



Bologna  
ROYAL HOTEL CARLTON  
October 25-26, 2022

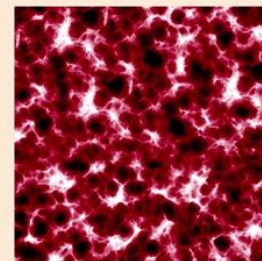


ALMA MATER STUDIORUM  
UNIVERSITÀ DI BOLOGNA  
DIPARTIMENTO DI MEDICINA SPECIALISTICA  
DIAGNOSTICA E Sperimentale

POLICLINICO DI **SANT'ORSOLA**

SERVIZIO SANITARIO REGIONALE  
EMILIA-ROMAGNA  
Azienda Ospedaliera - Università di Bologna

# 2018... 2022 T-Cell Lymphomas: Finally vision and mission!



**Breast implant-associated ALCL**  
**Stefano A. Pileri**  
European Institute of Oncology  
Member of the Committee of the Italian  
Public Health Ministry on BIA-ALCL

President: **Pier Luigi Zinzani**

Co-President: **Michele Cavo**

# Disclosures

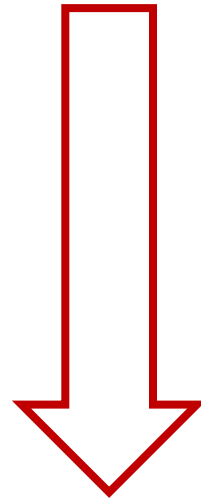
## Disclosures of Stefano A. Pileri

---

Company name	Research support	Employee	Consultant	Stockholder	Speaker bureau	Advisory board	Other
BeiGene						X	
Takeda						X	
Roche					X		
Diatech						X	
Stemline					X		

# Chronology

1997: Keech and Creech (PRS; 100:554-5)



2022: ICC and WHO 5<sup>th</sup> Edition: accepted entity



breast implant associated anaplastic large cell lymphoma



Search

[Advanced](#) [Create alert](#) [Create RSS](#)

[User Guide](#)

Save

Email

Send to

Sorted by: Publication date ↓

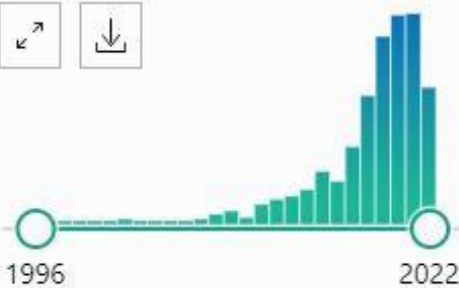
Display options ⚙️

MY NCBI FILTERS

636 results

Page 1 of 64

RESULTS BY YEAR



**Breast** lymphomas, **breast implants** and capsules The timeline of BIA-ALCL with respect to surgical consent: the UK perspective.

1

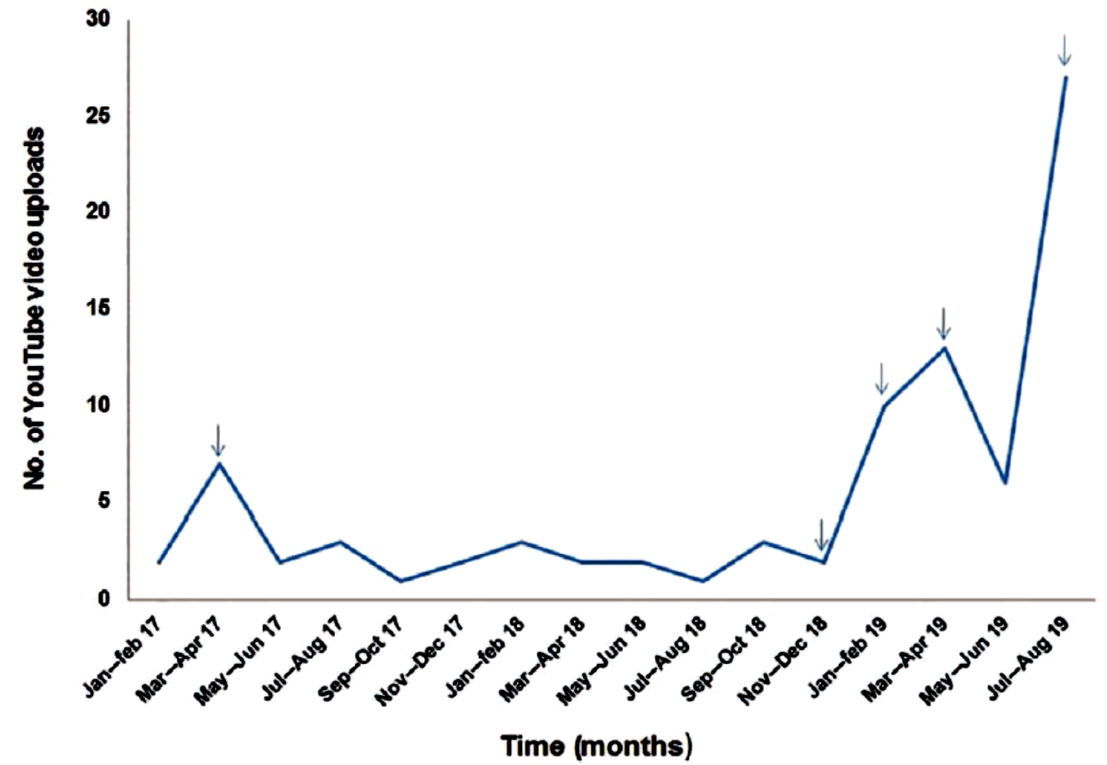
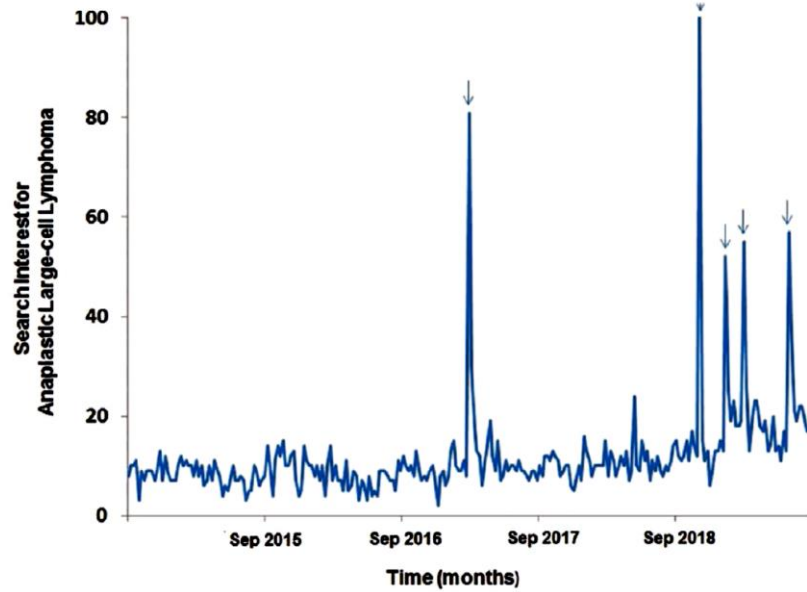
Cite Allison K, Gilmour A.

JPRAS Open. 2022 Jul 11;34:41-50. doi: 10.1016/j.jptra.2022.07.001. eCollection 2022 Dec.

Share

PMID: 36164587 [Free PMC article.](#)

**Breast Implant-Associated Anaplastic Large Cell Lymphoma** (BIA-ALCL) is a rare type of T-Cell (non-Hodgkin's) **lymphoma associated** with the use of silicone **breast implants**. Recent widespread awarene



OPEN



IDEAS AND INNOVATIONS

Breast

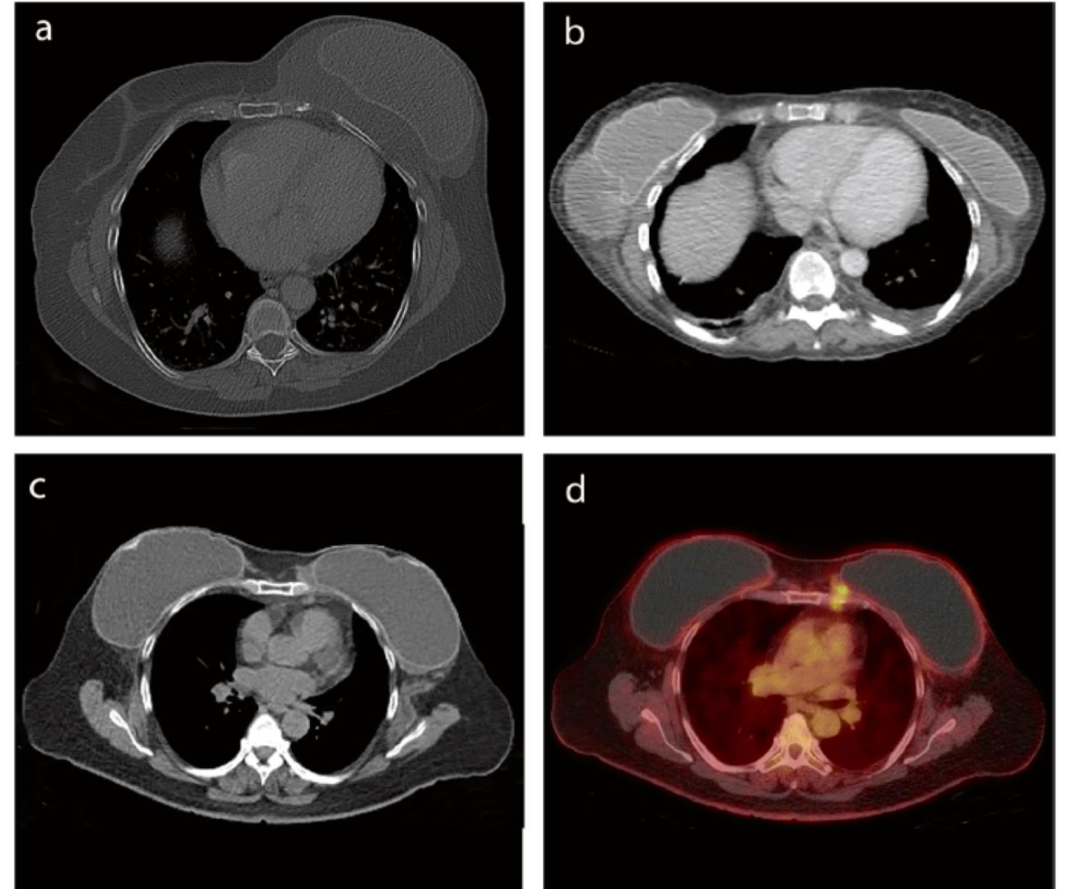
Impact of FDA Updates on Public Interest in Breast Implant-associated Anaplastic Large Cell Lymphoma

# Clinical Features

- Patients: Females (with a few exceptions) with a mean age of 52 yrs. and a history of breast implant following mastectomy for a breast cancer or for cosmetic reasons.
- 80% of patients present with an effusion adjacent to the implant (seroma BIA-ALCL)
- 20% of patients present with a tumour mass (tumour BIA-ALCL)



Marra A et al. Cancer Treat. Rev. 2020; 84:101963.



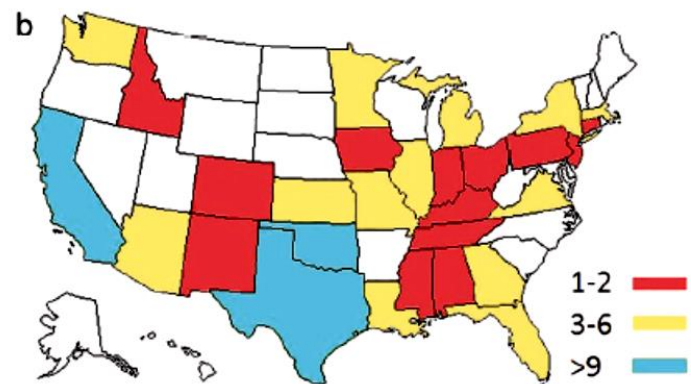
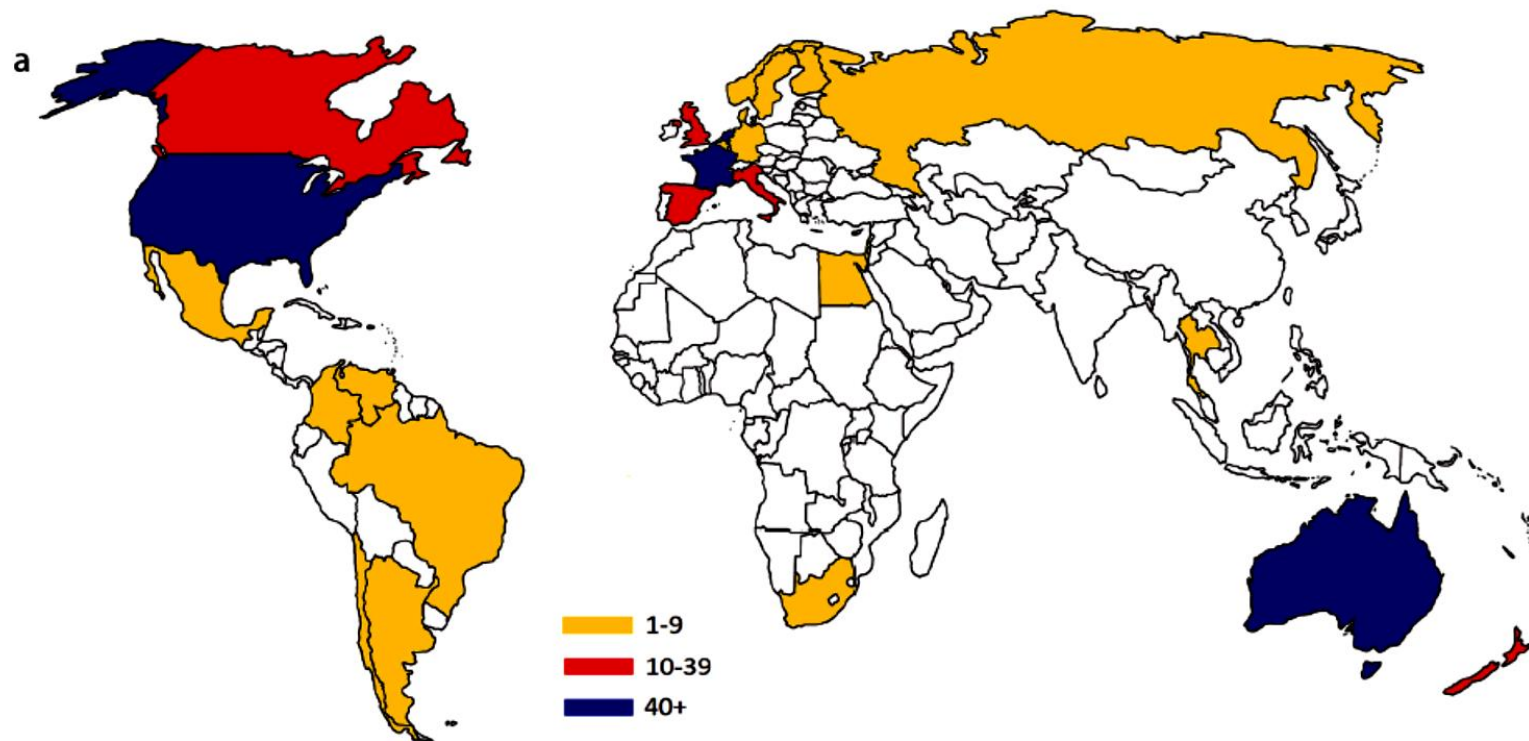
Quesada AE et al. Modern Pathol. 2019; 32:166-88.

