CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, Starhotels Anderson
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PATOLOGIE KSHV/HHV8 RELATE

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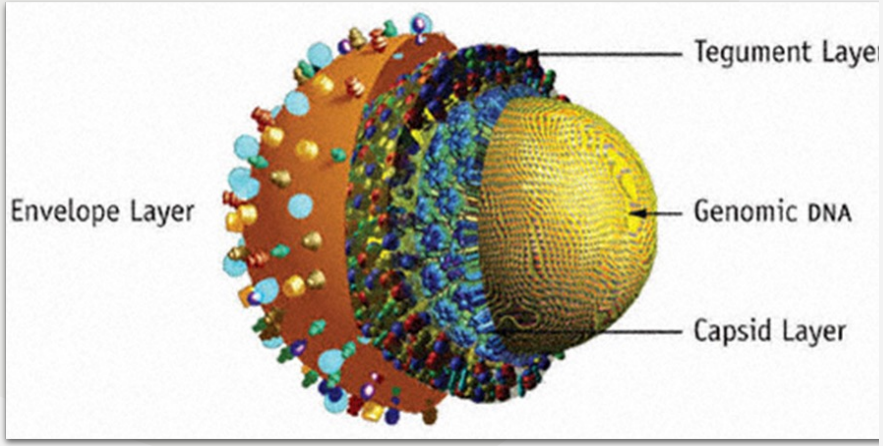
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Pfizer					√		
Eusapharma					√		

KSHV/HHV8 CARATTERISTICHE

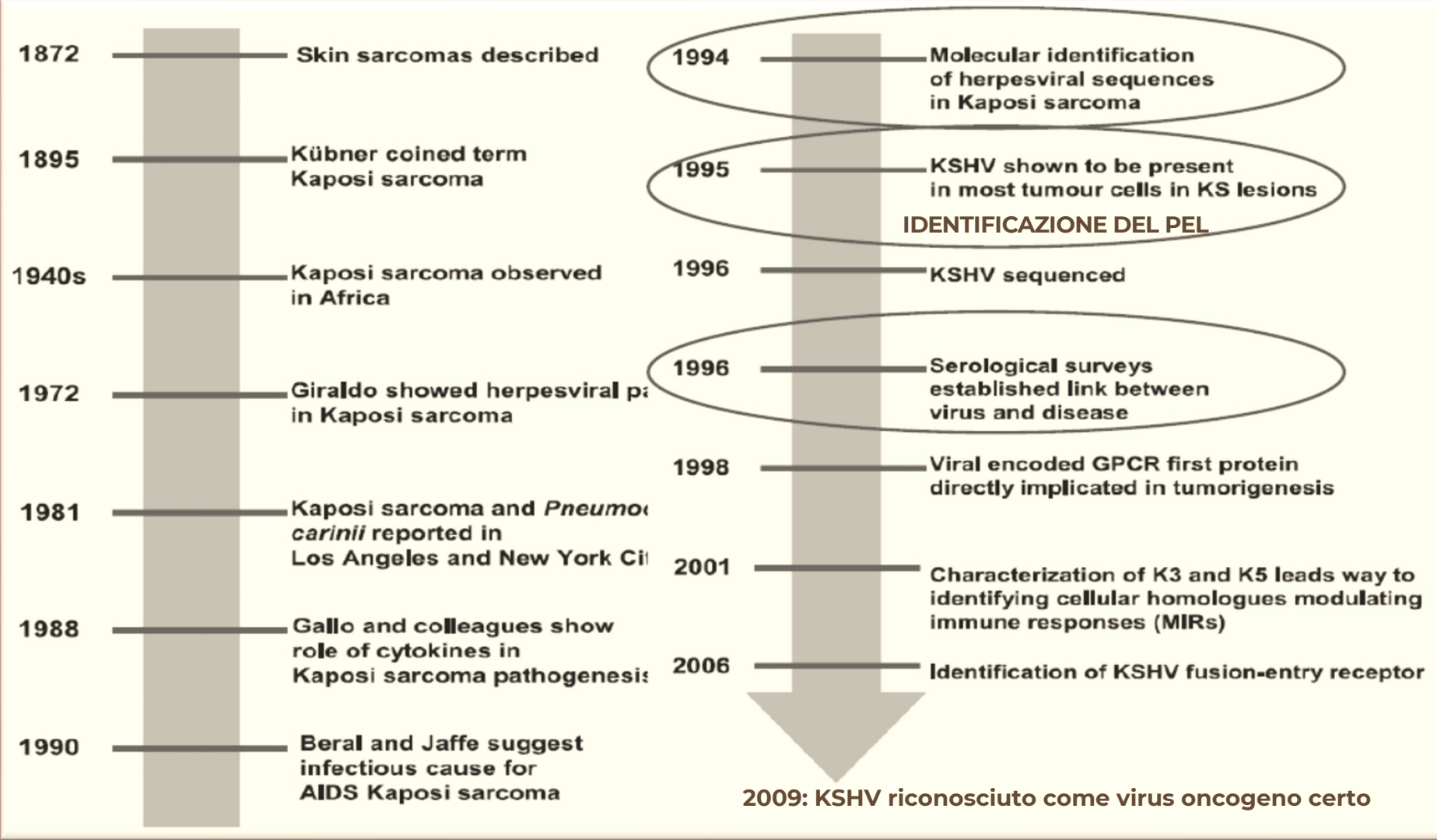


- **KAPOSI SARCOMA ASSOCIATED HERPESVIRUS (KSHV) o human gammaherpesvirus 8 (HHV-8)** è un virus oncogenico a DNA a doppio filamento di circa 165 kilobasi, con capside a simmetria icosaedrica, rivestito, appartenente alla famiglia Herpesviridae e alla sottofamiglia dei gamma herpes virus.

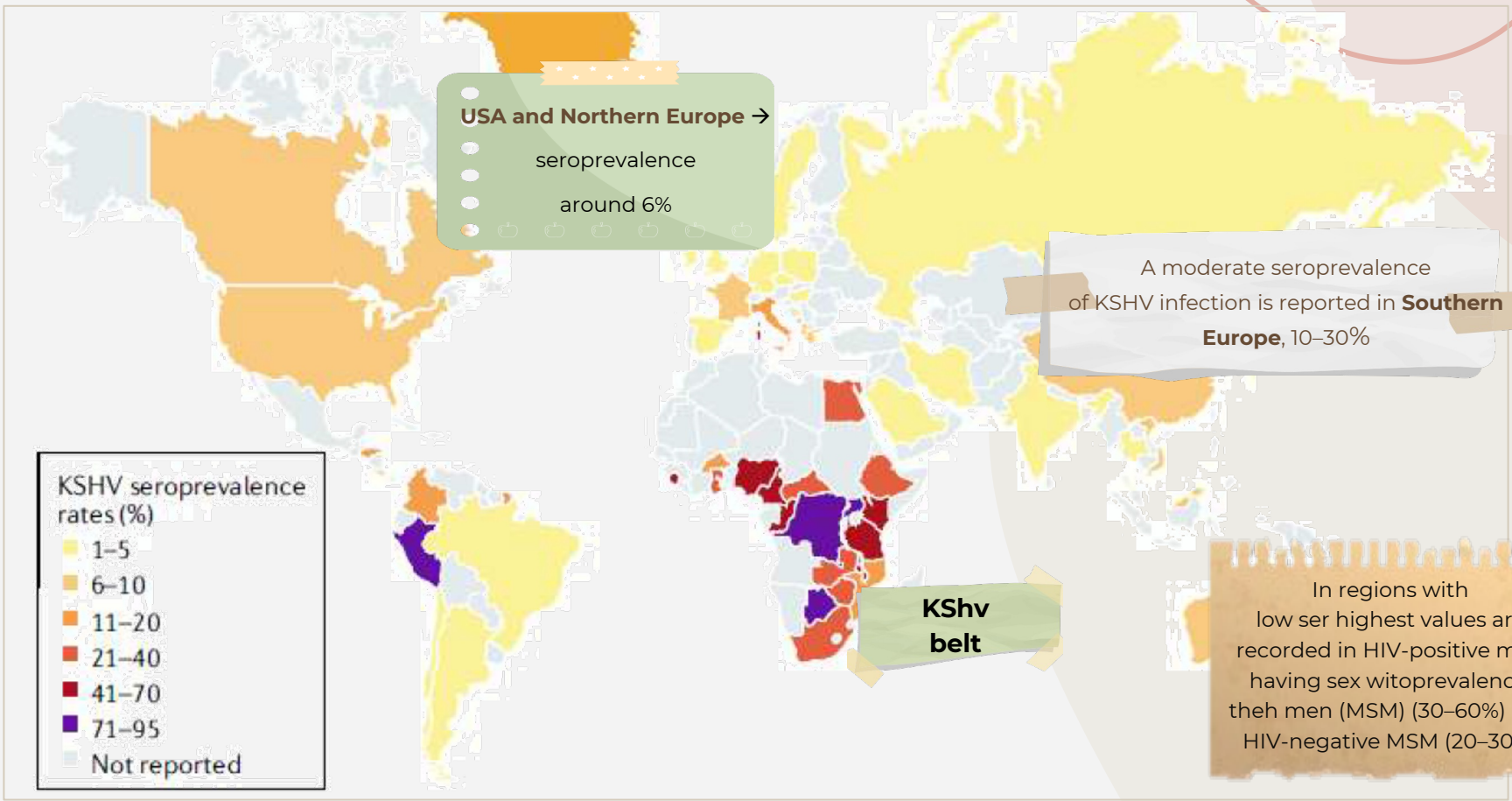
- HHV-8 **è capace di infettare diversi tipi** di cellule: cellule B, cellule endoteliali, macrofagi, cellule epiteliali, attraverso un meccanismo di fusione di membrana mediato da GP.

TAXONOMY AND CLASSIFICATION:

ORDER: Herpesvirales
FAMILY: Herpesviridae
SUBFAMILY: Gammaherpesvirinae
GENUS: Rhadinovirus
SPECIES: Human Gammaherpesvirus 8


1872
Skin sarcomas described
1895
Kübner coined term
Kaposi sarcoma
1940s
Kaposi sarcoma observed
in Africa
1972
Giraldo showed herpesviral pa
in Kaposi sarcoma
1981
Kaposi sarcoma and Pneumoc
carinii reported in
Los Angeles and New York Cit
1988
Gallo and colleagues show
role of cytokines in
Kaposi sarcoma pathogenesis
1990
Beral and Jaffe suggest
infectious cause for
AIDS Kaposi sarcoma
1994
Molecular identification
of herpesviral sequences
in Kaposi sarcoma
1995
KSHV shown to be present
in most tumour cells in KS lesions
IDENTIFICAZIONE DEL PEL
1996
KSHV sequenced
1996
Serological surveys
established link between
virus and disease
1998
Viral encoded GPCR first protein
directly implicated in tumorigenesis
2001
Characterization of K3 and K5 leads way to
identifying cellular homologues modulating
immune responses (MIRs)
2006
Identification of KSHV fusion-entry receptor
2009: KSHV riconosciuto come virus oncogeno certo

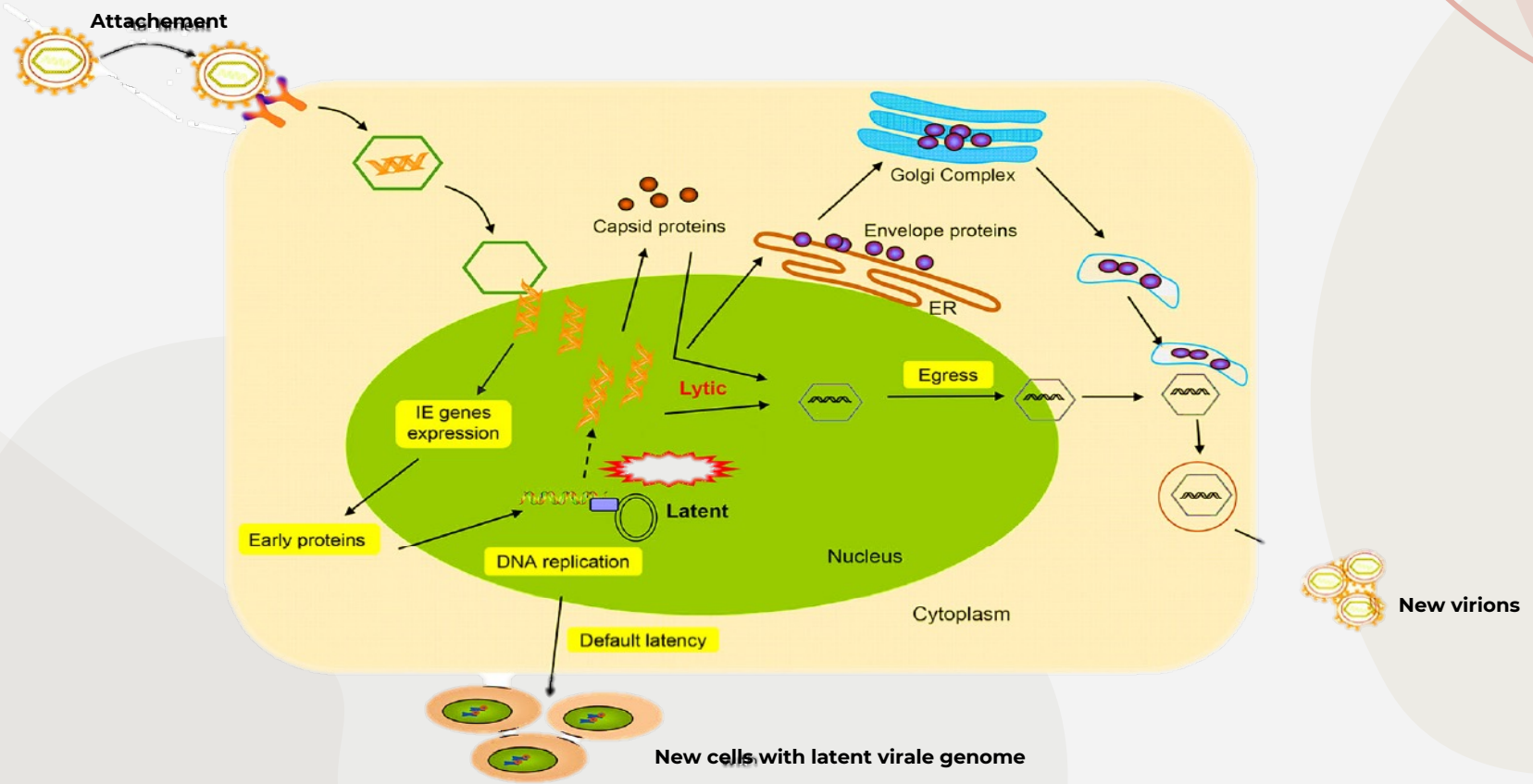
KSHV EPIDEMIOLOGY



TRANSMISSION

Presence of KSHV in potentially infectious body	HSHV+		
	KS+	KS-HIV+	KS- HIV-
saliva	22	20-35	10-20
semen	6	<1	<1
Vaginal fluid	NA	1	1
feces	0	NA	<1

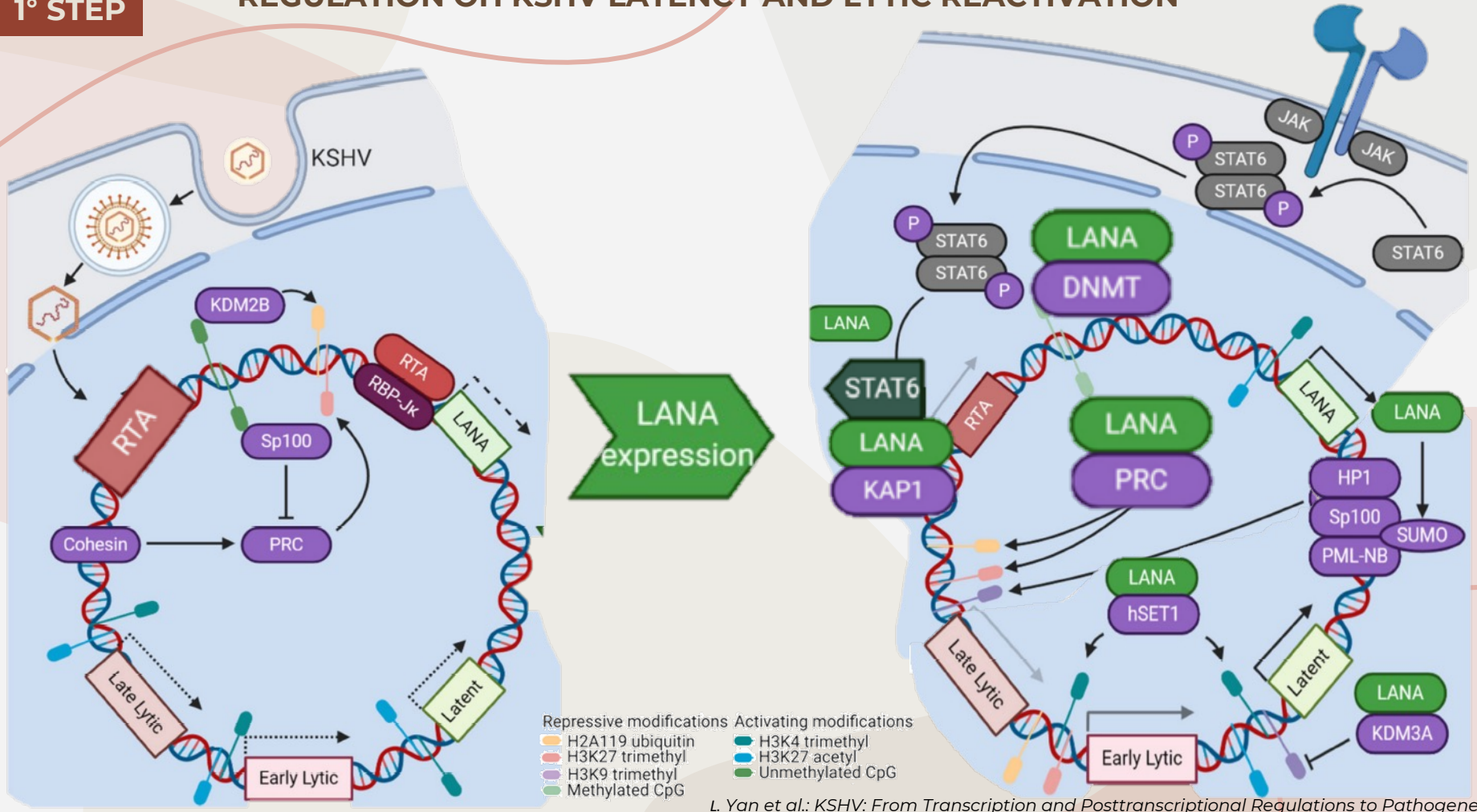
REGULATION OH KSHV LATENCY AND LYTIC REACTIVATION



