8th POSTGRADUATE
Lymphoma
Conference

Signaling pathways and immune evasion mechanisms in HL

Stefano Pileri

Bologna University and European Institute of Oncology (Milan)

Naples,
March 21-22, 2024

Grand Hotel Santa Lucia

President:
P.L. Zinzani

Disclosures of STEFANO PILERI

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Lilly					+	+	
BeiGene					+		
Stemline					+	+	
Roche					+		
Takeda					+		
Diatech						+	

blood

American Society of Hematology
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Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee

Leukemia

www.nature.com/leu

REVIEW ARTICLE OPEN

Check for updates

LYMPHOMA

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

Hodgkin lymphoma		
WHO – 4th Ed.	**WHO – 5th Ed.**	**ICC**
Classic Hodgkin lymphoma	Classic Hodgkin lymphoma (subtypes maintained as in 4th WHO edition)	Classic Hodgkin lymphoma (subtypes maintained as in 4th WHO edition)
Nodular lymphocyte predominant Hodgkin lymphoma	Nodular lymphocyte predominant Hodgkin lymphoma	Nodular lymphocyte predominant B-cell lymphoma (see DLBCL)

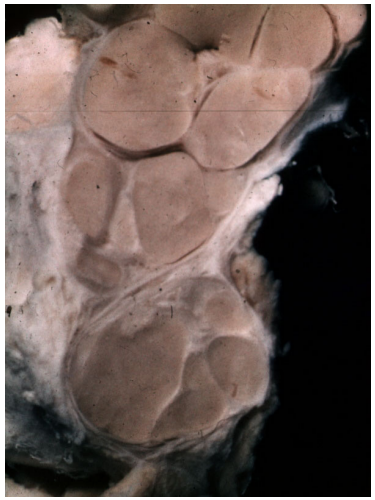
WHO-HAEM5 continues to list **nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)** under the family of Hodgkin lymphoma; the existing terminology of NLPHL (Hodgkin lymphoma) is maintained so as not to interfere with ongoing clinical trials. However, NLPHL may be more accurately called "nodular lymphocyte predominant B-cell lymphoma" since the neoplastic cells have a functional B-cell program, and therefore this term is now considered acceptable in preparation of future definitive adoption of the new nomenclature. An important issue in NLPHL is the recognition of the different growth patterns [176] overlapping with T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) at the extreme end (Table 6) [177]. These patterns occur across all age groups. Some variant patterns (patterns C, D and E) have been associated with more aggressive clinical behaviour in retrospective analyses [177–179] and may thus reflect the natural development and progression of the tumour [180, 181]. In some cases, a clear distinction between NLPHL Pattern E and THRLBCL may not be possible since both diseases present with advanced clinical stage. Distinction is especially difficult on small biopsies, which may not be representative.

Classical Hodgkin lymphoma

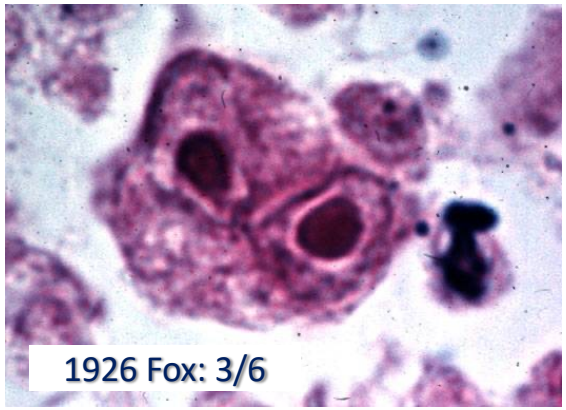
Lancet 2021; 398: 1518–27

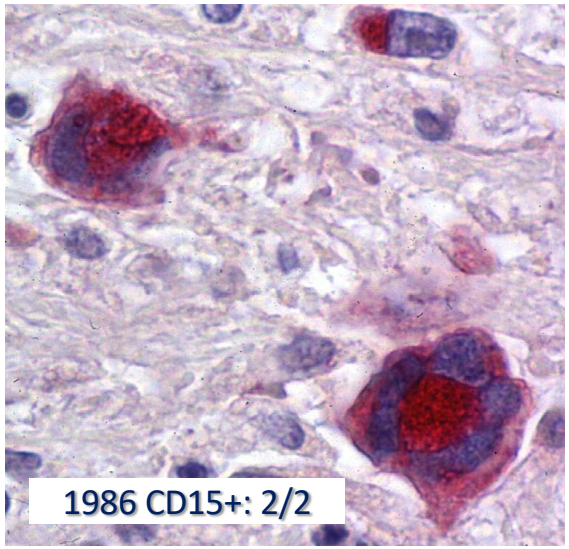
Pauline Brice, Eric de Kerviler, Jonathan W Friedberg

Neoplastic cells



Sir Thomas Hodgkin
January 10th, 1832





GENOMICS

Your Complete Web Guide to Tumors

Vice President Al Gore last week officially unveiled a new Web site that will help cancer researchers and physicians paint a complete genetic picture of tumor cells throughout the body. The site is part of the Cancer Genome Anatomy Project (CGAP) funded by the National Cancer Institute (NCI), the National Library of Medicine, and several

