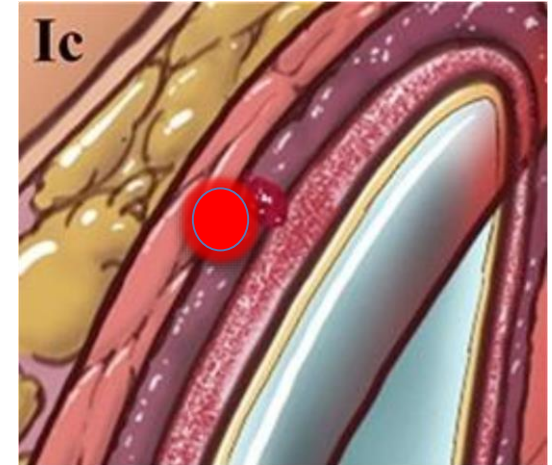
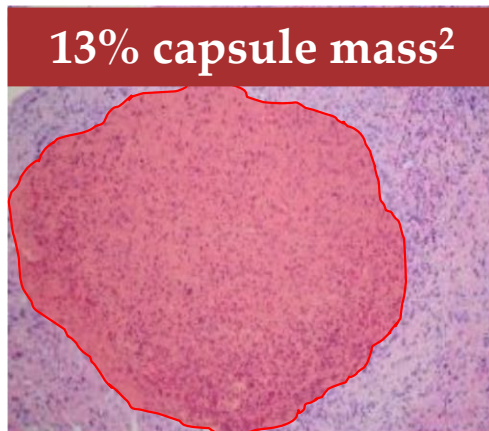


Image from Clemens MW, et al. J Clin Oncol 2016



Images courtesy of Dr Mark Clemens

MDACC BIA-ALCL staging: Stage 2A¹

- T4: invasive mass outside of capsule
- N0 M0



25% mass through capsule²

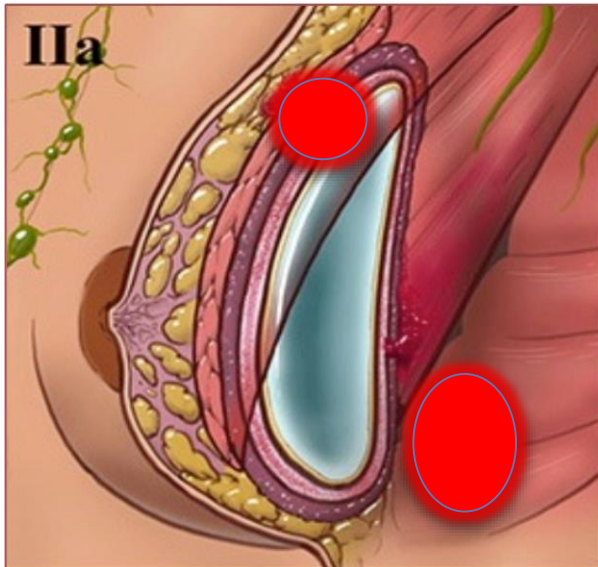
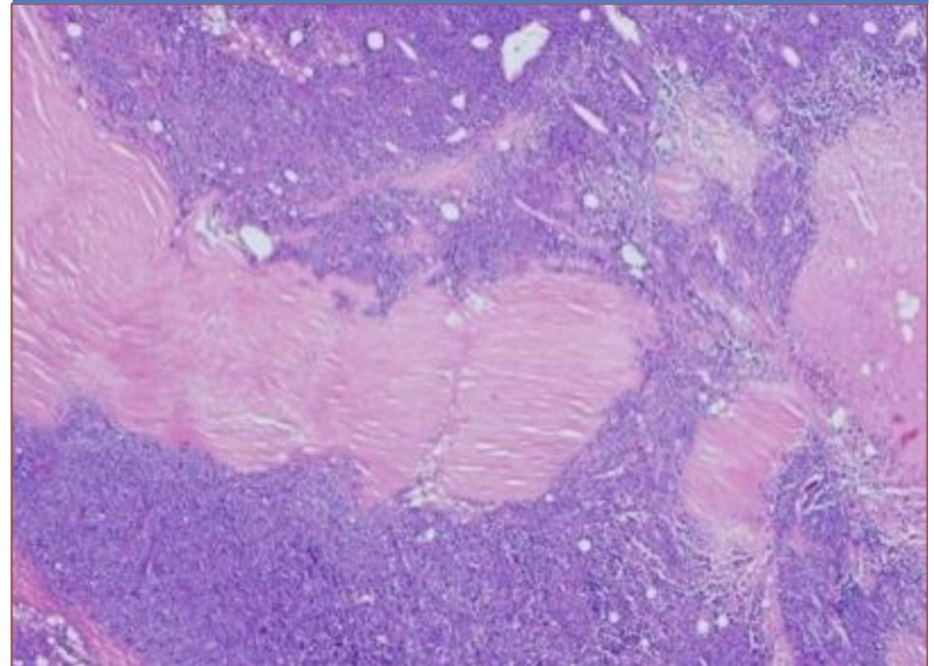


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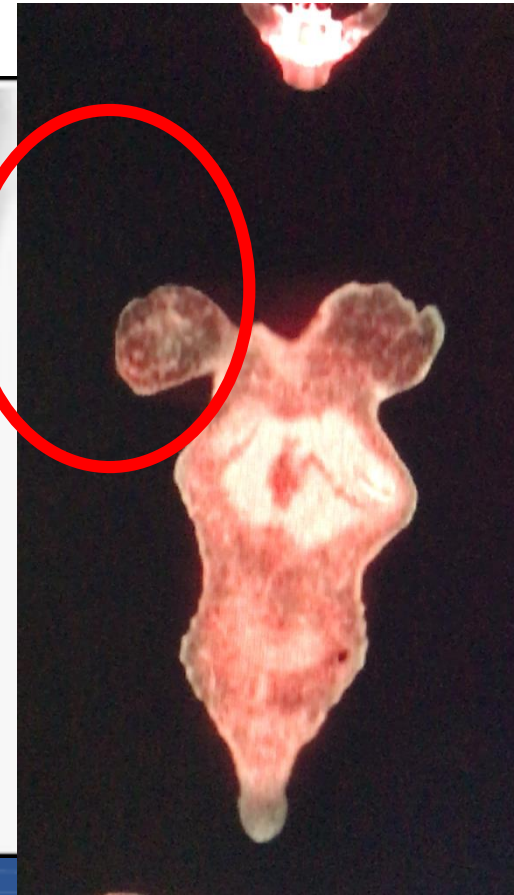
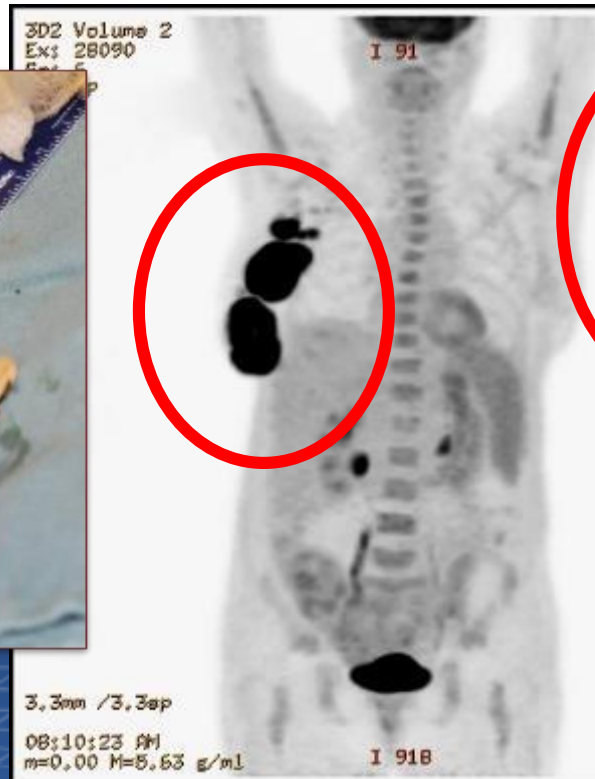


Images courtesy of Dr Mark Clemens

Mass 18-25% of BIA-ALCL

Worse Prognosis

- Important to image prior to surgery
- Must resect all of the malignancy

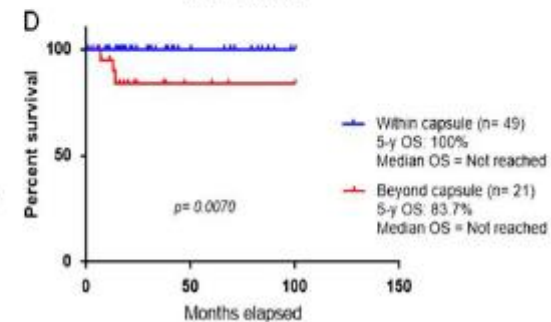
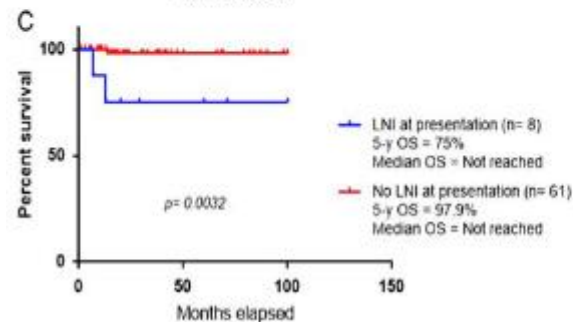
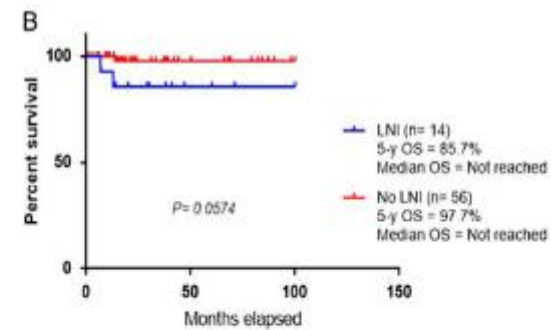
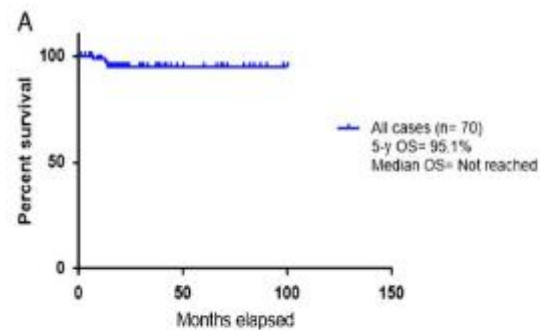
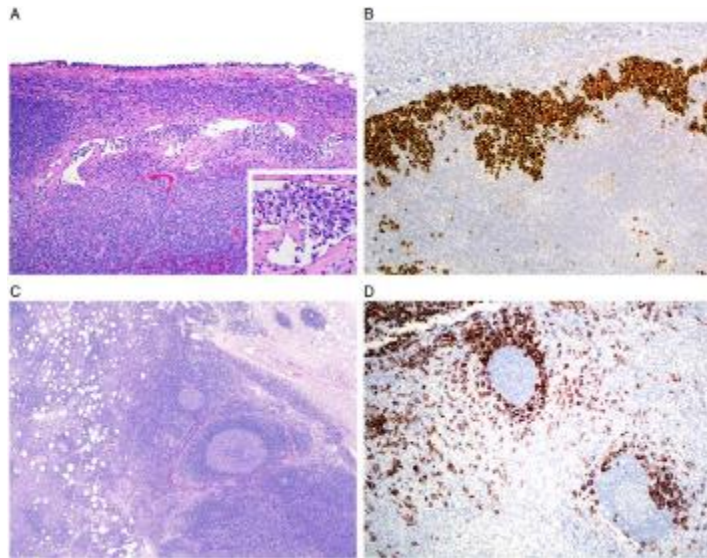


Patterns of Lymph Node Involvement

- 13% of BIA-ALCL Cases
- 85% Axillary, 10% Supraclav, 5% internal mammary
- Mass, LNI portend Worse Prognosis

Clinicopathologic Features and Prognostic Impact of Lymph Node Involvement in Patients With Breast Implant-associated Anaplastic Large Cell Lymphoma

Maria C. Ferrufino-Schmidt, MD,*† L. Jeffrey Medeiros, MD,* Hui Liu, MD, PhD,‡
Mark W. Clemens, MD,§ Kelly K. Hunt, MD,|| Camille Laurent, MD, PhD,¶ Julian Lofts, MD,‡



Reported Stage Presentations Worldwide

Study		Ann Arbor		MDA Solid Tumor TNM Stage						
		IE	IIE	IA	IB	IC	IIA	IIB	III	IV
Brody 2015 (n=173)	USA	89.6	10.4	NR	NR					
Clemens 2016 (n=87)	USA	86.2	13.8	35.6	11.5	13.8	25.3	4.6	9.2	0
Loch-Wilkinson 2017 (n=55)	Australia	96.4	3.6	76.4	0	10.9	9.1	0.0	1.8	1.8
De Boer 2017 (n=32)	Netherlands	81.3	18.8	45.2	NR					
Campanale 2017 (n=22)	Italy	81.8	18.2	68.2	0	4.5	9.0	9.0	0	9.0
				Effusion Only	Infiltrative					

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Is this like the spectrum of CD30+ Cutaneous Lymphomas?

Lymphomatoid papulosis = **in situ** ?



Primary Cutaneous ALCL = **invasive/spreading** ?

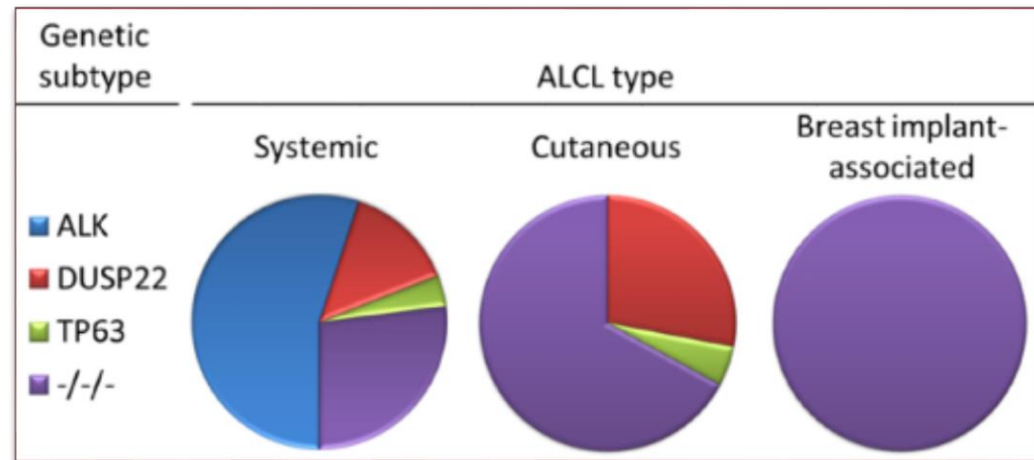
- *ALK* negative
- *DUSP22* positive or negative
- Indolent
- Can be self resolving
- Surgery and/or irradiation adequate
- Often do not require chemotherapy

Are there ALCL-like mutations in BIA-ALCL?

- Evaluated 36 cases BIA-ALCL
- All cases:
 - Negative for ALK
 - Negative for DUSP22
 - Negative for TP 63
- STAT3 IHC evaluated in 25 cases
 - 100% positive
 - EBV negative

Genetic subtyping of breast implant-associated anaplastic large cell lymphomas

Naoki Oishi^{a,b}, Garry Brody^c, Rhett P. Ketterling^a, Christopher A. Sattler^a, Rebecca L. Boddicker^a, Ellen D. McPhail^a, N. Nora Bennani^d, Cristin A. Harless^e, Kuldeep Singh^g, Mark W. Clemens^f, L. Jeffrey Medeiros^g, Roberto N. Miranda^{g*} and Andrew L. Feldman^{h*}



ASPS ASAPS Joint Statement

January 10, 2018

EDUCATION

BIA-ALCL Frequently Asked Questions
A Joint Project from the American Society of Breast Surgeons and the American Society of Plastic Surgeons



Q: What is BIA-ALCL?
A: BIA-ALCL (Breast Implant-Associated Anaplastic Large Cell Lymphoma) is a rare lymphoma that has only been reported in patients with a history of at least one breast implant device and is thought to be a cancer of the breast tissue itself. All government authorities and oncology groups have currently classified BIA-ALCL as a lymphoma. Ongoing research is needed to better understand and define BIA-ALCL, which contains a spectrum of subtypes. A CTSA-sponsored research consortium is currently conducting a clinical trial to evaluate treatment options for BIA-ALCL.

Q: What are the symptoms of BIA-ALCL?
A: BIA-ALCL usually develops as a swelling of the breast (lump) 5 years, or 2 to 28 years, after the insertion of breast implants, which may present as fluid collecting around the implant or as a lump in the breast or armpit.