L. Yan et al.: KSHV: From Transcription and Posttranscriptional Regulations to Pathogenesis

1° STEP

REGULATION OH KSHV LATENCY AND LYTIC REACTIVATION



L. Yan et al.: KSHV: From Transcription and Posttranscriptional Regulations to Pathogenesis

TRANSCRIPTION REGULATION OF GENES

Only a small portion of the latent KSHV genome is transcribed, and the major latency locus in latently infected cells include:

01

ORF 7 LANA

02

ORF72 (v-Cyclin)

regulates the cell cycle and cell proliferation by constitutive activation of cellular cyclin-dependent kinase 6 (CDK6)

03

ORF71 (K13, v-FLIP)

activates NF-kB pathway→ facilitates cell survival, proliferation and cell type-specific induced growth arrest and apoptosis during latency

04

Kaposins (K12)

Viral miRNA

05

a group of noncoding single stranded RNAs (20ncts) regulate gene expression by binding to the seed-matched regions of target mRNAs

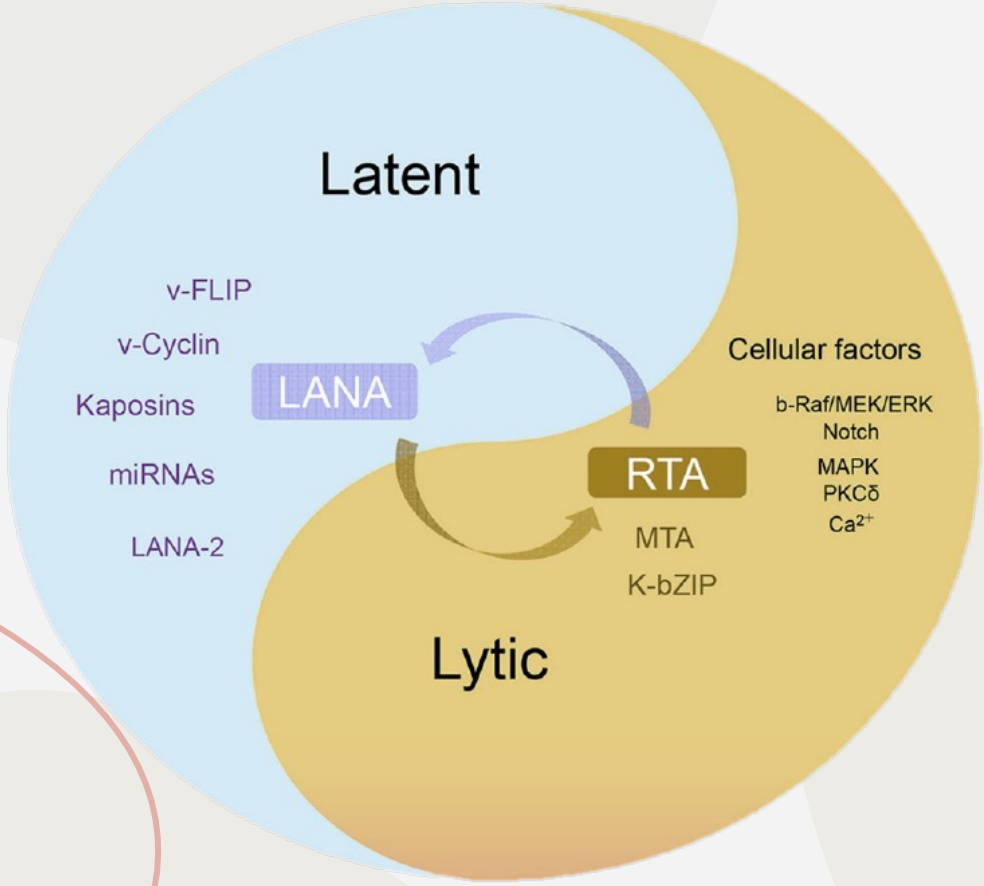
06

LYTIC GENES

ORF74, K14, vIL-6 and ORF59, are transcribed at low
→ leaky expression of viral lytic genes during latent infection.

2° STEP

KSHV LIFE CYCLE AND ONCOGENESIS

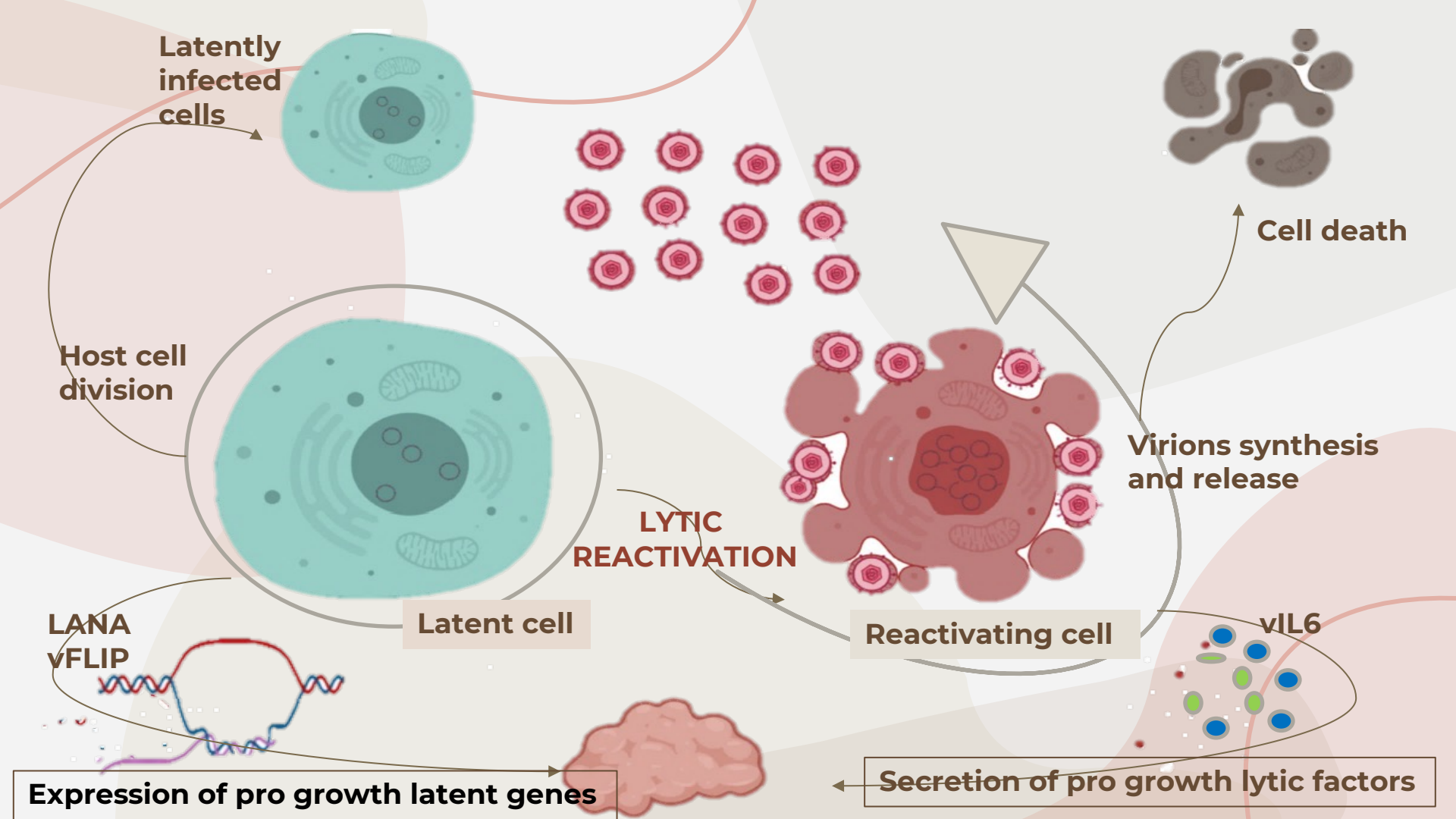


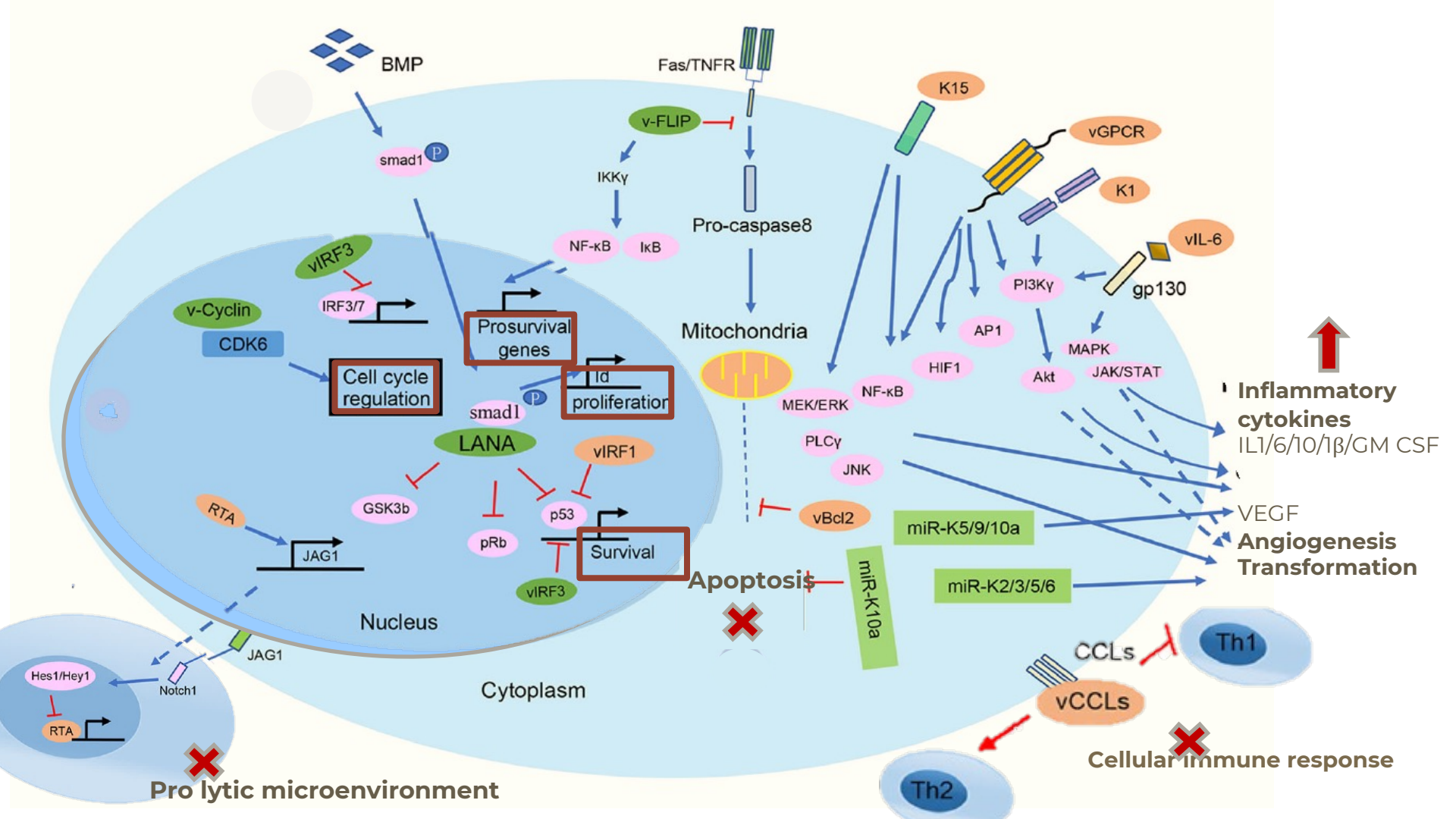
close association of KSHV with some human malignancies (KS, PEL and MCD) has caused virologists to consider KSHV as a human oncovirus.

The highlights of KSHV infection are:

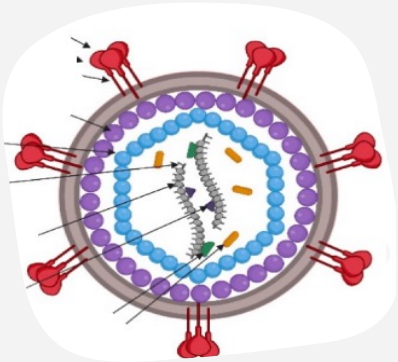
- higher cell growth rate with an extended lifespan,
- altered cell morphology,
- deregulated angiogenesis,
- elevated inflammation and
- immune evasion

to support tumor growth

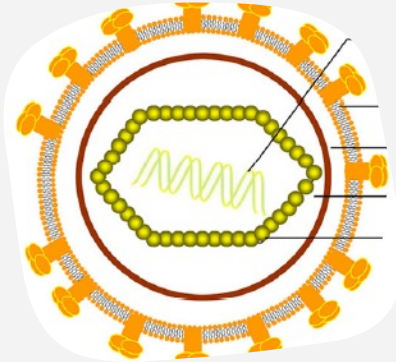

Latently infected cells
Cell death
Host cell division
Virions synthesis and release
LYTIC REACTIVATION
Latent cell
Reactivating cell
LANA
vFLIP
vIL6
Expression of pro growth latent genes
Secretion of pro growth lytic factors


BMP
smad1
P
Fas/TNFR
v-FLIP
IKKγ
NF-κB
IκB
Pro-caspase8
K15
vGPCR
K1
vIL-6
gp130
PI3Kγ
AP1
MAPK
Akt
JAK/STAT
HIF1
NF-κB
MEK/ERK
PLCγ
JNK
vIRF3
IRF3/7
v-Cyclin
CDK6
Cell cycle regulation
Prosurvival genes
Id
proliferation
smad1
P
LANA
vIRF1
GSK3b
p53
pRb
Survival
vIRF3
RTA
JAG1
Mitochondria
vBcl2
Apoptosis
miR-K10a
miR-K5/9/10a
miR-K2/3/5/6
Inflammatory cytokines
IL1/6/10/1β/GM CSF
VEGF
Angiogenesis
Transformation
Nucleus
Cytoplasm
JAG1
Hes1/Hey1
Notch1
RTA
CCLs
Th1
vCCLs
Th2
Cellular immune response
Pro lytic microenvironment

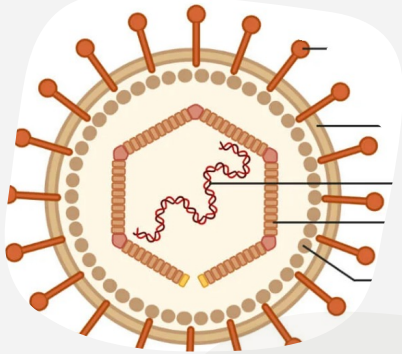
ONCOGENIC VIRUSES and hematology



HTLV-1



HHV8
KSHV



EBV

WHO 2022

KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas	ID (hiv)	EBV
Primary effusion lymphoma	80% hiv+	80%
KSHV/HHV8-positive diffuse large B-cell lymphoma	>90% hiv+	--
KSHV/HHV8-positive germinotropic lymphoproliferative disorder	Very few cases	
Tumour-like lesions with B-cell predominance		
Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma IgG4-related disease Unicentric Castleman disease Idiopathic multicentric Castleman disease		
KSHV/HHV8-associated multicentric Castleman disease	50-75%	

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

elderly patients without overt immunodeficiency

Immunodeficiency setting

HIV+pts

3° STEP

VIRAL COOPERATION

HIV infection and immunosuppression play an important role in the pathogenesis of both EBV and KSHV-associated cancers

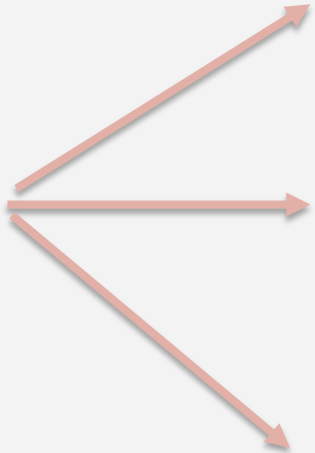
DEFINITION: a mechanism by which different viruses coinfecting human tissus, have synerigstic or regulatory effects on carcinogenesis

- detection of different viruses in the same neoplastic cells
- proof that immunodeficiency and/or chronic antigenic stimulation act in an indirect way in promoting tumor outgrowth

- the demonstration of viral-dependent molecular alterations induc-ing neoplastic transformation

VIRAL COOPERATION

Cooperazione virale



Direttamente sulla cellula nella trasformazione tumorale

Indirettamente sul microambiente tumorale

Indirettamente sul Mi(a)croambiente «umano»

VIRAL COOPERATION: PEL MODEL

Dually infected PEL cells

HIV

KSHV	EBV
RTA inhibits chemically-induced EBV lytic gene expression	**EBV ZTA inhibits chemically-induced KSHV lytic expression**
the KSHV RTA transactivates the EBV LMP-1 promoter	Expression of LMP1 ↓ KSHV and EBV lytic phase
RTA indirectly contributes to EBV and KSHV latency	LMP1 → negative-feedback loop that resulted in the expansion of PEL cells with no need of KSHV reactivation or lysis of the infected-cells

viral latency → expression of few low-immunogenic viral proteins

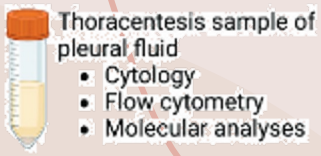
→ immune response against the virus diminished.