in the set of normal genes expres
ticular cell. But clinical diagnos
ment of cancer currently rely l
location of tumor tissue in th
appearance under
CGAP seeks to
check the active
in human tissu
earlier detecti
diagnosis and
The CG
plete data
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precanc
dexed
target
breas
with
pr
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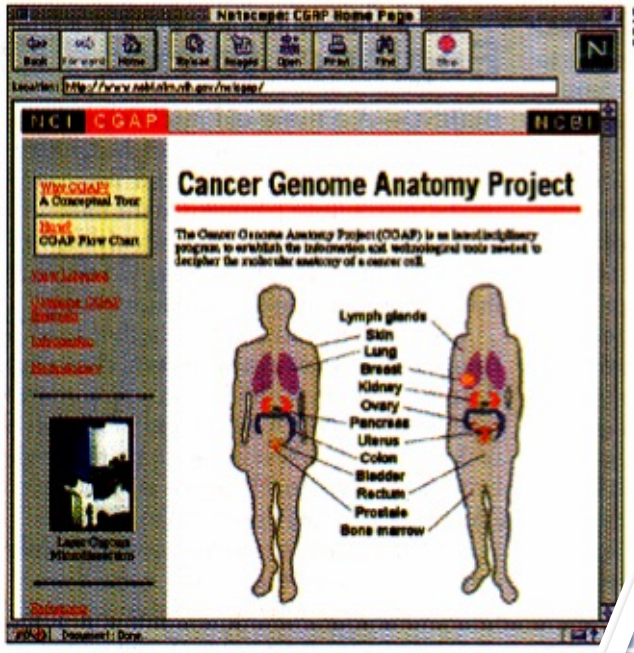
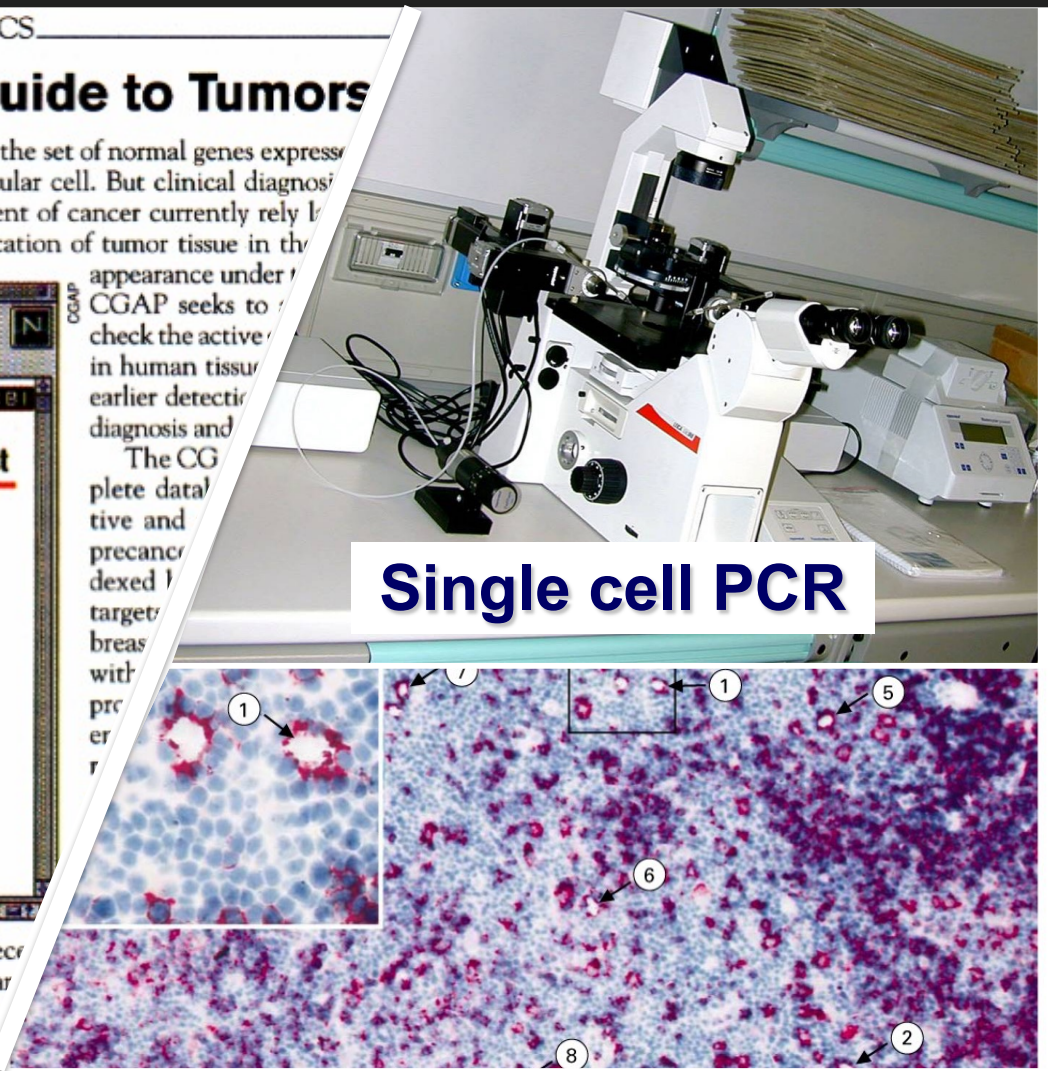
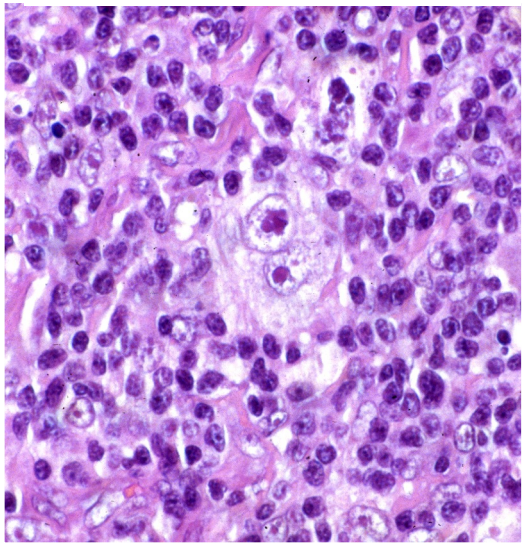
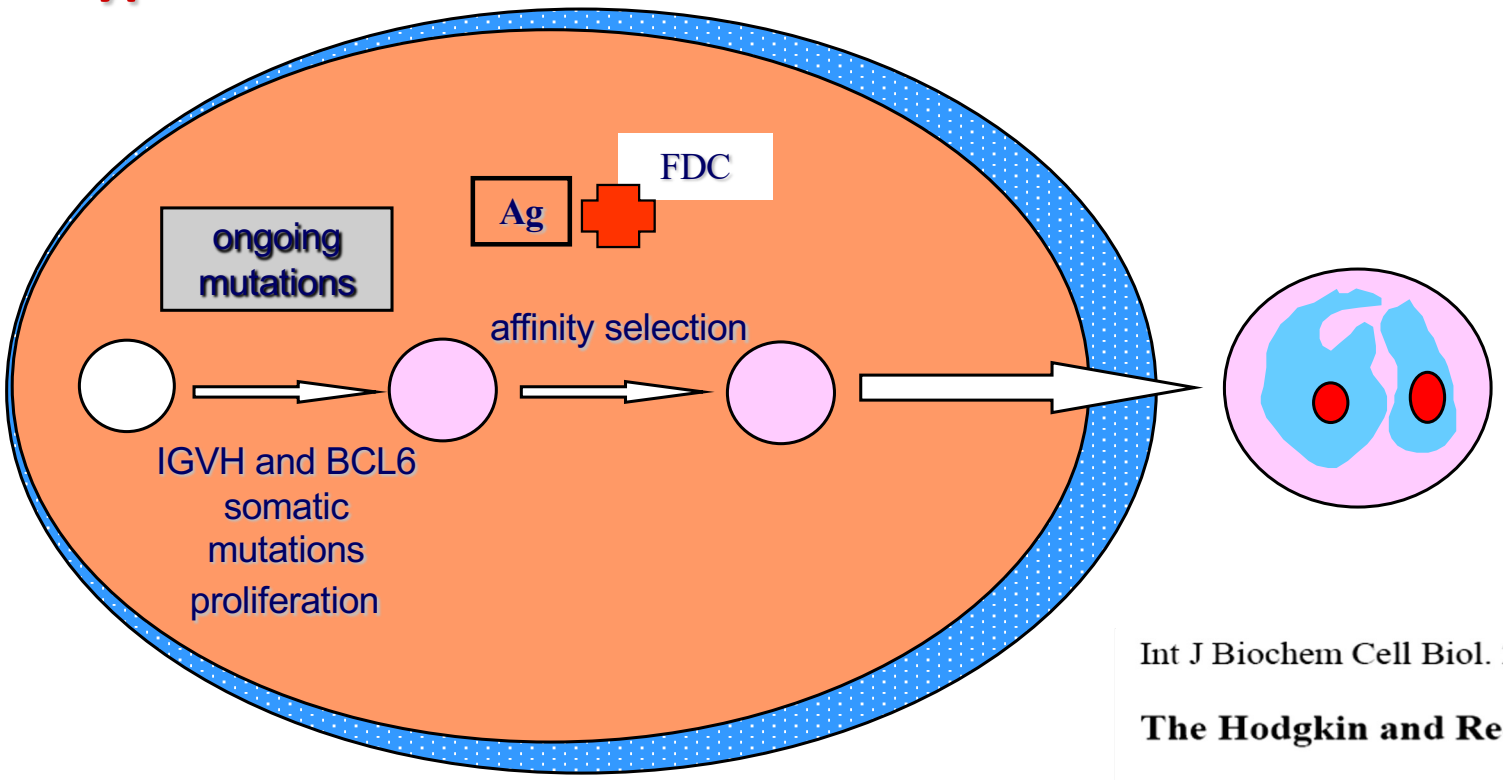