ASPS is a Society Member of the

1. All government authorities and oncology organizations classify BIA-ALCL as a lymphoma
2. To date, only noted to occur with textured implants.
3. Report confirmed cases to ASPS/FDA PROFILE Registry
4. FDA, ASPS, ASAPS support NCCN Guidelines for Diagnosis and Treatment
5. After PET/CT for oncologic workup, Treatment is surgery with removal of implant and capsule for most patients
6. For clinical situations where use of a smooth vs. textured device is equivocal, should consider a smooth device
7. Deaths and advanced cases emphasize need for prompt identification and proper treatment

EDUCATION

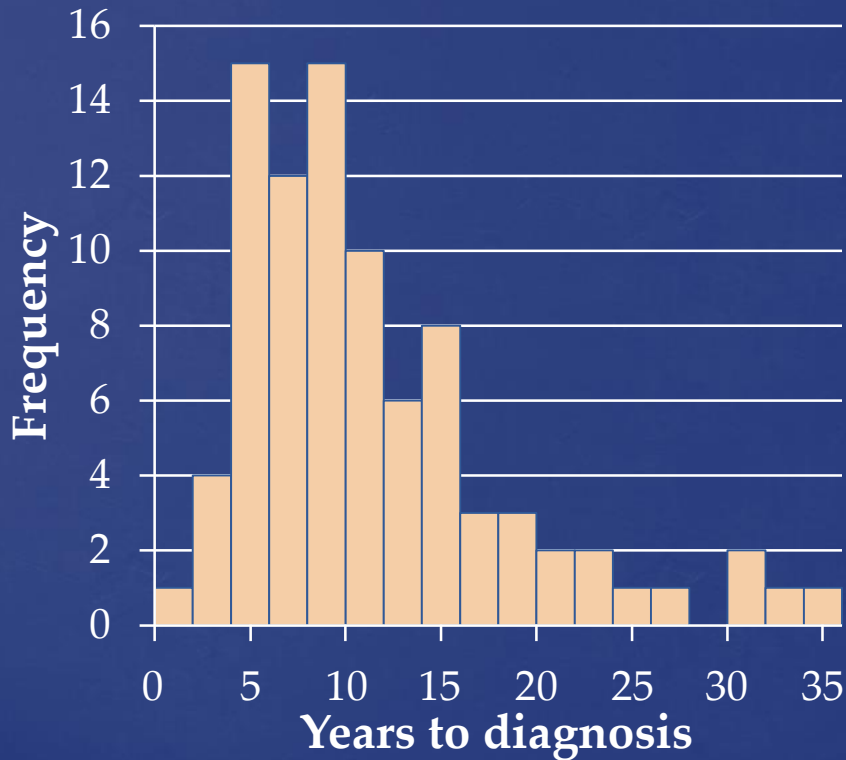
BIA-ALCL Frequently Asked Questions

BIA-ALCL Frequently Asked Questions



THE AMERICAN SOCIETY FOR
AESTHETIC PLASTIC SURGERY, INC.

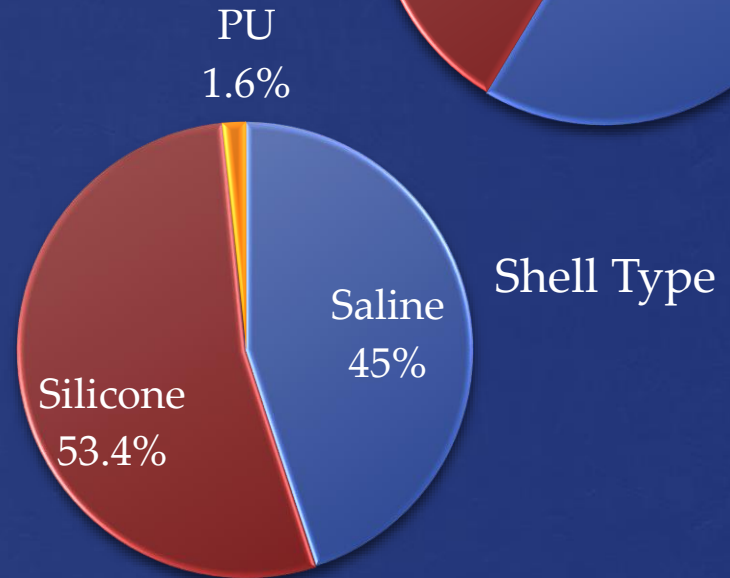
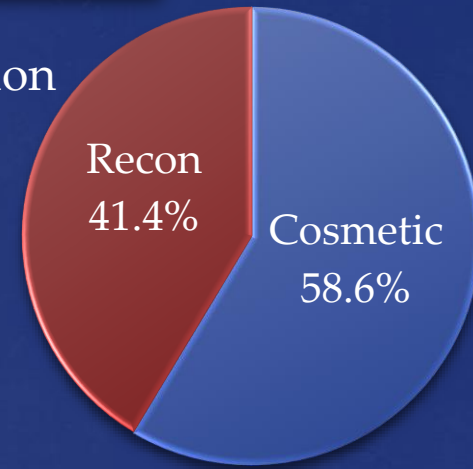
Implants



Median onset ALCL from implantation:
8 years (range, 2– 25 years)

Implant Characteristics

Implant Indication



No Confirmed Pure Smooth Cases To Date


Global Adverse Event Reports of Breast Implant-Associated ALCL: An International Review of 40 Government Authority Databases

Daisyo E. Saitono, M.D.
 Roberto N. Miranda, M.D.
 Aruninder Kaura, B.A.
 Ashleigh M. Francis, M.D.
 Alessandra Cagnavale, M.D.
 Beatrice Rodriguez, M.D.
 Justine Alexander, M.D.
 Anand K. Deva, M.D.
 Paula E. Garriba, M.D.
 L. Jeffrey Medeiros, M.D.
 Karen Noss, B.N.
 Charles E. Butler, M.D.
 Mack W. Gleason, M.D.

Background: Tracking world cases of breast implant-associated lymphoma (ALCL) is currently limited to patient device centers, dependent upon patient referral and clinic. The purpose of this study was to review and collate adverse event reports of breast implant-associated ALCL across breast implant markets worldwide.

Methods: Federal implantable device regulatory body database queries were performed for 40 countries. Data variables, pathology, treatment modalities, and outcomes available.

Results: For the countries searched, 365 unique cases of implant-associated ALCL. Search terms "implant-associated" of the U.S. Manufacturer and User Facility Device Information System.



Out of 359 adverse event reports, **28 reports of "smooth implants" cases.**

Smooth implant reports had either no clinical history or a very superficial unreliable history.

SPECIAL TOPIC

Anaplastic Large Cell Lymphoma Occurring in Women with Breast Implants: Analysis of 173 Cases

Garry S. Brody, M.D., M.Sc.
 Dennis Dracopis, Dr.Ph.
 Cline R. Taylor, M.D., D.Phil.
 Lauren Pinter-Brown, M.D.
 Sarah Rose House-Lightner, M.D.

Background: The first silicone breast implant was inserted in 1962. In 1997, the first case of anaplastic large cell lymphoma (ALCL) in association with a silicone breast implant was reported. The authors reviewed 37 articles in the world literature reporting on 79 patients and collected another 94 unreported cases as of the date of submission.

Methods: The world literature was reviewed. Missing clinical and laboratory information was obtained from the authors.

70 to 80 percent of implants sold in North America are smooth.

No cases of ALCL were found in patients with documented smooth devices only.³

274 Research paper

Risk of lymphoma in women with breast implants: analysis of clinical studies

Joan Largent^a, Michael Oefelein^a, Hilton M. Kaplan^a, Ted Okerson^a and Peter Boyle^b

Large studies suggest that the overall rate of lymphoma in women with breast implants is no greater than in women without breast implants. ALCL in women between 1996 and 2007 without a history of cancer, for an average annual incidence of 0.0001.

Age 71: left breast cancer (1980), treated with radiotherapy and reconstructive breast surgery (**device unknown**). Right breast cancer (1990) treated with mastectomy and reconstructive surgery (**device unknown**).¹

ALK-1–Negative Anaplastic Large Cell Lymphoma Associated With Breast Implants: A New Clinical Entity

Davide Lazzeri,^{1,2} Tommaso Agostini,³ Guido Bocci,⁴ Giordano Giannotti,¹ Giovanni Fanelli,⁵ Antonio Giuseppe Naccarato,³ Romano Danesi,⁴ Marco Tuccori,⁴ Marcello Pantaloni,¹ Carlo D'Aniello²

Abstract

Concerns have been raised recently regarding the increasing number of reports of non-Hodgkin lymphoma (NHL) that developed in close proximity to silicone or saline breast implants. In particular, an increased risk of anaplastic large

58-year-old woman who had undergone bilateral cosmetic breast augmentation with a smooth silicone gel breast implants 19 years previously. In 2006, her device had already been **replaced** for the same complication.²

1. Largent J, et al. Eur J Cancer Prev 2012; 21:274–280; Lazzeri D, et al. Clin Breast Cancer 2011;11(5):283–96; 3. Brody GS, et al. Plast Reconstr Surg 2015; 135:695–705.

Implant type

Type of implant varies from country to country

- US mostly smooth (70-80%)
- Europe and Australia mostly textured (70-90%)

Geographic variation?

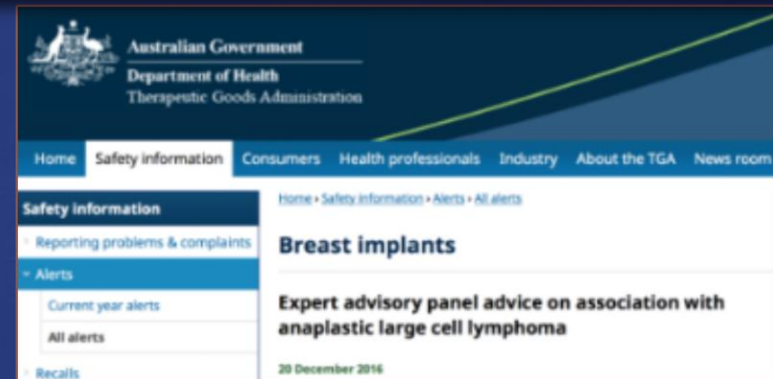
October, 2017

- ◆ US: 1:30,000 (100 cases, 2016)
- ◆ Netherlands 1:6920 (32 cases)
- ◆ Australia, New Zealand, 83 cases,^{1,2}
17 PU cases
 - ◆ Risk 1:1000-1:10,000?¹ for textured implants
 - ◆ Allergan Biocell (1:3705)
 - ◆ Silimed polyurethane (1:3894)
 - ◆ Mentor Siltex (1:60631)



13:46 BREAST-IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL): RELATIVE AND ABSOLUTE RISK ASSESSMENT BASED ON 100% OF ALL NATIONAL CASES OF BIA-ALCL IN THE NETHERLANDS

Mintsje DE BOER, René DAN DER HULST, Floor VAN LEEUWEN, Daphne DE JONG, Hinne RAKHORST
Maastricht University Medical Centre, Maastricht, The Netherlands



1. Therapeutic Goods Administration update, 20 December 2016; 2. Smith TJ. Breast 2012;21:102-4.

Australian Data

	Implants per ALCL	Rate per 10,000 implant	Rate per 10,000 implant-years
Single Implant analysis			
Biocell	4344 (3024,6486)	2.30 (1.54,3.31)	0.34 (0.23,0.49)
Siltex	60631 (10882,2397471)	0.17 (0.004,0.92)	0.028 (0.001,0.156)
Polyurethane 4% market share	2492 (1265,5772)	4.01 (1.73,7.91)	0.59 (0.26,1.17)
Polyurethane 6% market share	3738 (1897,8659)	2.67 (1.15,5.27)	0.40 (0.17,0.78)
Polyurethane 8% market share	4984 (2530,11545)	2.01 (0.87,3.95)	0.30 (0.13,0.59)
Multiple Implant analysis			
Biocell	4199 (2941,6223)	2.38 (1.61,3.40)	0.35 (0.24,0.50)
Siltex	30315 (8392,250330)	0.33 (0.01,1.19)	0.056 (0.007,0.203)
Polyurethane 4% market share	2215 (1167,4844)	4.51 (2.06,8.57)	0.68 (3.06,1.27)
Polyurethane 6% market share	3323 (1750,7267)	3.00 (1.38,5.71)	0.45 (0.20,0.85)
Polyurethane 8% market share	4430 (2334,9689)	2.26 (1.03,4.28)	0.33 (0.15,0.63)

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Biocell	4344 (3024,6486)	2.30 (1.54,3.31)	0.34 (0.23,0.49)
Siltex	60631 (10882,2397471)	0.17 (0.004,0.92)	0.028 (0.001,0.156)
Polyurethane 4% market share	2492 (1265,5772)	4.01 (1.73,7.91)	0.59 (0.26,1.17)
Polyurethane 6% market share	3738 (1897,8659)	2.67 (1.15,5.27)	0.40 (0.17,0.78)
Polyurethane 8% market share	4984 (2530,11545)	2.01 (0.87,3.95)	0.30 (0.13,0.59)
Multiple Implant analysis			
Biocell	4199 (2941,6223)	2.38 (1.61,3.40)	0.35 (0.24,0.50)
Siltex	30315 (8392,250330)	0.33 (0.01,1.19)	0.056 (0.007,0.203)
Polyurethane 4% market share	2215 (1167,4844)	4.51 (2.06,8.57)	0.68 (3.06,1.27)
Polyurethane 6% market share	3323 (1750,7267)	3.00 (1.38,5.71)	0.45 (0.20,0.85)
Polyurethane 8% market share	4430 (2334,9689)	2.26 (1.03,4.28)	0.33 (0.15,0.63)

Risk Factor Analysis for Capsular Contracture, Malposition, and Late Seroma in Subjects Receiving Natrelle 410 Form-Stable Silicor Breast Implants

Patricia McGuire, M.D.
Neal R. Reisman, M.D., J.D.
Diane K. Murphy, M.B.A.

Background: Natrelle 410 silicone breast implants are approved in the United States for breast augmentation, reconstruction, and revision.

Methods: In two ongoing, prospective, multicenter 10-year studies, 17,656 subjects received Natrelle 410 implants for augmentation ($n = 5059$), revision-augmentation ($n = 2632$), reconstruction ($n = 7502$), or revision-reconstruction ($n = 2463$). Capsular contracture, implant malposition, and late seroma were documented. Cox proportional hazards regression analyses evaluated potential associations between subject-, implant-, and surgery-related factors and these complications.

Results: Median follow-up was 4.1, 2.6, 2.1, and 2.3 years in the augmentation, revision-augmentation, reconstruction, and revision-reconstruction cohorts, respectively. Incidence of capsular contracture across cohorts ranged from 2.3 to 4.1 percent; malposition, 1.5 to 2.7 percent; and late seroma, 0.1 to 0.2 percent. Significant risk factors for capsular contracture were subglandular implant placement, periareolar incision site, and older device age in the augmentation cohort ($p < 0.0001$), older subject age in the revision-augmentation cohort ($p < 0.0001$), and higher body mass index ($p = 0.0026$) and no povidone-iodine pocket irrigation ($p = 0.0006$) in the reconstruction cohort. Significant risk factors for malposition were longer incision size in the augmentation cohort ($p = 0.0003$), capsulectomy at the time of implantation in the reconstruction cohort ($p = 0.0028$), and implantations performed in physicians' offices versus hospitals or standalone surgical facilities in both revision cohorts ($p < 0.0001$). The incidence of late seroma was too low to perform risk factor analysis.

Conclusions: These data reaffirm the safety of Natrelle 410 implants. Knowledge of risk factors for capsular contracture and implant malposition offers guidance for reducing complications and optimizing outcomes. (*Plast. Reconstr. Surg.* 139: 1, 2017.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, II.

mass index, device size, style, or incision site. Four cases of breast implant-associated anaplastic large cell lymphoma were reported. One case each was reported in the augmentation, revision-augmentation, reconstruction, and revision-reconstruction cohorts. In these four subjects, breast implant-associated anaplastic large cell lymphoma was diagnosed from approximately 3.5 to 11.6 years after implantation.