→ the immune escape and increased risk for the development of gammaherpesvirus-associated diseases

PRIMARY EFFUSION LYMPHOMA

DEFINITION

- Effusion-based, usually without a solid component
- Male, HIV +(md age 43)or elderly pts (md age 73)
- **Association with MCD and/or KS**
- **EBV+cases**→ severely immunocompromised HIV+
- EBV- cases → HIV- elderly men
- Post-transplant PEL → EBV -



MORPHOLOOGY and IP

- Large cells with plasmablastic/immunoblastic/anaplastic cytology;
- Terminal B lineage; IP: **CD30 CD38 CD138 EMA MUM1 HLA DR** +; CD45+
  (lack markers of b cell differ.: PAX5, CD19, CD20, CD79a CD45 –
  expression of T/NL markers may occur
  CD10/BCL6 neg
  IGH gene → clonally rearranged and hypermutated/TCR
  only occasionally express Ig with some lamda liht chain+ cases

Post GC profile

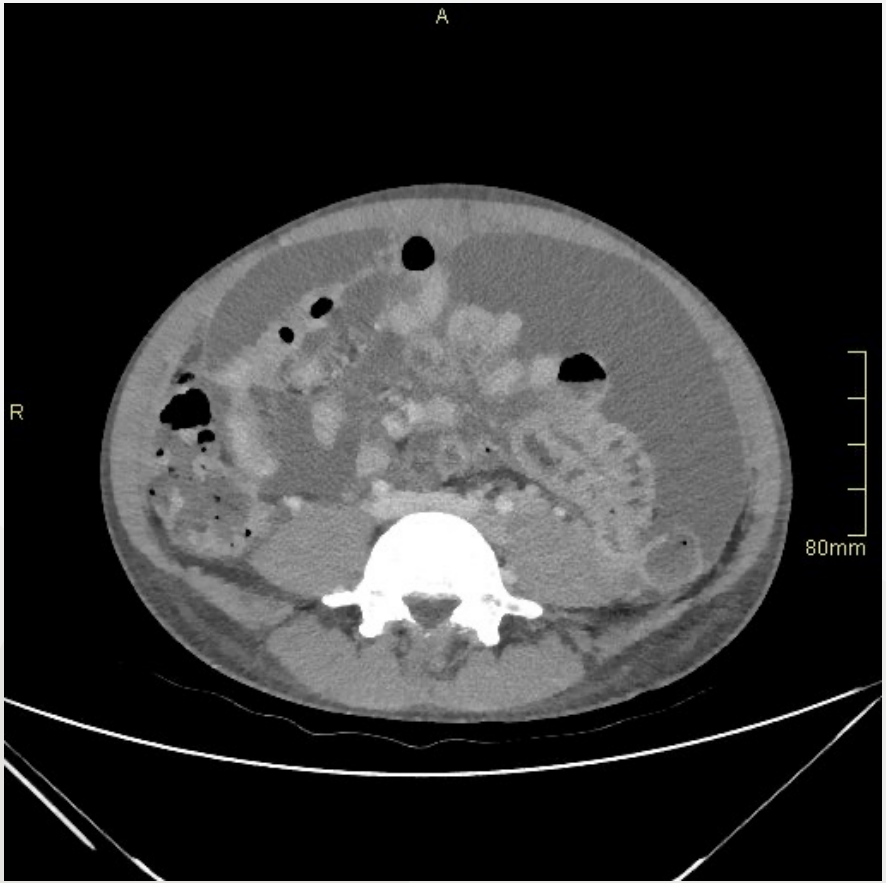
- NO MYC rearrangement
- Mutations in BCL6, MYC, pax5 RhoH/ITF

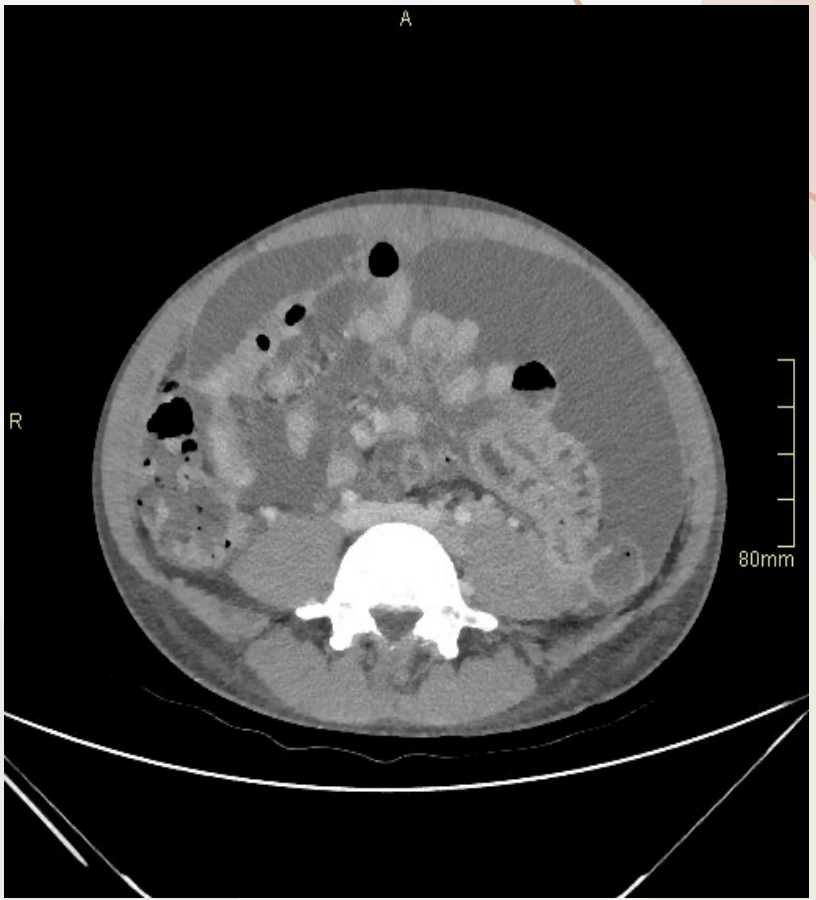
Caso 1

- Uomo di 30 anni con HIV di primo riscontro e ascite tesa.
- **Cd4 alla diagnosi: 8/mmc**

- Esame citologico su liquido peritoneale: numerosi elementi linfoidi ad abito plasmablastico di immunofenotipo MUM1+, HHV8+, EBER+, CD30+,CD79a+ focale, CD138-, CD20-, ALK-.

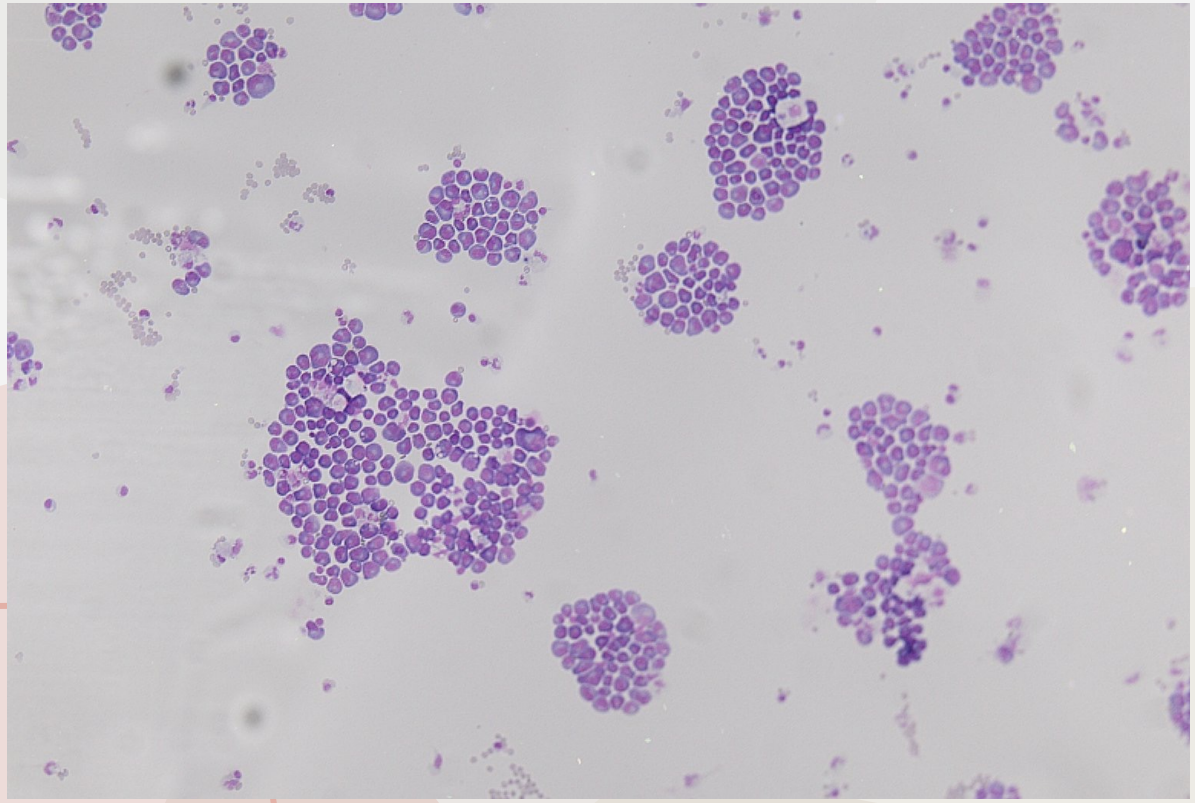
- Reperto compatibile con localizzazione sierosa di linfoma a cellule B mature CD30+ HHV8-EBV driven, tipo **PEL**.