1 – 3% Cellularity



Genotype



Int J Biochem Cell Biol. 2005 Mar;37(3):511-7.

The Hodgkin and Reed/Sternberg cell.

Kuppers R, Hansmann ML.

Gene expression profiling of microdissected Hodgkin Reed-Sternberg cells correlates with treatment outcome in classical Hodgkin lymphoma

Christian Steidl,[1,2] Arjan Diepstra,[3] Tang Lee,[1] Fong Chun Chan,[1,4] Pedro Farinha,[1] King Tan,[1] Adele Telenius,[1] Lorena Barclay,[5] Sohrab P. Shah,[2] Joseph M. Connors,[1] Anke van den Berg,[3] and Randy D. Gascoyne[1,2]

[1]Centre for Lymphoid Cancer, British Columbia Cancer Agency, Vancouver, BC; [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC; [3]Departments of Pathology and Medical Biology, University of Groningen, University Medical Center, Groningen, The Netherlands; [4]Bioinformatics Training Program, University of British Columbia, Vancouver, BC; and [5]Department of Cancer Imaging, British Columbia Cancer Agency, Vancouver, BC

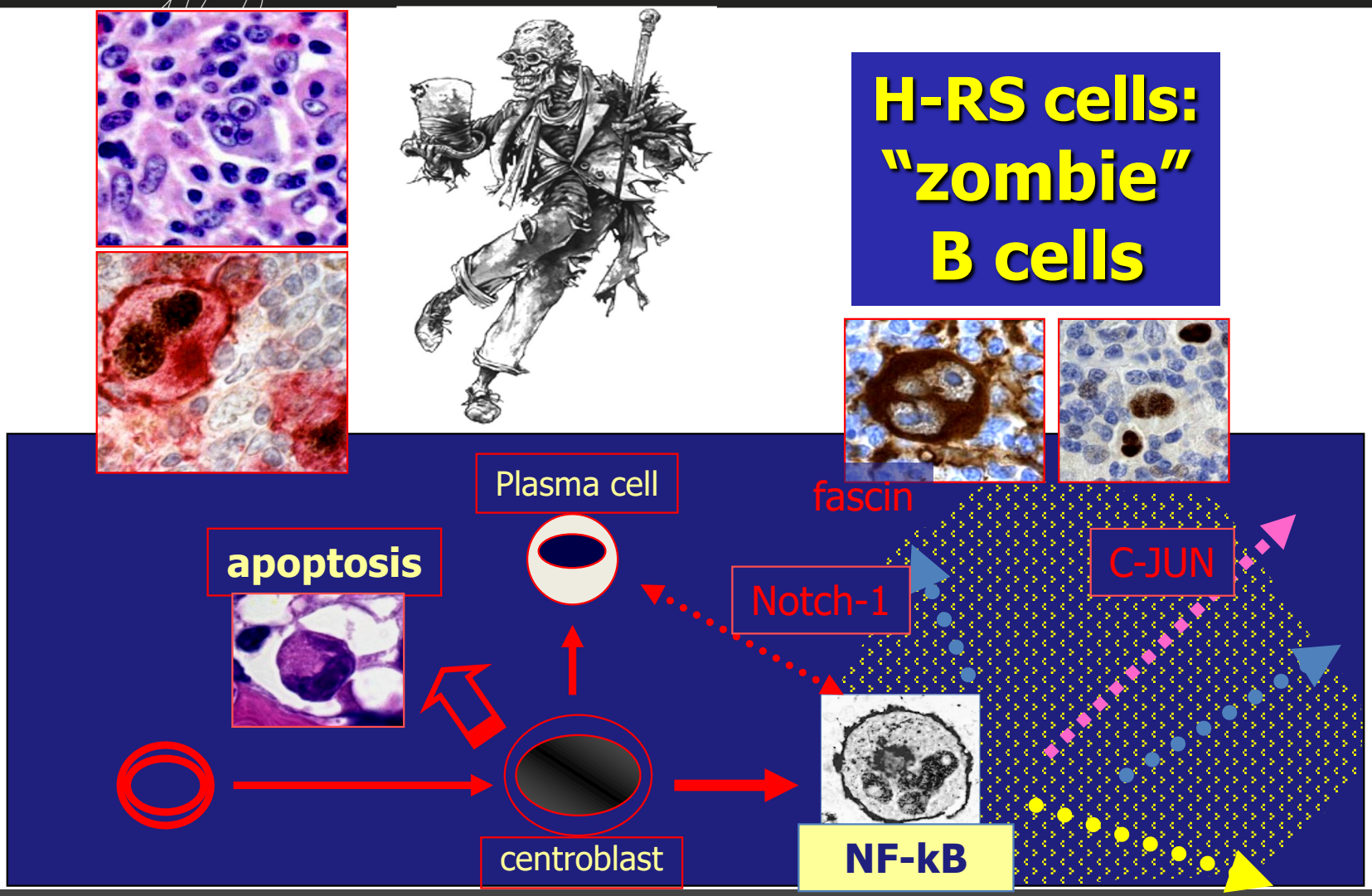
Blood 2012; 120:3530-40.

Analyzing primary Hodgkin and Reed-Sternberg cells to capture the molecular and cellular pathogenesis of classical Hodgkin lymphoma

Enrico Tiacci,[1] Claudia Döring,[2,3] Verena Brune,[1,2] Carel J. M. van Noesel,[4] Wolfram Klapper,[5] Gunhild Mechtersheimer,[6] Brunangelo Falini,[7] *Ralf Küppers,[1] and *Martin-Leo Hansmann[2]

[1]Institute of Cell Biology (Cancer Research), University of Duisburg-Essen Medical School, Essen, Germany; [2]Institute for Pathology, University of Frankfurt Medical School, Frankfurt, Germany; [3]Institute for Informatics, University of Frankfurt, Frankfurt, Germany; [4]Department of Pathology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [5]Institute for Pathology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; [6]Institute of Pathology, University of Heidelberg, Heidelberg, Germany; and [7]Institute of Hematology, University of Perugia, Perugia, Italy

Blood 2012; 120:4609-20.