# Incidence


- Highly variable
- Brody et al.(PRS 2015):  
0.01/1000 pts. (Metanalysis)
- Nelson et al. (AJSP 2020):  
1.79/1,000 pts. (USA/1 Inst.)
- Cordeiro et al. (JPRAS, 2020):  
0.311/1000 pts. (USA/1 Inst.)
- Allison & Gilmour (JPRAS,  
2022: about 0.2/1000 pts.  
(UK)

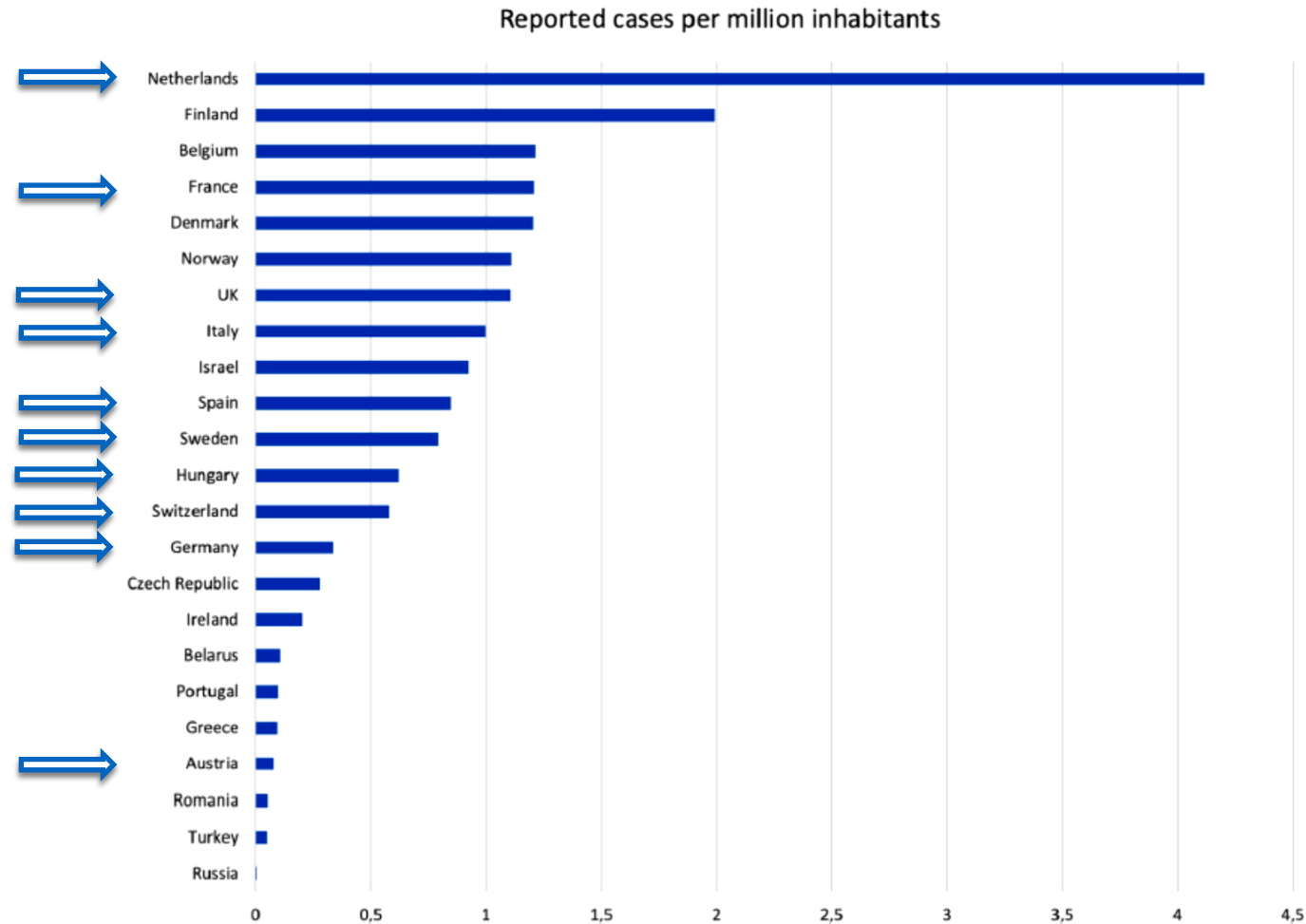
Years since textured device insertion	Cumulative risk of developing BIA-ALCL
5	0.000
10	0.0024
15	0.0066
20	0.0109





## Considerations on the Demography of BIA-ALCL in European Countries Based on an E(A)SAPS Survey

Birgit Stark<sup>1</sup>  · Martin Magnéli<sup>2</sup> · Ivar van Heijningen<sup>3</sup> · Carlos Parreira<sup>4,5</sup> · Urs Bösch<sup>6</sup> · Michel Rouif<sup>7</sup> · Martin Halle<sup>1</sup>



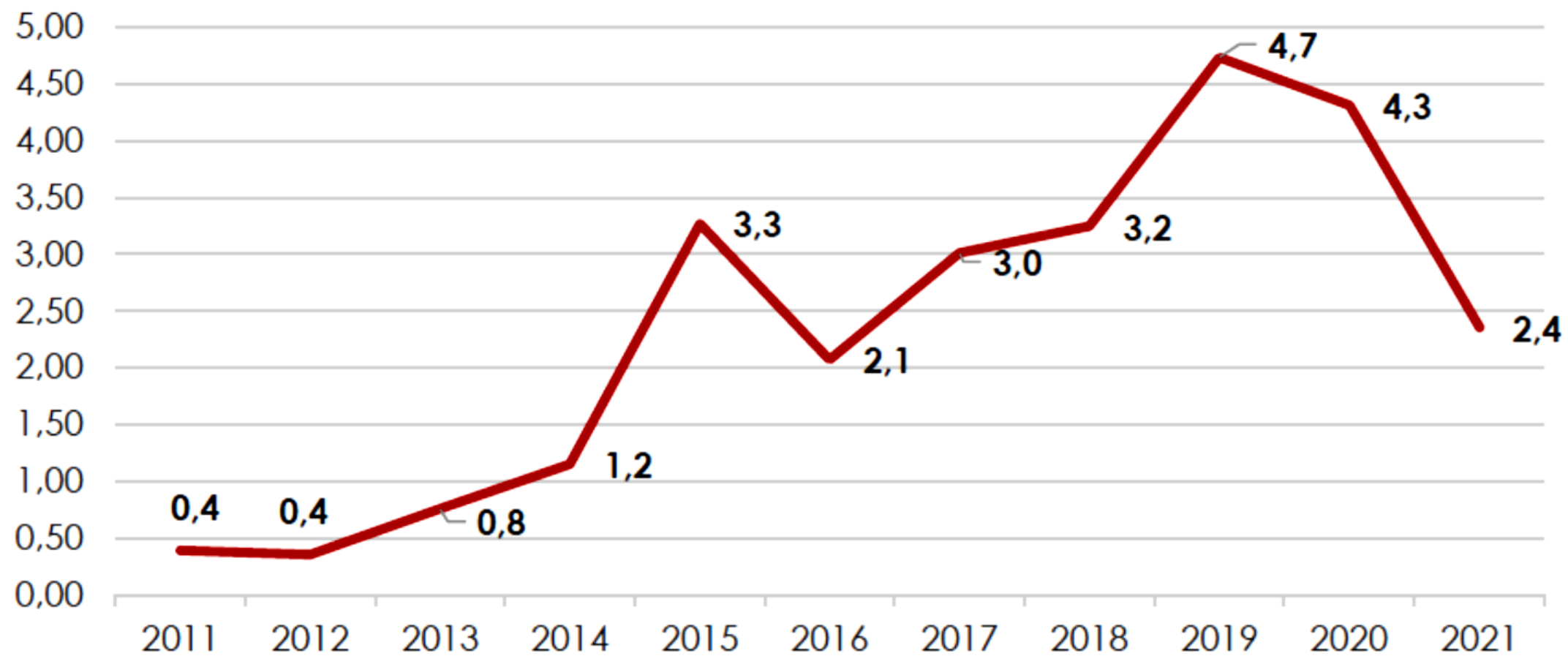
# Italian Ministry of Public Health

- Registry of implants and BIA-ALCL
- Permanent Commission on BIA-ALCL
- Guidelines for the diagnosis and treatment
  
- Registered BIA-ALCL cases (January 2010 up to now): 85
- Incidence: 1 case of BIA-ALCL/20,000 subjects, who received an implant (0.2/1,000)
- Lethal cases: 2/85



*Ministero della Salute*

DIREZIONE GENERALE DEI DISPOSITIVI MEDICI E DEL SERVIZIO FARMACEUTICO  
Ufficio 5 –Vigilanza sugli incidenti con dispositivi medici



Italian Ministry of Public Health: prevalence per 100,000 patients

**SYMPTOMS**

Breast implanted patient with at least one of the following symptoms suggesting BIA-ALCL:

- late seroma (> 1 year after implant), persistent and recurrent;
- breast mass;
- axillary lymphadenopathy;
- unilateral Baker IV capsular contracture associated with seroma;
- skin ulceration.

**MANAGEMENT**

Ultrasound of the breast and axilla (MRI or CT/PET scan if ultrasound is indeterminate or if prosthesis rupture is suspected or in the presence of a mass)

Peri-prosthetic effusion

- mass
- axillary lymphadenopathy;
- unilateral Baker IV capsular contracture associated with seroma;
- skin ulceration.

Breast Unit or other proper healthcare facility for a multidisciplinary evaluation and diagnosis

Ultrasound guided Fine Needle Aspiration for cytological examination

Biopsy and histological examination of the mass/ periprosthetic capsule

**HISTO-CYTOLOGICAL EXAM**

Negative for BIA-ALCL

Undetermined diagnosis

Positive for BIA-ALCL

Follow-up according to medical prescriptions

Second opinion by an Haematopathology Centre identified by the Italian Ministry of Health



VOLUME 34 • NUMBER 2 • JANUARY 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant–Associated Anaplastic Large-Cell Lymphoma

*Mark W. Clemens, L. Jeffrey Medeiros, Charles E. Butler, Kelly K. Hunt, Michelle A. Fanale, Steven Horwitz, Dennis D. Weisenburger, Jun Liu, Elizabeth A. Morgan, Rashmi Kanagal-Shamanna, Vinita Parkash, Jing Ning, Aliyah R. Sohani, Judith A. Ferry, Neha Mehta-Shah, Ahmed Dogan, Hui Liu, Nora Thormann, Arianna Di Napoli, Stephen Lade, Jorge Piccolini, Ruben Reyes, Travis Williams, Colleen M. McCarthy, Summer E. Hanson, Loretta J. Nastoupil, Rakesh Gaur, Yasuhiro Oki, Ken H. Young, and Roberto N. Miranda*

**Purpose**

Breast implant–associated anaplastic large-cell lymphoma (BI-ALCL) is a rare type of T-cell lymphoma that arises around breast implants. The optimal management of this disease has not been established. The goal of this study is to evaluate the efficacy of different therapies used in patients with BI-ALCL to determine an optimal treatment approach.

**Patients and Methods**

In this study, we applied strict criteria to pathologic findings, assessed therapies used, and conducted a clinical follow-up of 87 patients with BI-ALCL, including 50 previously reported in the literature and 37 unreported. A Prentice, Williams, and Peterson model was used to assess the rate of events for each therapeutic intervention.