A
R
80mm

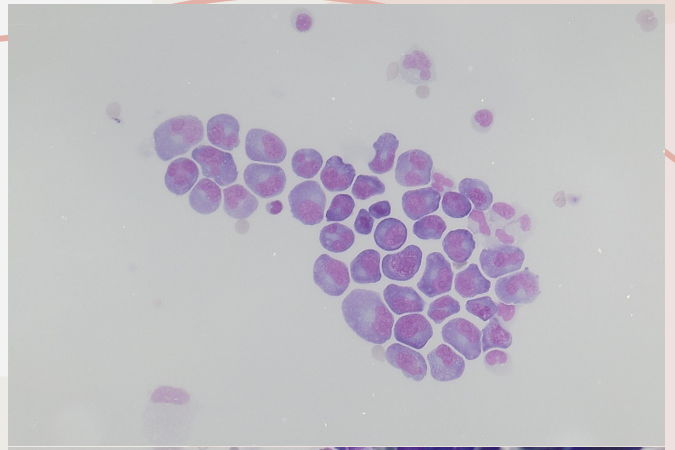

A
R
80mm

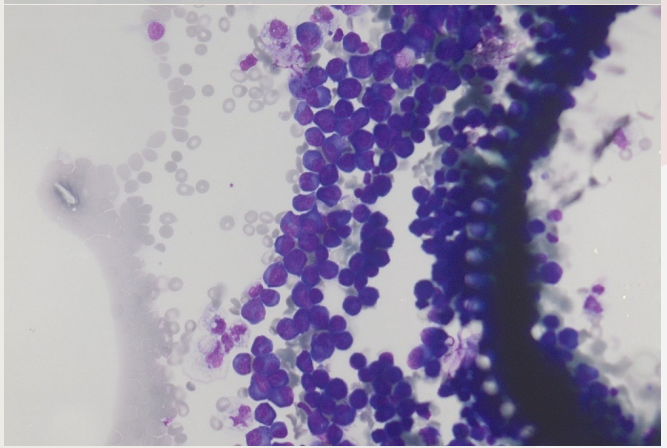
MGG

10X



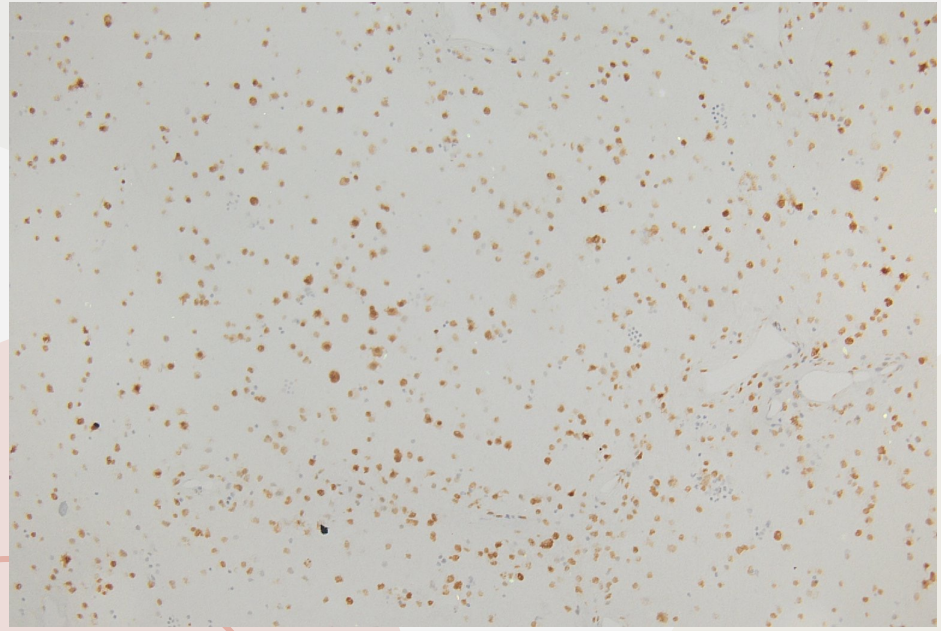
40X



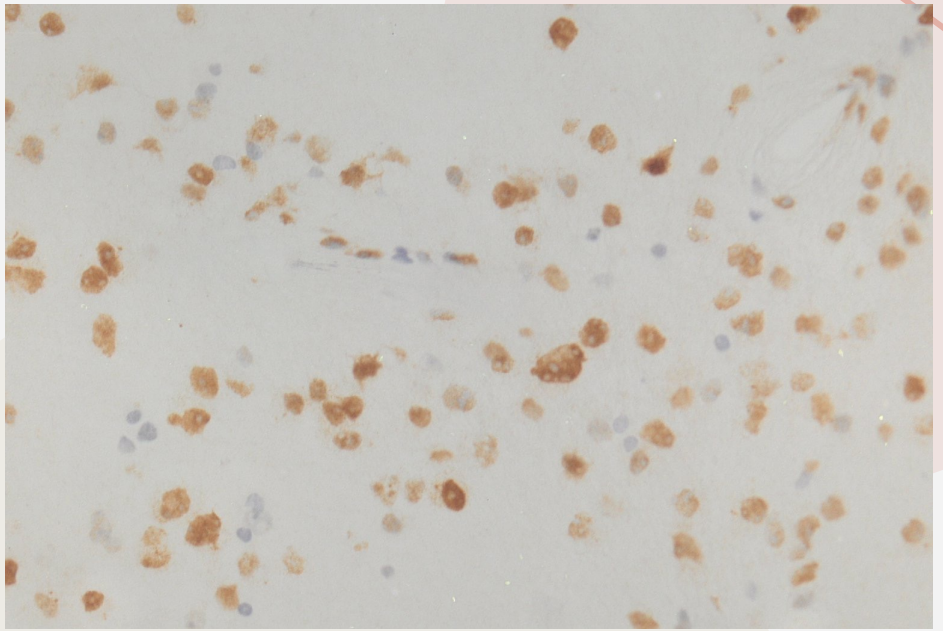


MUM1

10X

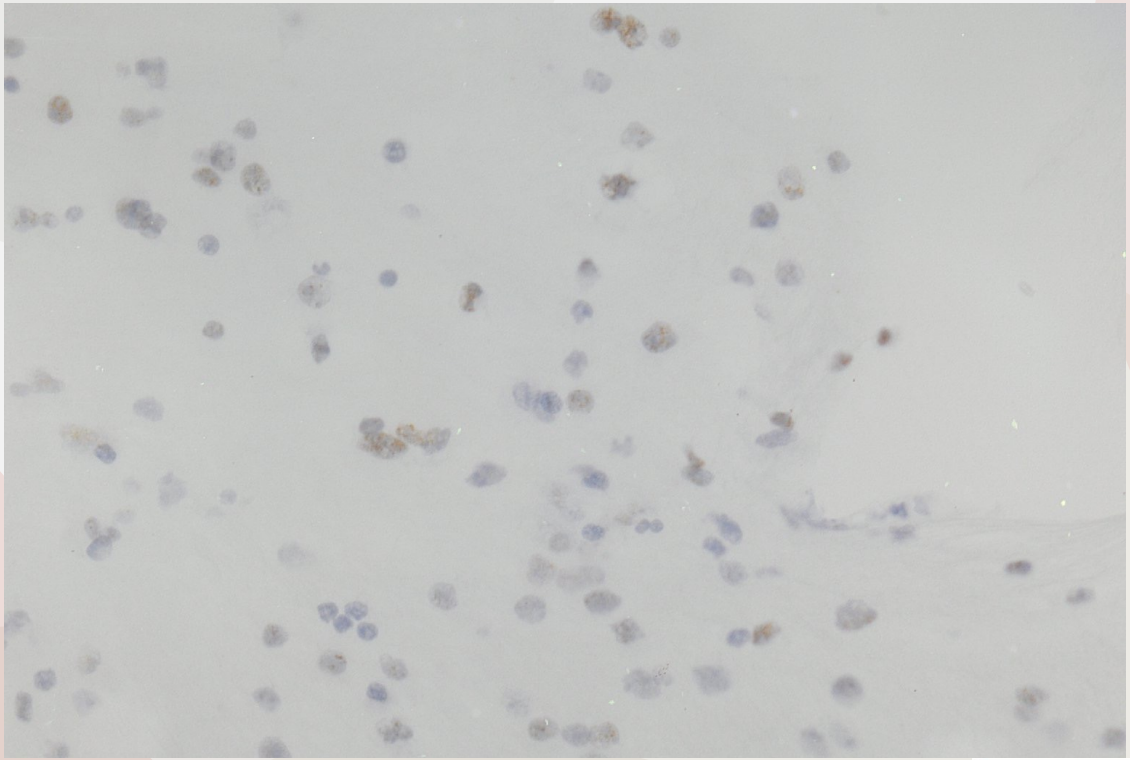


40X

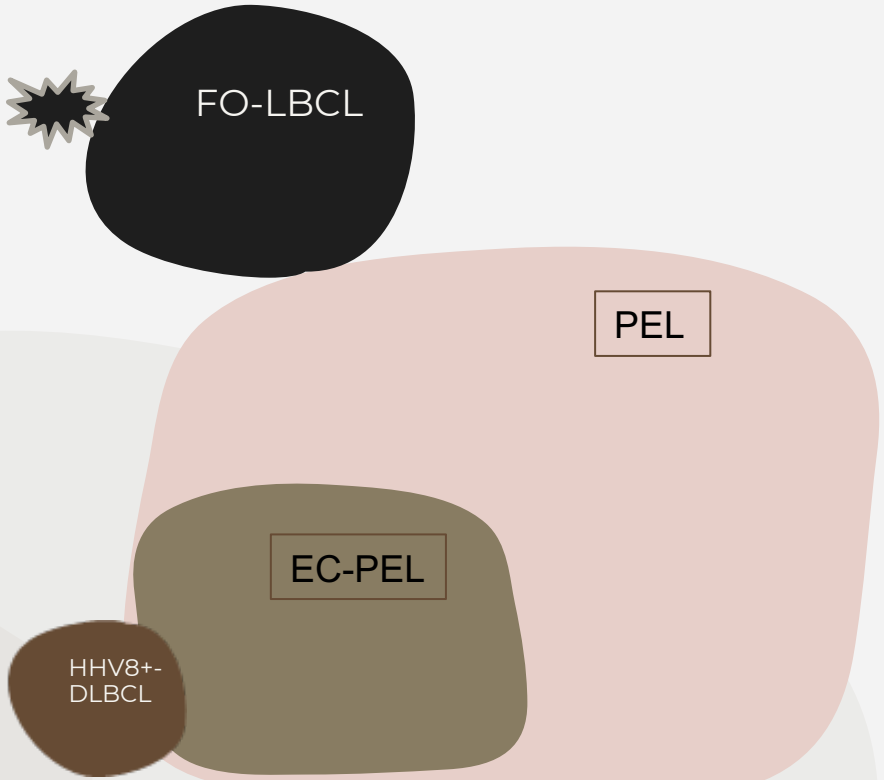


LANA

40X



CAVITY BASED LYMPHOMAs



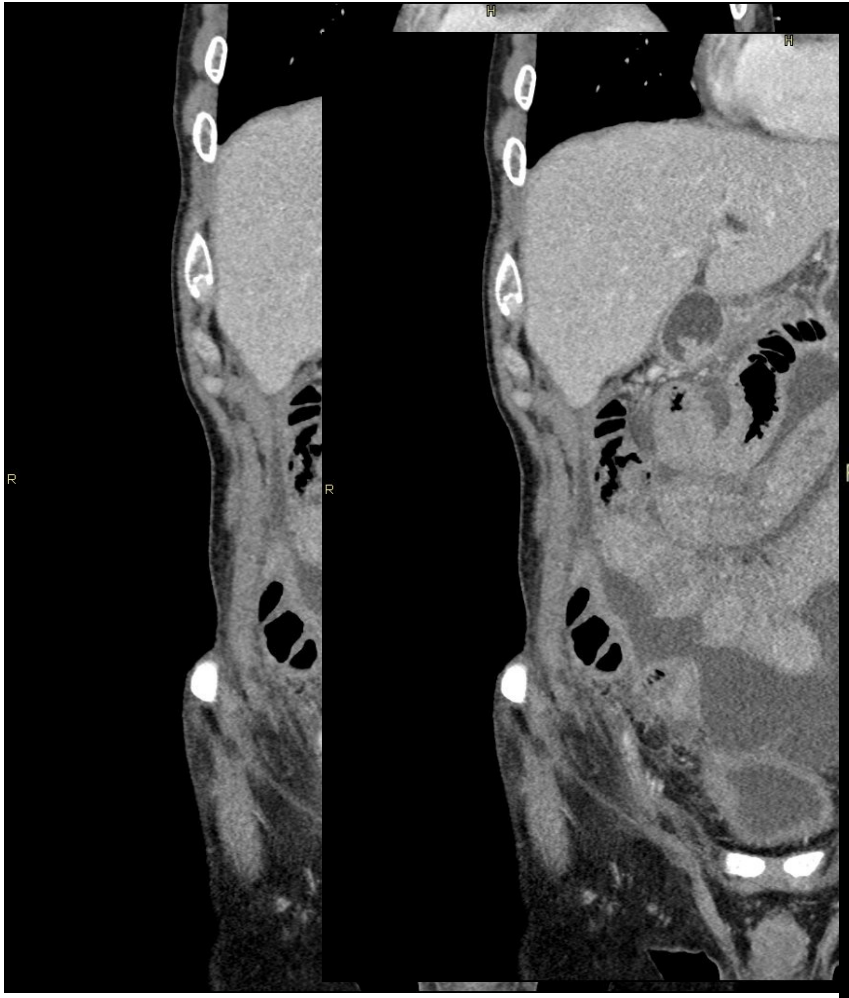
CI-DLBCL
FA-DLBCL
BIA-ALCL

PEL
EBV + (high)or -
EBV
LMP1/EBNA2
latency-
HIV+/-

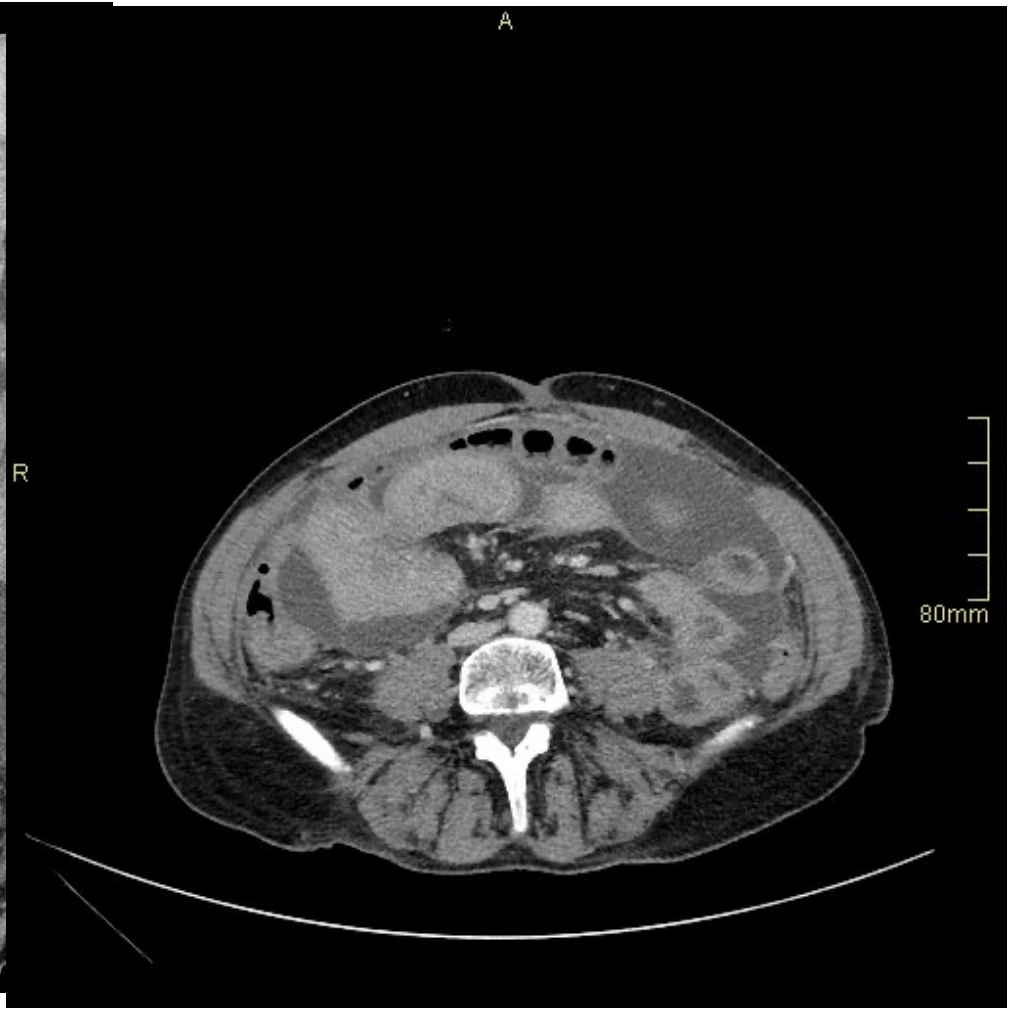
EC –PEL
EBV+ (permitted -)
HIV + most

HHV8+DLBCL
EBV-
HIV+

HHV8-effusion lymphoma
«FO-LBCL» (WHO)
HHV8 neg EBVneg PEBL
(ICC)
Elderly HIV-
Medical cond→ FO


R

R

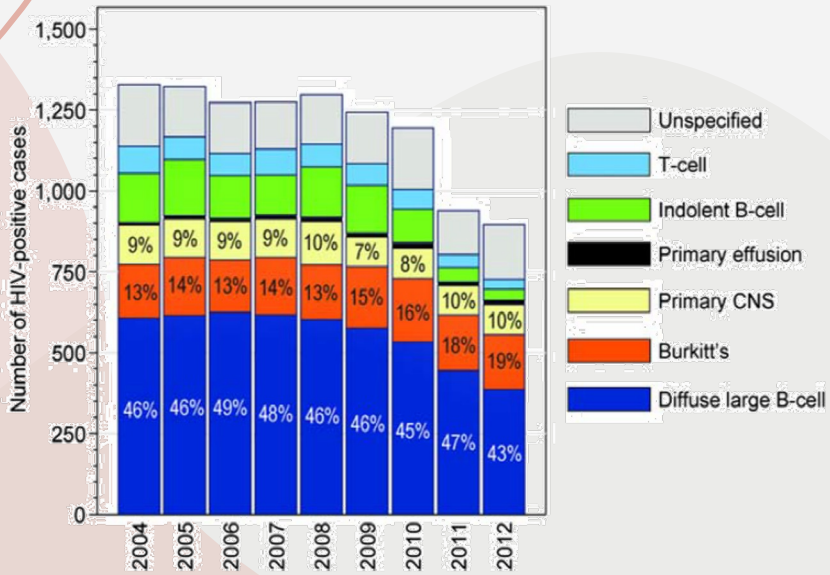

A
R
80mm

DISTRIBUTION OVER TIME

Histotype	1986-1995; London (158 patients)	1996-2005; London (200 patients)	2006-2015; London (257 patients)	1996-2000; CNICS (132 patients)	2001-2005; CNICS (201 patients)	2006-2010; CNICS (143 patients)
BL	3%	10%	20% ↑	7.6%	10.9%	16.8% ↑
DLBCL	63%	59%	37% ↓	43.9%	45.8%	35.7% ↓
HL	4%	11%	26% ↑	15.2%	15.4%	19.6% ↑
PCNSL				14.4%	10.4%	9.8% ↓
PBL	0	2%	6% ↑			
PEL	2%	1%	5% ↑			
Other				18.9%	17.4%	18.2%

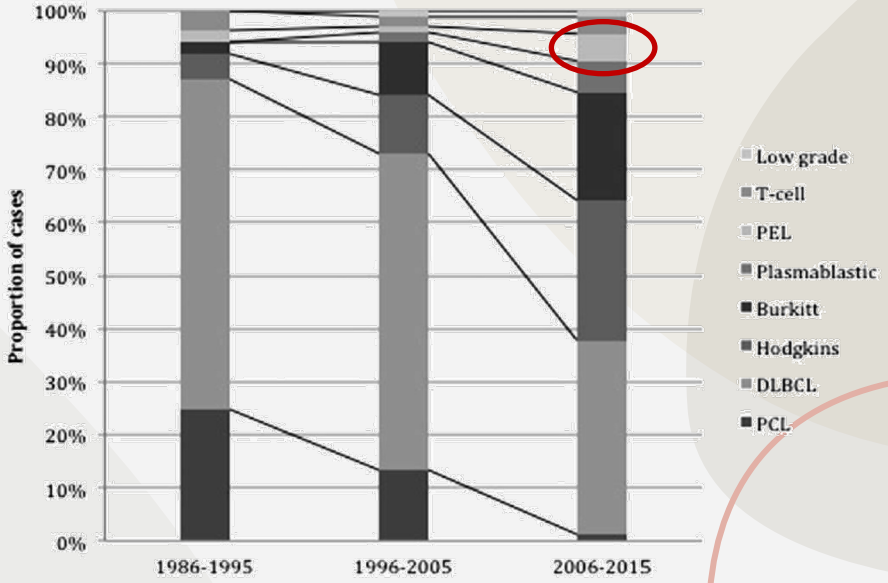
DISTRIBUTION OVER TIME

Human Immunodeficiency Virus-Associated Lymphoma in the Antiretroviral Therapy Era: Analysis of the National Cancer Data Base
Cancer, 2016



359,731 lymphomas between 2004 and 3.4% (10,769) were HIV-positive

Evolution of HIV-Associated Lymphoma Over 3 Decades
J Acquir Immune def Syndr,2016



615 pts; 158 with lymphomain the pre-cART decade (1986–1995), 200 pts in the earlycART era (1996–2005), and 257 patients in the late-cART era (2006–2015).

CLINICAL MANIFESTATIONS

PEL

- neoplastic effusions in body cavities without extracavitary tumor masses, and the most common sites are the pleural (60-90%) , peritoneal (30-60%) and pericardial cavities(till 30%). Typically, only a single cavity is involved.

- *Often concomitant* KSHVdiseases (KS -75%- and KSHV-MCD 33%)

Shortness of breath, abdominal distension,chest pain

- KSHV can also cause immune dysregulation, inducing elevations of huIL-10, huIL-6, and vIL-6, which can result in many of the constitutional and laboratory abnormalities, including fever, cachexia, edema, and anemia

EC-PEL

- Common sites: lymphnodes and GE tract
- Rare: skin presentation

THERAPY

No. of patients	301	51	28	11	8	20	7	6
Year of study	2001-2012	1996-2013	1993-2003	1987-2002	1987-2001	2000-2013	2010-2017	2020
PEL, %	100	67	100	100	0	18	100	67
Solid PEL, %	24	33	0	0	100	1	0	33
Median age, y	55	45	44	41	40	44	NA	38
HIV, %	67	100	100	100	100	100	100	100
ART, %		100	78	NA	20	100	100	100
Median (range) $CD4^+$ T-cell count, cells per μL	NA	204 (90-370)	133 (5-756)		NA*	125 (53-389)	NA	231 (3-403)
EBV, %	50	66	71	NA	NA	73	60	
KS, %	28	49	67	27	25	75	NA	66
MCD, %	4	35	32	NA		30	NA	17
Receiving chemotherapy, %	86	88†	79	73	75	95‡	100	100
Chemotherapy backbone	Various	CHOP-like	CHOP-like	CHOP	CHOP	DA-EPOCH	DA-EPOCH	DA-EPOCHR
CR, %	NA	62 classic, 41 solid	41	42	NA	53	71	50
Median OS, mo	6	10.2	6.2	6	11	22	NA	Data not mature
OS rate, %	NA	43 (classic) and 39 (EC) at 5y	39 at 1y	NA	40 at 5y	47 cancer-specific survival at 3y	NA	67 at 2y
EFS rate, %	NA	71 (classic) and 100% (EC) DFS at 2y	NA	NA	NA	NA	71 3y EFS	NA

Classic and extracavitary primary effusion lymphoma in 51 HIV-infected patients from a single institution

RETROSPECTIVE study

OS:doubled compared with CHOP-like treatment studies in the pre-ART/early ART era where ART was inconsistently or not administered either before or during treatment.