H-RS cells:
"zombie"
B cells
fascin
Plasma cell
apoptosis
Notch-1
C-JUN
centroblast
NF-kB

CLINICAL TRIALS AND OBSERVATIONS

Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma

Robert Chen,[1,*] Ajay K. Gopal,[2,*] Scott E. Smith,[3] Stephen M. Ansell,[4] Joseph D. Rosenblatt,[5] Kerry J. Savage,[6] Joseph M. Connors,[6] Andreas Engert,[7] Emily K. Larsen,[8] Dirk Huebner,[9] Abraham Fong,[8] and Anas Younes[10]

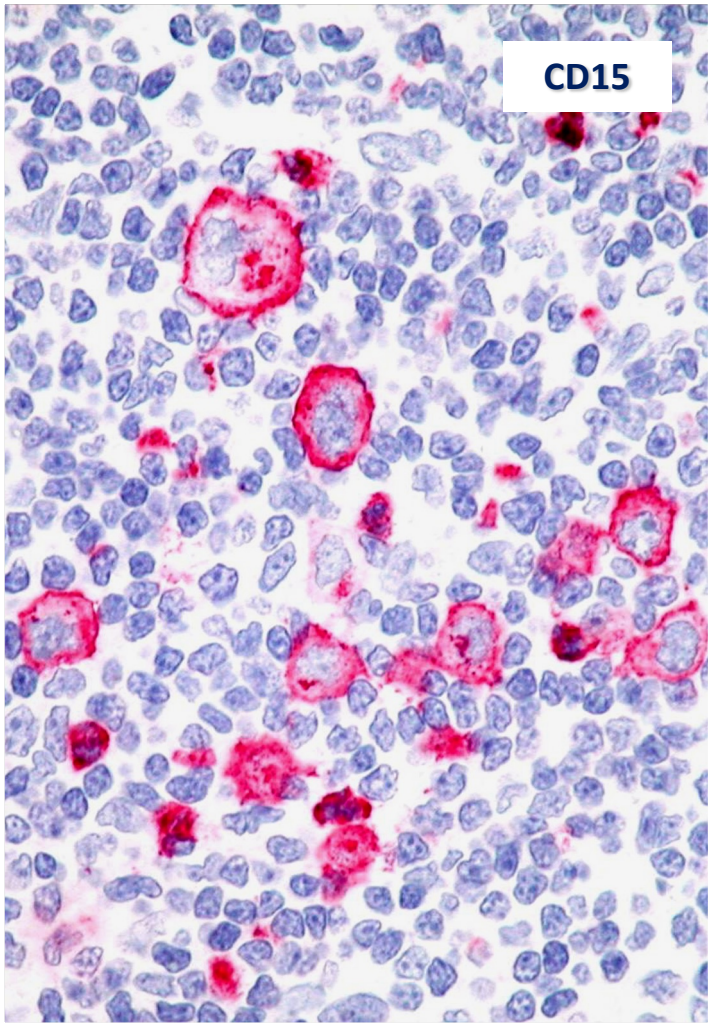
(*Blood*. 2016;128(12):1562-1566)

CLINICAL TRIALS AND OBSERVATIONS

Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study

David J. Straus,[1] Monika Długosz-Danecka,[2] Sergey Alekseev,[3] Árpád Illés,[4] Marco Picardi,[5] Ewa Lech-Maranda,[6] Tatyana Feldman,[7] Piotr Smolewski,[8] Kerry J. Savage,[9,10] Nancy L. Bartlett,[11] Jan Walewski,[12] Radhakrishnan Ramchandren,[13] Pier Luigi Zinzani,[14] Martin Hutchings,[15] Joseph M. Connors,[9,10] John Radford,[16,17] Javier Munoz,[18] Won Seog Kim,[19] Ranjana Advani,[20] Stephen M. Ansell,[21] Anas Younes,[1] Harry Miao,[22] Rachael Liu,[22] Keenan Fenton,[23] Andres Forero-Torres,[23] and Andrea Gallamini[24]

(*Blood*. 2020;135(10):735-742)