**Results**

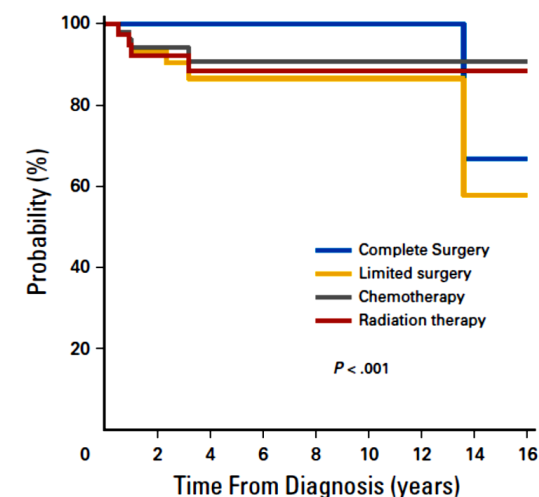
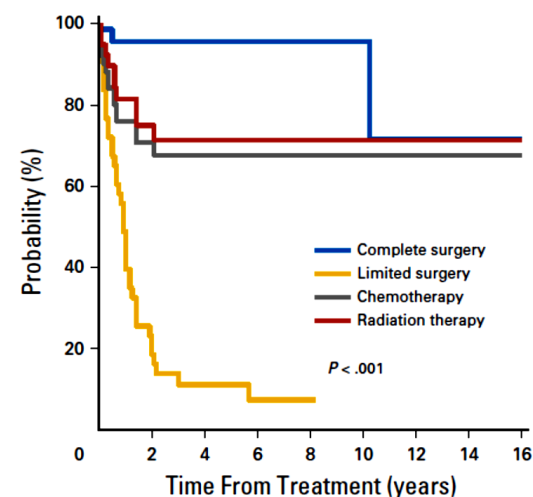
The median and mean follow-up times were 45 and 30 months, respectively (range, 3 to 217 months). The median overall survival (OS) time after diagnosis of BI-ALCL was 13 years, and the OS rate was 93% and 89% at 3 and 5 years, respectively. Patients with lymphoma confined by the fibrous capsule surrounding the implant had better event-free survival (EFS) and OS than did patients with lymphoma that had spread beyond the capsule ( $P = .03$ ). Patients who underwent a complete surgical excision that consisted of total capsulectomy with breast implant removal had better OS ( $P = .022$ ) and EFS ( $P = .014$ ) than did patients who received partial capsulectomy, systemic chemotherapy, or radiation therapy.

**Conclusion**

Surgical management with complete surgical excision is essential to achieve optimal EFS in patients with BI-ALCL.

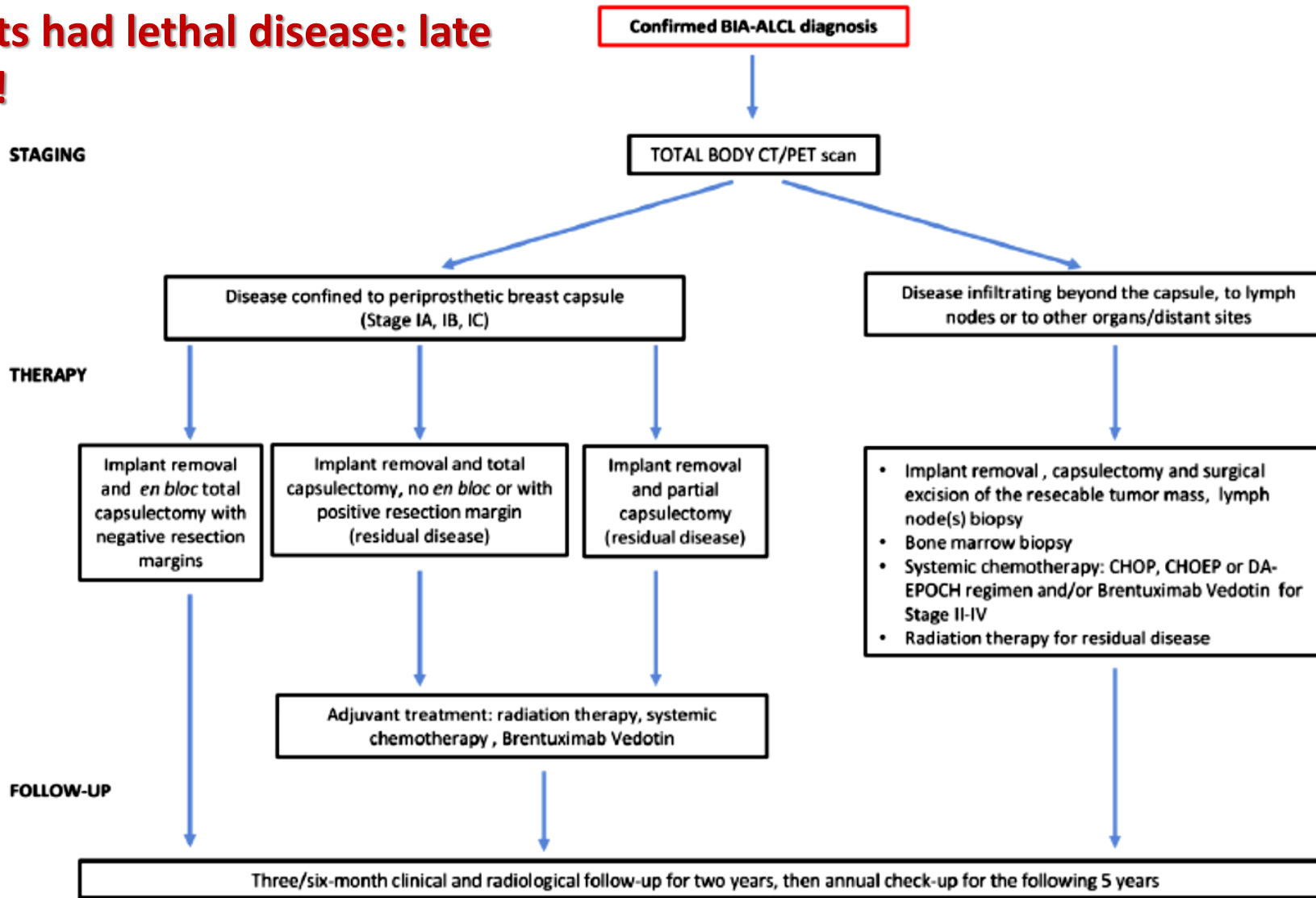
**Table 1.** Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma

TNM or Stage Designation	Description
<b>T: tumor extent</b>	
T1	Confined to effusion or a layer on luminal side of capsule
T2	Early capsule infiltration
T3	Cell aggregates or sheets infiltrating the capsule
T4	Lymphoma infiltrates beyond the capsule
<b>N: lymph node</b>	
N0	No lymph node involvement
N1	One regional lymph node (+)
N2	Multiple regional lymph nodes (+)
<b>M: metastasis</b>	
M0	No distant spread
M1	Spread to other organs/distant sites
<b>Stage</b>	
IA	T1N0M0
IB	T2N0M0
IC	T3N0M0
IIA	T4N0M0
IIB	T1-3N1M0
III	T4N1-2M0
IV	TanyNanyM1





## 2/85 patients had lethal disease: late diagnoses!!!



# The Crucial Role of Surgical Treatment in BIA-ALCL Prognosis in Early- and Advanced-Stage Patients

Antonella Campanale, M.D.  
Alessandra Spagnoli, Ph.D.  
Lucia Lispi, S.D.  
Rosaria Boldrini, S.D.  
Marcella Marletta, M.D.

*Rome, Italy*



**Background:** Studies on breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) are trying to optimize medical and surgical treatments for early and advanced stages of this disease. The aim of this article is to share the experience gathered on the authors' prospectively collected 46 well-documented cases.

**Methods:** Italian physicians are obliged to report BIA-ALCL cases to the Italian Ministry of Health. Because of this cooperation with health care professionals, the competent authority has coordinated and centralized the collection of information for each patient in 46 cases of BIA-ALCL. Statistical analyses with cumulative incidence and corresponding 95 percent confidence interval are provided for each year, dividing the number of new cases that occurred in a defined year and the population at risk of experiencing BIA-ALCL during the same year.

**Results:** The mean time to the onset of symptoms is reduced to  $6.4 \pm 3.77$  years (range, 1 to 22 years). Increased knowledge has also shortened the average time to diagnosis, at  $7.2 \pm 3.71$  years (range, 2 to 22 years). A late seroma appears in 91 percent of cases. The patient who died underwent limited surgery. The Italian incidence has been estimated as 2.8 per 100,000 patients receiving implants (95 percent CI, 0.88 to 4.84) in 2015; 2.1 (95 percent CI, 0.43 to 3.86) in 2016; 3.2 (95 percent CI, 1.11 to 5.31) in 2017; and 3.5 (95 percent CI, 1.36 to 5.78) in 2018.

**Conclusion:** Although the number of cases has risen slightly, BIA-ALCL is still a rare disease with a stable incidence, easily recognized and with a favorable prognosis also in advanced stages if complete surgical excision is performed. (*Plast. Reconstr. Surg.* 146: 530e, 2020.)



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.ejcancer.com](http://www.ejcancer.com)

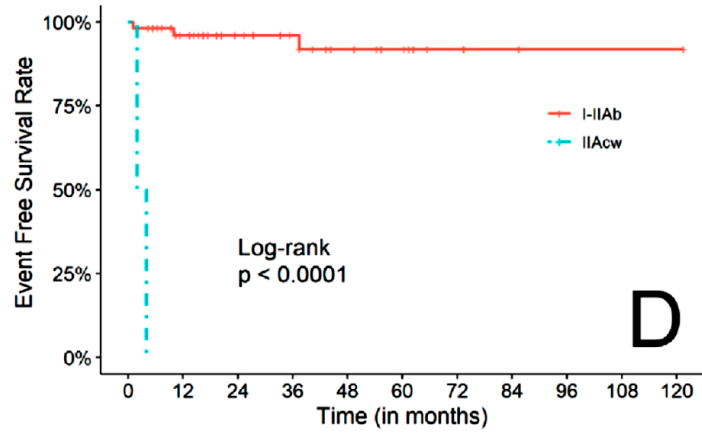


Original Research

## Chest wall infiltration is a critical prognostic factor in breast implant-associated anaplastic large-cell lymphoma affected patients



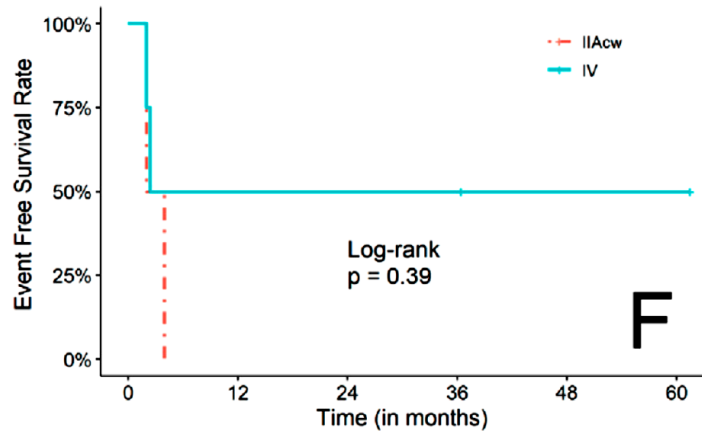
Antonella Campanale <sup>a,b</sup>, Arianna Di Napoli <sup>b,c</sup>, Marco Ventimiglia <sup>a</sup>,  
Stefano Pileri <sup>b,d</sup>, Daniela Minella <sup>a</sup>, Giuseppe Curigliano <sup>b,e,f,\*</sup>,  
Maurizio Martelli <sup>b,g</sup>, Roy De Vita <sup>b,h</sup>, Paola Di Giulio <sup>b,i</sup>,  
Marco Montorsi <sup>b,j</sup>, Paolo Veronesi <sup>b,f,k</sup>, Silvia Giordano <sup>b,l</sup>,  
Achille Iachino <sup>a,b</sup>, Lucia Lispi <sup>a,b</sup>



Number at risk

I-IIAb	54	41	29	23	16	13	6	3	1	1	1
IIACw	2	0	0	0	0	0	0	0	0	0	0
	0	12	24	36	48	60	72	84	96	108	120

Time (in months)



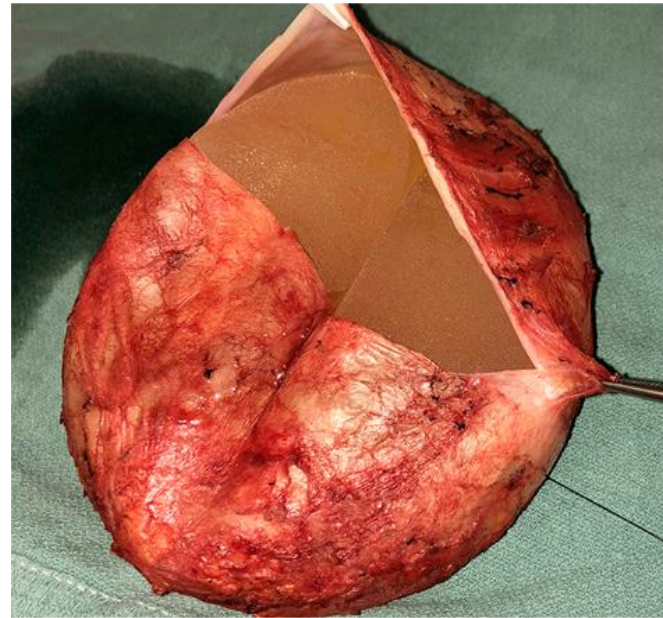
Number at risk

IIACw	2	0	0	0	0	0
IV	4	2	2	2	1	1
	0	12	24	36	48	60

Time (in months)