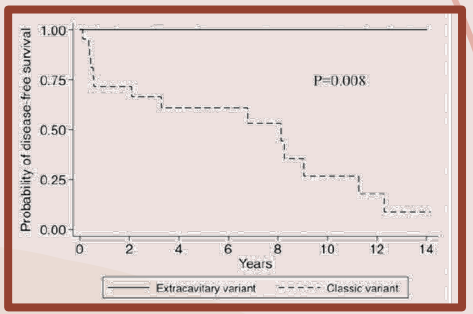
Pts characteristics

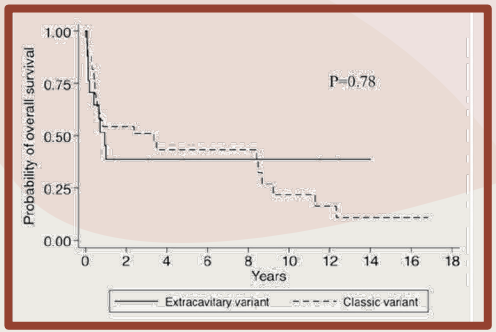
Characteristics	All patients ($n = 51$)	Classic group ($n = 34$)	Extracavitary group ($n = 17$)
Demographic characteristics			
Sex male, *n* (%)	47 (92)	31 (91)	16 (94)
Median age, years (IQR)	45 (39–53)	45 (40–54)	41 (36–48)
HIV characteristics			
Mode of HIV transmission, *n* (%)			
Sexual	45 (88)	30 (88)	15 (88)
IVDU	5 (10)	3 (9)	2 (12)
Unknown	1 (2)	1 (3)	0
Median HIV duration, years (IQR)	8 (1.5–15.7)	4 (1–12)	10 (8–16)
Prior AIDS, *n* (%)	33 (64.7)	24 (70.6)	9 (53)
cART at diagnosis, *n* (%)	35 (68.6)	24 (70.6)	11 (64.7)
Median cART duration, months (IQR)	40 (18–63.4)	30 (12.3–52.6)	62 (49.3–123)
Undetectable plasma HIV-RNA, *n* (%)	25 (49)	16 (47)	9 (53)
CD4 cell count			
Median, $\times 10^9$ L^{-1}, median (IQR)	204 (90–370)	185 (90–343)	207 (103–377)
Nadir, $\times 10^6$ mL^{-1}, median (IQR)	99 (45–180)	99 (56–145)	159 (35–228)
KS, *n* (%)	25 (49)	19 (56)	6 (35.3)
Castleman disease, *n* (%)	18 (35.3)	11 (32.3)	7 (41)
PEL characteristics			
IPI > 2, *n* (%)	34 (67)	25 (80)	9 (53)
PS > 2, *n* (%)	29 (57)	18 (53)	11 (65)
LDH > normal, *n* (%)	26 (52)	16 (48.5)	10 (59)
ICU stay, *n* (%)	14 (29)	10 (32)	4 (23.5)
EBV + PEL, *n* (%)	34 (66.6)	24 (70.6)	10 (59)
CR, *n* (%)	28 (56)	21 (63.6)	7 (41)
Treatment			
Standard chemo, *n* (%)	45 (88.2)	28 (82.3)	17 (100)
With HD-MTX, *n* (%)	32 (62.7)	23 (67.6)	9 (53)
Without HD-MTX, *n* (%)	13 (25.5)	5 (14.7)	8 (47)
Low dose/no chemo, *n* (%)	6 (11.7)	6 (17.6)	0 (0)

5-year OS:43% in the classic group
39% in the extracavitary group

Outcome

CR : 21 pts (62%) in the classic group
7(41%) in the extracavitary variant group



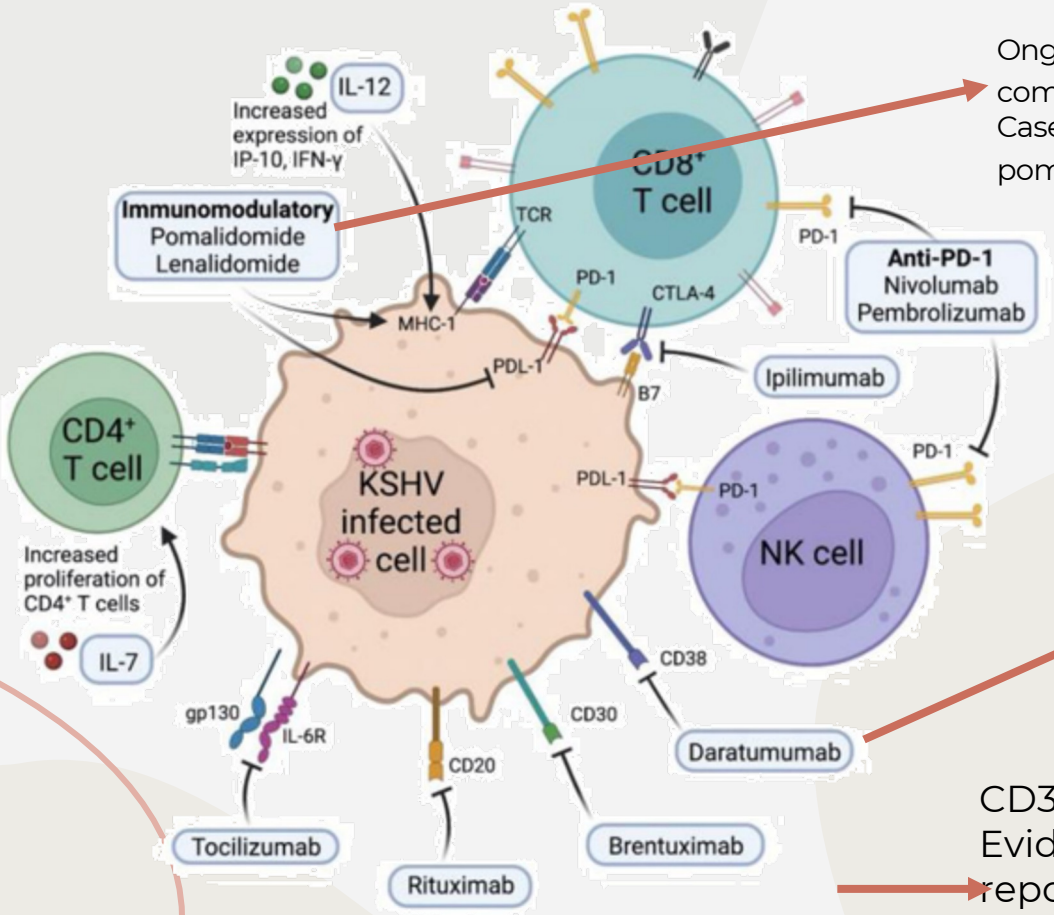


All but two of the 13 patients who relapsed died with a 2-year OS: 8.5%.
median follow-up of 10 years: 34 pts have died
median OS: 10.2 months.

THERAPY

No. of patients	301	51	28	11	8	20	7	6
Year of study	2001-2012	1996-2013	1993-2003	1987-2002	1987-2001	2000-2013	2010-2017	2020
PEL, %	100	67	100	100	0	18	100	67
Solid PEL, %	24	33	0	0	100	1	0	33
Median age, y	55	45	44	41	40	44	NA	38
HIV, %	67	100	100	100	100	100	100	100
ART, %		100	78	NA	20	100	100	100
Median (range) $CD4^+$ T-cell count, cells per μL	NA	204 (90-370)	133 (5-756)		NA*	125 (53-389)	NA	231 (3-403)
EBV, %	50	66	71	NA	NA	73	60	
KS, %	28	49	67	27	25	75	NA	66
MCD, %	4	35	32	NA		30	NA	17
Receiving chemotherapy, %	86	88†	79	73	75	95‡	100	100
Chemotherapy backbone	Various	CHOP-like	CHOP-like	CHOP	CHOP	DA-EPOCH	DA-EPOCH	DA-EPOCHR
CR, %	NA	62 classic, 41 solid	41	42	NA	53	71	50
Median OS, mo	6	10.2	6.2	6	11	22	NA	Data not mature
OS rate, %	NA	43 (classic) and 39 (EC) at 5y	39 at 1y	NA	40 at 5y	47 cancer-specific survival at 3y	NA	67 at 2y
EFS rate, %	NA	71 (classic) and 100% (EC) DFS at 2y	NA	NA	NA	NA	71 3y EFS	NA

IMMUNOTHERAPY FOR KSHV-ASSOCIATED DISEASES



Ongoing study of patients with untreated PEL, lenalidomide is combined with rituximab and dose- adjusted EPOCH ;
Case series of pembrolizumab alone and in combination with pomalidomide demonstrated clinical benefit

pembrolizumab alone and in combination with pomalidomide demonstrated clinical benefit

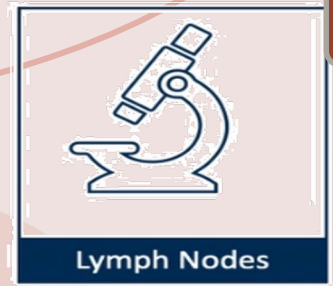
Preclinical studies demonstrate increases in PEL cell killing and NK mediated cytotoxicity

CD30 is expressed in the majority of PEL. Evidence from preclinical studies and case reports that suggest the clinical benefit of bretuximab in PEL

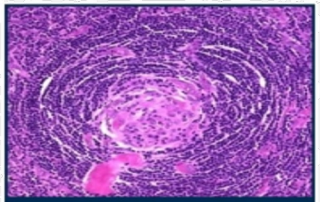
KSHV-MCD

Excisional lymph node biopsy

Excisional lympho node biopsy

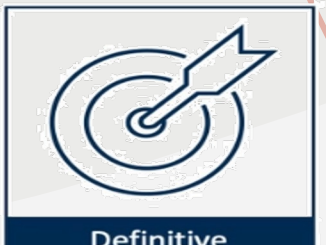


Lymph Nodes



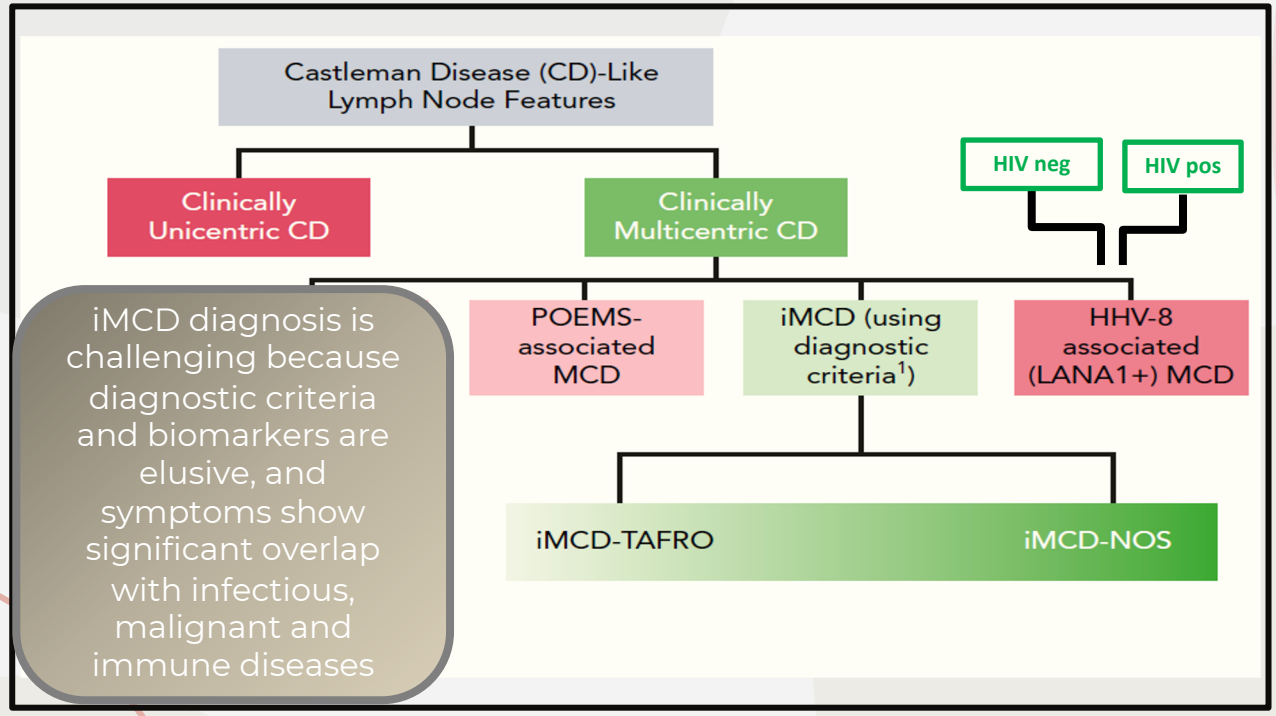
Pathological features suggestive of Castleman Disease

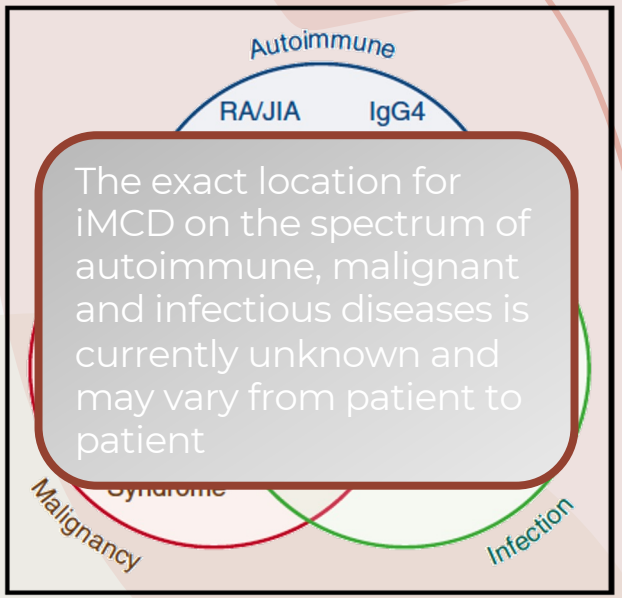
Report: Possible / Likely Castleman Disease



Definitive Diagnosis ? Look for specific markers

HETEROGENEITY of CASTLEMAN DISEASE



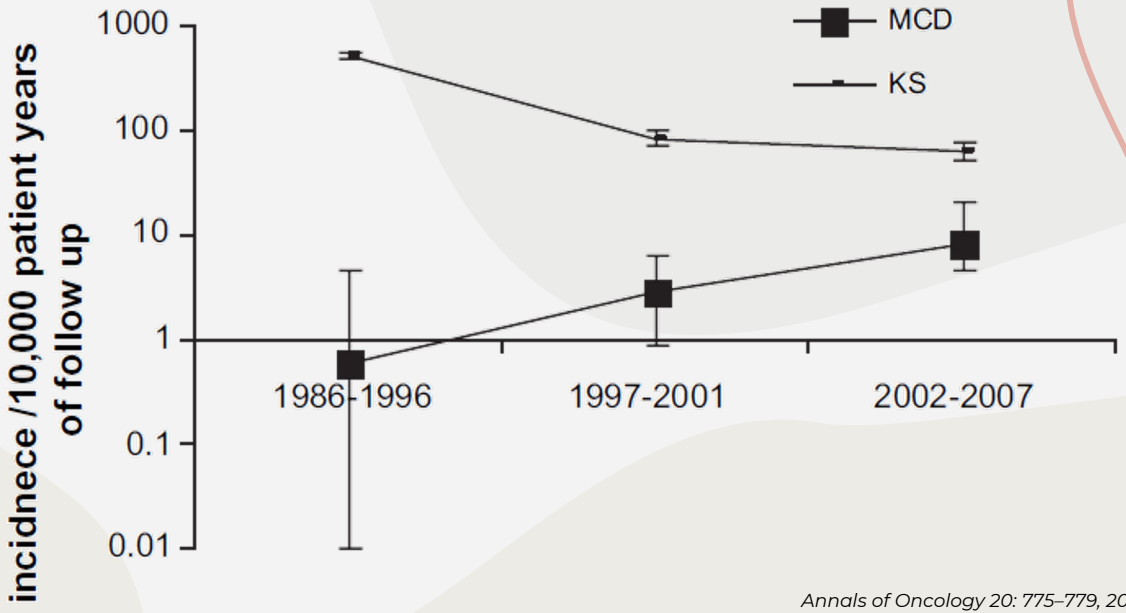


kSHV-MCD EPIDEMIOLOGY

- The estimated incidence of CD is 6500 to 7700 cases/year in the United States, with ~ 1650 cases of MCD
- ITALY: Expected annual incidence: 204 *cases;* Expected prevalence: 414 *cases* KSHV-MCD
- MCD cases are thought to be divided almost evenly betweenKSHV-MCD and iMCD lack of data in Italy

- nadir CD4 count >200/mm3,
- increased age,
- no previous HAART exposure and
- non-Caucasian ethnicity

associated with an increased risk of MCD.