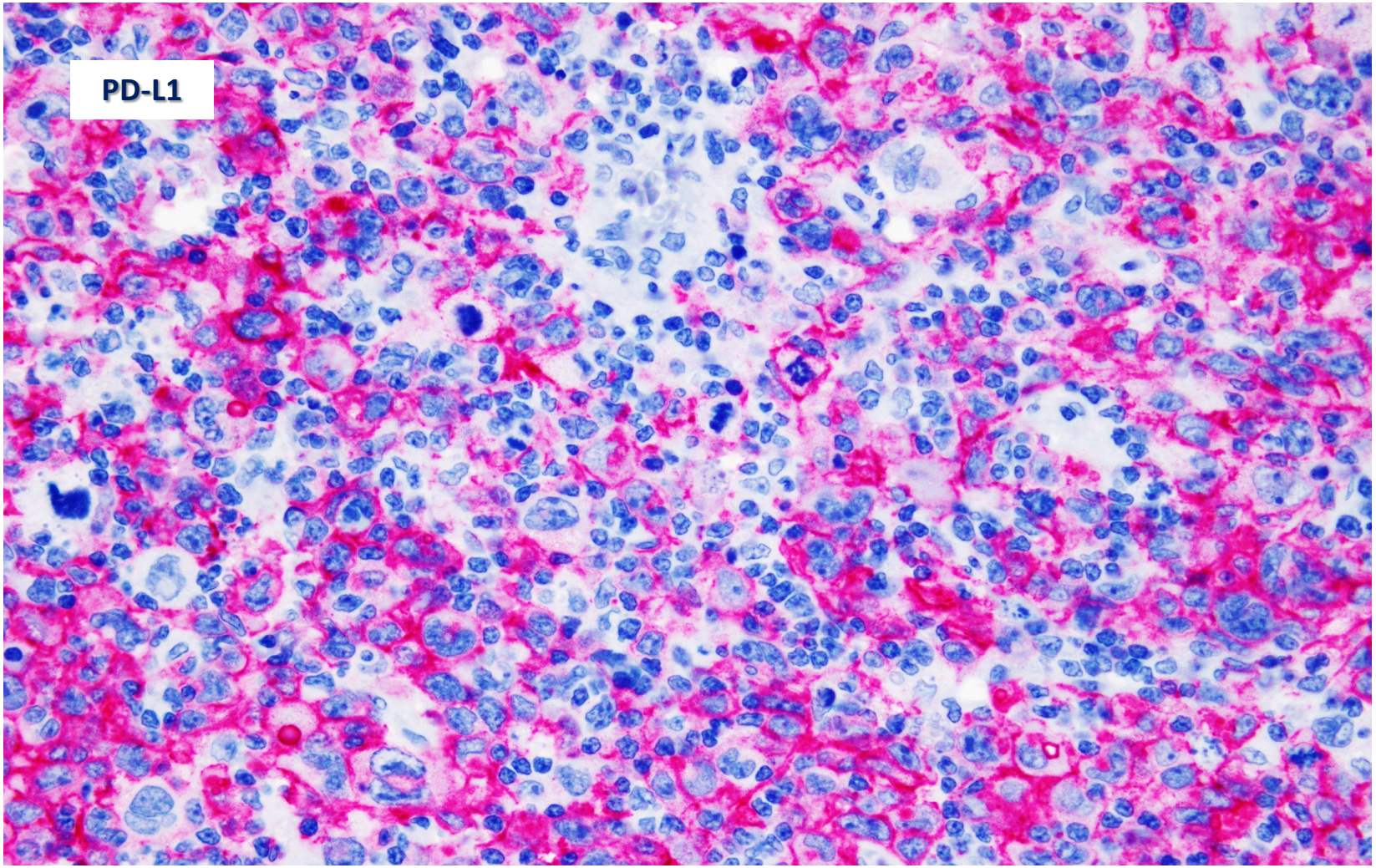


LYMPHOID NEOPLASIA

Autocrine LTA signaling drives NF-κB and JAK-STAT activity and myeloid gene expression in Hodgkin lymphoma

Linda von Hoff,[1] Eva Kärgel,[1] Vedran Franke,[2] Erik McShane,[3] Kathrin W. Schulz-Beiss,[4] Giannino Patone,[5] Nikolai Schleussner,[6,7] Marina Kolesnichenko,[1] Norbert Hübner,[5] Oliver Daumke,[4] Matthias Selbach,[3] Altuna Akalin,[2] Stephan Mathas,[6,7] and Claus Scheidereit[1]

(*Blood.* 2019;133(13):1489-1494)


PD-L1

KEY POINTS

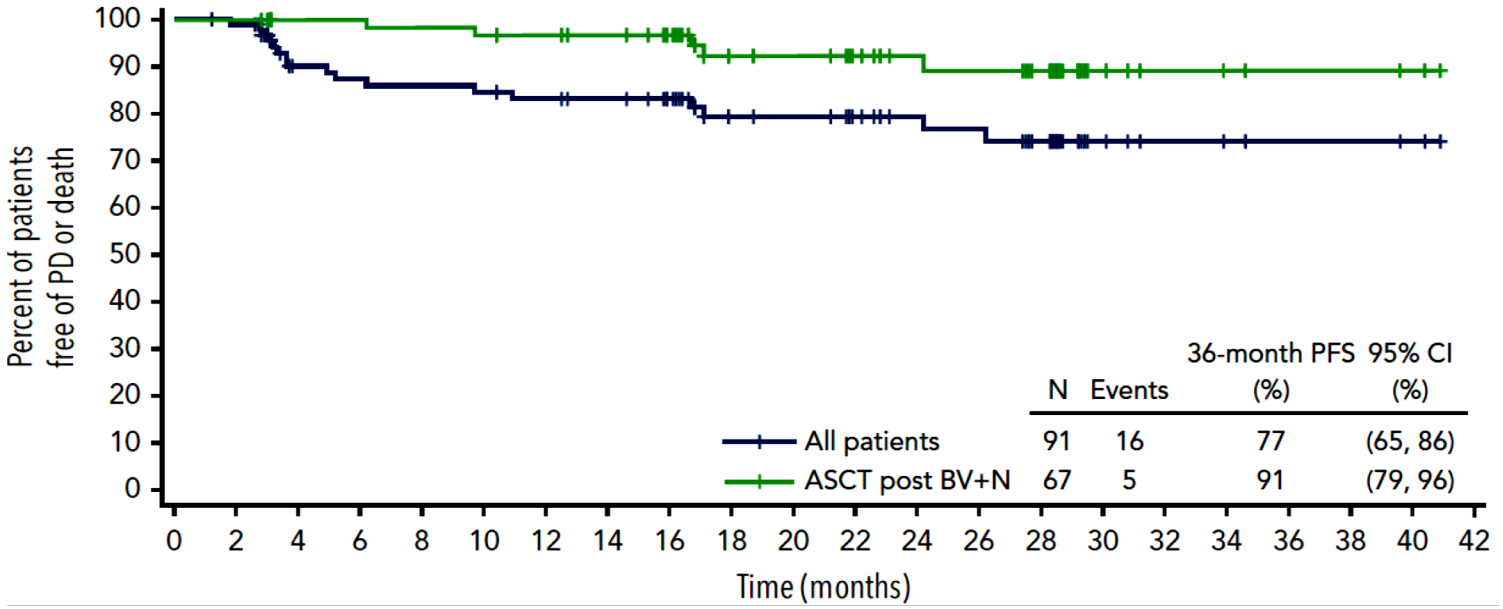
- **BV and Nivo with staggered or concurrent dosing were active and well tolerated when used as first salvage therapy in patients with r/r cHL.**
- **The ORR and CR rate were 85% and 67%, with a 3-year PFS rate of 91% in patients who proceeded directly to transplant.**