BIA-ALCL

$N = 4 (5^*)/17,656 = 3,531$

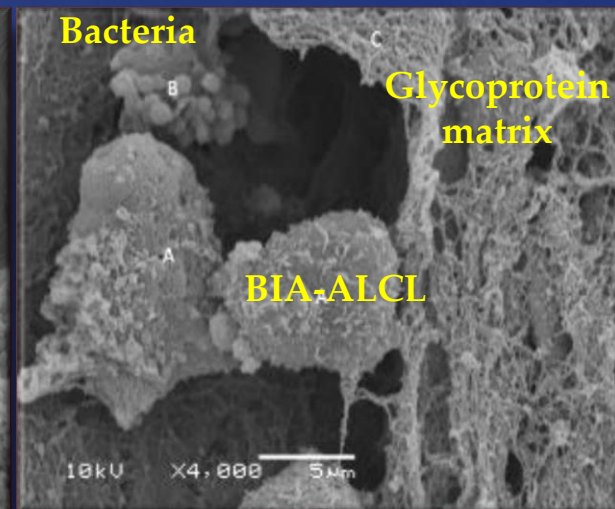
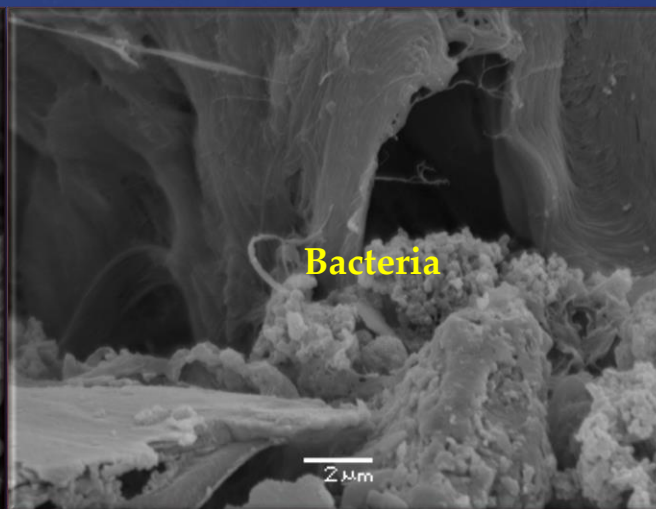
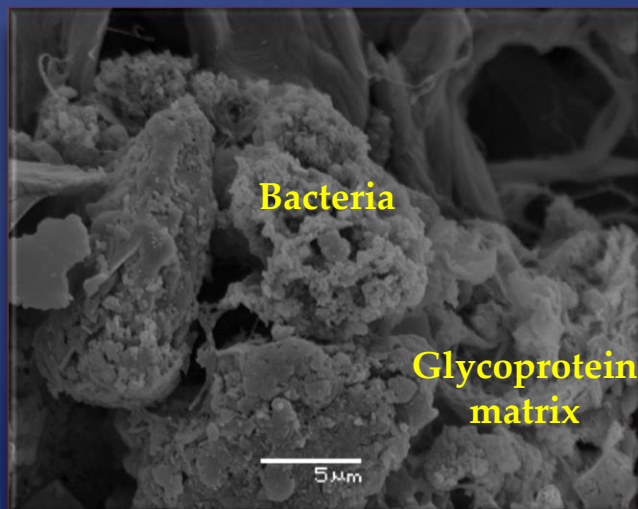
Geography/Ethnic/HLA

- Variables that may be important?
 - Usually 4 years + post implant – will it increase?
 - Geography - suggests a region/ethnic/HLA? - effect
 - 1 asians only reported (Thailand)
 - 1 Native American
 - few African American
 - Relatively few in Sth America
 - Australia/NZ over-represented

Biofilm Theory



- ◆ Picketti *Ralstonia*¹: Common in BIA-ALCL
- ◆ Precedence: *Helicobacter pylori* and GALT¹
- ◆ Distinct Microbiome may chronically stimulate T-cells



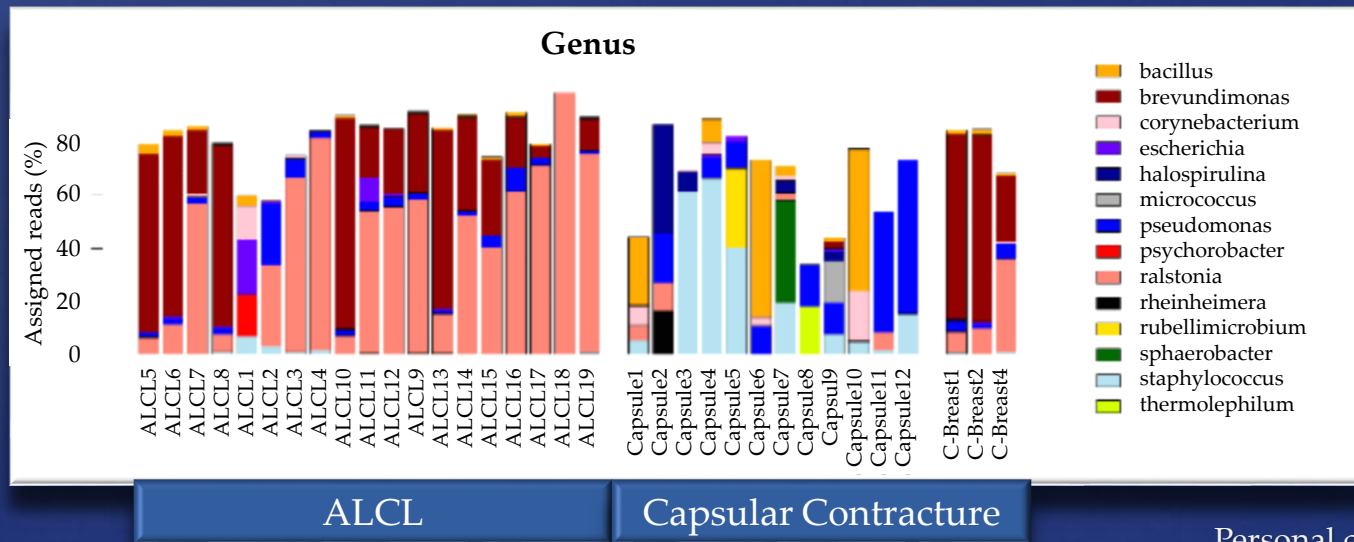
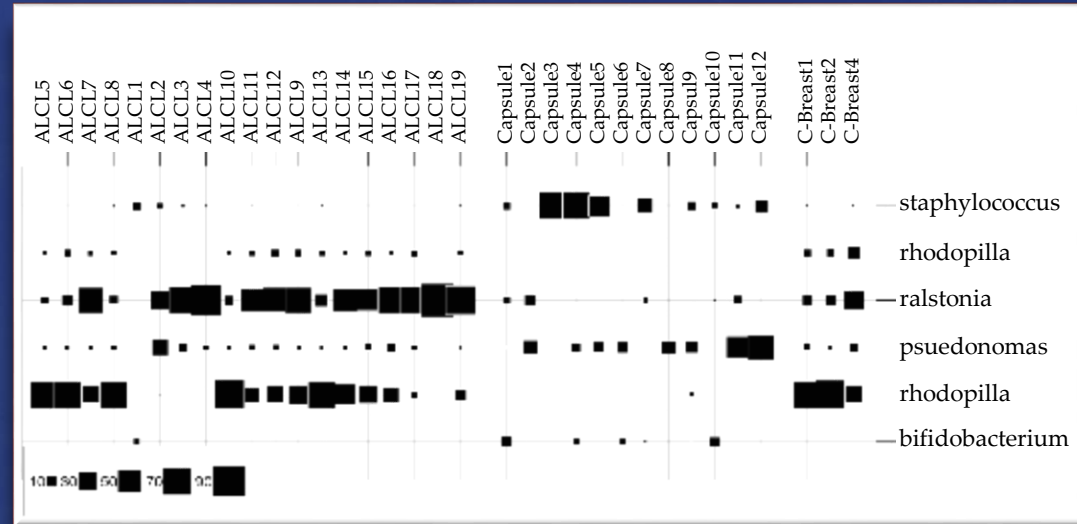
Images courtesy of Dr Mark Clemens.

GALT = gut-associated lymphoid tissue.

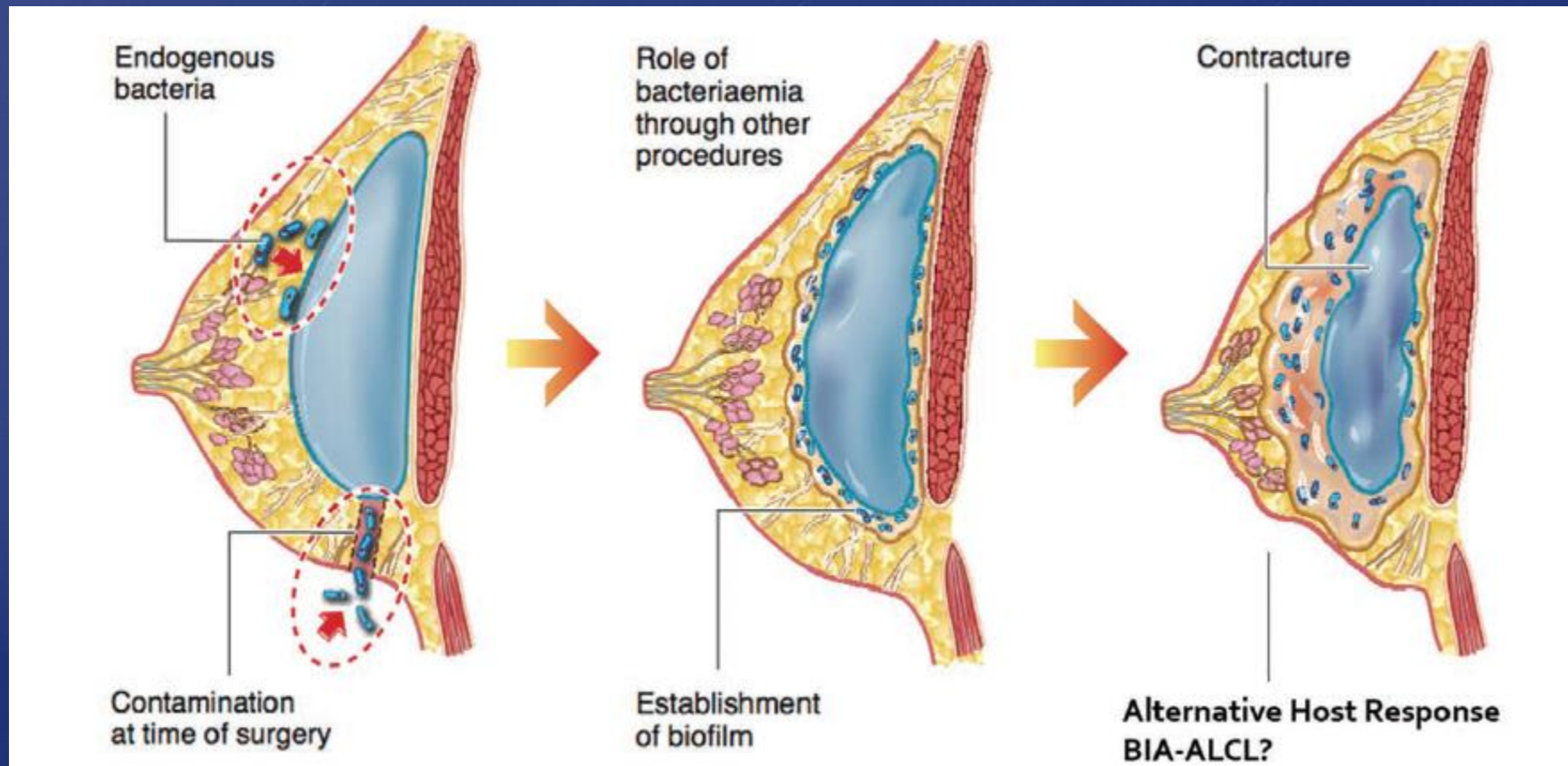
1. Hu H, et al. *Plast Reconstr Surg* 2015;135(2):319–29; 2. Personal communication, Dr Mark Clemens, July 2015.

Biofilm

- ◆ 26 Samples analyzed for biofilm
 - ◆ Locations: USC, MDA, PMC, WM, IPS
 - ◆ SEM, PCR, FISH
- ◆ Compared to 62 capsular contracture specimens
- ◆ Distinct microbiome



Biofilm causes a microbiome:
results in contracture and BIA-ALCL
.....but due to different host response.



Signalling pathways in BIA-ALCL.

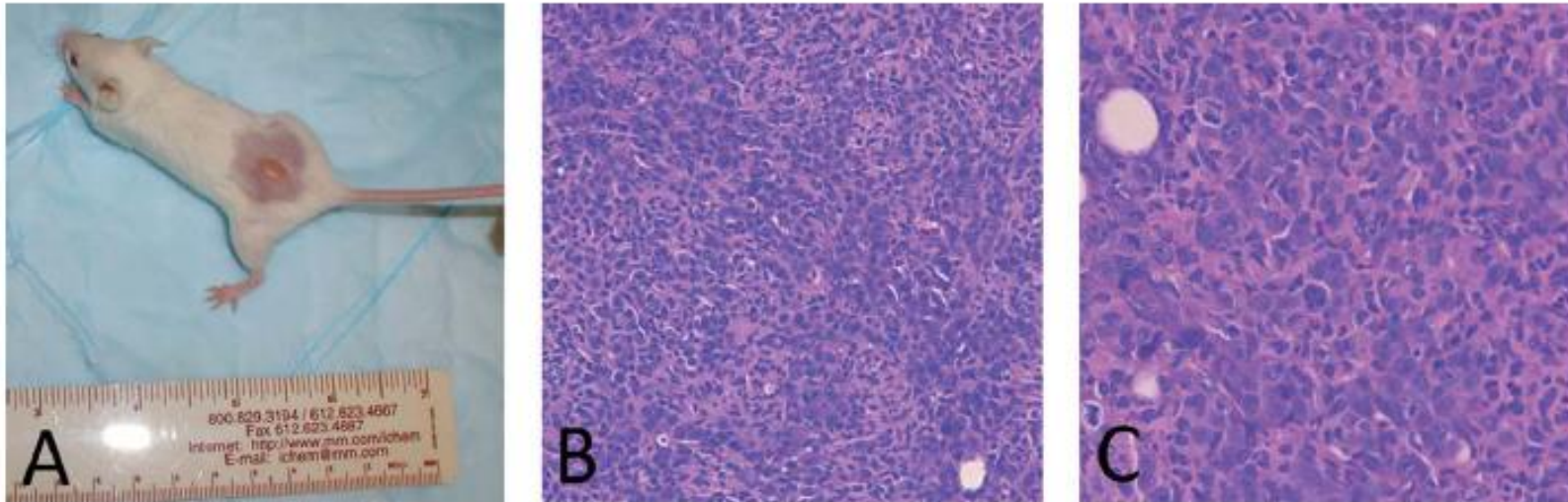
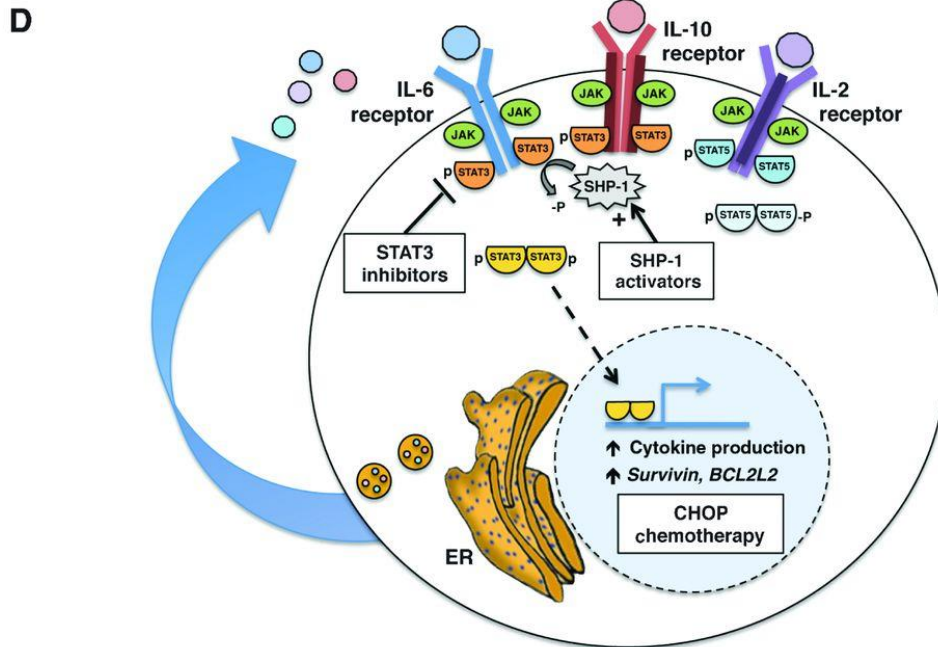
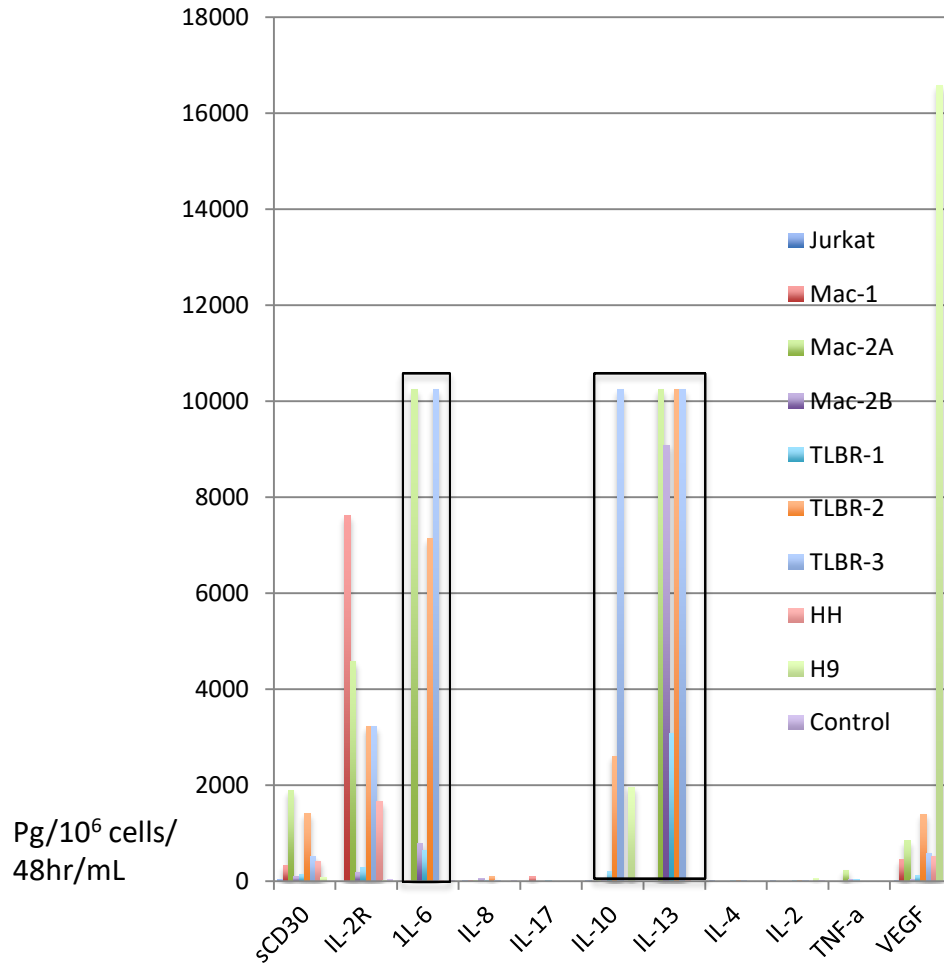


Figure 3. Heterotransplantation of TLBR-1 cell line. (A) Appearance of subcutaneous TLBR-1 tumor in SCID mouse. (B and C) Low and high magnification of TLBR-1 SCID tumor demonstrating similar morphological features to the original biopsy (hematoxylin and eosin [H&E] stain $\times 200$ and $\times 400$ original magnification).