Annals of Oncology 20: 775–779, 2009

CONSENSUS DIAGNOSTIC CRITERIA for iMCD

A patient must fulfil the **major**, **minor,** and **exclusion** criteria

Major criteria

Both features **must be present**

- **Histopathological lymph node features** consistent with the iMCD
  Enlarged lymph nodes (≥1 cm in short-axis diameter) in ≥2 lymph node stations

Minor Criteria:

≥2 of the following 11 features (including ≥1 laboratory condition) must be present

- LABORATORY (6 FEATURES)
- CLINICAL (5 FEATURES)

Exclusion criteria

Each of the following diseases/disorders must be ruled out:

- **Infection-related disorders**
- **Malignant/ lymphoproliferative disorders**
- **Autoimmune diseases**

MINOR CRITERIA for iMCD

≥2 of the following 11 features (including ≥1 laboratory condition) must be present:

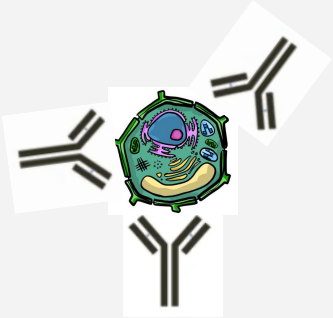
LABORATORY

- ☐ Elevated CRP or ESR
- ☐ Anemia
- ☐ Thrombocytopenia or thrombocytosis
- ☐ Hypoalbuminemia
- ☐ Renal dysfunction or proteinuria
- ☐ Polyclonal hypergammaglobulinemia

CLINICAL

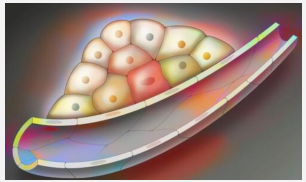
- ☐ Constitutional symptoms such as night sweats, fever, weight loss or fatigue
- ☐ Hepatomegaly and/or splenomegaly
- ☐ Fluid accumulation: oedema, anasarca, ascites or pleural effusion
- ☐ Eruptive cherry hemangiomatosis or violaceous papules
- ☐ Lymphocytic interstitial pneumonitis

PATHOGENESIS iMCD

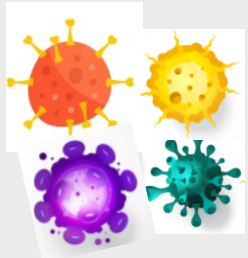


AUTOIMMUNE HYPOTESIS

AUTOINFLAMMATORY HYPOTESIS



NEOPLASTIC HYPOTESIS



PATHOGEN HYPOTESIS

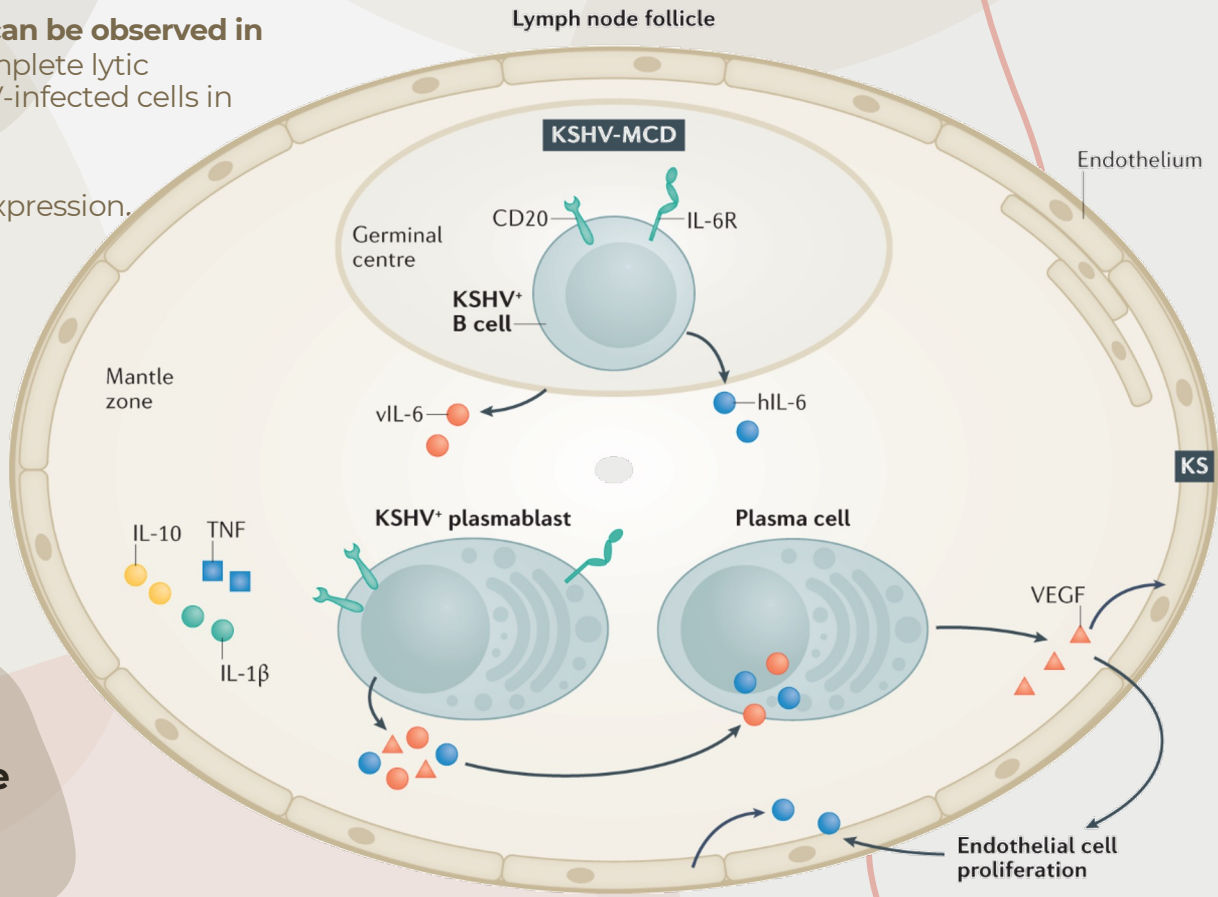
Proinflammatory cytokine(s)

IL-6

PATHOGENESIS

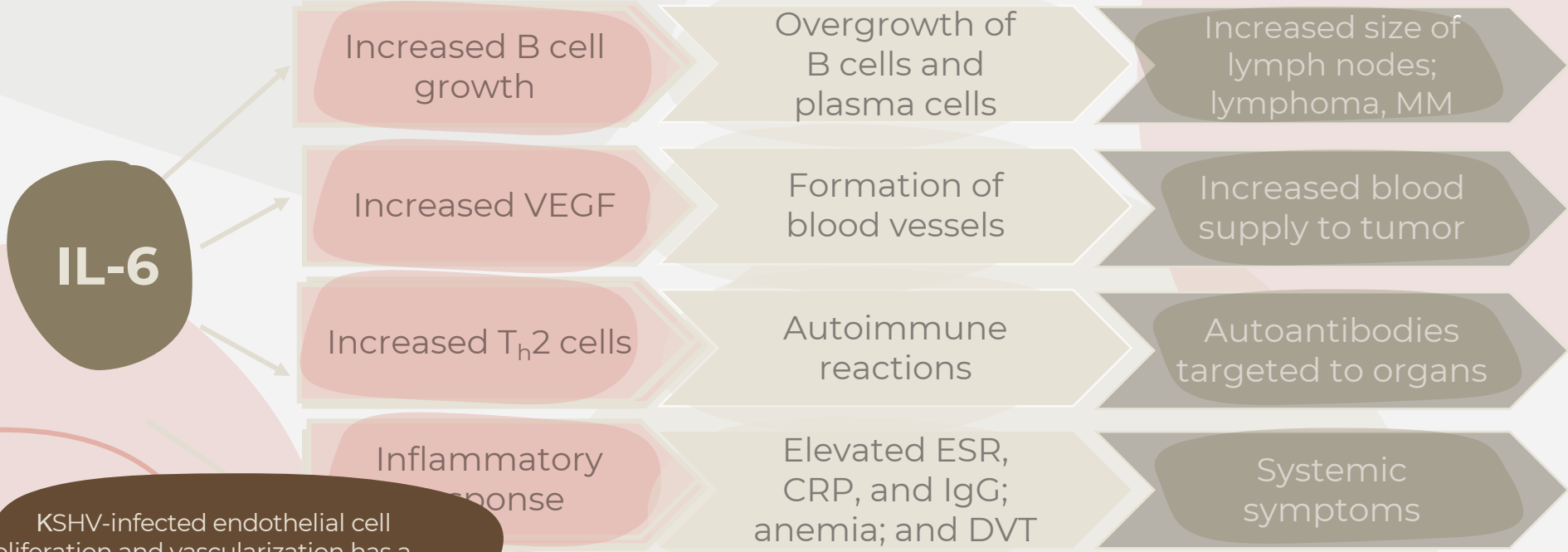
- **Both latent and lytic KSHV viral proteins can be observed in KSHV-MCD lymph nodes** → abortive or complete lytic replication is occurring in some of the KSHV-infected cells in the lymph node
- LANA, but above all SHV viral lytic protein expression.
- Central role of vIL-6, hIL-6, IL-10, IL-1β, TNF
- **CD20**→ expressed in the lymph nodes
- Higher viral load in peripheral blood than KS or PEL

KSHVaMCD: «bandierina» che ci informa che il virus sta iniziando ad avere azione oncogena.
Il patologo non ha trovato ciò che ancora non è emerso



Nat Rev Dis Primers. ; 7(1): 84.

PATHOGENESIS, THE ROLE OF IL-6



KSHV-infected endothelial cell proliferation and vascularization has a central role in both KSHV-MCD and Kaposi sarcoma andcytokine expression seems to drive disease progression.

cyte sedimentation rate; IgG, immunoglobulin G; IL-6, interleukin 6; iMCD, idiopathic multicentric Castleman disease; T_h2, T helper type 2; VEGF, vascular endothelial growth factor.

1. Dispenzieri A *et al. Blood* 2020; 135 (16): 1353–1364. 2. van Rhee F *et al. Clin Adv Hematol Oncol* 2010; 8 (7): 486–498.

Cytokine storm. Clinical presentation

Symptoms may be due
- directly to **cytokine induced tissue damage**

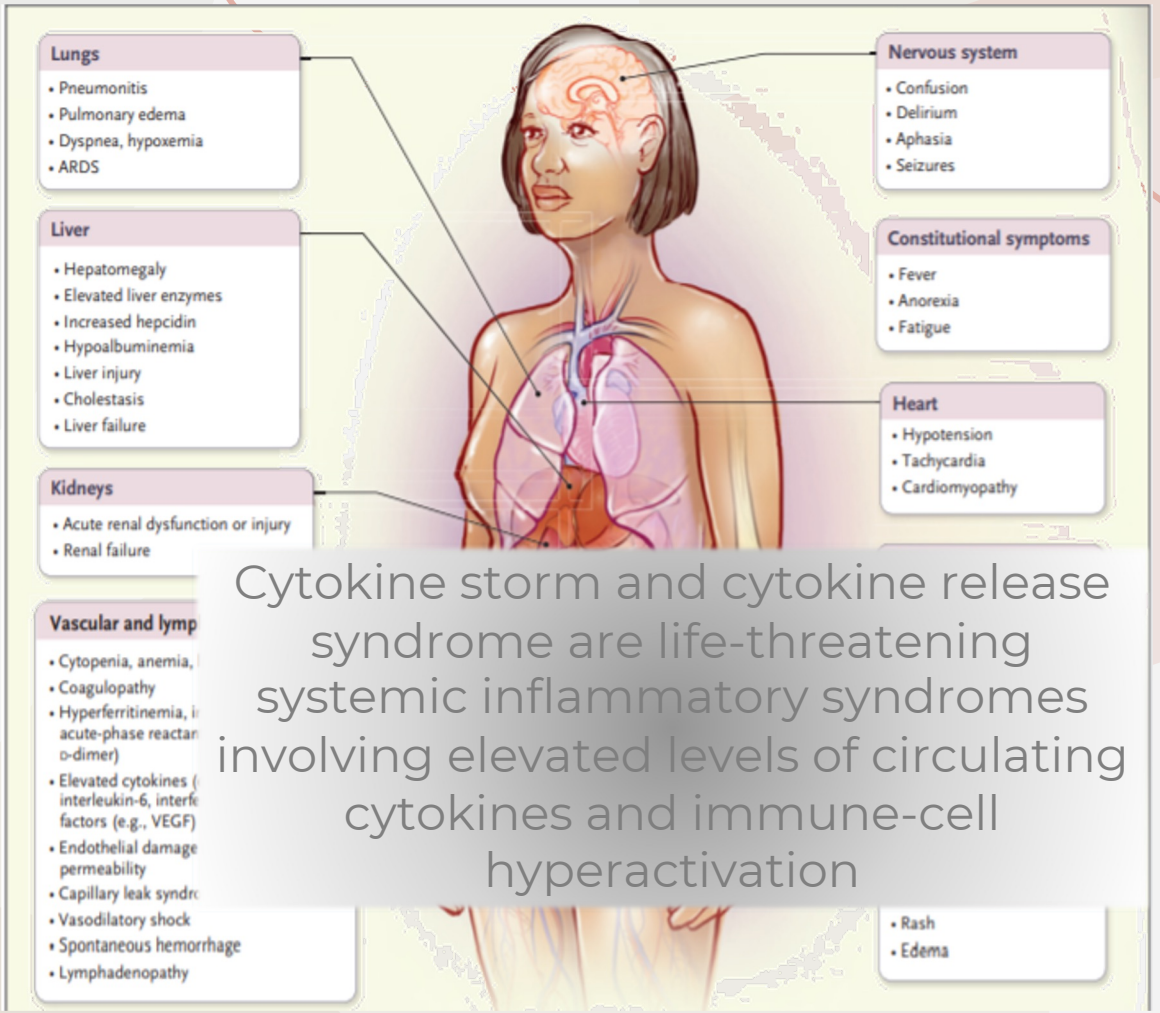
or
- may result from **immune cell–mediated responses**.

HLH

Progressione to **disseminated intravascular coagulation**

vascular occlusion
catastrophich emorrhages
dyspnea
hypoxemia
hypotension

takotsubo-like cardiomyopathy
vasodilatory shock, and death.

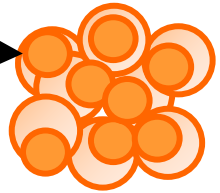


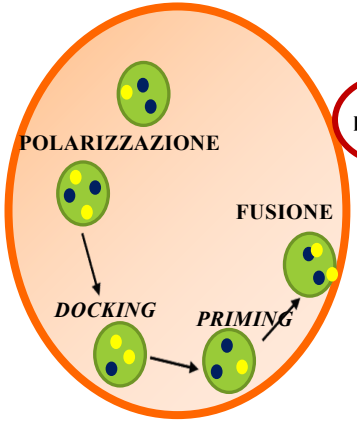
Cytokine storm and cytokine release syndrome are life-threatening systemic inflammatory syndromes involving elevated levels of circulating cytokines and immune-cell hyperactivation

RISPOSTA IMMUNITARIA NORMALE

ATTIVAZIONE ED ESPANSIONE CTL E NK

TRIGGER





perforina

***KILLING* DEL TARGET**

SPEGNIMENTO RISPOSTA

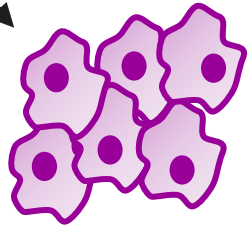
CITOCHINE (INF-gamma)

Perforina (-)

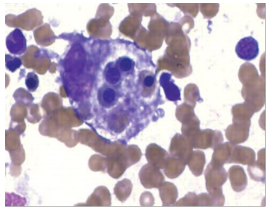
(-)

FLOGOSI SISTEMICA e DANNO TISSUTALE (EMOFAGOCITOSI)

ATTIVAZIONE MACROFAGI



CITOCHINE



***STORM* CITOCHINICO**

HLH:

- **NO *KILLING***
- **NO *FEEDBACK NEGATIVO***
- **NO SPEGNIMENTO RISPOSTA**

THERAPY

Prospective Study of Rituximab in Chemotherapy- Dependent HIV-ass-MCD: ANRS 117 CastlemaB Trial

AIM: To evaluate the efficacy of **four weekly rituximab infusions (375 mg/m2)** after discontinuation of chemotherapy in HIV-associated MCD,
WHO: 24 pts
Prospective open-label trial.