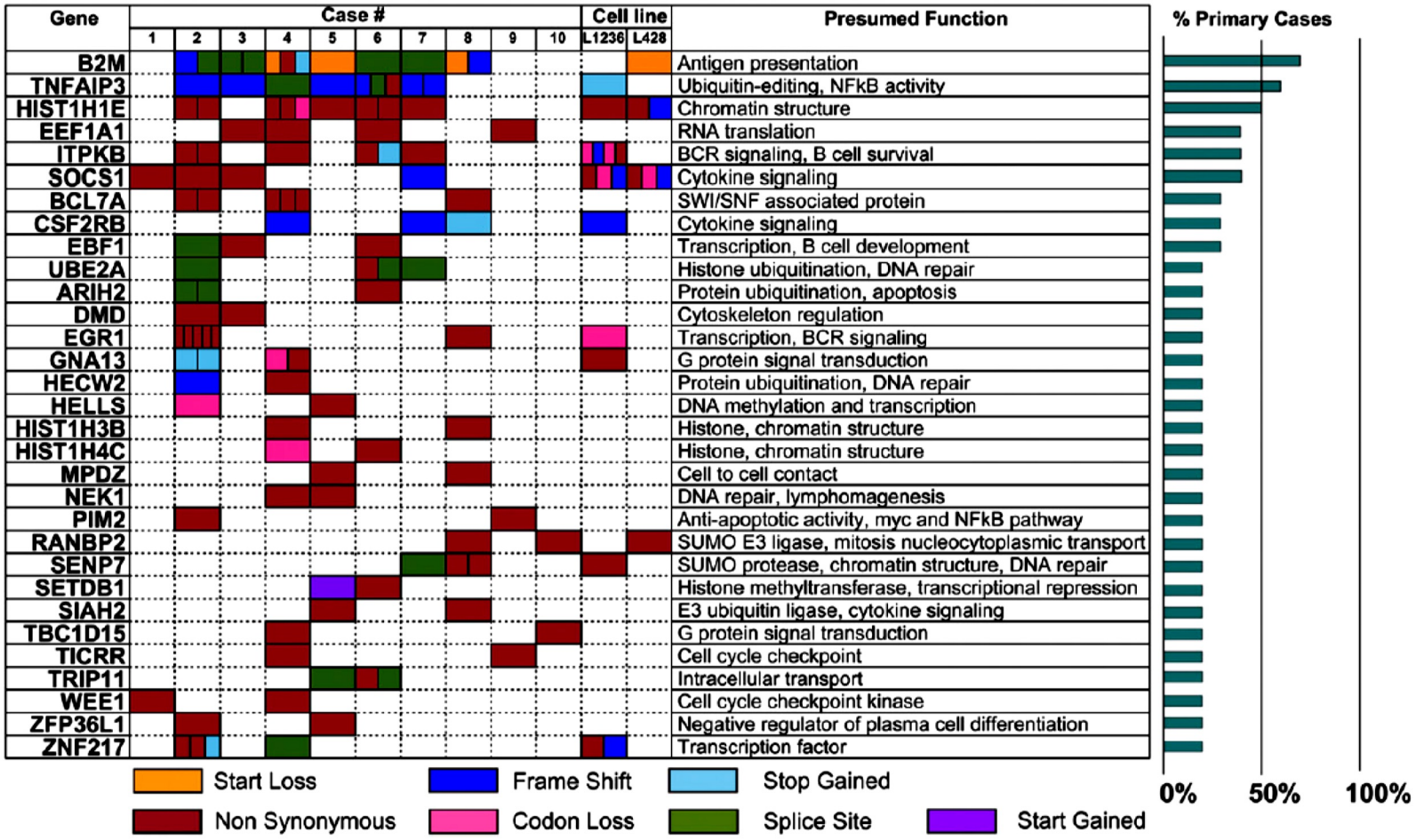
CLINICAL TRIALS AND OBSERVATIONS

blood® 12 AUGUST 2021 | VOLUME 138, NUMBER 6 427

Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results

Ranjana H. Advani,[1] Alison J. Moskowitz,[2] Nancy L. Bartlett,[3] Julie M. Vose,[4] Radhakrishnan Ramchandren,[5] Tatyana A. Feldman,[6] Ann S. LaCasce,[7] Beth A. Christian,[8] Stephen M. Ansell,[9] Craig H. Moskowitz,[10] Lisa Brown,[11] Chiyu Zhang,[11] David Taft,[11] Sahar Ansari,[11] Mariana Sacchi,[12] Linda Ho,[11] and Alex F. Herrera[13]




Gene
Case #
1
2
3
4
5
6
7
8
9
10
Cell line
L1236
L428
Presumed Function
% Primary Cases
B2M
Antigen presentation
TNFAIP3
Ubiquitin-editing, NFkB activity
HIST1H1E
Chromatin structure
EEF1A1
RNA translation
ITPKB
BCR signaling, B cell survival
SOCS1
Cytokine signaling
BCL7A
SWI/SNF associated protein
CSF2RB
Cytokine signaling
EBF1
Transcription, B cell development
UBE2A
Histone ubiquitination, DNA repair
ARIH2
Protein ubiquitination, apoptosis
DMD
Cytoskeleton regulation
EGR1
Transcription, BCR signaling
GNA13
G protein signal transduction
HECW2
Protein ubiquitination, DNA repair
HELLS
DNA methylation and transcription
HIST1H3B
Histone, chromatin structure
HIST1H4C
Histone, chromatin structure
MPDZ
Cell to cell contact
NEK1
DNA repair, lymphomagenesis
PIM2
Anti-apoptotic activity, myc and NFkB pathway
RANBP2
SUMO E3 ligase, mitosis nucleocytoplasmic transport
SENP7
SUMO protease, chromatin structure, DNA repair
SETDB1
Histone methyltransferase, transcriptional repression
SIAH2
E3 ubiquitin ligase, cytokine signaling
TBC1D15
G protein signal transduction
TICRR
Cell cycle checkpoint
TRIP11
Intracellular transport
WEE1
Cell cycle checkpoint kinase
ZFP36L1
Negative regulator of plasma cell differentiation
ZNF217
Transcription factor
0%
50%
100%
Start Loss
Frame Shift
Stop Gained
Non Synonymous
Codon Loss
Splice Site
Start Gained

EUROPEAN HEMATOLOGY ASSOCIATION

Ferrata Storti Foundation

A phase II study of the oral JAK1/JAK2 inhibitor ruxolitinib in advanced relapsed/refractory Hodgkin lymphoma

Eric Van Den Neste,[1] Marc André,[2] Thomas Gastinne,[3] Aspasia Stamatoullas,[4] Corinne Haioun,[5] Amine Belhabri,[6] Oumedaly Reman, [7]Olivier Casasnovas,[8] Hervé Ghesquieres,[9] Gregor Verhoef,[10] Marie-José Claessen,[11] Hélène A. Poirel,[12] Marie-Christine Copin,[13] Romain Dubois,[13] Peter Vandenberghe,[14] Ioanna-Andrea Stoian,[15] Anne S. Cottereau,[16] Sarah Bailly,[1] Laurent Knoops[17] and Franck Morschhauser[18]

Haematologica 2018
Volume 103(5):840-848

CHL and Tissue Microenvironment

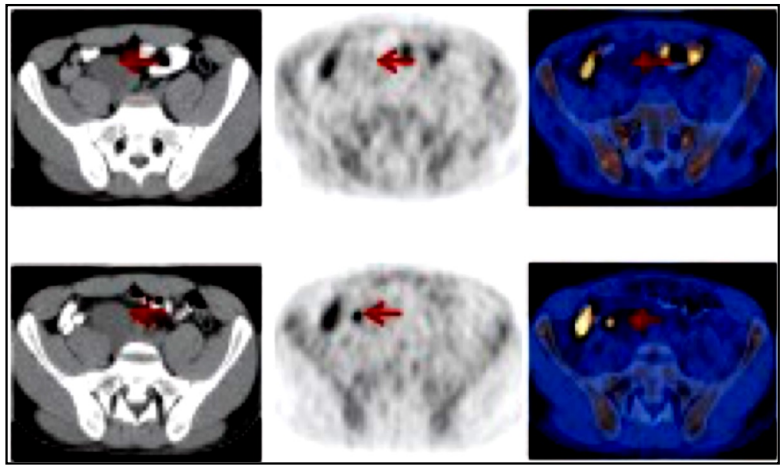
Interim PET (PET-2)

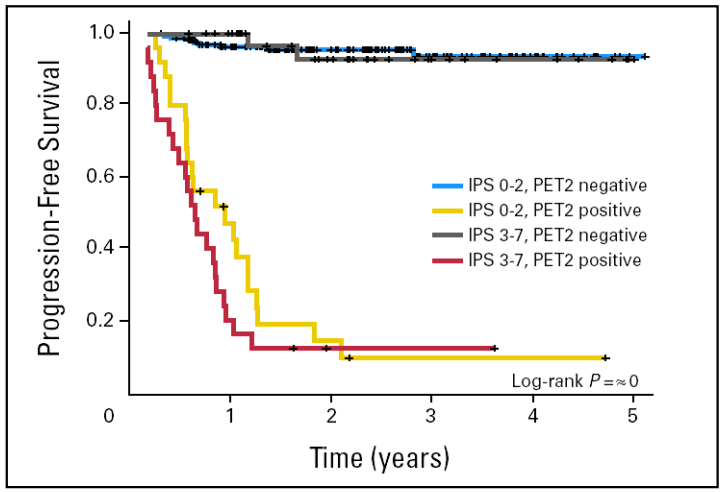
5%-12% PET2 negative pts
experience a treatment failure