# Sampling

- Seroma: fine needle aspiration with cytology and phenotyping
- En bloc removal: sampling of the oriented capsule by ordered sections (two scenarios: no mass, presence of a mass)
- Fragments of the capsule and pericapsular tissue: complete sampling
- Lymph node examination



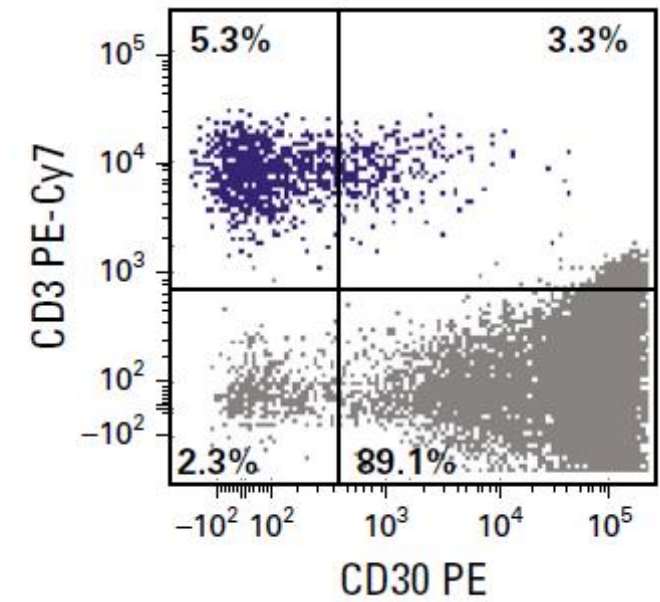
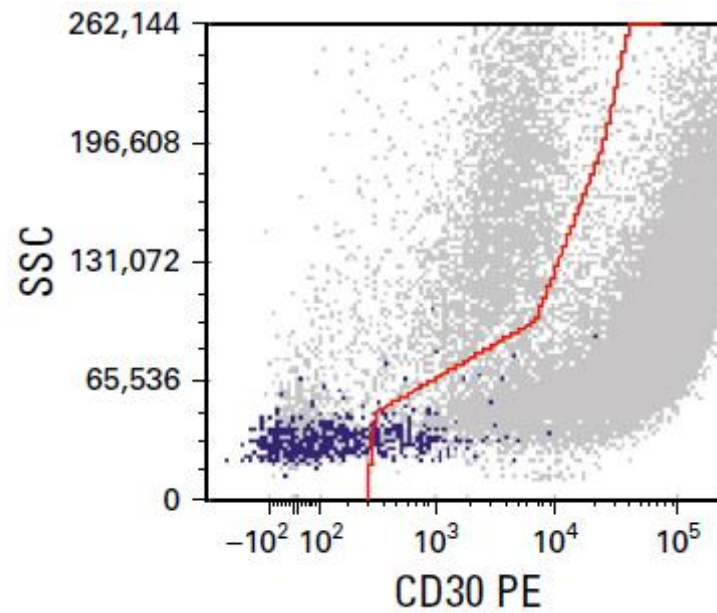
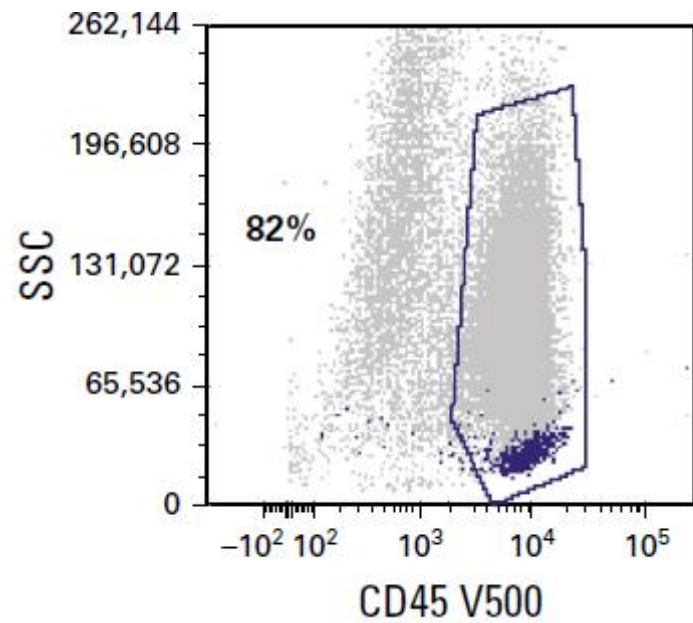
Jaffe ES et al. JCO 2020; 38:1102-11. Best practice guidelines

# Morphology & Phenotype

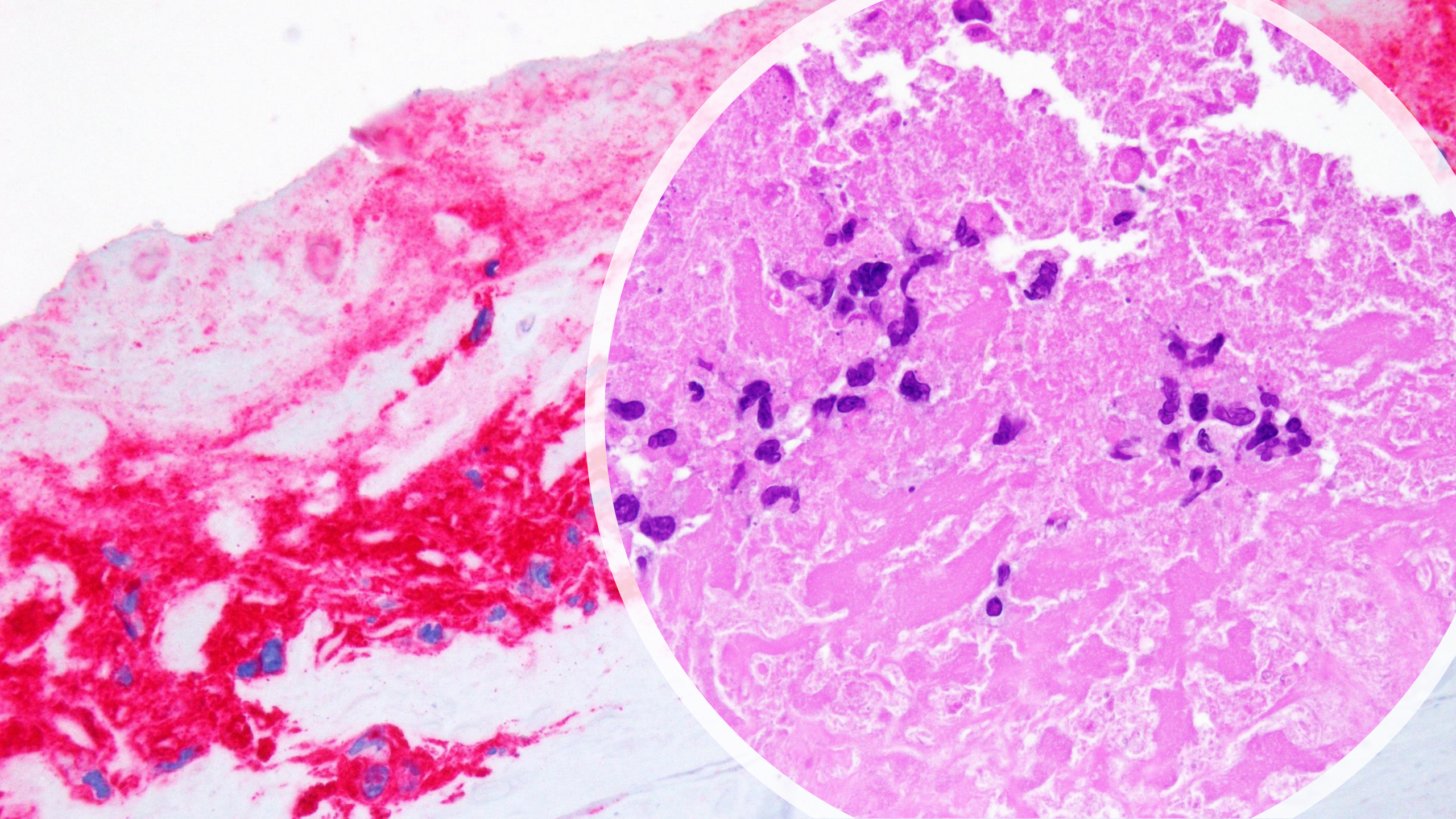
- Typical hallmark cells
- CD30-positivity of most if not all cells
- EMA-positivity
- Variable defectivity of T-cell associated antigens
- Cytotoxic profile
- IRF4-positivity (unrelated to *DUSP22* rear.)
- ALK-negativity
- PAX5/BSAP negativity
- EBV negativity

<i>TRB</i> (n = 12)	5	41.7
<i>TRG</i> (n = 34)	26	76.5

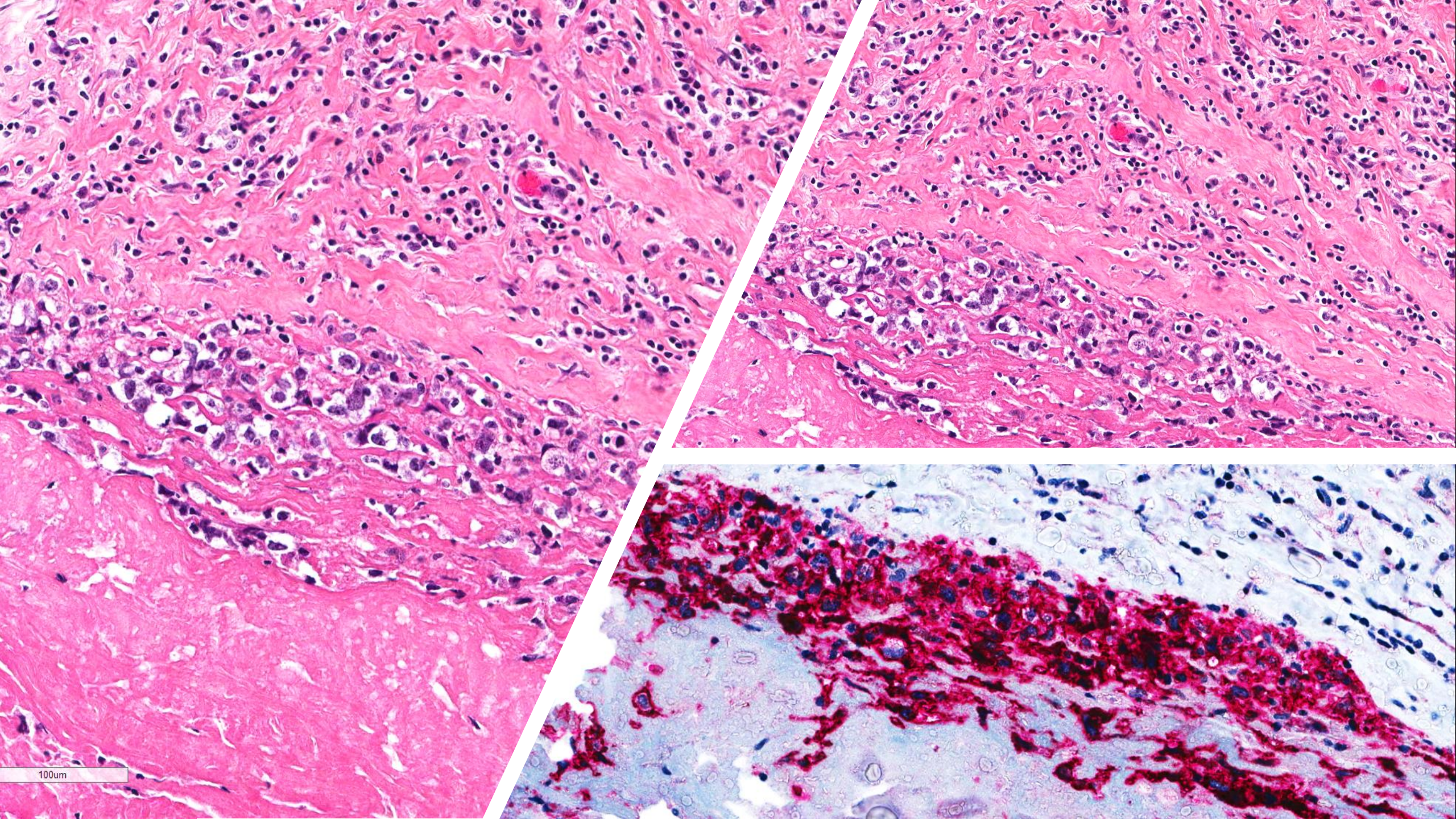
Marra A et al. Cancer Treat. Rev. 2020; 84:101963.  
Quesada EA et al. Modern Pathol. 2019; 32:166-8.