Patient No.	Delay From MCD Diagnosis (months)	Associated KS	No. of Previous Different Chemotherapy Regimens	Splenectomy	MCD Treatment at Entry	Outcome at Day 365
1	7	No	1	No	Vinblastine	Alive, SR
2	20	No	2	No	Vinblastine	Alive, SR
3	8	No	2	No	Etoposide	Alive, SR
4	76	Yes	5	No	Etoposide	Death, day 15
5	7	Yes	5	Yes	Etoposide	Alive, SR
6	7	No	3	No	Etoposide	Failure, day 23
7	31	Yes	2	No	Liposomal doxorubicin	Alive, SR
8	42	Yes	5	Yes	Etoposide	Relapse, day 271
9	8	Yes	2	Yes	Etoposide	Alive, SR
10	4	No	4	No	Etoposide	Alive, SR
11	107	Yes	4	Yes	Etoposide	Alive, SR
12	52	Yes	4	Yes	Etoposide	Death, day 112
13	29	Yes	5	Yes	Liposomal doxorubicin	Alive, SR
14	5	No	1	No	Vinblastine	Alive, SR
15	84	No	5	Yes	Etoposide	Relapse, day 299
16	5	No	3	No	Etoposide	Alive, SR
17	109	No	3	Yes	Etoposide	Alive, SR
18	3	No	2	No	Etoposide	Alive, SR
19	9	No	1	Yes	Etoposide	Relapse, day 76
20	142	Yes	2	Yes	Vinblastine	Alive, SR
21	7	No	2	No	Etoposide	Alive, SR
22	22	Yes	1	No	Etoposide	Alive, SR
23	73	Yes	5	Yes	Etoposide	Relapse, day 173
24	26	Yes	2	No	Etoposide	Alive, SR

In another cohort study of 61 patients with HIV1MCD

OS of 46 pts treated with rituximab-based treatment

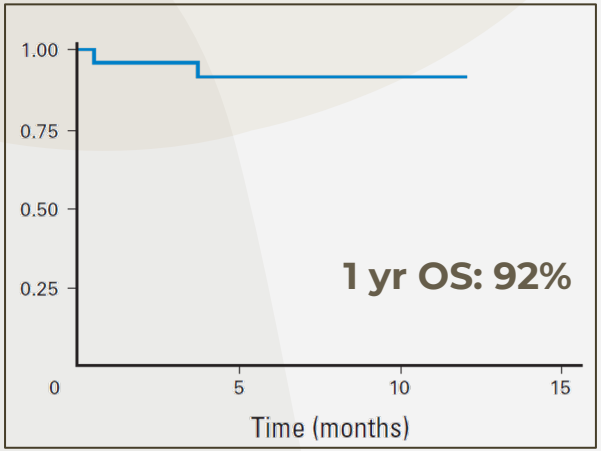
90% at 5 yrs vrs 33% before the introduction of rituximab

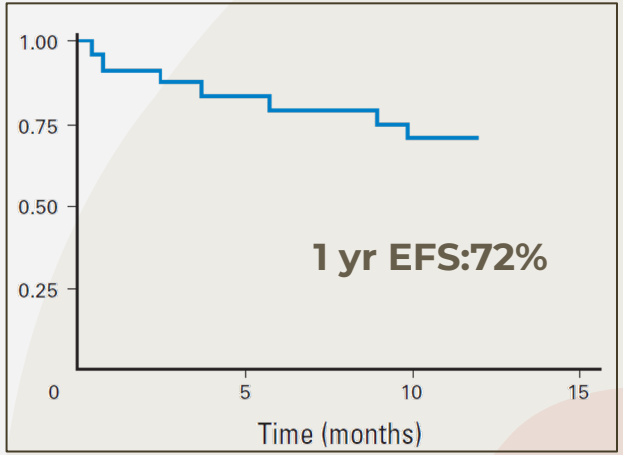
Annals of Oncology 20: 775–779, 2009

THERAPY

Prospective Study of Rituximab in Chemotherapy- Dependent HIV-ass-MCD: ANRS 117 CastlemaB Trial

D+60: 22 pts alive and free of MCD-related symptoms after discontinuation of chemotherapy → SR rate of 92%





All the pts were in cART

WARNING 1 relapse.

WARNING 2 Exacerbation of KS lesions was noted in eight of 12 patients who had a previous history of KS

- Treatment modified according the severity of the disease
- in the rituximab studies, worsening KS was observed in 35% to 67% of pts with baseline KS. v

Annals of Oncology 20: 775–779, 2009

THERAPY

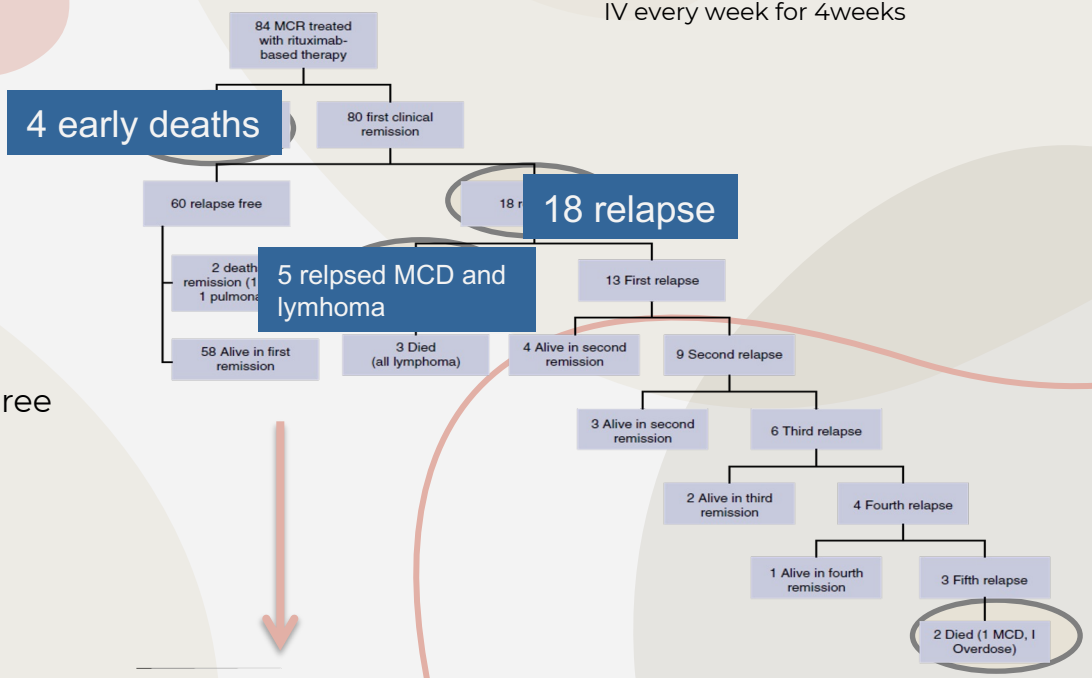
WARNING 1 relapse.

KSHV MCD

- PS 0-1, No end organ damage → Rituximab
- PS ≥ 2, end organ damage → Etoposide and Rituximab

rituximab, 375mg/m2;
etoposide, 100mg/m2 both administered IV every week for 4weeks

Relapse of HHV8-positive multicentric Castleman disease following rituximab-based therapy in HIV-positive patients



Follow up:

- clinical examination and blood tests
- plasma HHV8 viral

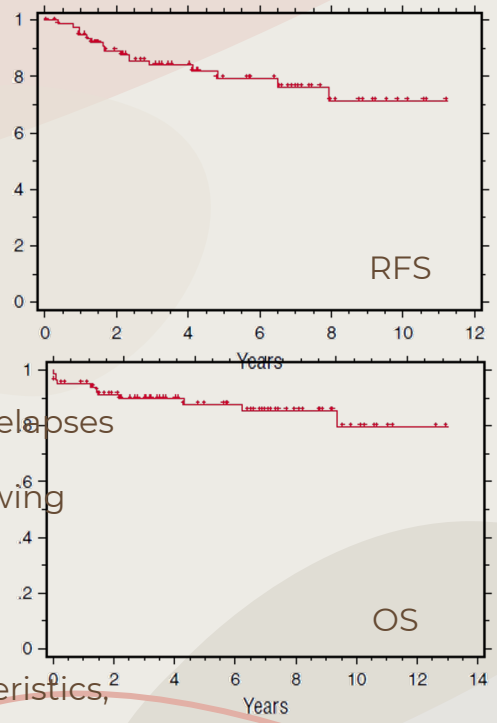
} Every three mnths

- Radiological examinations for relapse are based on symptoms and laboratory findings
- relapses are confirmed by repeat biopsy and histological examination

BLOOD, 13 APRIL 2017 x VOLUME 129, NUMBER 15

THERAPY

Relapse of HHV8-positive multicentric Castleman disease following rituximab-based therapy in HIV-positive patients



- With a median follow-up of 6.9 years, **5-year OS for the entire cohort is 88%**
- Four patients died of progressive refractory MCD **before completing** the 4-week course oF treatment and only 1 other patient died of MCD following 5 relapses
- 5 patients developed HHV8-associated **lymphoma**. The relapse rate at 5 years following first remission is 18%, and all achieved a second remission
- the **median time to first relapse** is 30 months; all pts with detectable viremia
- **The risk of relapse** of HIV1MCD was not significantly influenced by patient characteristics, use of cART, plasma HIV viral load, or lymphocyte subset counts
- Retreatment of patients with **histologically confirmed** HIV1MCD relapse with rituximab-based therapy achieved second remissions

BLOOD, 13 APRIL 2017 x VOLUME 129, NUMBER 15

THERAPY

Rituximab plus liposomal doxorubicin in HIV-infected patients with KSHV-aMCD

RESPONSE

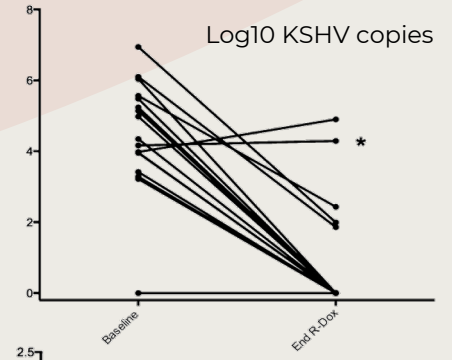
NCI-KSHV-MCD Response Criteria

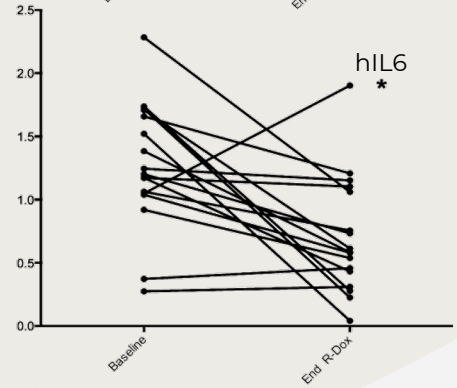
Response category	Response	n(%)
Clinical response	Complete response	15 (88)
	Symptom-free disease	1 (6)
	Progressive disease§	1 (6)
	Major clinical response*	16 (94)
Biochemical response	Complete response	13 (76)
	Partial response	2 (12)
	Major biochemical response†	15 (88)
	Stable disease	1 (6)
	Progressive disease§	1 (6)
Radiographic response	Complete response	
	Nodes	13 (76)
	Spleen	8 (47)
	Partial response	
	Nodes	4 (24)
	Spleen	7 (41)
	Major radiographic response‡	15 (88)
	Stable disease (spleen)	1 (6)
	Progressive disease§ (spleen)	1 (6)
Overall response	Complete response	5 (29)
	Partial response	9 (53)
	Stable disease	2 (12)
	Progressive disease§	1 (6)
KSHV-MCD Clinical Benefic Criteria	Complete response	14 (82)
	Partial response	1 (6)
	Stable disease	1 (6)
	Progressive disease	1 (6)

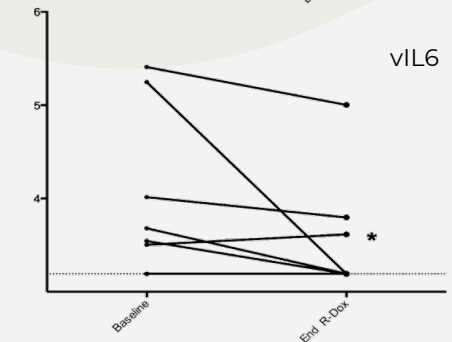
- **recurrent symptomatic KSHV-MCD** requiring therapy developed in 4 patients. Improved predictive factors for recurrence are needed
- The roles of **consolidation or maintenance therapy** as well as optimal management of patients with residual radiographic findings or elevated KSHV viral load remain areas of clinical uncertainty

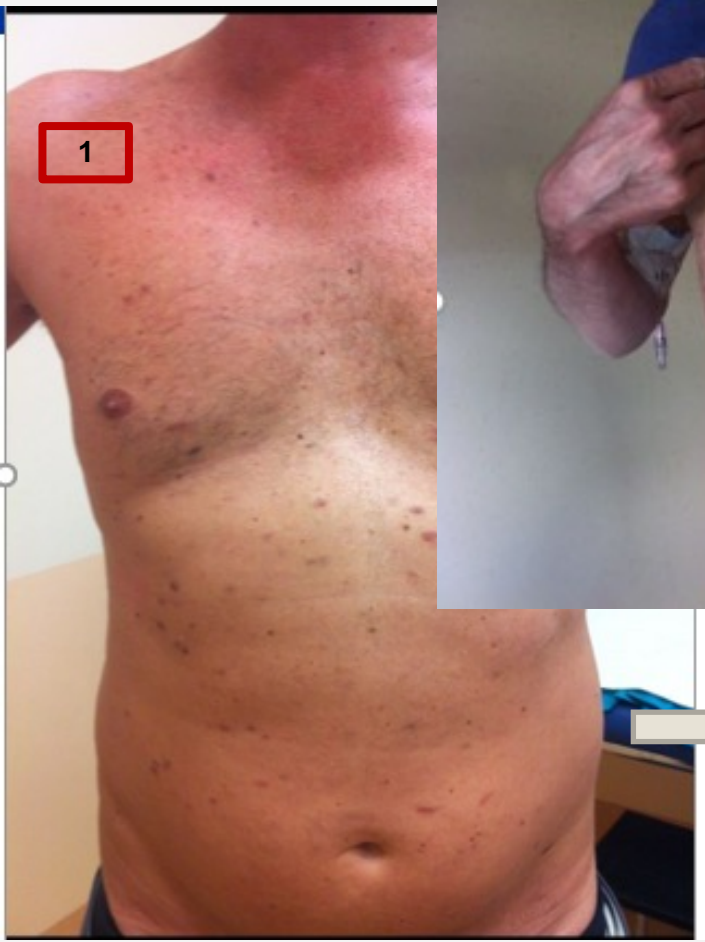
Supplemental Table 2: Kaposi sarcoma (KS) response in 12 patients with baseline KS or History of KS

Patient	Previous cutaneous KS	Baseline cutaneous KS	Baseline lymph node KS	Response end R-Dox (# cycles)	Response criteria	Consolidation (months)	Response long-term follow-up	Months follow-up	Response criteria
1 (BK)	N	T_1	Y	PR (5)	A	LD (14)	PR *	60	A
2 (ML)	N	T_1	Y	CI (6)	C	None	CW	3.5	C
3 (TK)	N	T_0	Y	CI (5)	C	IFN (10)	PR/cCR‡	85	A
4 (CC)	N	T_0	N	CI (7)	C	IFN (1)	CW/PR‡	55	A
3 (RP)	N	T_1	Y	SD (5)	A	AZT/VGC (4)	PD§	42	A
6 (DW)	N	T_0	N	PR (3)	A	IFN (4)	SD	6	A
7 (GB)	N	N	Y	NED (3)	-	IFN (10)	NED	91	A
8 (MC)	Y	N	Y	NED (3)	-	IFN (10)	NED	91	A
9 (MA)	N	N	Y	PD/PR‖ (3)	A	None	Lost to follow up	5	-
10 (KW)	N	N	Y	NED (5)	-	IFN (0.5)	NED	36	A
11 (JG)	Y	N	N	NED (3)	-	IFN (10)	NED	69	A
12 (RD)	Y	N	N	NED (4)	-	AZT/VGC (7)	NED	57	A





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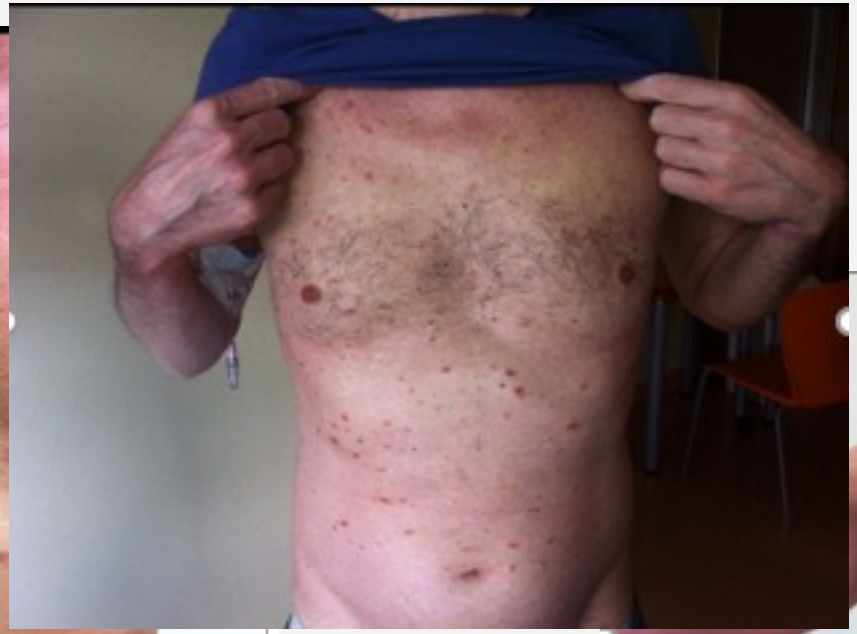