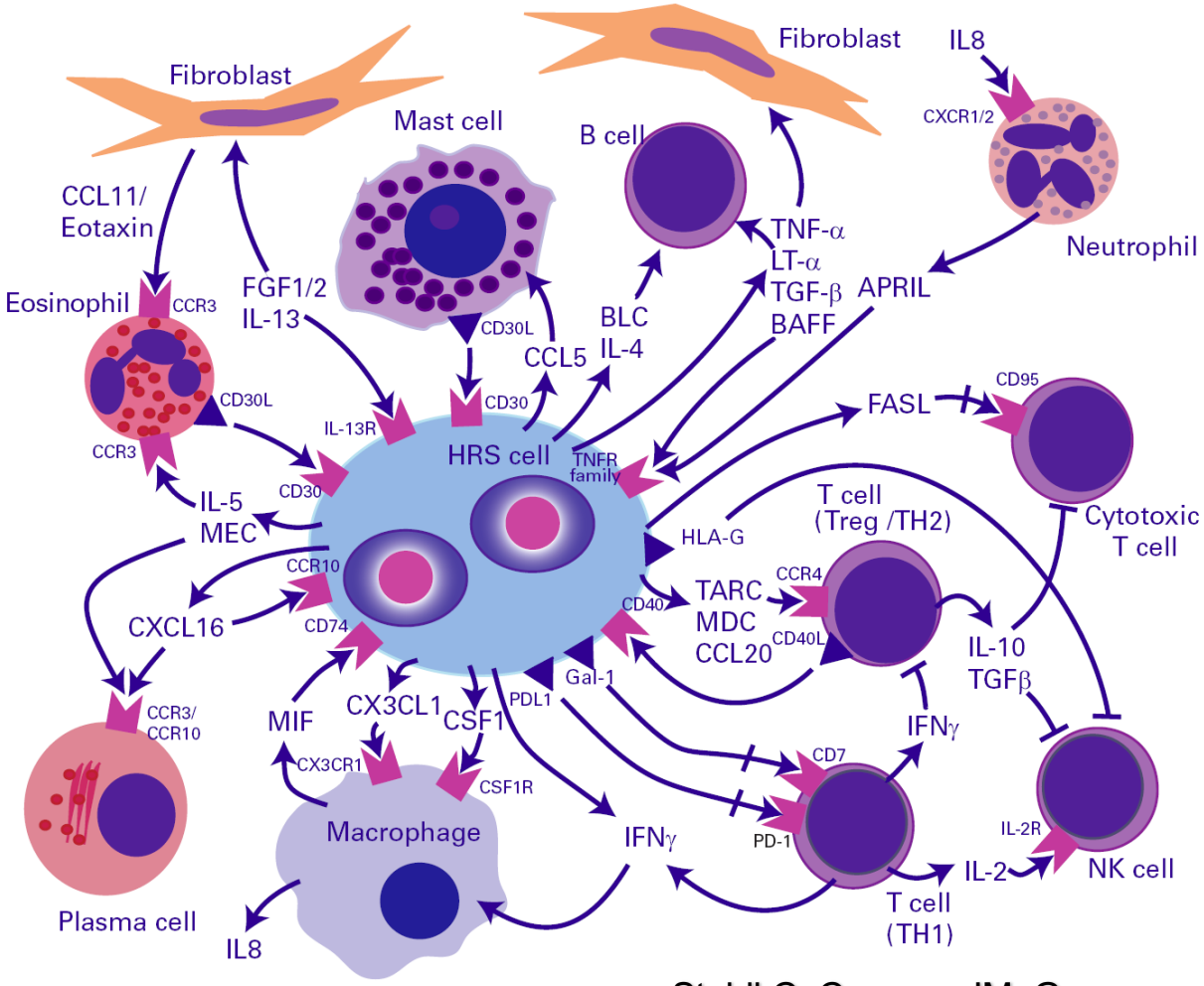
VOLUME 25 · NUMBER 24 · AUGUST 20 2007
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Early Interim 2-[^{18}F]Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography Is Prognostically Superior to International Prognostic Score in Advanced-Stage Hodgkin's Lymphoma: A Report From a Joint Italian-Danish Study

Andrea Gallamini, Martin Hutchings, Luigi Rigacci, Lena Specht, Francesco Merli, Mads Hansen, Caterina Patti, Annika Loft, Francesco Di Raimondo, Francesco D'Amore, Alberto Biggi, Umberto Vitolo, Caterina Stelitano, Rosario Sancetta, Livio Trentin, Stefano Luminari, Emilio Iannitto, Simonetta Viviani, Ivana Pierri, and Alessandro Levis