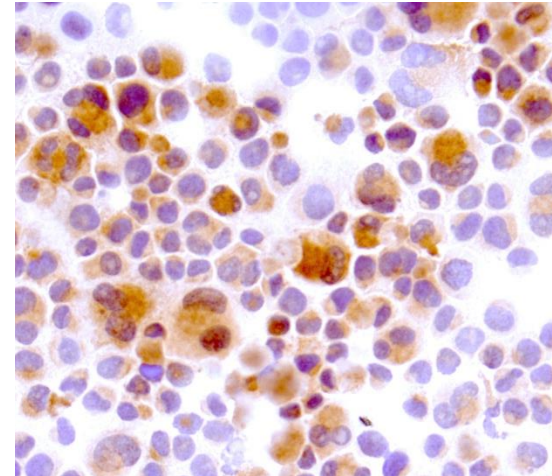


Cytokines secreted by cutaneous and BIA-ALCL lines

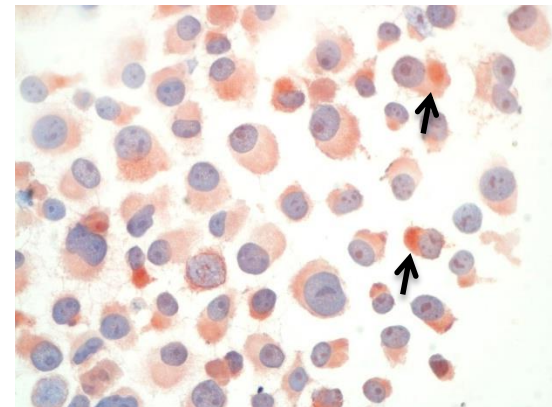


TLBR3

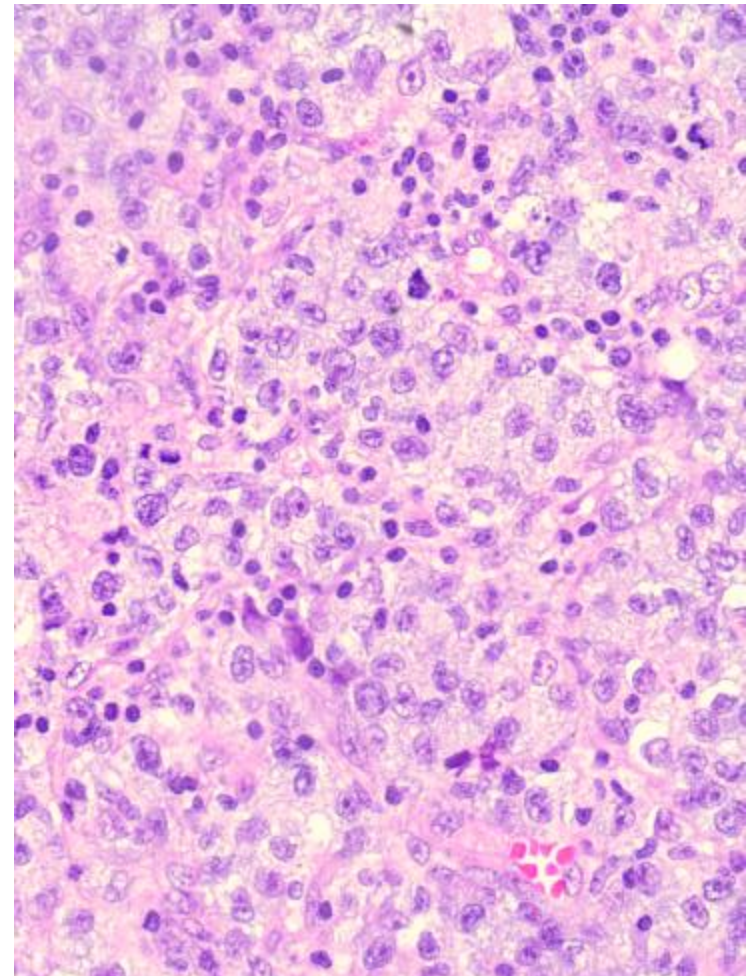
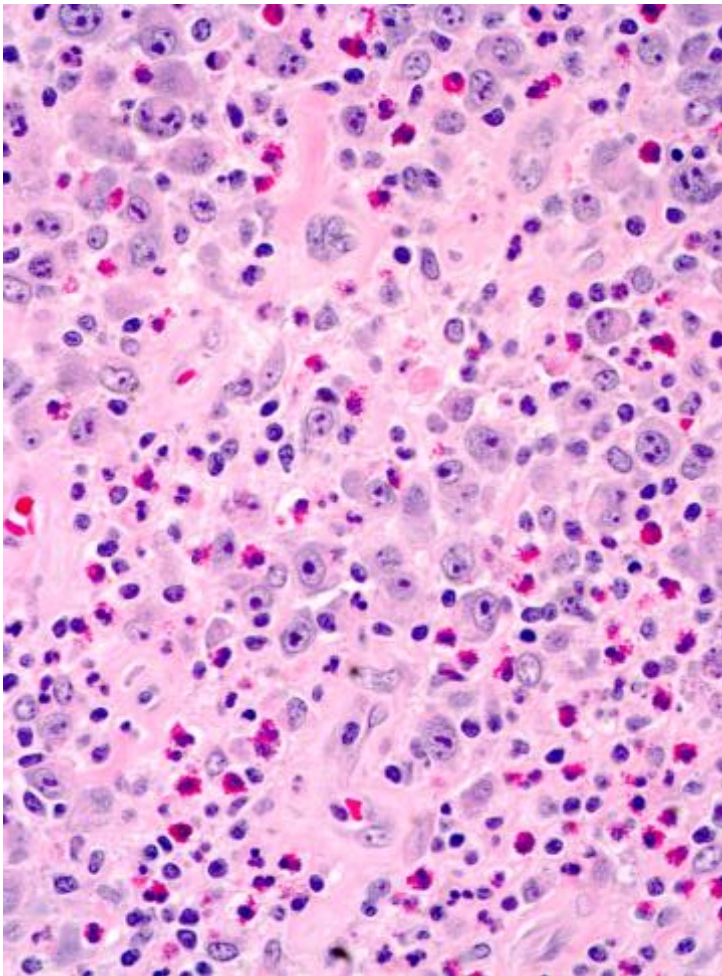
IL-13



IL-10

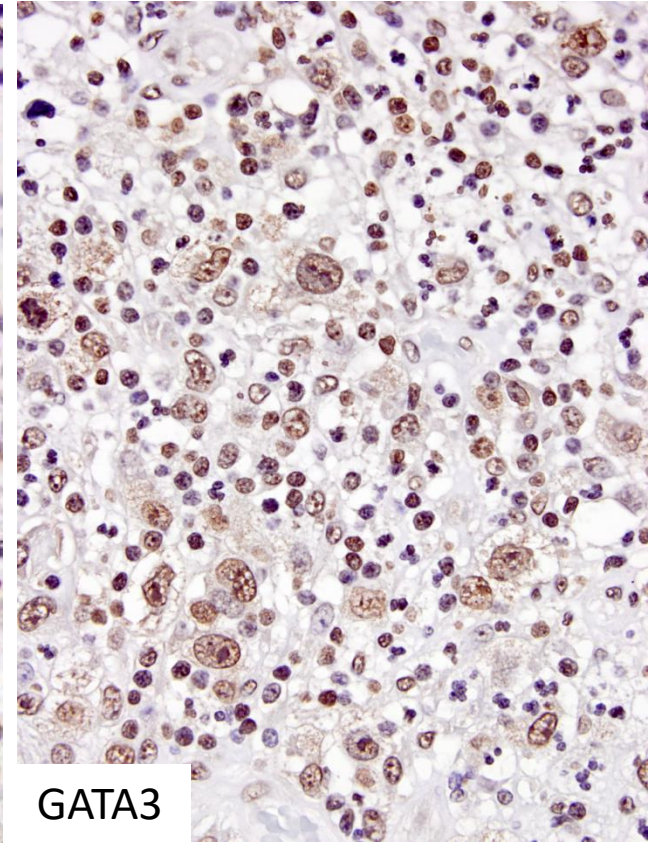
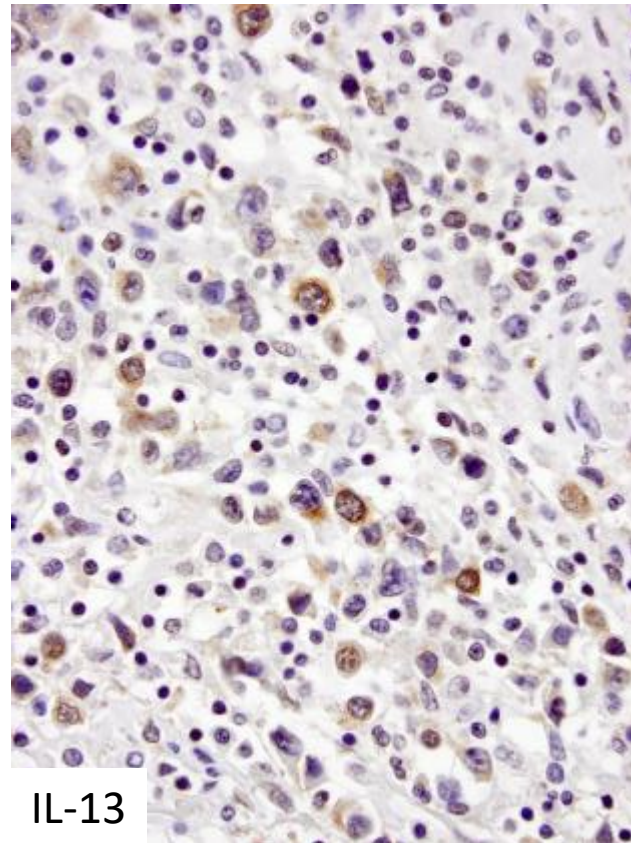
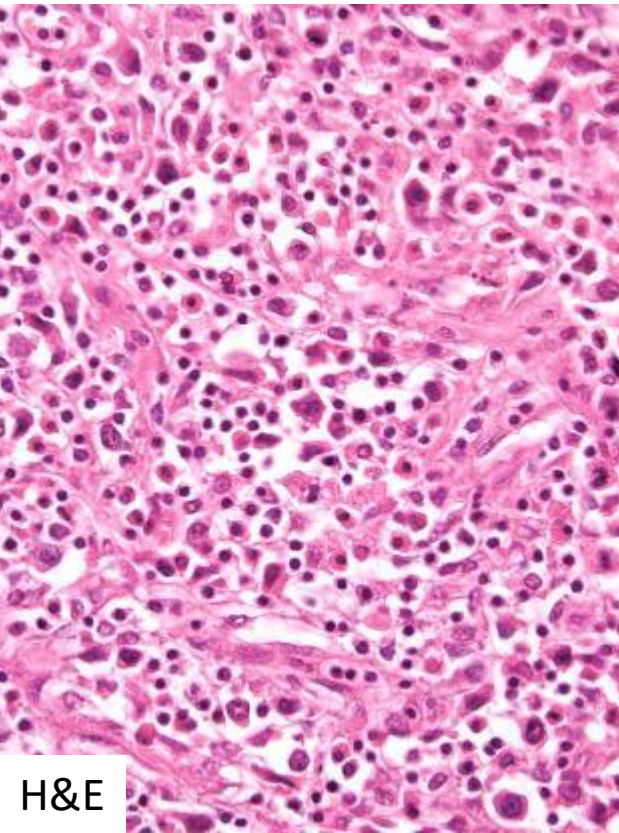


Eosinophils are characteristic of BIA-ALCL but not systemic ALCL



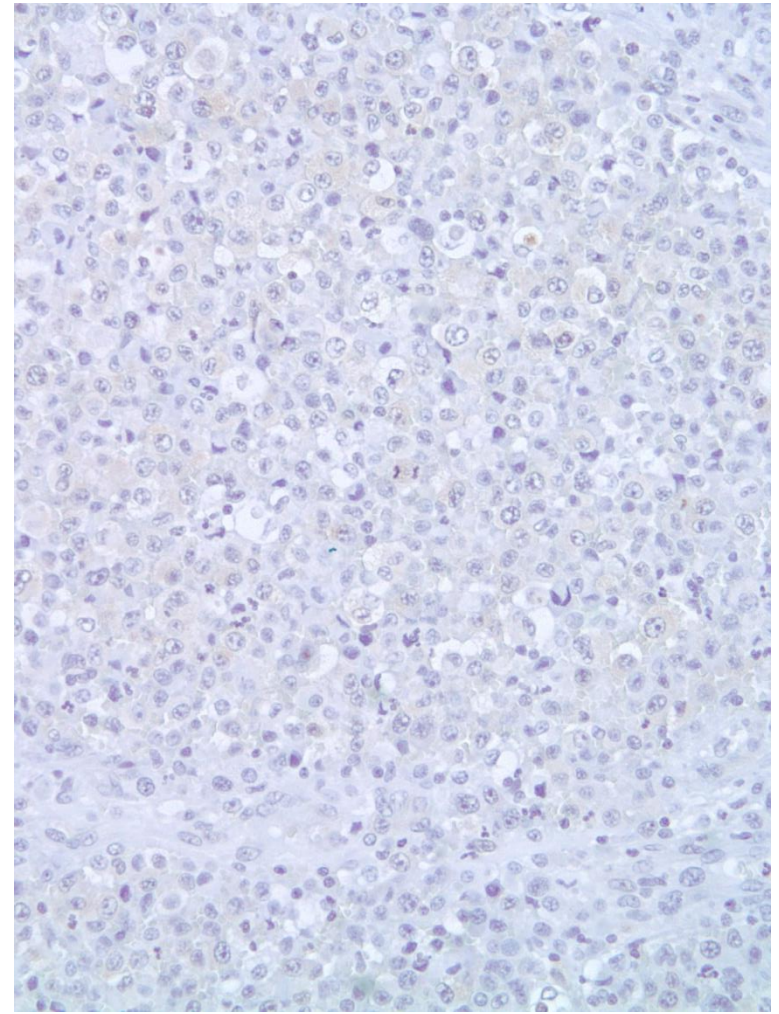
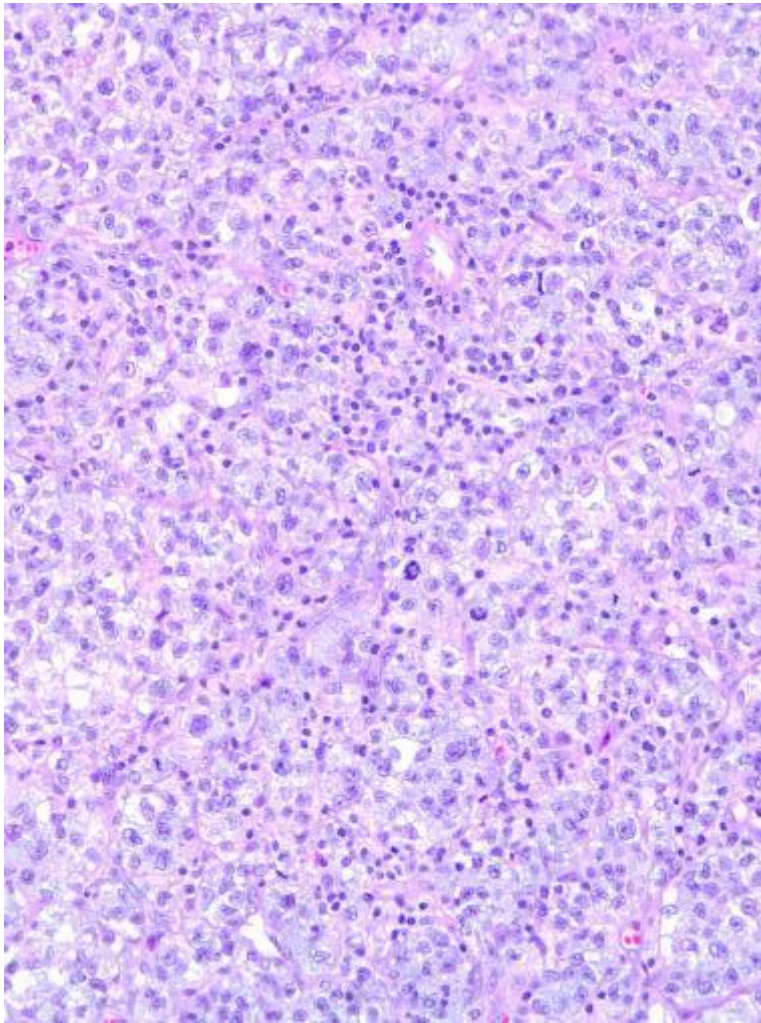
Difference in eosinophils between BIA- and systemic ALCL, $P=.003$, Kruskal-Wallis