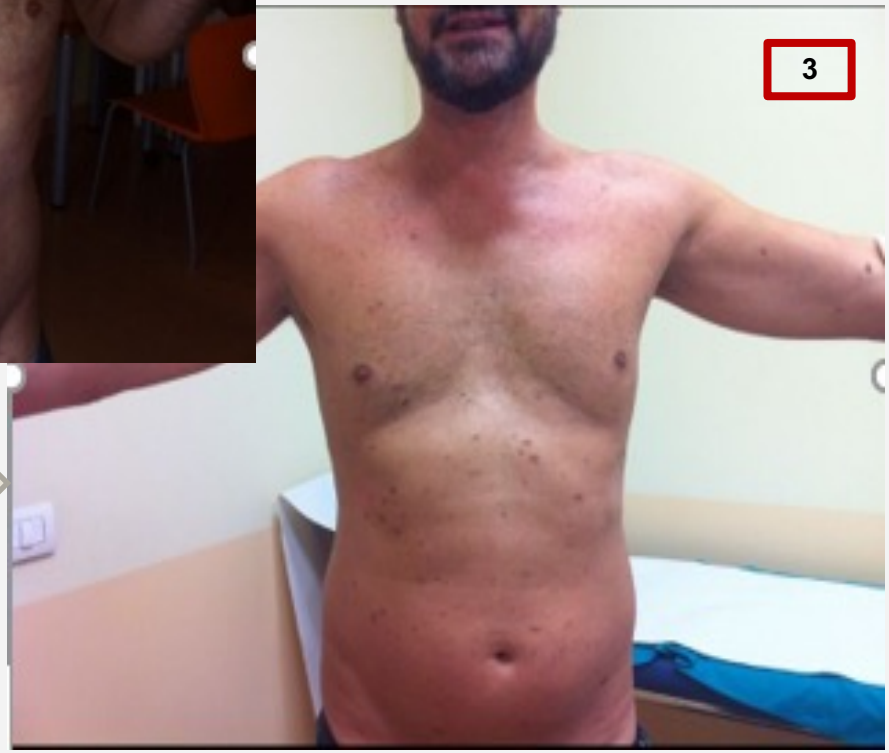
3

KSHVaMCD, THERAPY

	cART	RITUXIMAB	ETOPOSIDE	L-DOXOR.
HIVaMCD ECOG 0-1 Cut KS Y/N	✓	✓	×	×
HIVaMCD ECOG>2; EOD Cut KS Y/N	✓	✓	✓	?
HIVaMCD ECOG 0-1 Visc KS Y	✓	✓	?	✓
HIVaMCD ECOG ≥2 Visc KS Y	✓	✓	✓	Multidisciplinary approach

- Att.ne! Un numero non indifferente di pazienti **muore durante le prime fasi del trattamento**!
- Att.ne!! A monitoraggio delle lesioni cutanee!
- Non dimenticarsi delle recidive anche dopo anni!
- Manteniamo monitoraggio per possibilità di avere linfomi HHV8 relati!

KSHV INFLAMMATORY CYTOKINE SYNDROME (KICS)

First described 2010

DEFINITION:

- clinical symptoms and systemic inflammation, but **without KSHV-MCD**
- High KSHV viremia and levels of hIL-6, vIL-6, and IL-10 comparable to those seen in active KSHVMCD, significantly elevated compared with controls with KS only
- Mortality is high despite therapies directed at KSHV replication (including valganciclovir) or at KSHV-related tumors (including liposomal doxorubicin).

1. Clinical manifestations	
a. Symptoms	b. Laboratory abnormalities
Fever	Anemia
Fatigue	Thrombocytopenia
Edema	Hypoalbuminemia
Cachexia	Hyponatremia
Respiratory symptoms	c. Radiographic abnormalities
Gastrointestinal disturbance	Lymphadenopathy
Athralgia and myalgia	Splenomegaly
Altered mental state	Hepatomegaly
Neuropathy with or without pain	Body cavity effusions
2. Evidence of systemic inflammation	
Elevated C-reactive protein (≥3 g/dL)	
3. Evidence of KSHV viral activity	
Elevated KSHV viral load in plasma (≥1000 copies/mL) or peripheral blood mononuclear cells (≥100 copies/10^6 cells)	
4. No evidence of KSHV-associated multicentric Castleman disease	
Exclusion of MCD requires histopathologic assessment of lymphadenopathy if present.	

definition of KICS:

presence of at least **2 clinical manifestations drawn from at least 2 categories** (1a, b, and c), **+ each of the criteria in 2, 3, and 4.**

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KSHV INFLAMMATORY CYTOKINE SYNDROME (KICS)

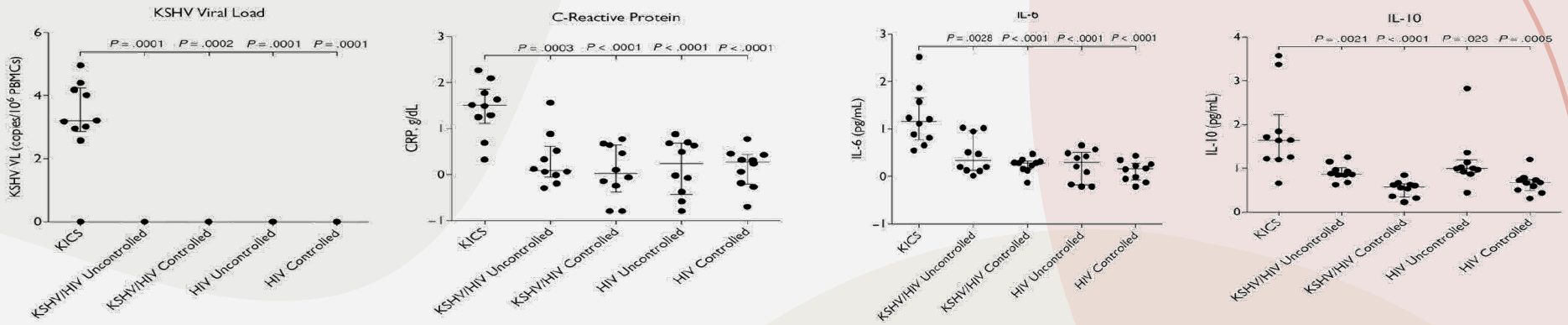
		KSHV and HIV Coinfected Subjects		HIV Infected Subjects	
	KICS Subjects (10)	HIV Uncontrolled (10)	HIV Controlled (10)	HIV Uncontrolled (10)	HIV Controlled (10)
Male sex	10 (100%)	9 (90%)	9 (90%)	8 (80%)	9 (90%)
Age (years)	36 (22–60)	38 (29–50)	46 (34–61)	37 (24–51)	37 (29–51)
Receiving ART	8 (80%)	0	10 (100%)	0	10 (100%)
HIV VL (copies/mL)	72 (<50–74 375)	61 600 (12 100–1 190 000)	<50 (<50–<50)	35 686 (1425–500 000)	<50 (<50–459)
CD4 (cells/μL)	88 (7–1308)	324 (75–568)	568 (261–972)	375 (12–860)	307 (100–577)

CRITICALLY ILL PTS

			KSHV and HIV Coinfected Subjects				HIV Infected Subjects			
	KICS Subjects (10)		HIV Uncontrolled (10)		HIV Controlled (10)		HIV Uncontrolled (10)		HIV Controlled (10)	
	Abnormal (N, %)	Median, Range	Abnormal (N, %)	Median, Range	Abnormal (N, %)	Median, Range	Abnormal (N, %)	Median, Range	Abnormal (N, %)	Median, Range
KSHV VL (copies/10^6 PBMCs)	NA	1569 (0–90 909)[a]	NA	0 (0–1) *P* = .0001[b]	NA	0 (0–1) *P* = .0002[b]	NA	0 (0–1) *P* = .0001[b]	NA	0 (0–1) *P* = .0001[b]
C-reactive protein (g/dL)	10 (100%)	37.8 (4.9–185.0)	3 (30%)	1.2 (0.5–36.3) *P* = .0003[b]	3 (30%)	1.1 (0.16–5.9) *P* < .0001[b]	5 (50%)	2.0 (0.16–7.6) *P* < .0001[b]	1 (10%)	1.9 (0.2–5.9) *P* < .0001[b]
Hemoglobin (g/dL)	10 (100%)	9.0 (6.5–10.2)	2 (20%)	14.1 (9.5–15.4) *P* = .0001[b]	3 (30%)	14.3 (9.5–15.6) *P* = .0001[b]	6 (60%)	13.3 (7.4–16.1) *P* = .0009[b]	4 (40%)	14.1 (11.1–15.6) *P* < .0001[b]
White Cell Count	4 (40%)	5.2 (2.5–13.9)	3 (30%)	5.0 (2.5–7.8) *P* = .8[b]	4 (40%)	5.2 (3.5–8.9) *P* = .91[b]	4 (40%)	5.7 (1.7–6.6) *P* = .48[b]	2 (20%)	5.0 (2.6–8.0) *P* = .85[b]
Platelet Count	6 (60%)	138 (27–371)	0	204 (161–286) *P* = .22[b]	1 (10%)	211 (156–253) *P* = .29[b]	3 (30%)	194 (47–314) *P* = .74[b]	1 (10%)	244 (154–291) *P* = .15[b]
Albumin	10 (100%)	2.4 (1.6–3.1)	4 (40%)	3.8 (2.5–4.1) *P* = .0002[b]	3 (30%)	3.9 (3.3–4.4) *P* < .0001[b]	4 (40%)	3.7 (2.2–4.2) *P* = .0002[b]	0	4.0 (3.7–4.3) *P* < .0001[b]
Sodium	1 (10%)	136 (126–143)	0	138 (135–141) *P* = .58[b]	1 (10%)	138 (133–140) *P* = .34[b]	0	139 (135–144) *P* = .29[b]	0	139 (135–140) *P* = .42[b]

KSHV INFLAMMATORY CYTOKINE SYNDROME (KICS)

Systemic inflammation, KSHV activation, (IL)-6 and IL-10 elevation in patients with KIC compared with controls



Other typical characteristics (to guide the clinician):

- HIV viremia (high)
- advanced CD4 lymphocytopenia
- the widespread adenopathy and splenomegaly that characterize KSHV-MCD are rare

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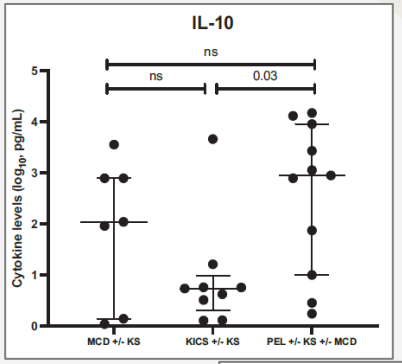
Characteristics of patients admitted to the ICU with Kaposi sarcoma herpesvirus-associated diseases

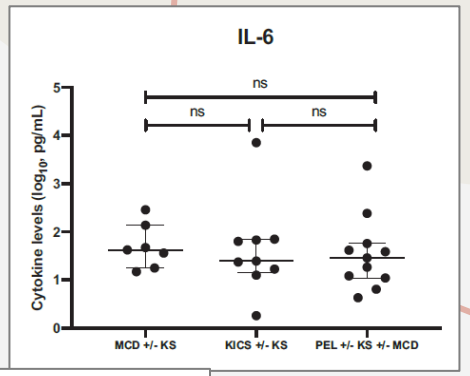
Retrospective study

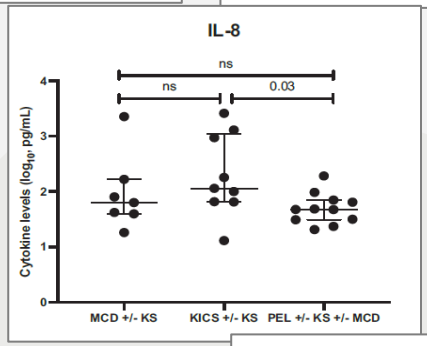
WHO: Forty-seven patients with KADs admitted to the ICU at the NIH Clinical Center between 2010 and 2021

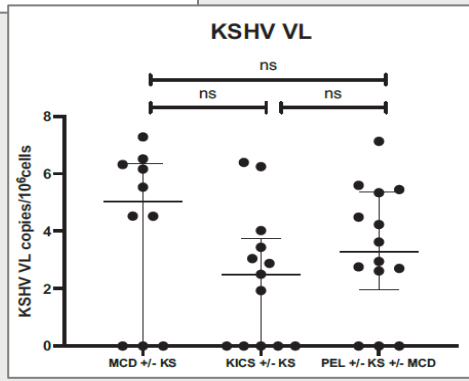
HOW: evaluate the pts at ICU entry and ICU dishcharge/death

	All patients	Alive at 60 days	Died within 60 days
Reasons for ICU admission [*n* (%)]			
Respiratory failure	***26 (55)***	***17 (52)***	***9 (64)***
Alone	9 (19)	7 (21)	2 (14)
+ Hypotension	8 (17)	3 (9)	5 (36)
+ Fever	2 (4)	2 (6)	0 (0)
+ Cardiac condition	1 (2)	1 (3)	0 (0)
+ Altered mental status (AMS)	2 (4)	1 (3)	1 (7)
+ Fever and AMS	3 (6)	3 (9)	0 (0)
+ Fever, hypotension, and AMS	1 (2)	0 (0)	1 (7)
Hypotension	***10 (21)***	***6 (18)***	***4 (29)***
Alone	5 (11)	2 (6)	3 (21)
+ Fever	2 (4)	1 (3)	1 (7)
+ Cardiac condition	1 (2)	1 (3)	0 (0)
+ Hemorrhage	2 (4)	2 (6)	0 (0)
Cardiac condition	***4 (9)***	***4 (12)***	***0 (0)***
Alone	2 (4)	2 (6)	0 (0)
+ Fever	1 (2)	1 (3)	0 (0)
+ Fever and AMS	1 (2)	1 (3)	0 (0)
ICU interventions [*n* (%)]			
Intubation	16 (34)	7 (21)	9 (64)
CRRT/dialysis/CVVH	13 (28)	8 (24)	5 (36)
Vasopressors	24 (51)	14 (42)	10 (71)
>1 intervention as above	19 (40)	9 (27)	10 (71)
ICU chemotherapy/KAD therapy	20 (43)	13 (39)	7 (50)







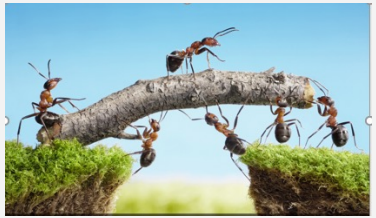



SOLO TU
MI CAPISCI
EH?
DON


CAPIRSI È PER POCHI
COURTESY OF TRUSTA.DON LONDON, UK

CYTOKINE STORM RELATED SIGNS AND SYMPTOMS/ CRITICALLY ILL PATIENTS

Though none of the cytokine levels were of prognostic value, **the measurement of these cytokines in combination with KSHV viral load levels** may aid critical care and infectious disease teams in **identifying KAD as a potential cause of multiorgan dysfunction** in PWH , especially **when patients present with a sepsis-like clinical picture but no identifiable source of infection**



- INFETTIVOLOGO
- PATOLOGO
- INTENSIVISTA
- CHIRURGO
- INTERNISTA

WORK UP DIAGNOSTICO RAPIDO MA COMPLETO!!

High viral load of KSHV/high level of cyotkines and inflammatory markers +/- HIV+

NO LPD

KICS

Siltuximab/tocilizumab? +
Etoposide? +
Rituximab?

SI LPD

PEL

KICS/CRS/HLH PEL ASSOCIATED

DA-EPOCH (R???)

KSHV aMCD

HLH syndrome + KSHVa MCD

R+ ETOPOSIDE, +L-DOXO

TAKE HOME MESSAGE

- LE PATOLOGIE LINFOPROLIFERATIVE HHV8 RELATE rappresentano un gruppo di **patologie rare MA estremamente complesse**, e spesso sono un «continuum» ;

- Il **trattamento** di molte di queste patologie è a tutt'oggi «**aperto»**, tuttavia la maggiore conoscenza della loro patogenesi ci può aiutare ad indirizzare i nostri sforzi terapeutici;

- L'approccio vincente è SICURAMENTE quello **multidisciplinare**. Da soli non bastiamo! E' pertanto indispensabile educare gli altri specialisti e /o internisti alla loro conoscenza perché esse spesso degenerano in situazioni «life-threatening»

- Forse è giunto il momento di abolire la definizione di «linfomi AIDS definenti e di sostituirla con «neoplasie associate ad infezione dal virus dell'HIV»

luisa.verga@irccs-sangerardo.it

J. Pollock In my Head II

THANKS TO

I miei colleghi ematologi, specializzandi compresi

Il dr Rindone, la dr Rossi, la dr Sabbatini e la dr Columpsi

I colleghi della FIL per questa opportunità

Il prof Pagni, il dr L'Imperio

Un particolare ringraziamento al Prof Carbone per il tempo dedicatomi

Tutti i pazienti, quelli che ci sono ancora e quelli che sono nel cuore