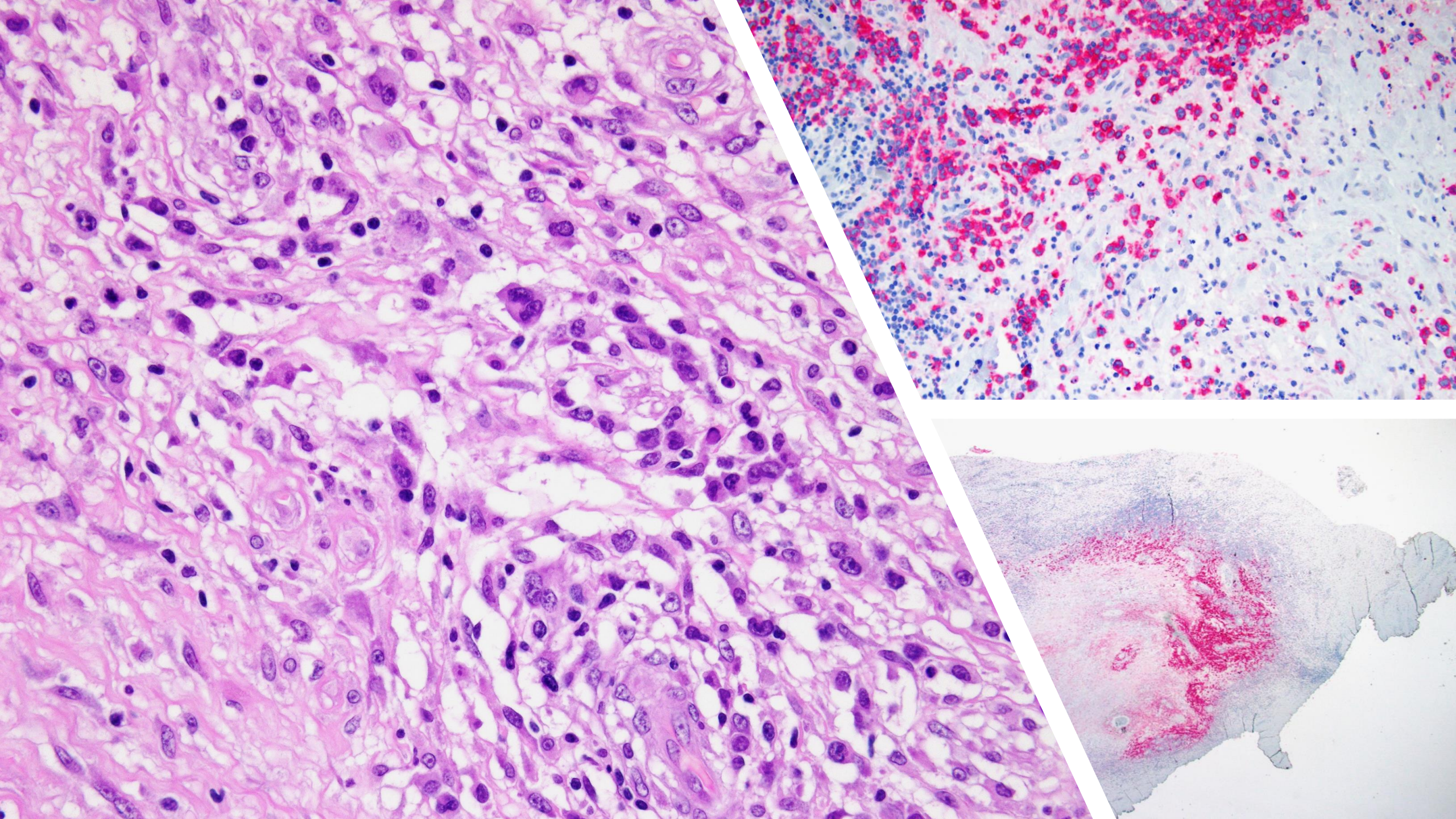
Jaffe ES et al. JCO 2020; 38:1102-11.

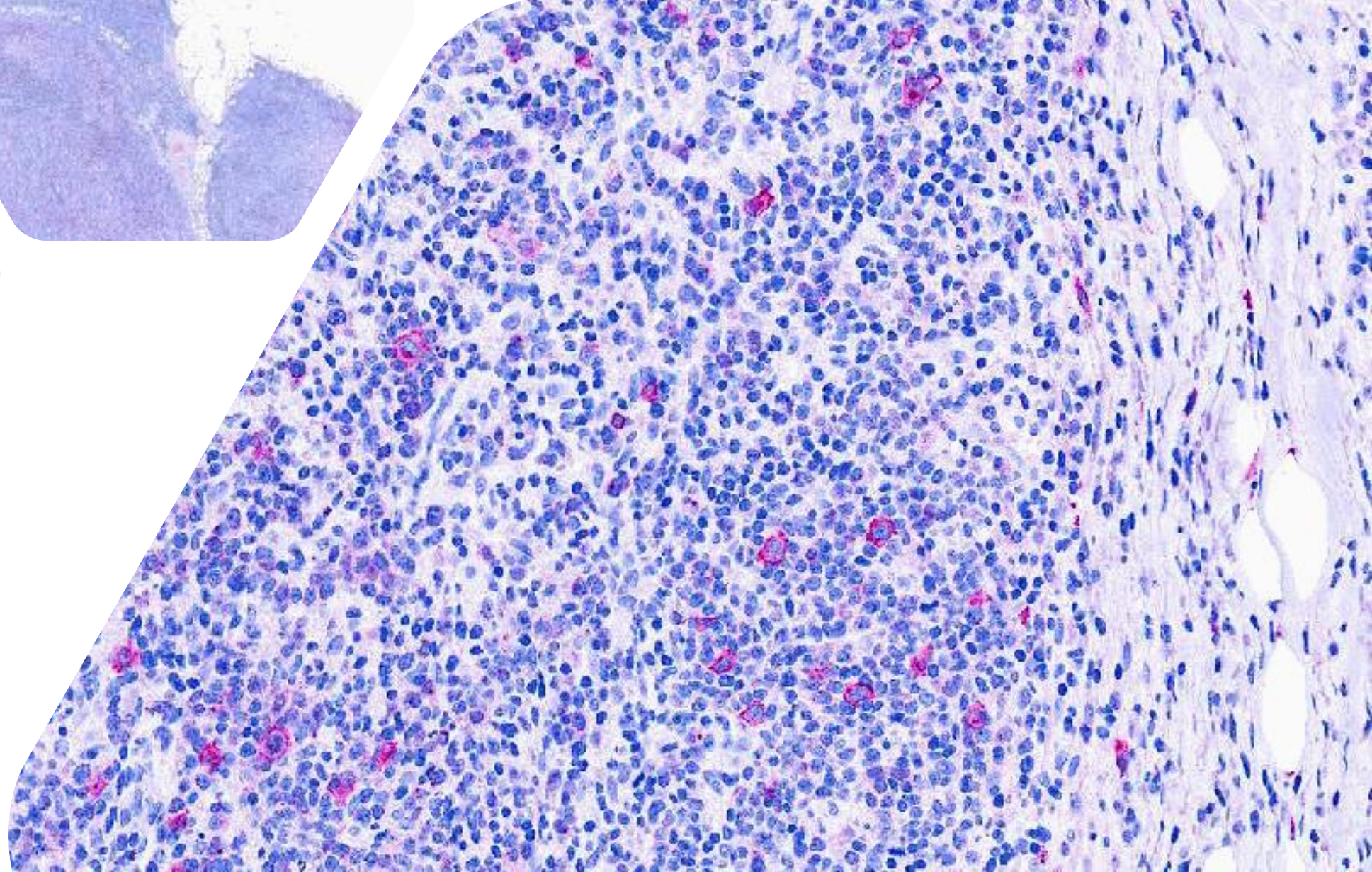
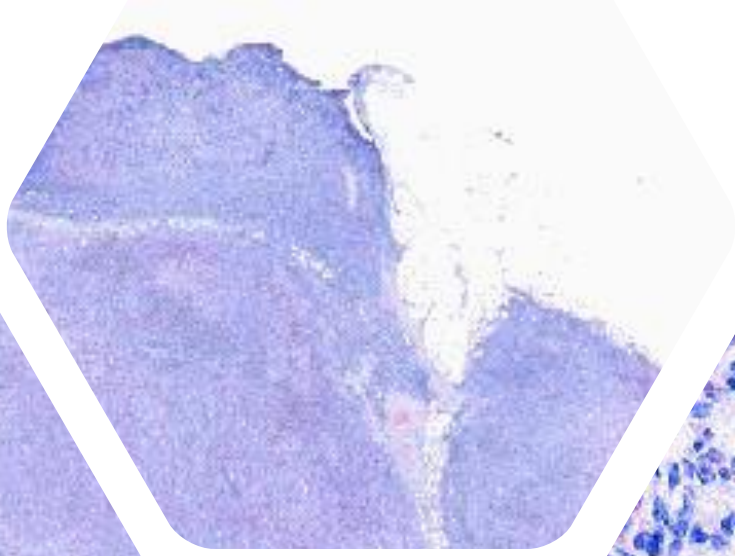
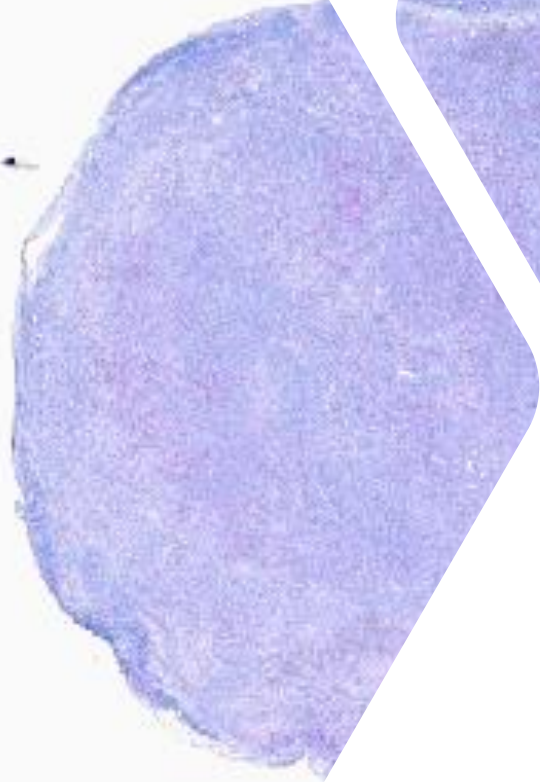






100µm



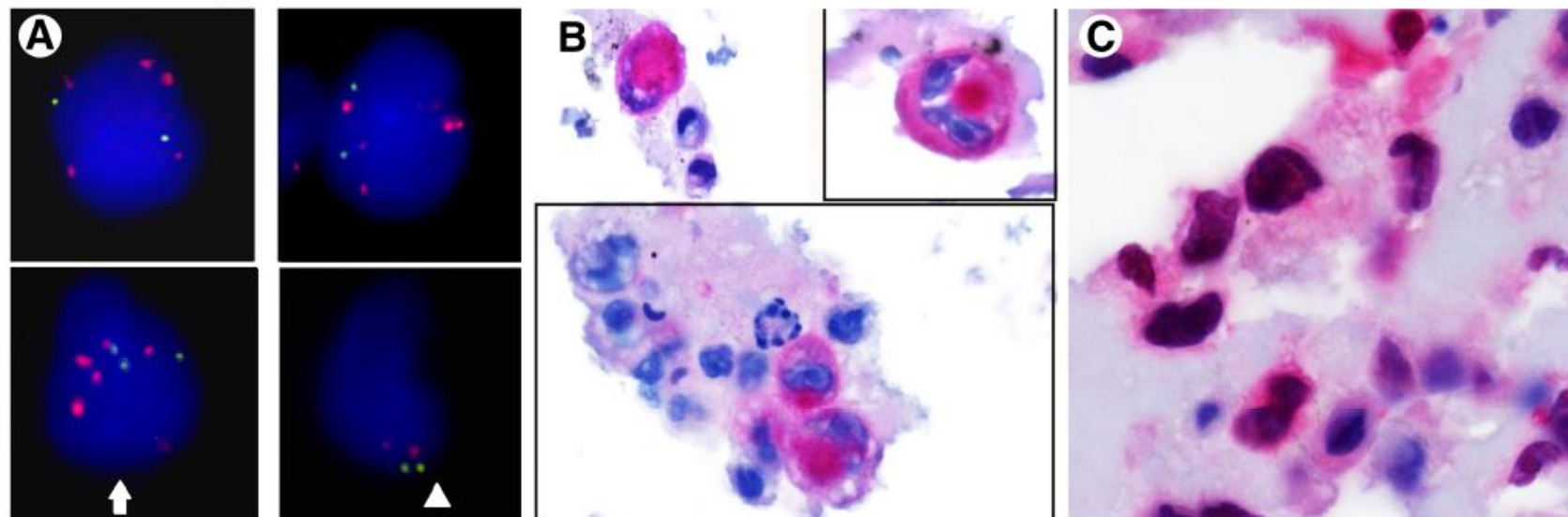


Recurrent PDL1 expression and PDL1 (CD274) copy number alterations in breast implant-associated anaplastic large-cell lymphomas

Valentina Tabanelli, Chiara Corsini, Stefano Fiori, Claudio Agostinelli, Angelica Calleri, Stefania Orecchioni, Federica Melle, Giovanna Motta, Anna Rotili, Arianna Di Napoli, Stefano A. Pileri