Anaplastic cells surrounded by eosinophils produce IL-13



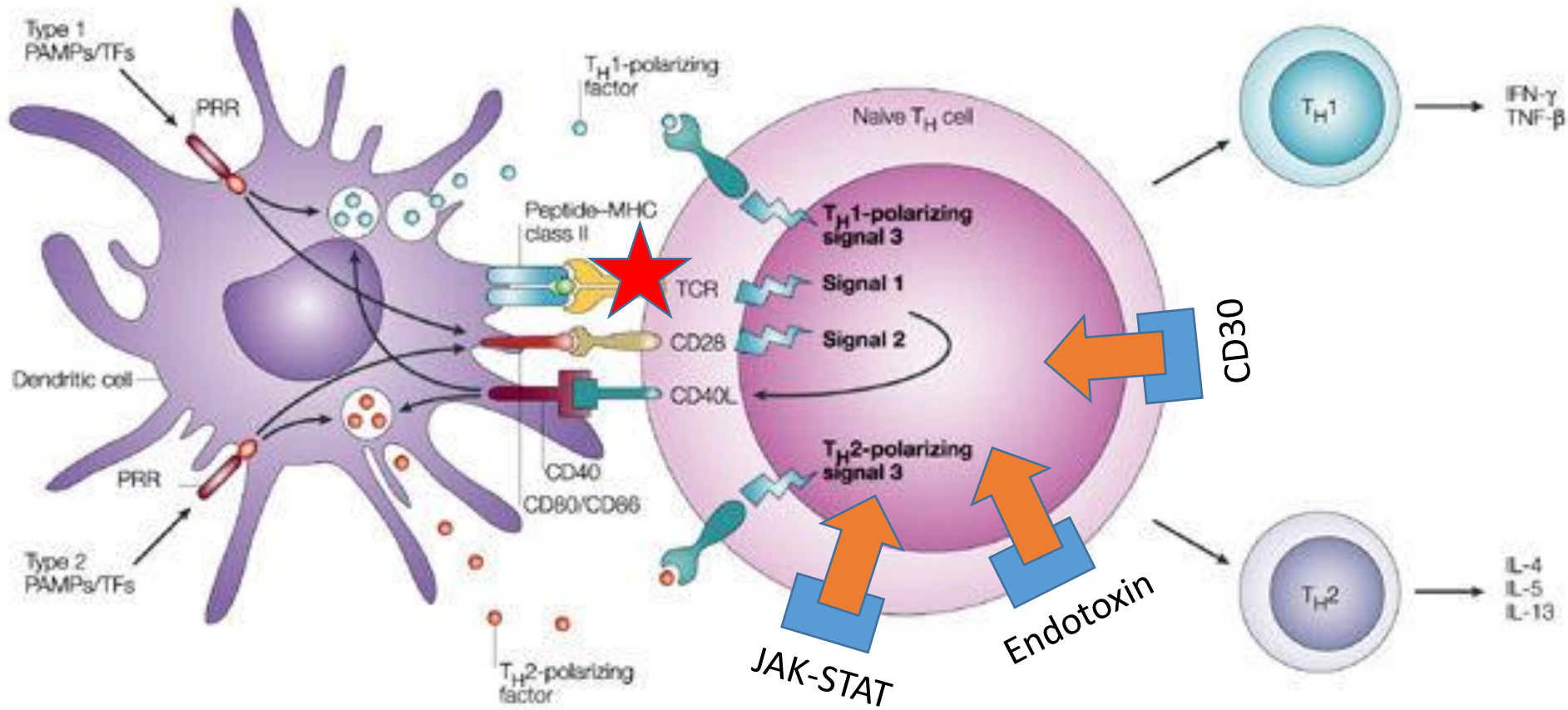
Tumor cells surrounded
by eosinophils

Systemic ALCL negative for IL-13



Only 2 of 18 systemic ALCL contained neoplastic cells expressing IL-13 ($P < .001$)

Proliferation to malignancy



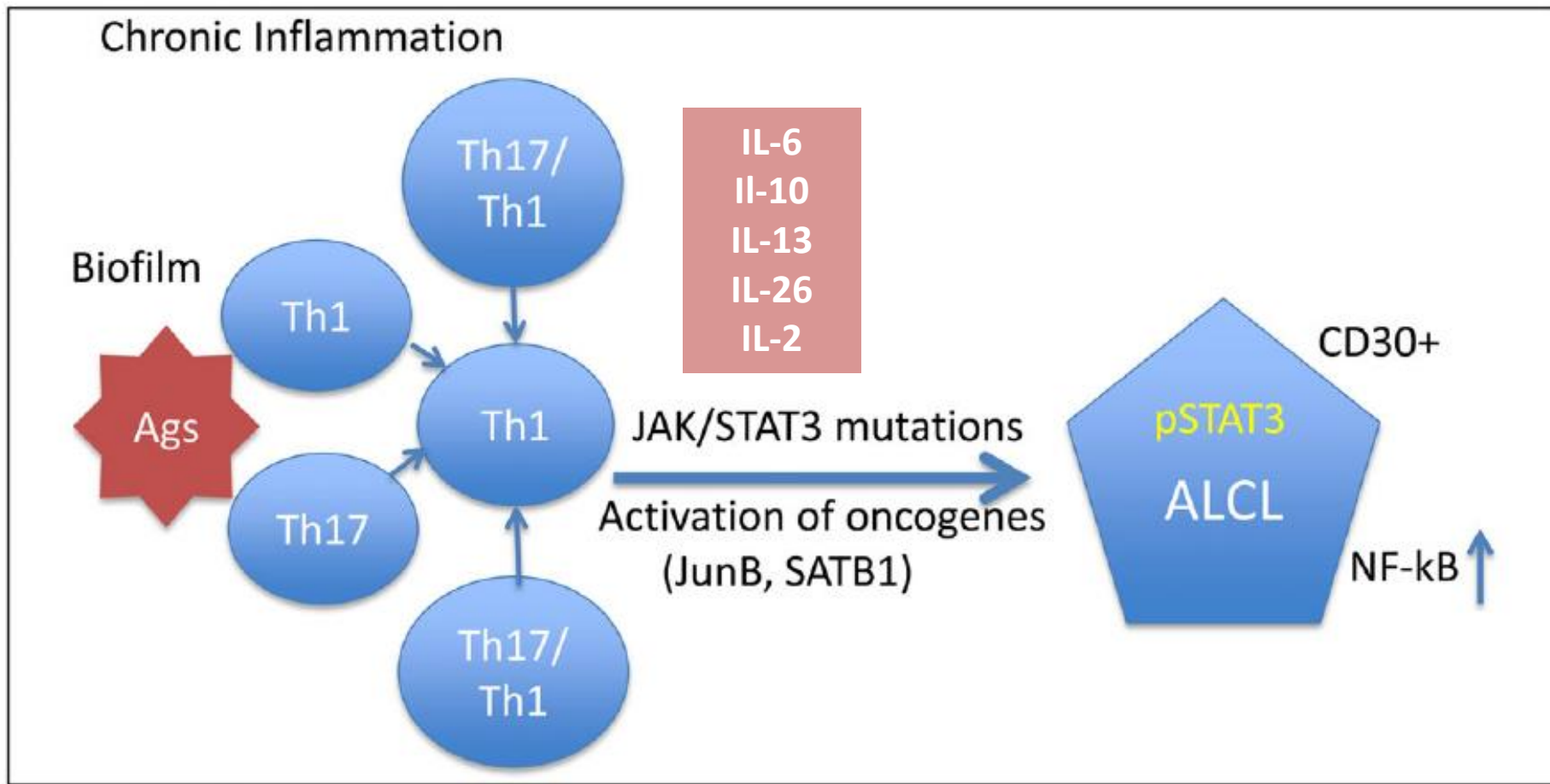


Figure 13. Working hypothesis for progression of immune responding T lymphocytes to BIA-ALCL.

Molecular studies



EUROPEAN
HEMATOLOGY
ASSOCIATION

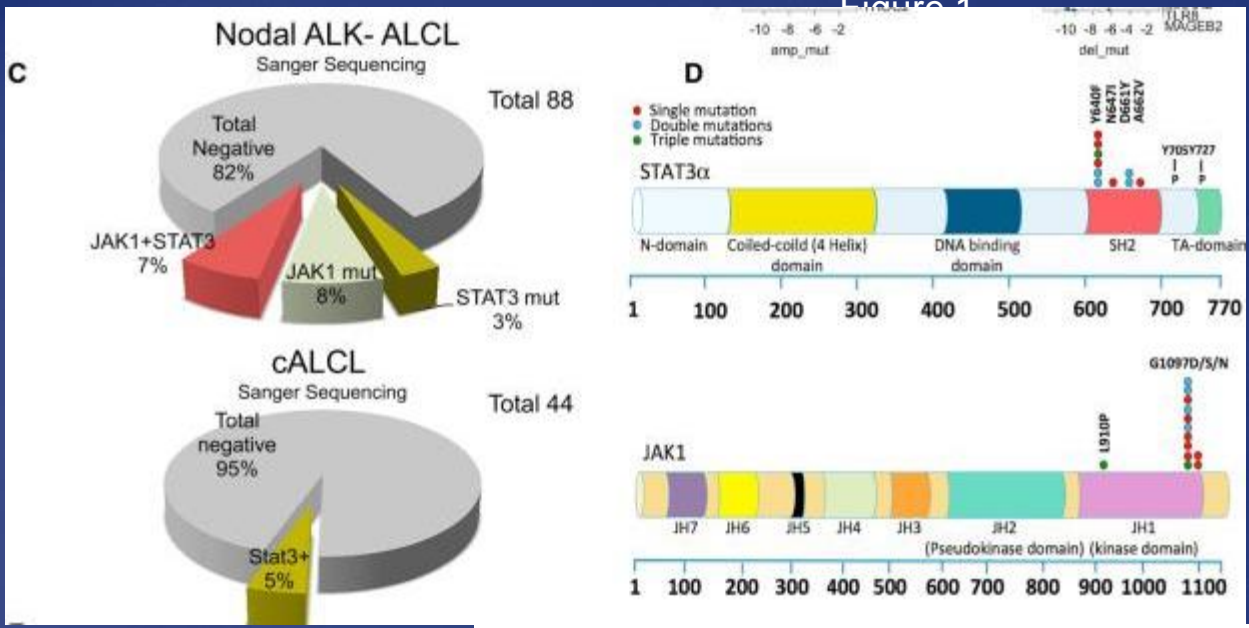
 **haematologica**

Journal of the European Hematology Association

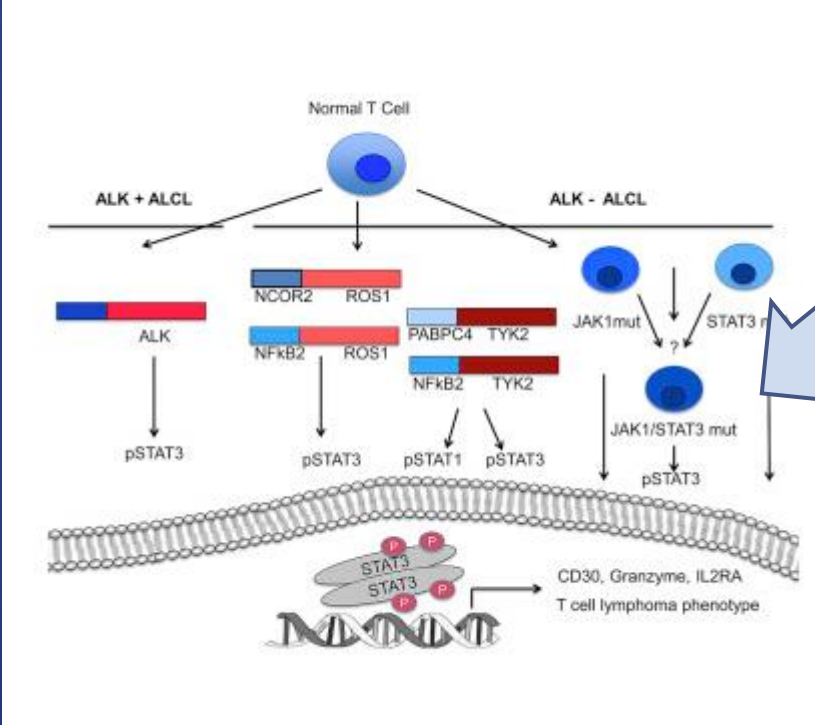
Whole exome sequencing reveals activating JAK1 and STAT3 mutations in breast-implant associated anaplastic large cell lymphoma

by Piers Blombery, Ella Thompson, Kate Jones, Gisela Mir Arnau, Stephen Lade, John F. Markham, Jason Li, Anand Deva, Ricky W. Johnstone, Amit Khot, H. Miles Prince, and David Westerman

Figure 1












In vitro data
Indicates that
this alone will
not result in
autonomous
growth






Summary of mutations found in 10 cases from PMCC

BALCL1	<i>STAT3</i>	NM_139276.2:c.1981G>T; p.(Asp661Tyr)	
BALCL1	<i>BCOR</i>	NM_017745.5:c.4424G>A; p.(Trp1475*)	(bcl-6 path)
BALCL2	<i>STAT3</i>	NM_139276.2:c.1919A>T; p.(Tyr640Phe)	
BALCL3	<i>TP53</i>	NM_000546.5:c.673-1G>A	Confirmed germline
BALCL3	<i>OBSCN</i>	NM_052843.3:c.19411G>A; p.(Asp6471Asn)	calmodulin
BALCL4	<i>SOCS1</i>	NM_003745.1:c.518dup; p.(Leu174Alafs*79)	
BALCL5	<i>STAT3</i>	NM_139276.2:c.1981G>T; p.(Asp661Tyr)	
BALCL5	<i>BRIP1</i>	NM_032043.2:c.487C>G; p.(Pro163Ala)	With BRCA-1
BALCL6	<i>TP53</i>	NM_000546.5:c.524G>A; p.(Arg175His)	
BALCL6	<i>STAT3</i>	NM_139276.2:c.1229A>G; p.(His410Arg)	
BALCL6	<i>TP53</i>	NM_000546.5:c.746G>A; p.(Arg249Lys)	Confirmed germline
BALCL6	<i>SETD2</i>	NM_014159.6:c.2893G>T; p.(Glu965*)	HMT
BALCL7	<i>STAT3</i>	NM_139276.2:c.1840A>C, p.(Ser614Arg)	
BALCL8	<i>JAK1</i>	NM_002227.2:c.3290_3291delinsTT; p.(G1097V)	
BALCL8	<i>JAK3</i>	NM_000215.3:c.2164G>A, p.(Val722Ile)	Confirmed germline
BALCL9	<i>STAT3</i>	NM_139276.2:c.1981G>T; p.(Asp661Tyr)	
BALCL10	<i>STAT3</i>	NM_139276.2:c.1842C>A; p.(Ser614Arg)	


Summary of mutations found in 10 cases from PMCC

BALCL1	<i>STAT3</i> 	NM_139276.2:c.1981G>T; p.(Asp661Tyr)	
BALCL1	<i>BCOR</i>	NM_017745.5:c.4424G>A; p.(Trp1475*)	(bcl-6 path)
BALCL2	<i>STAT3</i> 	NM_139276.2:c.1919A>T; p.(Tyr640Phe)	
BALCL3	<i>TP53</i>	NM_000546.5:c.673-1G>A	Confirmed germline
BALCL3	<i>OBSCN</i>	NM_052843.3:c.19411G>A; p.(Asp6471Asn)	calmodulin
BALCL4	<i>SOCS1</i> 	NM_003745.1:c.518dup; p.(Leu174Alafs*79)	
BALCL5	<i>STAT3</i> 	NM_139276.2:c.1981G>T; p.(Asp661Tyr)	
BALCL5	<i>BRIP1</i>	NM_032043.2:c.487C>G; p.(Pro163Ala)	With BRCA-1
BALCL6	<i>TP53</i>	NM_000546.5:c.524G>A; p.(Arg175His)	
BALCL6	<i>STAT3</i> 	NM_139276.2:c.1229A>G; p.(His410Arg)	
BALCL6	<i>TP53</i>	NM_000546.5:c.746G>A; p.(Arg249Lys)	Confirmed germline
BALCL6	<i>SETD2</i>	NM_014159.6:c.2893G>T; p.(Glu965*)	HMT
BALCL7	<i>STAT3</i> 	NM_139276.2:c.1840A>C, p.(Ser614Arg)	
BALCL8	<i>JAK1</i> 	NM_002227.2:c.3290_3291delinsTT; p.(G1097V)	
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BALCL9	<i>STAT3</i> 	NM_139276.2:c.1981G>T; p.(Asp661Tyr)	
BALCL10	<i>STAT3</i> 	NM_139276.2:c.1842C>A; p.(Ser614Arg)	

Summary of mutations found in 10 cases from PMCC

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BALCL3	<i>TP53</i>	NM_000546.5:c.673-1G>A	Confirmed germline 
BALCL3	<i>OBSCN</i>	NM_052843.3:c.19411G>A; p.(Asp6471Asn)	calmodulin
BALCL4	<i>SOCS1</i>	NM_003745.1:c.518dup; p.(Leu174Alafs*79)	
BALCL5	<i>STAT3</i>	NM_139276.2:c.1981G>T; p.(Asp661Tyr)	
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BALCL6	<i>STAT3</i>	NM_139276.2:c.1229A>G; p.(His410Arg)	
BALCL6	<i>TP53</i>	NM_000546.5:c.746G>A; p.(Arg249Lys)	Confirmed germline 
BALCL6	<i>SETD2</i>	NM_014159.6:c.2893G>T; p.(Glu965*)	HMT
BALCL7	<i>STAT3</i>	NM_139276.2:c.1840A>C, p.(Ser614Arg)	
BALCL8	<i>JAK1</i>	NM_002227.2:c.3290_3291delinsTT; p.(G1097V)	
BALCL8	<i>JAK3</i>	NM_000215.3:c.2164G>A, p.(Val722Ile)	Confirmed germline 
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Summary of mutations found in 10 cases from PMCC

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BALCL6	<i>STAT3</i>	NM_139276.2:c.1229A>G; p.(His410Arg)	
BALCL6	<i>TP53</i>	NM_000546.5:c.746G>A; p.(Arg249Lys)	Confirmed germline
BALCL6	<i>SETD2</i>	NM_014159.6:c.2893G>T; p.(Glu965*)	HMT  Enteropathy -TCL
BALCL7	<i>STAT3</i>	NM_139276.2:c.1840A>C, p.(Ser614Arg)	
BALCL8	<i>JAK1</i>	NM_002227.2:c.3290_3291delinsTT; p.(G1097V)	
BALCL8	<i>JAK3</i>	NM_000215.3:c.2164G>A, p.(Val722Ile)	Confirmed germline
BALCL9	<i>STAT3</i>	NM_139276.2:c.1981G>T; p.(Asp661Tyr)	
BALCL10	<i>STAT3</i>	NM_139276.2:c.1842C>A; p.(Ser614Arg)	

Peter MacCallum Cohort

	Case 1	Case 2	Case 3	Case 4	Case 5
Investigation	WES	WES	PanHaem	PanHaem	PanHaem
Tumour	STAT3 S614R	JAK1 G1097V JAK3 V722I	STAT3 H410R TP53 R175H TP53 R249K	STAT3 D661Y	STAT3 D661Y
CNV	Multiple	None	Multiple (MYC amp.)	N/A*	N/A*
Germline	N/A**	JAK3 V722I	TP53 R249K	N/A**	N/A**

Di Napoli et al, Br J Haem. Rome Cohort

	Case 1	Case 2	Case 3	Case 4	Case 5
Investigation	Targeted seq	Targeted seq	Targeted seq	Targeted seq	Targeted seq
Tumour	STAT3 S614R TP53 D259Y SOCS1 P83fs	DNMT3A W176X	Nil	Nil	Nil
CNV	N/A	N/A	N/A	N/A	N/A
Germline	N/A	N/A	N/A	N/A	N/A

Peter MacCallum Cohort

	Case 1	Case 2	Case 3	Case 4	Case 5
Investigation	WES	WES	PanHaem	PanHaem	PanHaem
Tumour	STAT3 S614R	JAK1 G1097V JAK3 V722I	STAT3 H410R TP53 R175H TP53 R249K	STAT3 D661Y	STAT3 D661Y
CNV	Multiple	None	Multiple (MYC amp.)	N/A*	N/A*
Germline	N/A**	JAK3 V722I	TP53 R249K	N/A**	N/A**

Di Napoli et al, Br J Haem. Rome Cohort

	Case 1	Case 2	Case 3	Case 4	Case 5
Investigation	Targeted seq	Targeted seq	Targeted seq	Targeted seq	Targeted seq
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CNV	N/A	N/A	N/A	N/A	N/A
Germline	N/A	N/A	N/A	N/A	N/A

Peter MacCallum Cohort

	Case 1	Case 2	Case 3	Case 4	Case 5
Investigation	WES	WES	PanHaem	PanHaem	PanHaem
Tumour	STAT3 S614R	JAK1 G1097V JAK3 V722I	STAT3 H410R TP53 R175H TP53 R249K	STAT3 D661Y	STAT3 D661Y
CNV	Multiple	None	Multiple (MYC amp.)	N/A*	N/A*
Germline	N/A**	JAK3 V722I	TP53 R249K	N/A**	N/A**

Di Napoli et al, Br J Haem. Rome Cohort

	Case 1	Case 2	Case 3	Case 4	Case 5
Investigation	Targeted seq	Targeted seq	Targeted seq	Targeted seq	Targeted seq
Tumour	STAT3 S614R TP53 D259Y SOCS1 P83fs	DNMT3A W176X	Nil	Nil	Nil
CNV	N/A	N/A	N/A	N/A	N/A
Germline	N/A	N/A	N/A	N/A	N/A



Breast implant-associated anaplastic large cell lymphoma in a patient with Li–Fraumeni syndrome

DOI: 10.1111/his.12737

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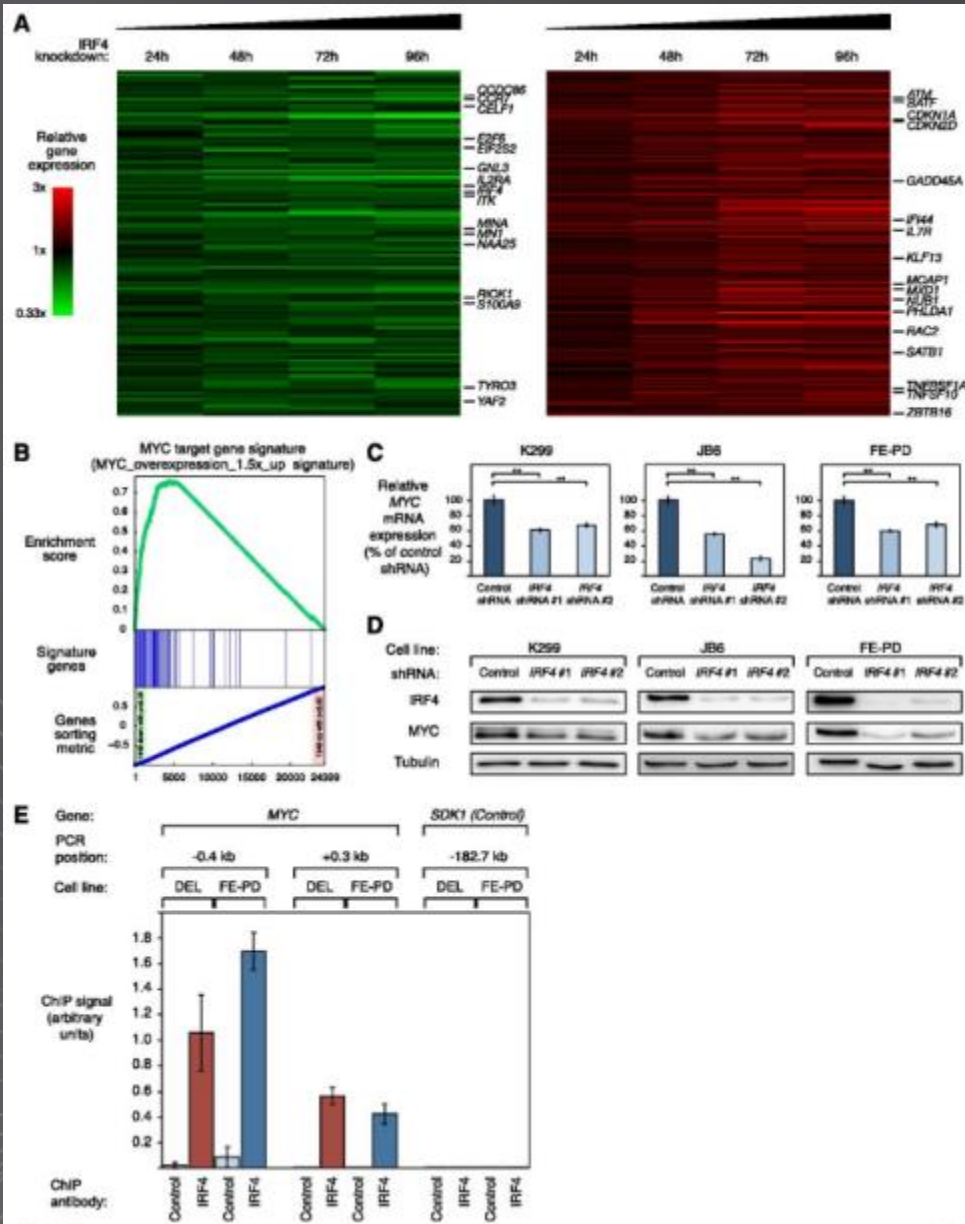
*Laboratory of Pathology, Center for Cancer Research,
National Cancer Institute, Bethesda, MD, USA, and
¹Genito-urinary Malignancies Branch, Center for Cancer
Research, National Cancer Institute, Bethesda, MD, USA*

Peter MacCallum Cohort

	Case 1	Case 2	Case 3	Case 4	Case 5
Investigation	WES	WES	PanHaem	PanHaem	PanHaem
Tumour	STAT3 S614R	JAK1 G1097V JAK3 V722I	STAT3 H410R TP53 R175H TP53 R249K	STAT3 D661Y	STAT3 D661Y
CNV	Multiple	None	Multiple (MYC amp.)	N/A*	N/A*
Germline	N/A**	JAK3 V722I	TP53 R249K	N/A**	N/A**

Di Napoli et al, Br J Haem. Rome Cohort

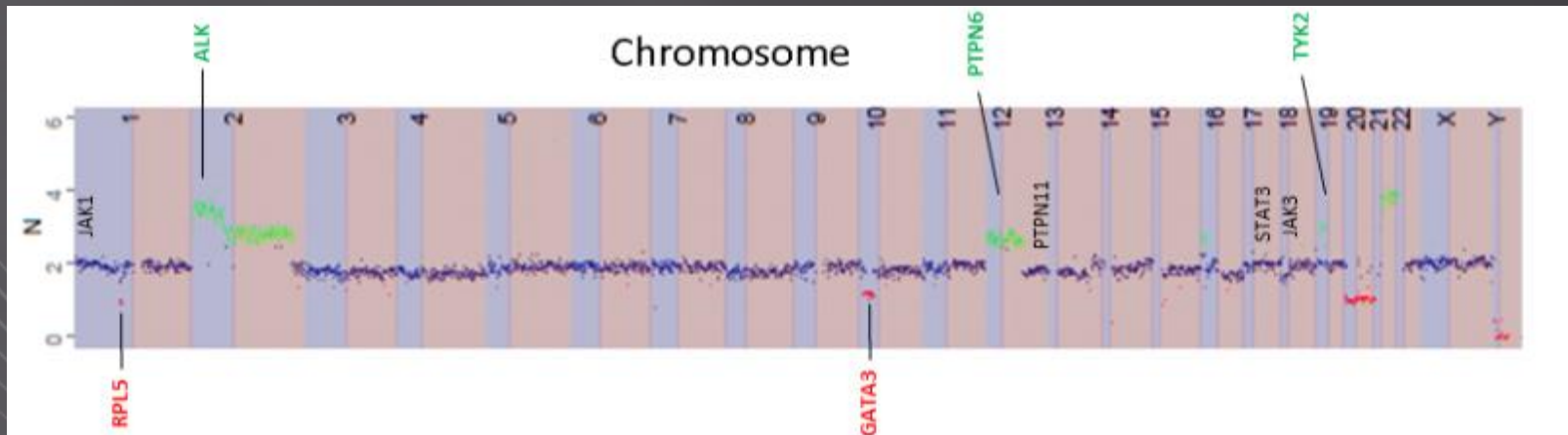
	Case 1	Case 2	Case 3	Case 4	Case 5
Investigation	Targeted seq	Targeted seq	Targeted seq	Targeted seq	Targeted seq
Tumour	STAT3 S614R TP53 D259Y SOCS1 P83fs	DNMT3A W176X	Nil	Nil	Nil
CNV	N/A	N/A	N/A	N/A	N/A
Germline	N/A	N/A	N/A	N/A	N/A



MYC expression is central to ALK-ve and ALK+ve ALCL pathogenesis

Case 1 - Molecular

- Multiple somatic **copy number alterations**



1p copy number loss*	Somatic	Focal deleted region containing tumour suppressor gene RPL5
10p copy number loss*	Somatic	Focal deleted region containing tumour suppressor gene GATA3
19p copy number gain*	Somatic	Focal gained region containing JAK-family kinase TYK2

HLA?

- Only T cell lymphoma associated with infection is Coeliac disease – Enteropathy-associated T cell lymphoma
 - Coeliac disease is very anglo-saxon/HLA disease
- Geography of BIA-ALCL: suggests region/ethnic/HLA? - effect
 - 1 asians (Thailand) only reported
 - 1 Native American
 - few African American
 - Relatively few in Sth America
 - Australia/NZ over-represented
- If this is like coeliac disease – what is the antigen?

HLA Distribution in BIA-ALCL

- Prospectively evaluated 11 BIA-ALCL patients
- Probe based sequence specific testing and sequence based typing
- Compared to Caucasian European-descent general population obtained from the National Marrow Donor Program
- Age range 37-76 yo

Table: Frequencies of HLA Alleles in Patients with BIA-ALCL and the General Population

HLA Allele	# of Allele Haplotypes N = 22	BIA-ALCL Allele Frequency	General Population Allele Frequency*
A*01	2	0.09091	0.17206
A*02	10	0.45455	0.30806
A*03	2	0.09091	0.14639
A*11	1	0.04545	0.05686
A*24	1	0.04545	0.08812
A*26	1	0.04545	0.2992
A*29	1	0.04545	0.03495
A*32	2	0.09091	0.03133
A*68	2	0.09091	0.0336
B*07	6	0.27273	0.14272
B*15	3	0.13636	0.07282
B*27	1	0.04545	0.03621
B*35	1	0.04545	0.08787
B*38	1	0.04545	0.02186
B*39	1	0.04545	0.01531
B*40	2	0.09091	0.0664
B*44	4	0.18182	0.14285
B*49	1	0.04545	0.01341
B*51	1	0.04545	0.04695
B*57	1	0.04545	0.03902
C*01	1	0.04545	0.02928
C*02	1	0.04545	0.03729
C*03	5	0.22727	0.13836
C*04	2	0.09091	0.10546
C*05	2	0.09091	0.09161
C*07	9	0.40909	0.32806
C*12	1	0.04545	0.05851
C*16	1	0.04545	0.03882
DRB1*01	2	0.09091	0.11741
DRB1*03	2	0.09091	0.12922
DRB1*04	4	0.18182	0.15877
DRB1*07	3	0.13636	0.13767
DRB1*13	3	0.13636	0.11536
DRB1*14	1	0.04545	0.02503
DRB1*15	7	0.31818	0.15235
DQB1*02	3	0.13636	0.23030
DQB1*03	7	0.31818	0.32675
DQB1*05	2	0.09091	0.16214
DQB1*06	10	0.45455	0.25552

HLA Distribution in BIA-ALCL

- 7 DRB1 alleles and 4 DQB1 alleles in the BIA-ALCL patients
- More than 2x vs gen population:
 - A*32, A*68, B*38, B*39, B*49, and DRB1*15
- More than 6x in gen population
 - A*26 allele

Table: Frequencies of HLA Alleles in Patients with BIA-ALCL and the General Population

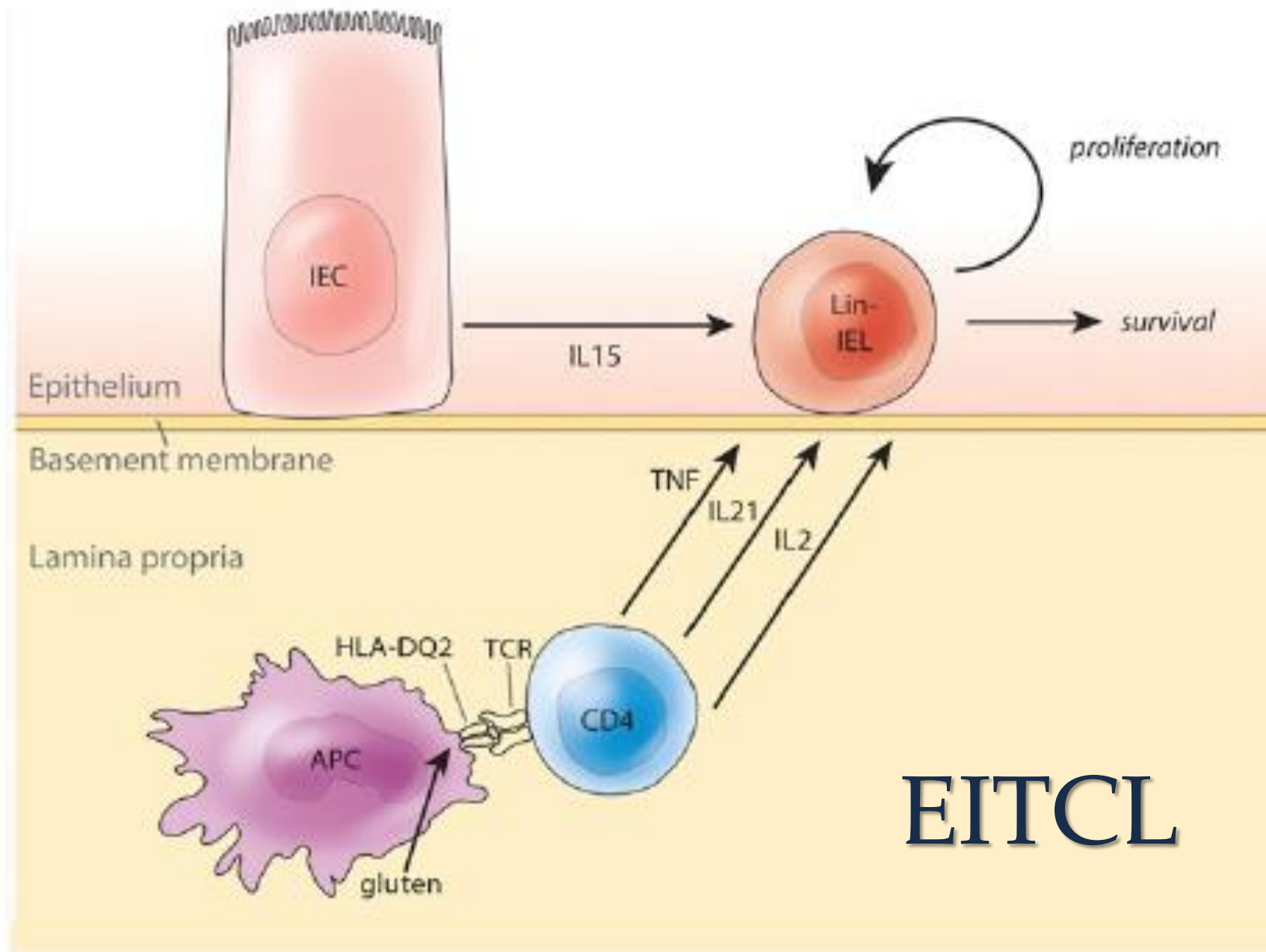
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DQB1*06	10	0.45455	0.25552

HLA?