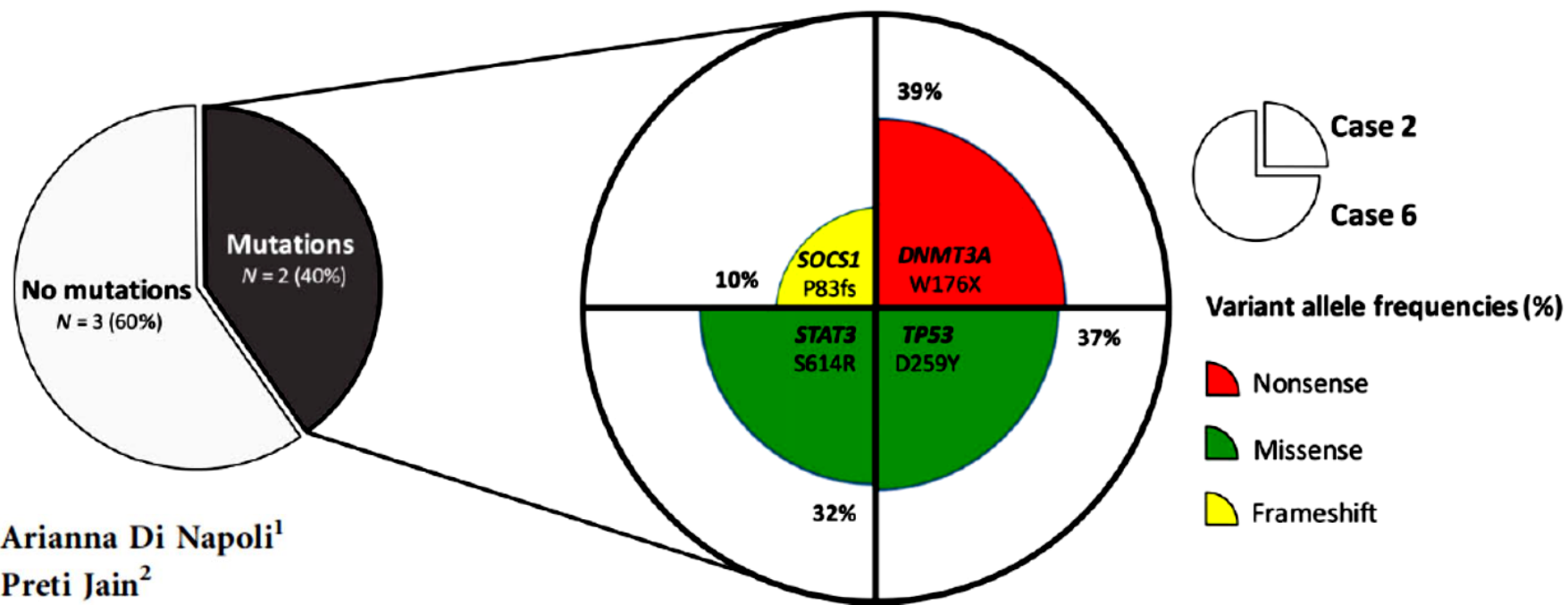
Copy Gain



Reference	Karyotype
George EV et al. [70]	45, XX [cp19]dup(X)(q11q28),+1, del(1)(q32), i(1)(q10), add(3)(p11), der(3), t(2;3)(p12;p26), +6, der(6)t(6;8)(q12;q21.3)x2, add(8)(q11.2), add(11)(q23), add(14)(p11.1), -15, -17, -20, 80~91, idem [cp2]
Alobeid B et al. [48]	116–123,55N4,XX,71, add(1)(p36.3),i(1)(q10),hsr(1)(q21q25),p2,p362, p6,hsr(7)(q32q35)62,i(8)(q10),p9,p10, inv(11)(p15.1q22.1)63,add(12)(q24.1),713,714,715,i(17)(q10),p19,720,p1*8mar[cp13]/46,XX,inv(11)(p15.1q22.1)[7].
Lechner MG et al. [75]	48,XX, = add(2)(q21),dup(2)(q31q35),add(5)(p13),del(10)(p11.2p13), + der(?12)t(12;17)(q13;q21),-16,-20, + mar1-2[5]
Lechner MG et al. [75]	76 < 3 N > ,XXX, + 1, + 2,der(4)t(1;4)9q42;q25),der(4)t(4;4)9p16;q31.3), + 5, + der(6)t(6;13)(q13;q22),der(7)t(7;19)(p13;q13.4)t(16;19)(q22;?q13.1)?trp(19)(q13.1q13.4),del(8)(p21p23), + del(10)(p11.2p13)x1 or x2, der(15)t(9;15)(p13;p11.2)x2, + 17,18,t(18;20)(q11.2;q13.1),der(19)t(18;19)(q21.3;q13.1)[23]
Lechner MG et al. [75]	81,3n.,XXX, + der(X)t(X;11)(q28;p14),del(1)(q21),der(1)del(1)(p13p34)inv(1)(p13q42)t(1;6)(q42;p23), + 2, + 5,der(6)t(1;6)(q42;p23),der(7)t(7;1)(q32;p32)t(1;2)(p36.3;p23), + der(7)t(7;1)(q32;p23), + der(7)t(7;1)(q32;p23)dup(1)(p32p36.3)t(1;2)(p36.3;p23),del(8)(q21q22),der(8)inv(8)(p21q11.2)dup(8)(q11.2q13)x2, + der(8)t(6; (karyotype cuts off), also + 10, + 11, + der12, -16, + 19, -20, + der20, + 21 x 2 (based on images of G-banded metaphases)
Hart AM et al. [76]	Complex; no details

	Gene rearrangements		
Reference	Method	<i>DUSP22</i>	<i>TP63</i>
Oishi et al <sup>7</sup>	FISH + IHC	0/36	0/36
Letourneau et al <sup>6</sup>	FISH	0/1	0/1
Blombery et al <sup>3</sup>			
Laurent et al <sup>5</sup>	FISH	0/9	
Di Napoli et al <sup>4</sup>			
Total		0/46	0/37

# Targeted next generation sequencing of breast implant-associated anaplastic large cell lymphoma reveals mutations in JAK/STAT signalling pathway genes, *TP53* and *DNMT3A*



Arianna Di Napoli<sup>1</sup>  
Preti Jain<sup>2</sup>  
Enrico Duranti<sup>1</sup>  
Elizabeth Margolskee<sup>2</sup>  
Walter Arancio<sup>3</sup>  
Fabio Facchetti<sup>4</sup>  
Bachir Alobeid<sup>2</sup>  
Fabio Santanelli di Pompeo<sup>5</sup>  
Mahesh Mansukhani<sup>2</sup>  
Govind Bhagat<sup>2</sup>

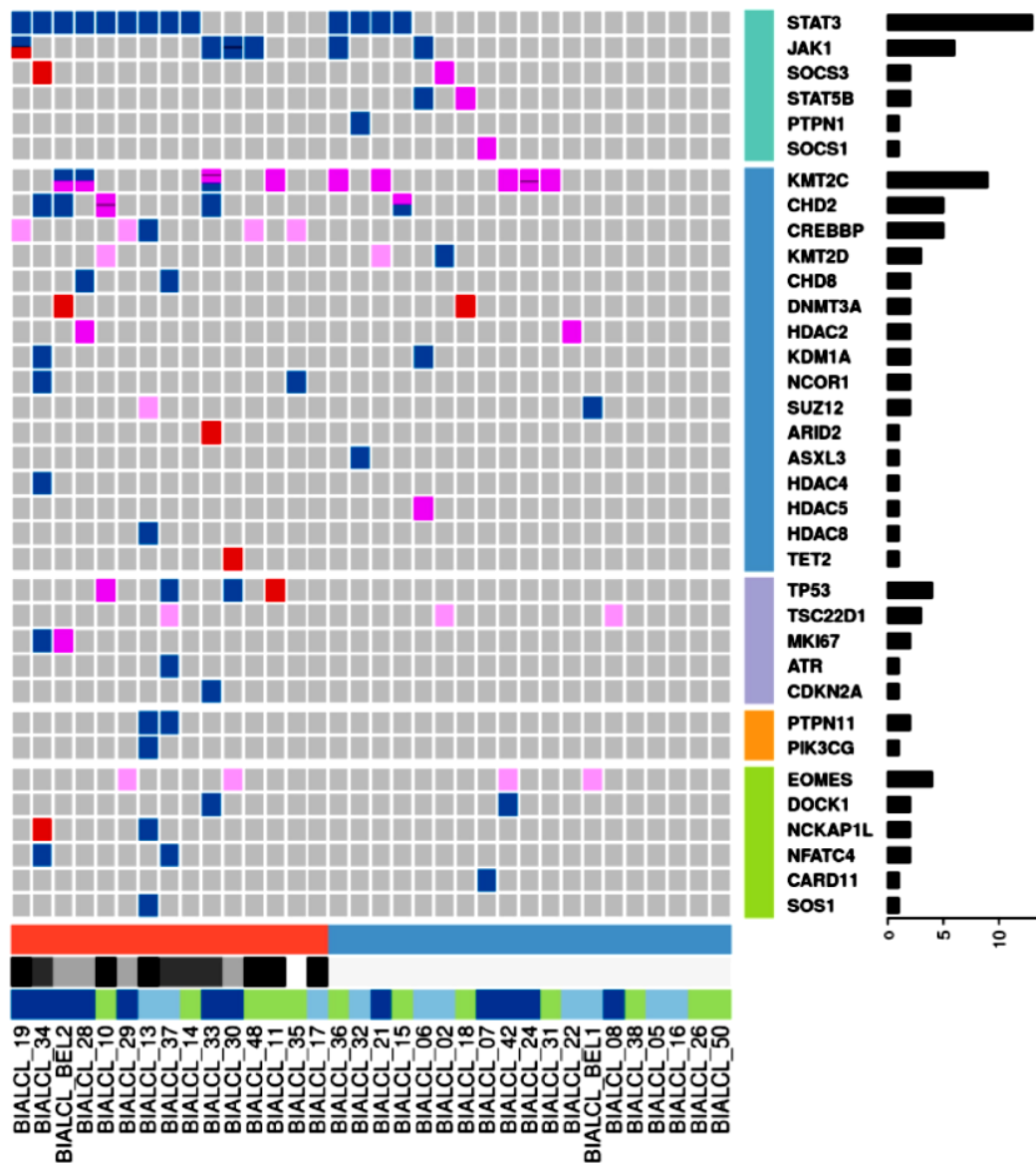
**Table 1.** Summary of key sequence variants reported in BIA-ALCL case-series.

Study	No. of Cases	Methodology	Sequence Variants in JAK/STAT Pathway (% of Patients; Genes Containing Variants)	Sequence Variants in Epigenetic Regulators (% of Patients; Genes Containing Variants)	Other Genes of Interest
Di Napoli et al. [10]	5	Targeted sequencing (465 gene panel)	20% ( <i>SOCS1</i> , <i>STAT3</i> )	20% ( <i>DNMT3A</i> )	<i>TP53</i> (1 case)
Blombery et al. [7]	11	Targeted sequencing (180 gene panel) WES (2 cases)	91% ( <i>JAK2</i> , <i>STAT3</i> )	9% ( <i>SETD2</i> )	<i>TP53</i> (2 cases), <i>PTPN1</i> (1)
Oishi et al. [5]	15	Targeted sequencing of <i>JAK1</i> , <i>JAK3</i> , <i>STAT3</i> , <i>STAT5A</i> , <i>STAT5B</i>	27% ( <i>JAK1</i> , <i>STAT3</i> )	Not assessed	Not assessed
Quesada et al. [9]	9	Targeted sequencing (400 and 199 genes)	78% ( <i>JAK1</i> , <i>STAT3</i> , <i>SOCS1</i> , <i>STAT5B</i> )	78% ( <i>SMARCB1</i> , <i>KDM5C</i> , <i>TET2</i> , <i>TET3</i> , <i>ARID4B</i> , <i>KDM6A</i> , <i>KMT2C</i> , <i>KMT2B</i> )	<i>TP53</i> (1 case), <i>PIK3CA</i> (1), <i>AXIN1</i> (1), <i>GNAS</i> (1)
Laurent et al. [8]	34	WES (22 cases) Targeted sequencing (400 gene panel) (24 cases)	59% ( <i>STAT3</i> , <i>JAK1</i> , <i>SOCS3</i> , <i>STAT5B</i> , <i>PTPN1</i> , <i>SOCS1</i> )	74% ( <i>KMT2C</i> , <i>CHD2</i> , <i>CREBBP</i> , <i>KMT2D</i> , <i>CHD8</i> , <i>DNMT3A</i> , <i>KDM1A</i> , <i>NCOR1</i> , <i>SUZ12</i> , <i>ARID2</i> , <i>ASXL3</i> , <i>HDAC2</i> , <i>HDAC4</i> , <i>HDAC5</i> , <i>HDAC8</i> , <i>TET2</i> )	<i>TP53</i> (4 cases), <i>EOMES</i> (4), <i>PTPN11</i> (2), <i>PIK3CG</i> (1), <i>CDKN2A</i> (1)
Los-de Vries et al. [11]	29	sWGS (29 cases) WES (7 cases)	43% (3/7 cases) ( <i>STAT3</i> , <i>JAK1</i> )	29% (2/7 cases) ( <i>KMT2C</i> )	<i>MEF2A</i> (1 case)

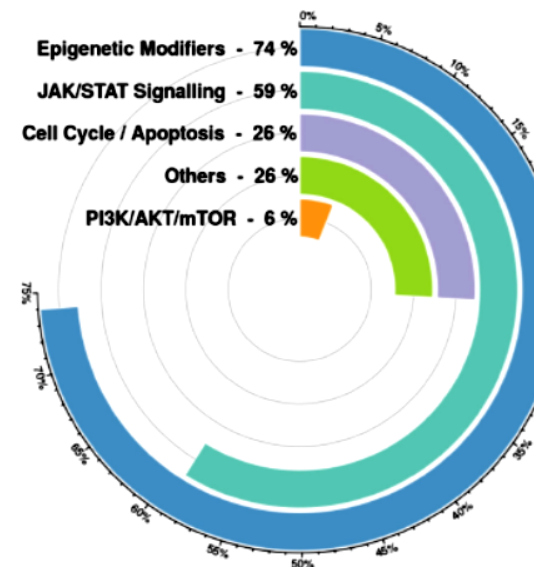
WES, whole exome sequencing; sWGS, shallow whole genome sequencing.