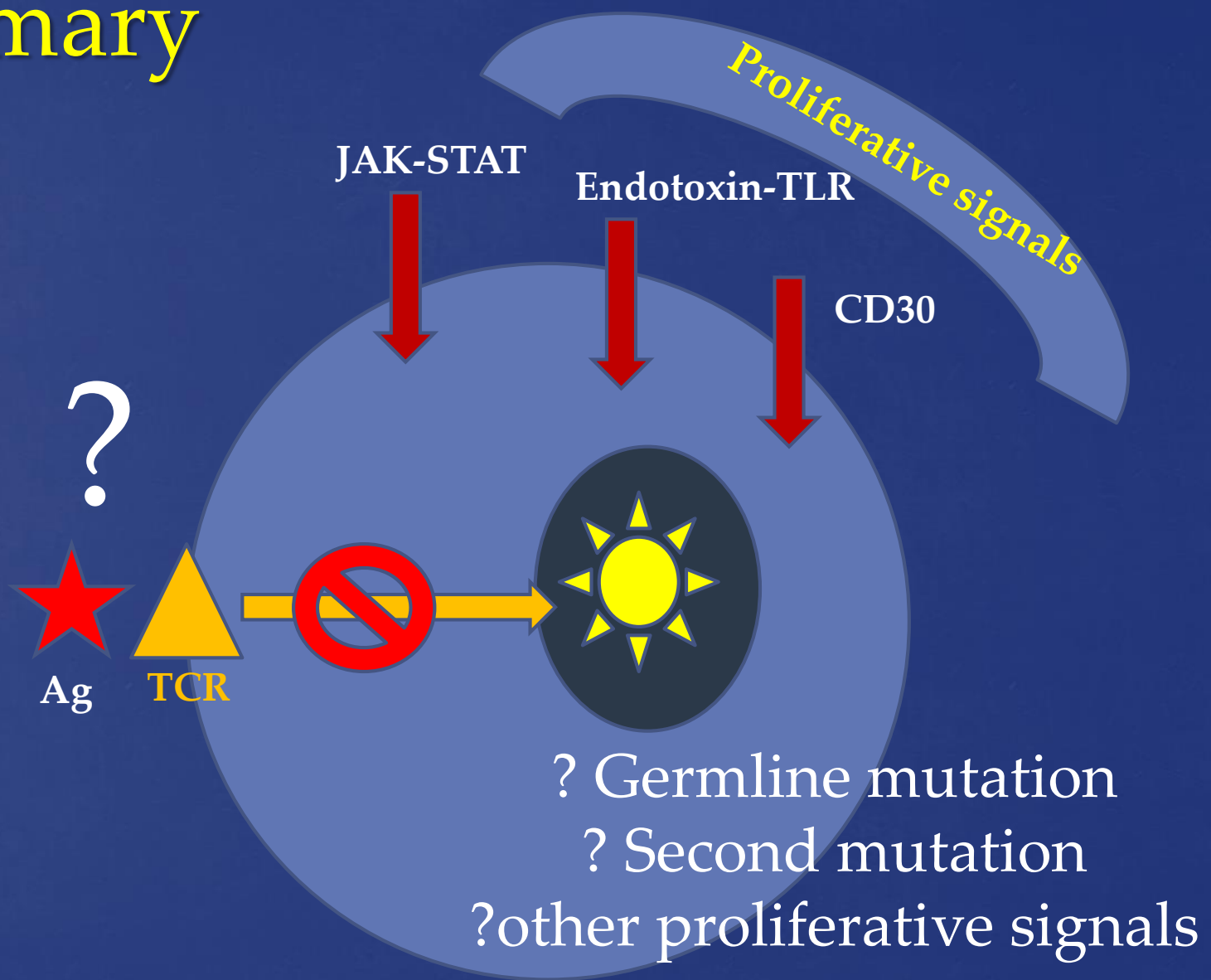
- Only T cell lymphoma associated with **non-viral antigen stimulation is Coeliac disease** – Enteropathy-associated T cell lymphoma

EITCL

Could a double-hit be required – like coeliac disease?

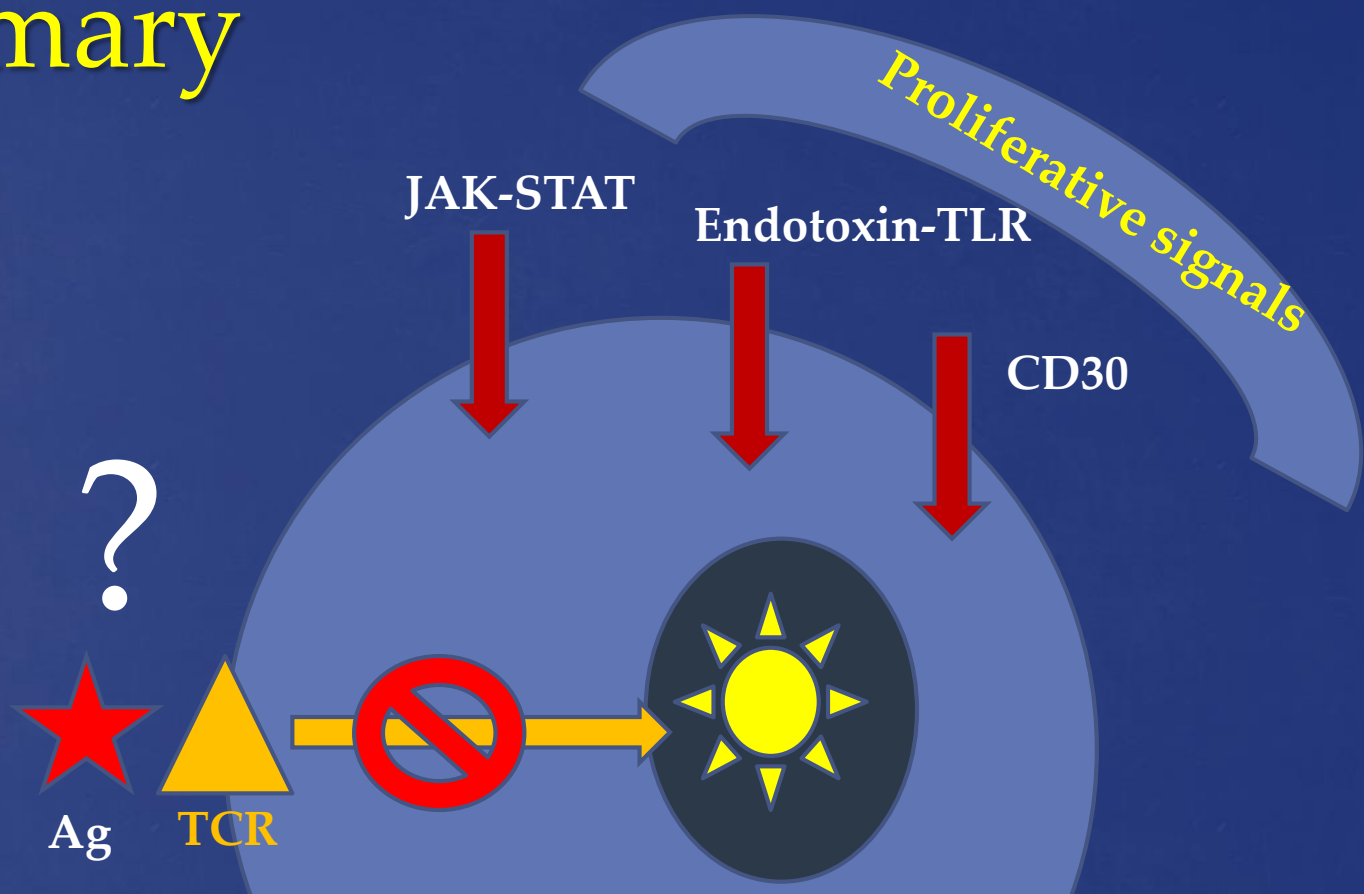


Summary



Autonomous/neoplastic growth

Summary



Is the TCR functioning?

- ? Germline mutation
- ? Second mutation
- ? other proliferative signals

Autonomous/neoplastic growth

Anaplastic large cell lymphomas lack the expression of T-cell receptor molecules or molecules of proximal T-cell receptor signaling

Irina Bonzheim, Eva Gelsinger, Sabine Roth, Andreas Zeffl, Alexander Marx, Andreas Rosenwald, Hans Konrad Müller-Hermelink, and Thomas Rodiger

Anaplastic large cell lymphoma (ALCL) designates a heterogeneous group of CD30⁺ (systemic or primary cutaneous) peripheral T-cell lymphomas (PTCLs). A subgroup of systemic ALCL is transformed by anaplastic lymphoma kinase (ALK). We compared 24 ALK⁺, 15 ALK⁻ systemic, and 7 cutaneous ALCLs with 29 nonanaplastic PTCLs in terms of T-cell receptor (TCR) rearrangements, expression of TCRs and TCR-associated mol-

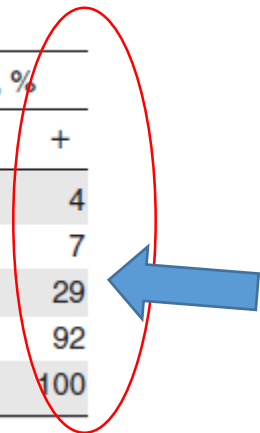
ecules (CD3, ZAP-70 [zeta-associated protein 70]). Despite their frequent clonal rearrangement for TCR β , only 2 (4%) of 47 ALCLs expressed TCR β protein, whereas TCRs were detected on 27 of 29 nonanaplastic PTCLs. Moreover, both TCR β ⁺ ALCLs lacked CD3 and ZAP-70 (i.e., molecules indispensable for the transduction of cognate TCR signals). Defective expression of TCRs is a common characteristic of all types of ALCL, which may

contribute to the dysregulation of intracellular signaling pathways controlling T-cell activation and survival. This molecular hallmark of ALCL is analogous to defective immunoglobulin expression distinguishing Hodgkin lymphoma from other B-cell lymphomas. (Blood. 2004; 104:3358-3360)

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Table 1. Expression of TCRs and molecules involved in proximal TCR signaling in ALCL and other PTCLs

Diagnosis	ALK1	No.	β F1, %	δ F1, %	CD3, %	ZAP-70, %		
						-	-/+	+
ALCL, systemic	+	24	4	0	4	71	25	4
ALCL, systemic	—	15	7	0	60	80	13	7
ALCL, cutaneous	—	7	0	0	29	71	0	29
NOS	—	22	86	5	71	0	8	92
AILT	—	7	100	0	80	0	0	100



TCR deep sequencing
– TCR* is rearranged –
?functional - TBD

Sample	TRB V/D/J	CDR3
16M6440	TRBV5-1*01/D1*01/J1-2*01	CASSLGHQLNYGYTF
17M2091	TRBV14*01/D1*01/TRBJ1-6*02	CASATSTLYNSPLHF
17M8738	TRBV13*01/D2*02/J1-1*01	CASSLGWGGGSEAFF
17M8778	TRBV30*01/D1*01/J2-4*01	CAWANWGNIQYF
09M1965	TRBV30*01/D2*02/J1-1*01	CAWGIGGGGEAFF
15M5441	TRBV11-1*01/D1*01/J2-1*01	CASSGSGNHEQFF
08189437	TRBV5-4*01/D1*01/J2-6*01	CASSLGGSAGANVLTFF

•note: TCRBeta tested – this is frequently (1/3) NOT rearranged in Alk pos disease but common in ALCL in general (90%). Flow expression in ALCL from 30-70%

Summary



?reversible

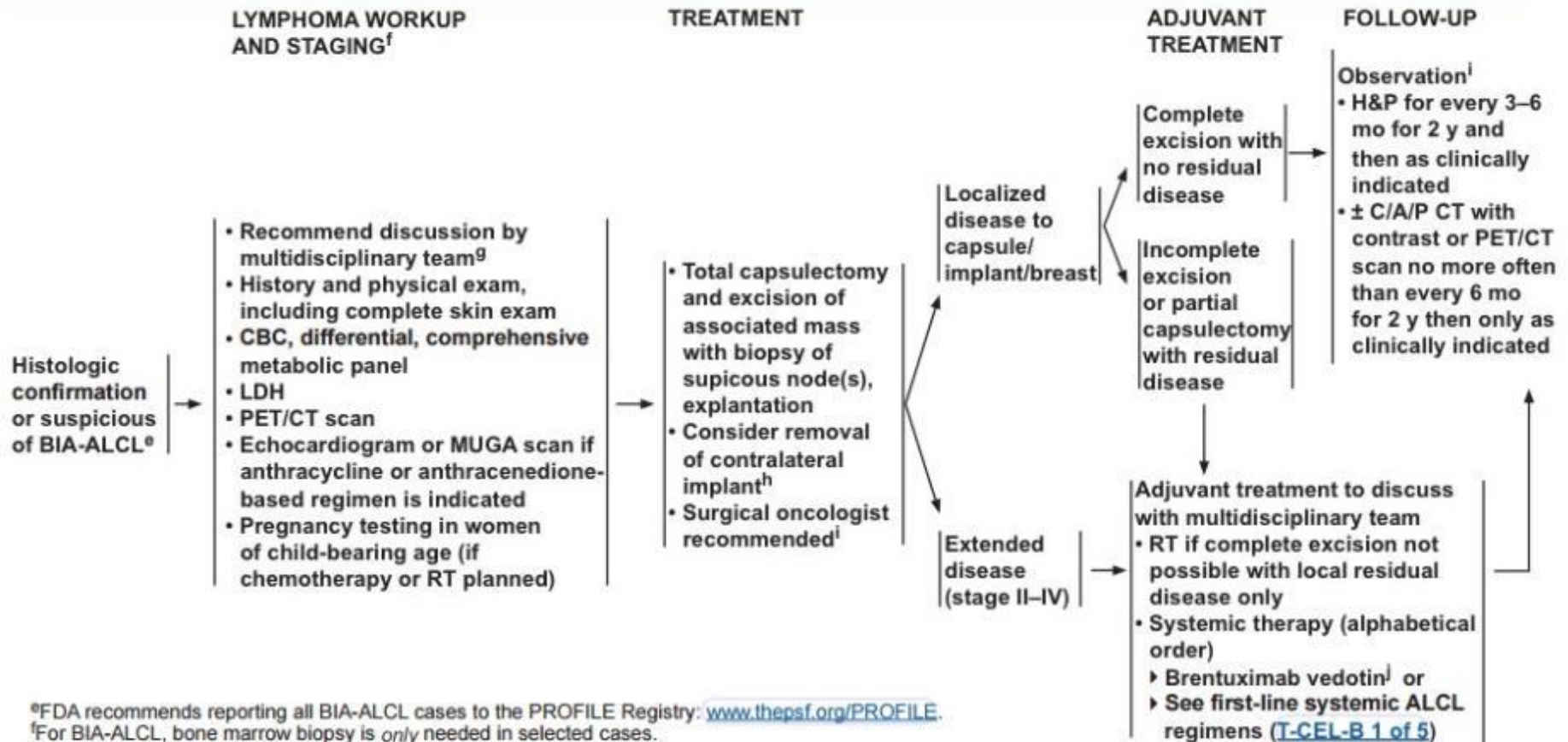
Treatment

Prevention first

Macrotextured Breast Implants with Defined Steps to Minimize Bacterial Contamination around the Device: Experience in 42,000 Implants

Results: A total of 42,035 Biocell implants were placed in 21,650 patients; mean follow-up was 11.7 years (range, 1 to 14 years). A total of 704 polyurethane implants were used, with a mean follow-up of 8.0 years (range, 1 to 20 years). The overall capsular contracture rate was 2.2 percent. There were no cases of implant-associated ALCL. All surgeons routinely performed all 13 perioperative components of the 14-point plan; two surgeons do not routinely prescribe prophylaxis for subsequent unrelated procedures.

William P. Adams, Jr., M.D.
Eric J. Culbertson, M.D.
Anand K. Deva, F.R.A.C.S.
Mark R. Magnusson, M.D.
Craig Layt, F.R.A.C.S.
(Plast)
Mark L. Jewell, M.D.
Patrick Mallucci, M.D.,
F.R.A.C.S. (Plast)
Per Hedén, M.D.



^gFDA recommends reporting all BIA-ALCL cases to the PROFILE Registry: www.thepsf.org/PROFILE.

^fFor BIA-ALCL, bone marrow biopsy is *only* needed in selected cases.

^gEg, oncologist, surgical oncologist, plastic surgeon, hemepathologist.

^hIn approximately 4.6% of cases, lymphoma was found in the contralateral breast (Clemens MW, Medeiros LJ, Butler CE, et al. Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large-cell lymphoma. *J Clin Oncol* 2016; 34:160-168).

ⁱClemens MW, Medeiros LJ, Butler CE, et al. Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large-cell lymphoma. *J Clin Oncol* 2016; 34:160-168.

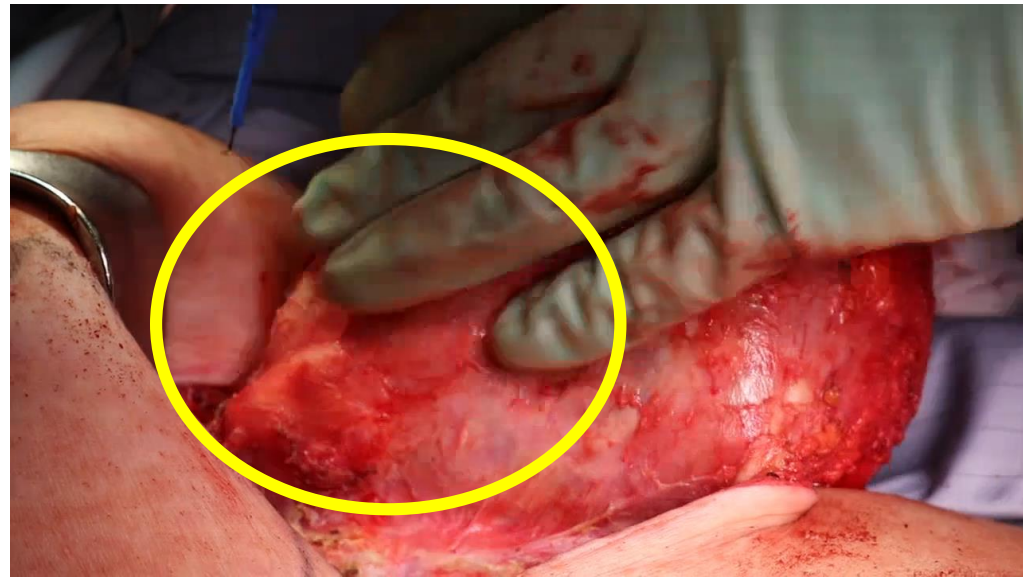
^jPro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol* 2012;30:2190-2196. Pro B, Advani R, Brice P, et al. Four-year survival data from an ongoing pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma [abstract]. *Blood* 2014 124:Abstract 3095.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Total capsulectomy implant removal

- Oncologic technique¹
- Orientation sutures
- Surgical clips in tumor bed
- Excision of suspicious lymph nodes¹
- Complete resection of capsule, including posterior wall
 - Tumescence may aid in removal of the back wall
- No role for sentinel lymph node biopsy



Images courtesy of Dr Mark Clemens

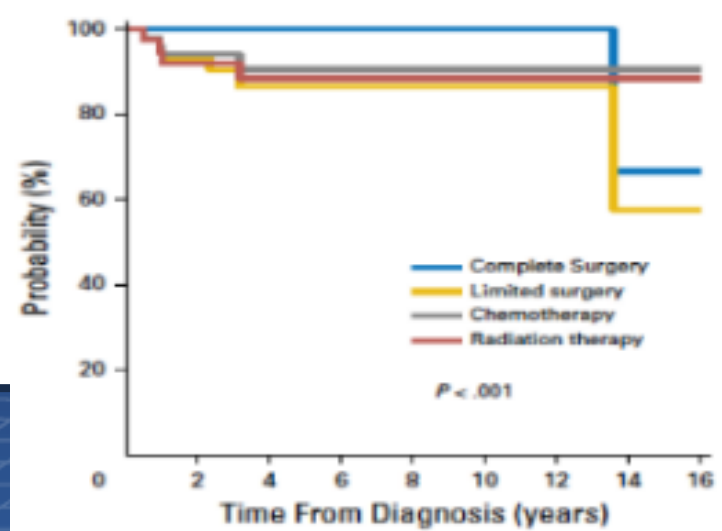
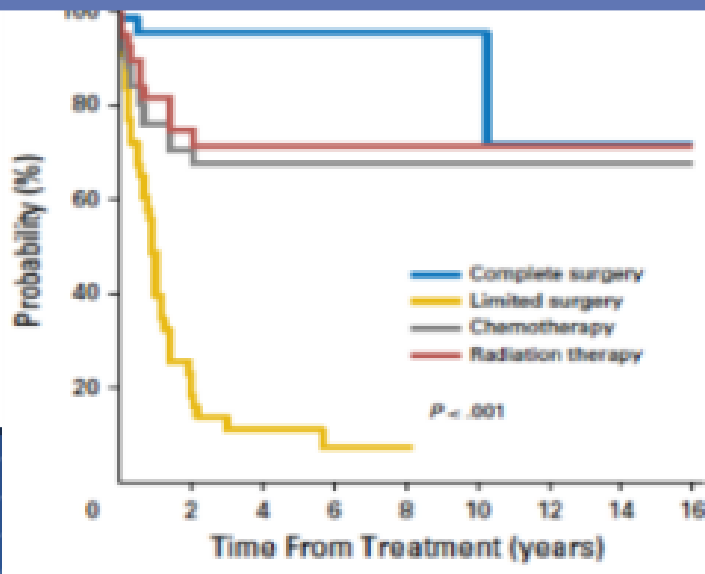
Surgery Essential for Cure

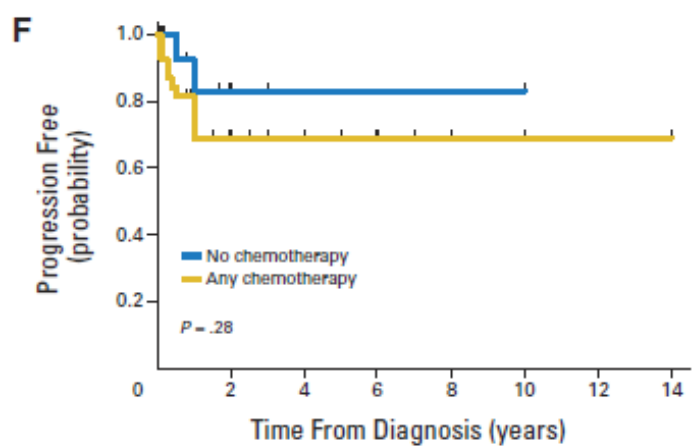
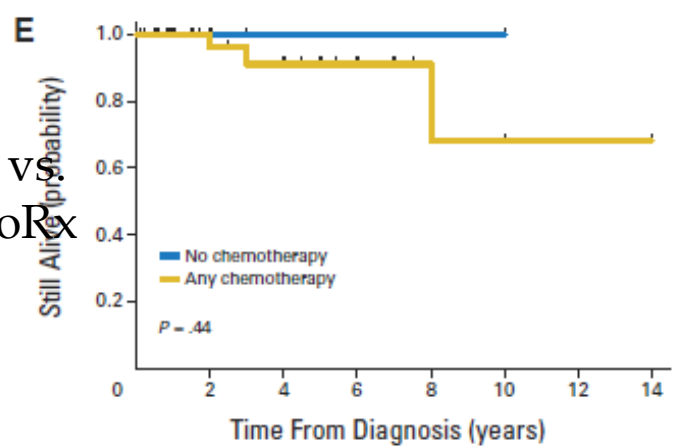
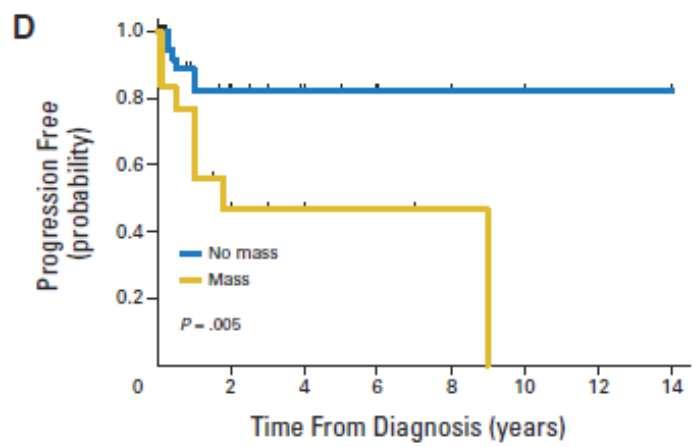
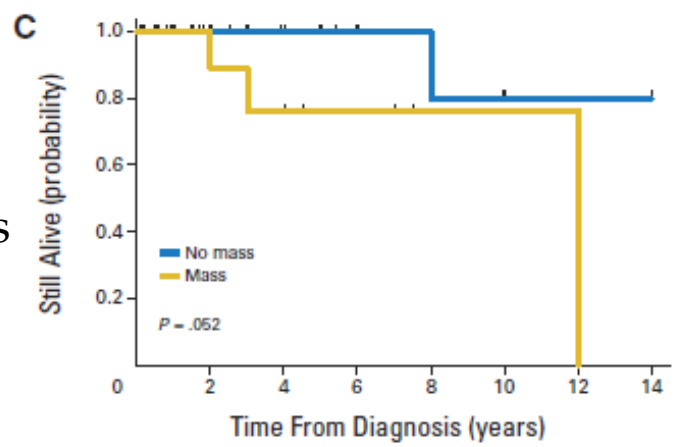
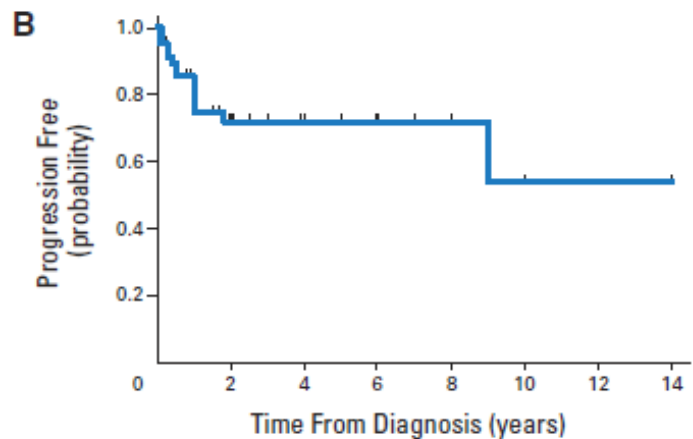
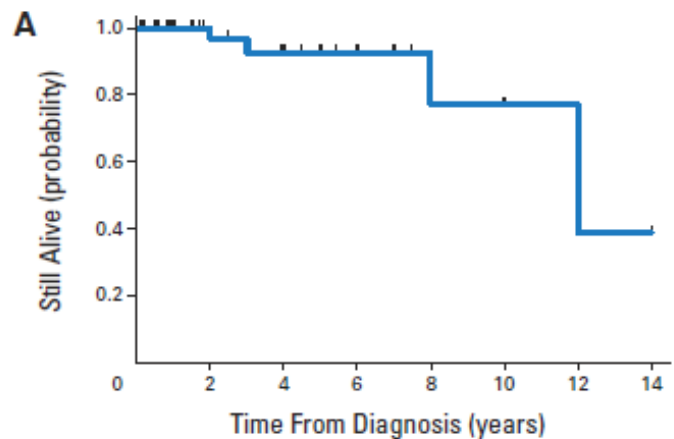
Patients can progress or up-stage if untreated

Treatment after diagnosis	Number	%
Limited surgery	43	52.9
Complete surgery	74	85.1
Radiation	39	44.8
Chemotherapy	51	58.6
ASCT	6	6.9
Immunotherapy	2	2.3

Treatment	1 year (%)	3 years (%)	5 years (%)
Overall	35	50.8	50.8
Limited surgery	60	89	89
Complete surgery	4	4	4
Radiation	18	28	28
Chemotherapy	24	32	32

Event-free survival



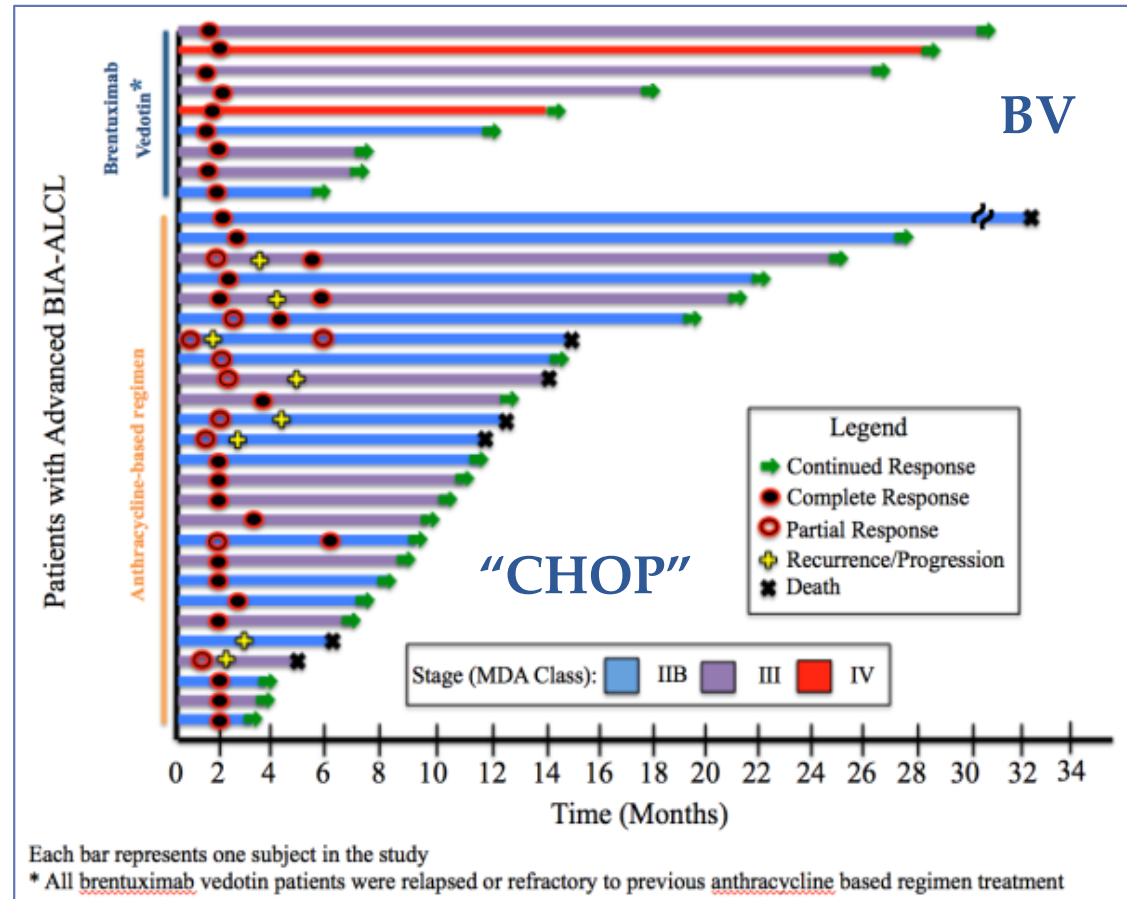


Mass vs.
No-mass

chemoRx vs
No-chemoRx

Brentuximab vedotin

- **BIA-ALCL: nine R/R patients treated achieved complete remission**
- **Complete remission in relapsed and refractory BIA-ALCL with BV**
- **Versus 32% recurrence rate at 3 years with anthracycline-based regimen**



A Perfect Storm?

Contaminated-implant

- Surgical implications-

Textured Implant



Microbiome



Chronic

Inflammation

BIA-
ALCL



JAK-STAT
activation

Germ-line
HLA (racial)
predisposition



Big Questions

- What is the Cell of Origin?
- What is the cell phenotype?
- Is there pre-malignant population
- Is it reversible?
- What is the cytokine profile – does it change?
- Is the TCR signalling active?
- Is there a driving antigen?
- When in the process is JAK-STAT mutated?
 - Proliferative population vs malignant transformation
- Are there other pathways driving? – **two steps**
 - TLR
 - CD30
 - Others – Aryl hydrocarbon receptors, others
- Is there an HLA association?
- Are there germ-line predispositions?

Prosthesis-associated?

- Tibial Implant
- Dental implant ALCL²
- Chest port ALCL³
- Total hip arthroplasties have higher rates of lymphoma⁴
- Shoulder repair ALCL
- Lap Band ALCL

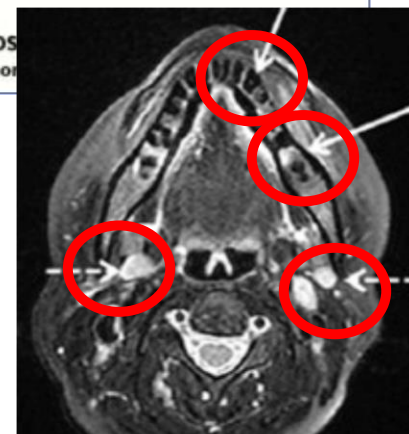


Tibial implant ALCL¹

Case Report

Mucosal CD30-Positive T-Cell Lymphoproliferative Disorder Arising in the Oral Cavity Following Dental Implants: Report of the First Case

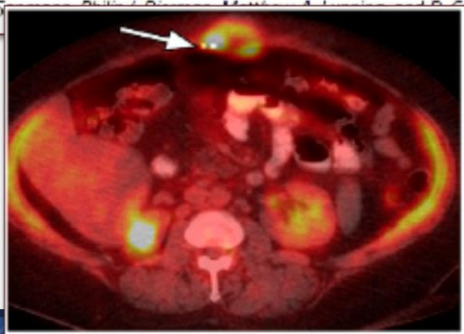
Hye-Jung Yoon, DDS and Yoon Kyung Jeon



Dental implant ALCL²

Bariatric Implant-Associated Anaplastic Large-Cell Lymphoma

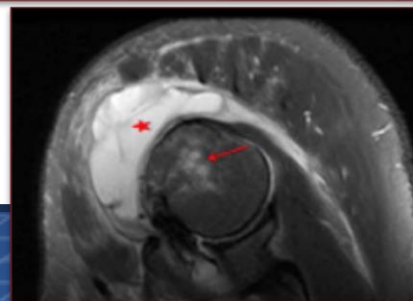
Jayadev Manikkam Umakanthan, Corrigan L. McBride, Timothy Greiner, Ji Yoon, Jennifer S. ... Gregory Bociek



CASE REPORT

Anaplastic large cell lymphoma masquerading as osteomyelitis of the shoulder: an uncommon presentation

Matthew Tuck,^{1,2} Jane Lim,³ Jose Lucar,⁴ Debra Benator²



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Development of a Plaque Infiltrated With Large CD30+ T Cells Over a Silicone-Containing Device in a Patient With History of Sézary Syndrome

Anna K. Engberg, Christ ... Michael Girardi



Chest port ALCL³

1. Palraj B, et al. J Foot Ankle Surg 2010;49:561-4; 2. Yoon HJ, et al. Int J Surg Pathol 2015;23:656-61; 3. Engberg A, et al. J Clin Oncol 2013;31:e87-e89. 4. Kellogg B et al. Annals Plastic Surgery 2013; 73(4).

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