**A**



**B**



# 12 Patients Sequenced with Panel T

Sample ID	Index	RICHIESTA	NOME PAZIENTE
21-L-2995	H1	LINFOCHIP T	BI-ALCL LA-4668
22-L-1574	A2	LINFOCHIP T	BI-ALCL LO-GD07
22-L-1580	B2	LINFOCHIP T	BI-ALCL LO-BWMM
22-L-1583	C2	LINFOCHIP T	BI-ALCL LA-GY4W
21 L 2991	D2	LINFOCHIP T	BI-ALCL LA-GB3B
21 L 2994	E2	LINFOCHIP T	BI-ALCL C-A2V7
21 L 3028	F2	LINFOCHIP T	BI-ALCL LA-MCFK
BI-ALCL TR-7JEW-C	B6	LINFOCHIP T	BI-ALCL TR-7JEW-C
BI-ALCL LOTZ2Q-C1	D6	LINFOCHIP T	BI-ALCL LOTZ2Q-C1
BI-ALCL VE-D5E2-C	E6	LINFOCHIP T	BI-ALCL VE-D5E2-C
BI-ALCL CA-Z28F-C	F6	LINFOCHIP T	BI-ALCL CA-Z28F-C
BI-ALCL LO-NMVO-C	G6	LINFOCHIP T	BI-ALCL LO-NMVO-C

## Filtering criteria:

- Germline Variants
- Variants not annotated or benign in COSMIC
- Annotated in 1000 Genomes Project with minor allele frequency  $\geq 0.01$
- Variants present in > 7 samples (70%) or with a VAF <1%
- Mutations outside the coding region
- Sequencing errors

### Acute Lymphoblastic T Cell Leukaemia

AKT1  
BCL11B  
CDKN2A  
CREBBP  
CSNK2A1  
DNM2  
ETV6  
EZH2  
FAT3  
FBXW7  
FLT3  
HERC1  
IL7R  
JAK1  
JAK3  
LEF1  
MYB  
NOTCH1  
NOTCH2  
NRAS  
NT5C2  
PHF6  
PTEN  
RELN  
RUNX1  
TP53  
TYK2  
WHSC1  
WT1

### Adult T Cell Lymphoma- Leukaemia

CARD11  
CCR4  
CCR7  
CD58  
CDKN2A  
CSNK2A1  
EP300  
FAS  
FAT4  
GATA3  
IRF2BP2  
JAK3  
KIT  
MUC16  
NOTCH1  
NOTCH2  
PCLO  
PLCG1  
POT1  
PRKCB  
RHOA  
SMARCA2  
STAT3  
SYNE1  
TBL1XR1  
TET2  
TP53  
VAV1

### Mycosis Fungoides-Sezary Syndrome

ARID1A  
ARID1B  
AARID2  
ATM  
ATXN1  
BCOR  
CARD11  
CD36  
CDKN2A  
DMD  
DNMT3A  
EPHA7  
FAT4  
FSIP2  
FYN  
IRF4  
JAK1  
JAK3  
MKI67  
MUC16  
PCLO  
PLCG1  
POT1  
PRKCB  
RHOA  
SMARCA2  
STAT3  
SYNE1  
TBL1XR1  
TET2  
TNFRSF1B  
TP53  
UGT1A7  
UNC5C  
UNC5D  
ZEB1

### Peripheral T Cell Lymphoma Unspecified

APC  
ARID1A  
ARID1B  
ARID2  
ASXL3  
ATM  
BCORL1  
BIRC6  
CD28  
CHD1  
CHD8  
CREBBP  
CTNNB1  
DDX3X  
DNMT3A  
ERBB2  
FAT1  
FOXO1  
FYN  
HDAC6  
IDH2  
KDM6A  
KMT2A  
KMT2C  
KMT2D  
MBD4  
NF1  
NFRKB  
NOTCH2  
PCLO  
PDCD11  
PLCG1  
PRDM2  
RHOA  
SETD2  
STAT3  
STAT6  
TET2  
TLX3  
TNFAIP3  
TNFRSF14  
TP53  
TP63  
TRAF3  
TTC3  
ZAP70

**Panel T**

### Anaplastic Large Cell Lymphoma

AKT1  
ALK  
DNMT3A  
JAK1  
NOTCH1  
NOTCH2  
NRAS  
PRDM1  
STAT3  
TET2  
TP53

### NK-T Cell Lymphoma

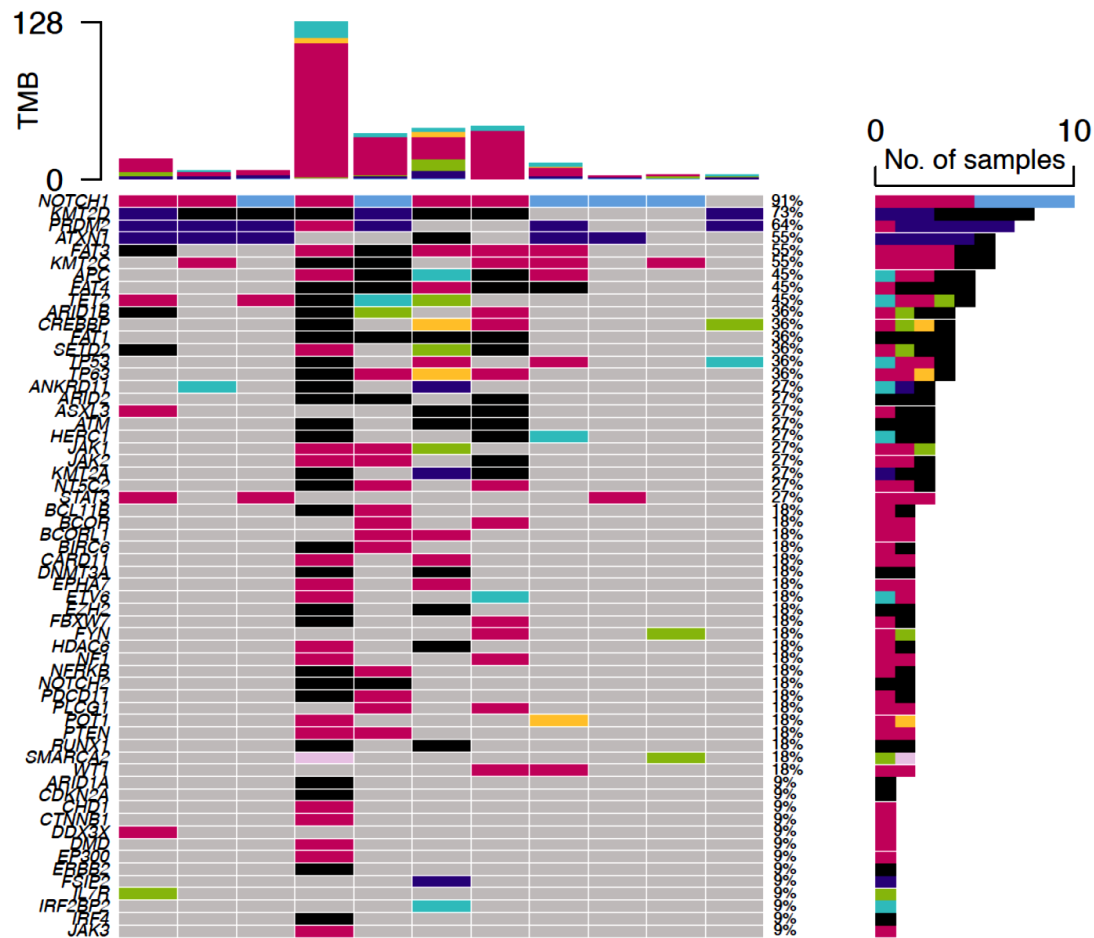
CTNNB1  
JAK3  
KIT  
STAT3  
STAT5B  
TP53

### Angioimmunoblastic T Cell Lymphoma

ANKRD11  
CD28  
CTNNB1  
DNMT3A  
EP300  
FAT4  
IDH2  
IRF4  
PLCG1  
RHOA  
TET2  
TP53  
VAV1

### T Cell Large Granular Lymphocytic Leukaemia

BCL11B  
KDM6A  
KRAS  
MED12  
NOTCH1  
NOTCH2  
STAT3  
STAT5B  
SUZ12  
WT1





- Stop Gain
- Missense Variant
- Frameshift Variant
- Disruptive Inframe Deletion
- Conservative Inframe Deletion
- Disruptive Inframe Insertion
- Multiple Type
- Multi Hit

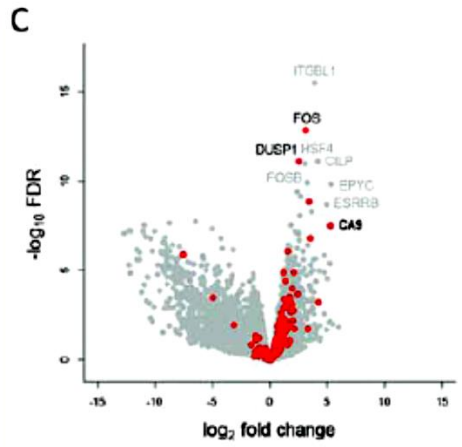
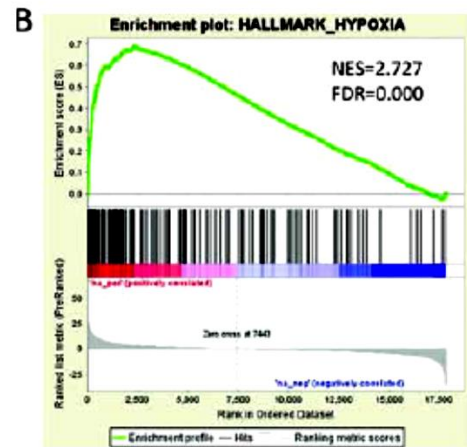
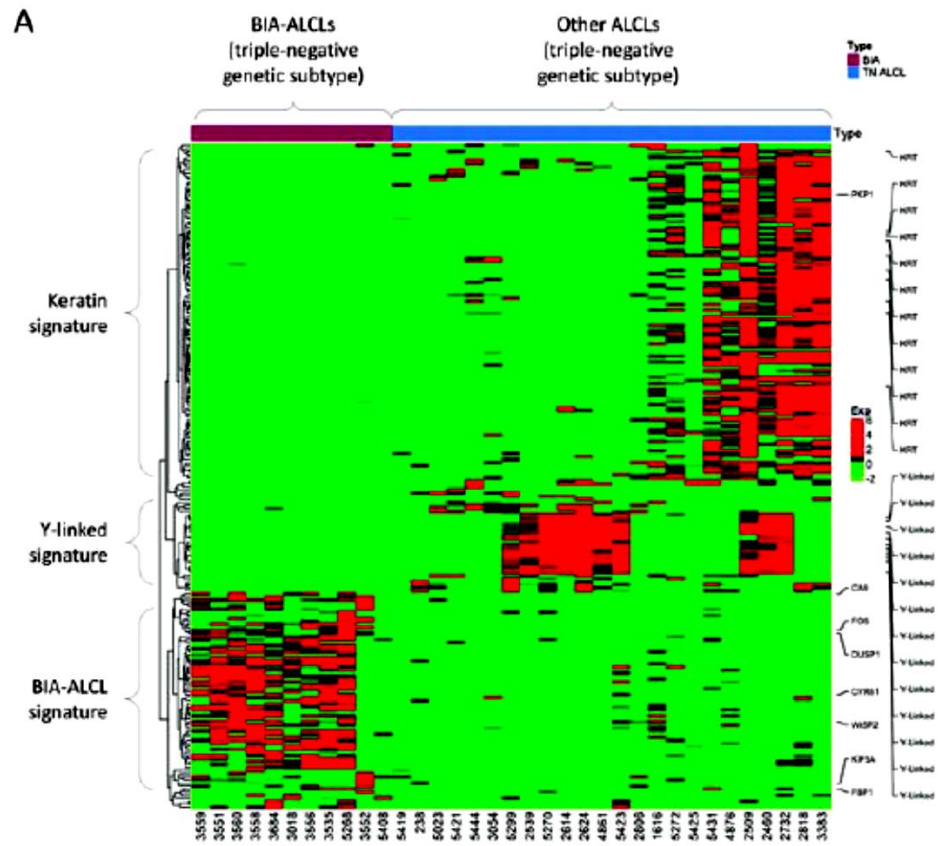
- OncoPrint depicting top 60 mutated genes sorted and ordered by decreasing frequency
- VAF  $\geq$  1%.

ARTICLE



## Whole exome sequencing reveals mutations in *FAT1* tumor suppressor gene clinically impacting on peripheral T-cell lymphoma not otherwise specified

Maria Antonella Laginestra<sup>1</sup> · Luciano Cascione<sup>2</sup> · Giovanna Motta<sup>3</sup> · Fabio Fuligni<sup>4</sup> · Claudio Agostinelli<sup>1</sup> · Maura Rossi<sup>1</sup> · Maria Rosaria Sapienza<sup>1</sup> · Simona Righi<sup>1</sup> · Alessandro Broccoli<sup>1</sup> · Valentina Indio<sup>5</sup> · Federica Melle<sup>3</sup> · Valentina Tabanelli <sup>3</sup> · Angelica Calleri<sup>3</sup> · Domenico Novero<sup>6</sup> · Fabio Facchetti<sup>7</sup> · Giorgio Inghirami<sup>8</sup> · Elena Sabattini<sup>1</sup> · Francesco Bertoni <sup>2</sup> · Stefano A. Pileri<sup>3</sup>




Cancer Immunology, Immunotherapy (2021) 70:1379–1392

<https://doi.org/10.1007/s00262-020-02778-3>

ORIGINAL ARTICLE

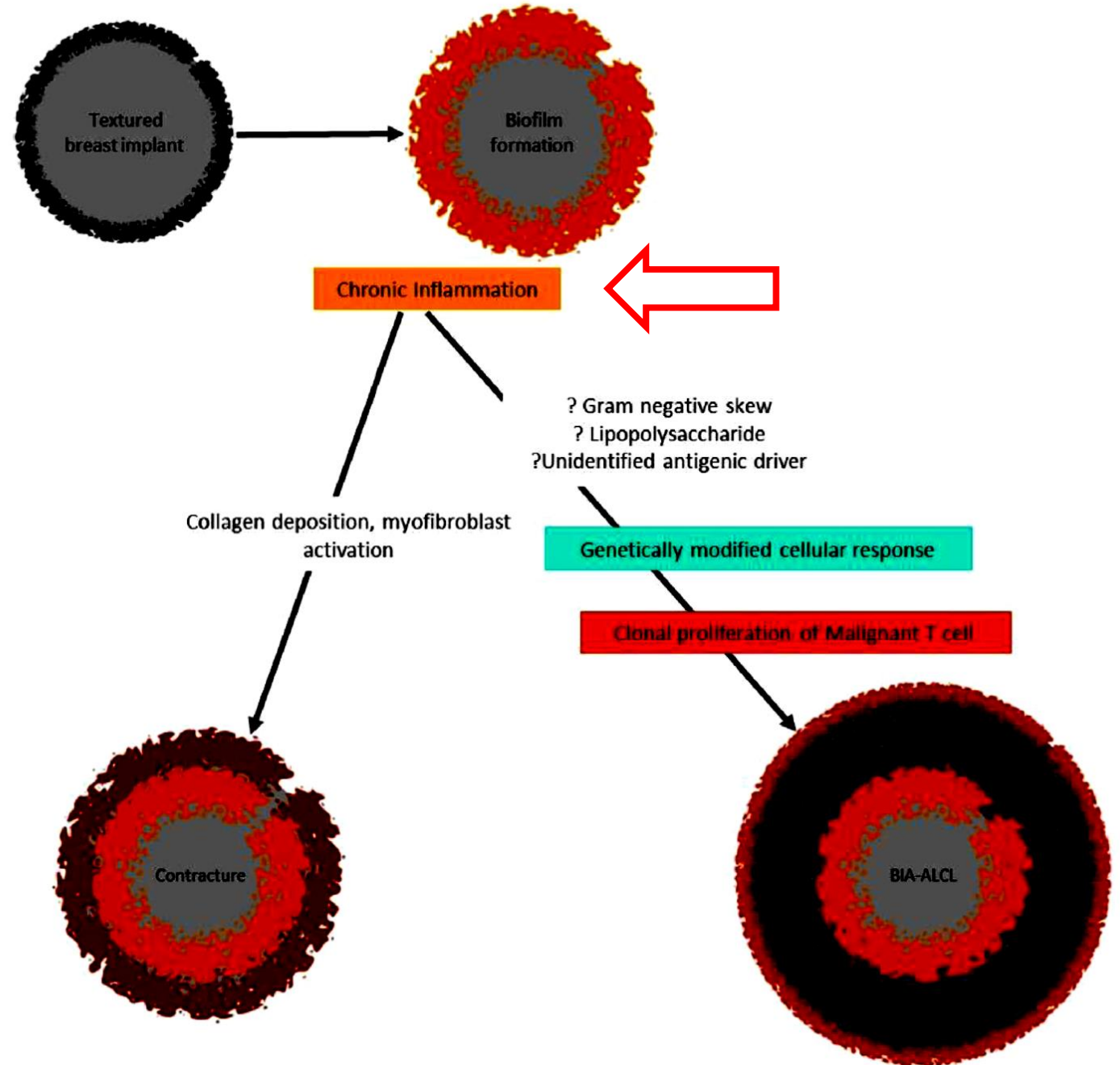


## **IL-10, IL-13, Eotaxin and IL-10/IL-6 ratio distinguish breast implant-associated anaplastic large-cell lymphoma from all types of benign late seromas**












**Arianna Di Napoli<sup>1</sup>  · Daniele Greco<sup>2</sup> · Giorgia Scafetta<sup>1</sup> · Francesca Ascenzi<sup>3</sup> · Alessandro Gulino<sup>2</sup> · Luigi Aurisicchio<sup>4</sup> · Fabio Santanelli Di Pompeo<sup>5</sup> · Adriana Bonifacino<sup>6</sup> · Enrico Giarnieri<sup>7</sup> · John Morgan<sup>8</sup> · Rita Mancini<sup>3</sup> · Marshall E. Kadin<sup>8</sup>**

# Etiology and pathogenesis

Lajevardi SS et al. JPRAS  
2022; 32:34-42.



# Epstein–Barr-virus-positive large B-cell lymphoma associated with breast implants: an analysis of eight patients suggesting a possible pathogenetic relationship

L. Jeffrey Medeiros <sup>1</sup>, Mario L. Marques-Piubelli <sup>2</sup>, Valentina F. I. Sangiorgio<sup>3</sup>, Roberto Ruiz-Cordero <sup>4</sup>, Francisco Vega <sup>1</sup>, Andrew L. Feldman <sup>5</sup>, Jennifer R. Chapman<sup>6</sup>, Mark W. Clemens<sup>7</sup>, Kelly K. Hunt <sup>8</sup>, Mark G. Evans<sup>1</sup>, Christine Khoo<sup>9</sup>, Stephen Lade<sup>9</sup>, Mark Silberman<sup>10</sup>, Jerzy Morkowski<sup>11</sup>, Edward M. Pina<sup>12</sup>, Daniel C. Mills<sup>13</sup>, Christopher M. Bates<sup>14</sup>, Winston B. Magno<sup>15</sup>, Aliyah R. Sohani <sup>16</sup>, Beth A. Sieling<sup>17</sup>, Joseph M. O'Donoghue<sup>18</sup>, Chris M. Bacon<sup>19</sup>, Neill Patani<sup>20</sup>, Despina Televantou<sup>21</sup>, Suzanne D. Turner <sup>22</sup>, Laura Johnson<sup>23</sup>, Fiona MacNeill<sup>24</sup>, Andrew C. Wotherspoon<sup>25</sup>, Swaminathan P. Iyer<sup>26</sup>, Luis E. Malpica<sup>26</sup>, Keyur P. Patel <sup>1</sup>, Jie Xu <sup>1</sup> and Roberto N. Miranda <sup>1</sup>✉

© The Author(s), under exclusive licence to United States & Canadian Academy of Pathology 2021

Breast implant anaplastic large cell lymphoma (ALCL) is a T-cell neoplasm arising around textured breast implants that was recognized recently as a distinct entity by the World Health Organization. Rarely, other types of lymphoma have been reported in patients with breast implants, raising the possibility of a pathogenetic relationship between breast implants and other types of lymphoma. We report eight cases of Epstein–Barr virus (EBV)-positive large B-cell lymphoma associated with breast implants. One of these cases was invasive, and the other seven neoplasms were noninvasive and showed morphologic overlap with breast implant ALCL. All eight cases expressed B-cell markers, had a non-germinal center B-cell immunophenotype, and were EBV+ with a latency type III pattern of infection. We compared the noninvasive EBV+ large B-cell lymphoma cases with a cohort of breast implant ALCL cases matched for clinical and pathologic stage. The EBV+ large B-cell lymphoma cases more frequently showed a thicker capsule, and more often were associated with calcification and prominent lymphoid aggregates outside of the capsule. The EBV+ B-cell lymphoma cells were more often arranged within necrotic fibrinoid material in a layered pattern. We believe that this case series highlights many morphologic similarities between EBV+ large B-cell lymphoma and breast implant ALCL. The data presented suggest a pathogenetic role for breast implants (as well as EBV) in the pathogenesis of EBV+ large B-cell lymphoma. We also provide some histologic findings useful for distinguishing EBV+ large B-cell lymphoma from breast implant ALCL in this clinical setting.

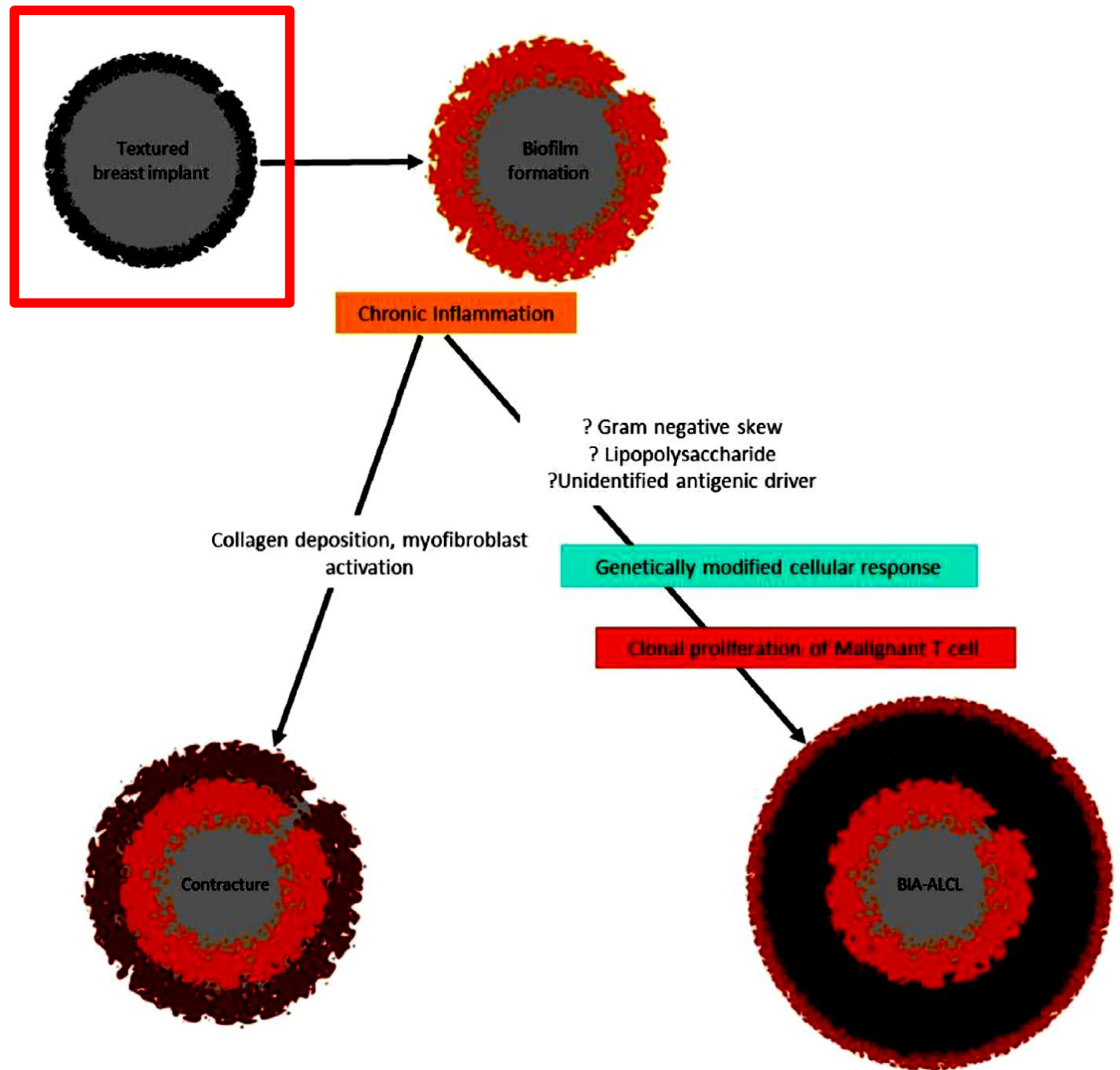
*Modern Pathology*; <https://doi.org/10.1038/s41379-021-00863-1>



# Etiology and pathogenesis

Lajevardi SS et al. JPRAS 2022; 32:34-42.

In 2018, EU did not renew the CE mark to one specific textured implant; however, further attention should be paid to the differences between macro and micro-textured devices.



Akhavan AA  
et al. PRS  
2021;  
148:299-303

Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is a malignancy associated with textured breast implants. BIA-ALCL is typically restricted to the periprosthetic capsule, presenting as a unilateral recurrent seroma years after placement of a textured breast implant. Current estimates suggest an incidence of one in 3300 for patients with Allergan Biocell textured implants. As of February 6, 2019, U.S. Medical Device Reporting associated with BIA-ALCL showed 457 unique cases of BIA-ALCL, with 24 "unverified and potentially inaccurate" cases associated with a nontextured implant. As of February of 2019, there were 688 reported cases to date worldwide. To date, there are no published case reports of BIA-ALCL associated exclusively with smooth implants or with smooth implants after textured expanders, and there has been no reported smooth-only case in any registry, database, or journal worldwide. The authors present a case of BIA-ALCL associated with smooth round implants and textured tissue expanders. A 56-year-old woman was treated for left stage IIA invasive ductal carcinoma with bilateral mastectomies and immediate reconstruction with bilateral subpectoral textured tissue expanders. She underwent exchange to Mentor smooth-round implants, and completed adjuvant chemotherapy. Magnetic resonance imaging and examination 4.5 years after implant placement showed no abnormal findings. The patient had left breast trauma 5 years following implant placement while taking adalimumab, and developed an open wound requiring explantation. A recurrent seroma developed, and tested positive for BIA-ALCL on cytology. Surgical pathologic examination after total capsulectomy demonstrated stage IA BIA-ALCL. To the authors' knowledge, this is the first case report of BIA-ALCL in a patient with textured expanders followed by prolonged exposure to smooth round implants.

Individual genetic factors should exist, if the prevalence of BIA-ALCL is indeed low by considering the number of women, who received implants. However, they are still largely unknown.