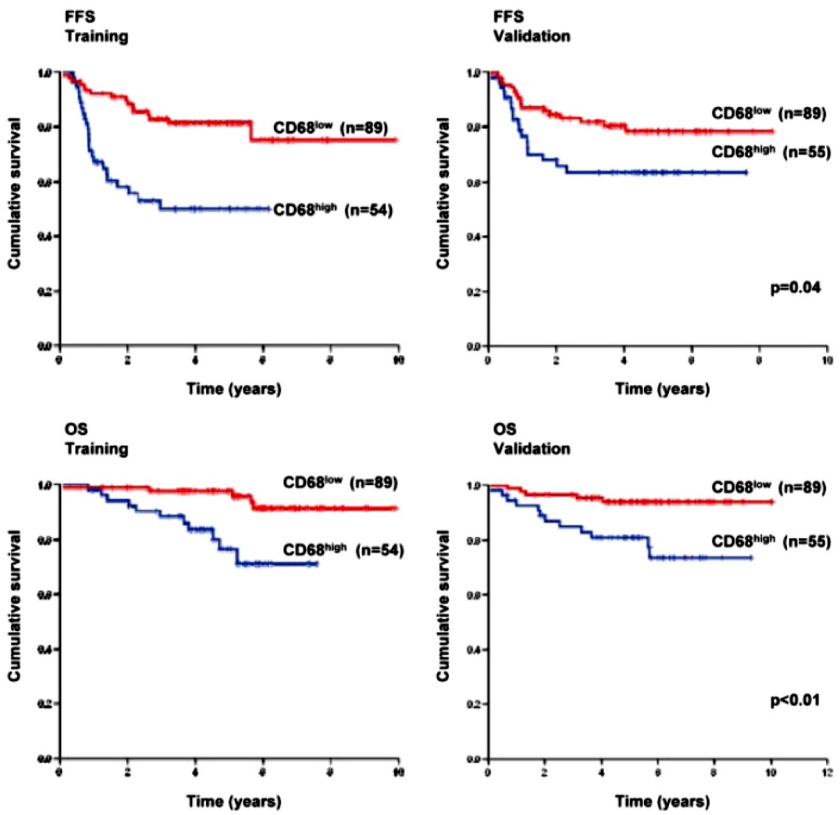


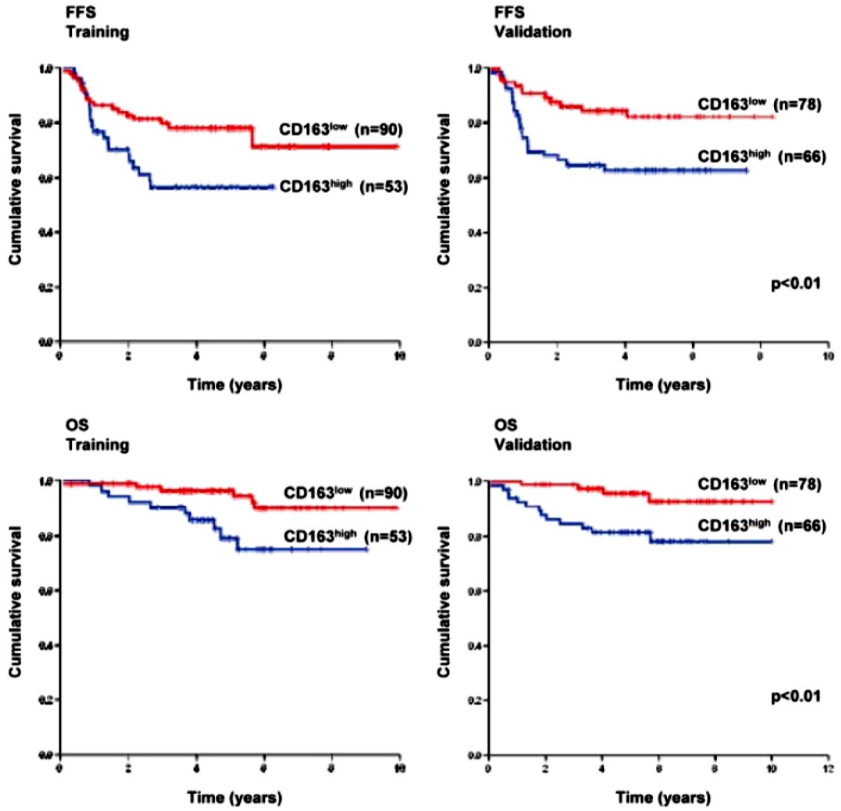
Steidl C, Connors JM, Gascoyne RD. JCO 2011, 29:1812-26

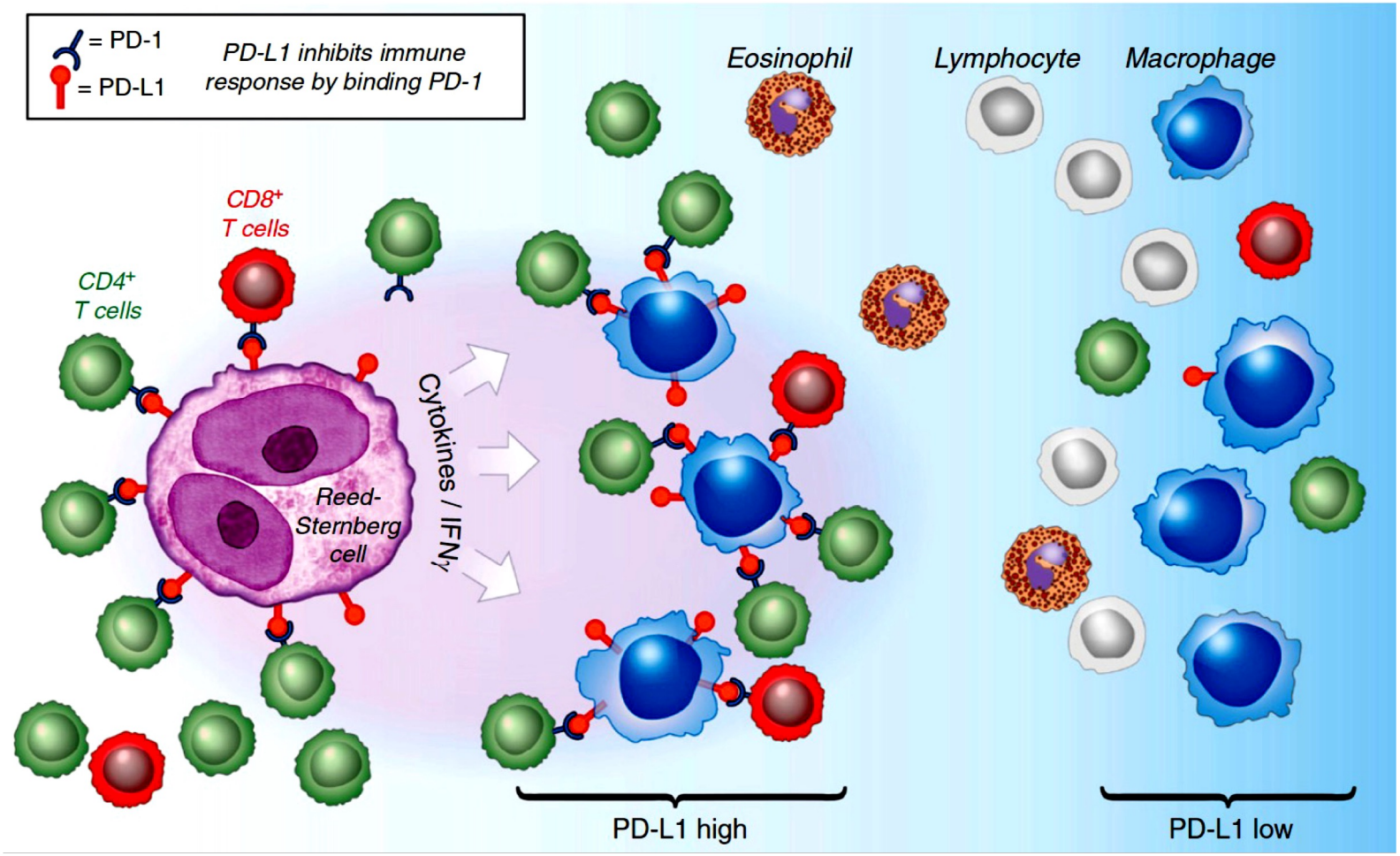
Tumor-associated macrophages predict inferior outcomes in classic Hodgkin lymphoma: a correlative study from the E2496 Intergroup trial

King L. Tan,[1] David W. Scott,[1] Fangxin Hong,[2] Brad S. Kahl,[3] Richard I. Fisher,[4] Nancy L. Bartlett,[5] Ranjana H. Advani,[6] Rena Buckstein,[7] Lisa M. Rimsza,[8] Joseph M. Connors,[1] Christian Steidl,[1] Leo I. Gordon,[9] Sandra J. Horning,[10] and Randy D. Gascoyne[1]

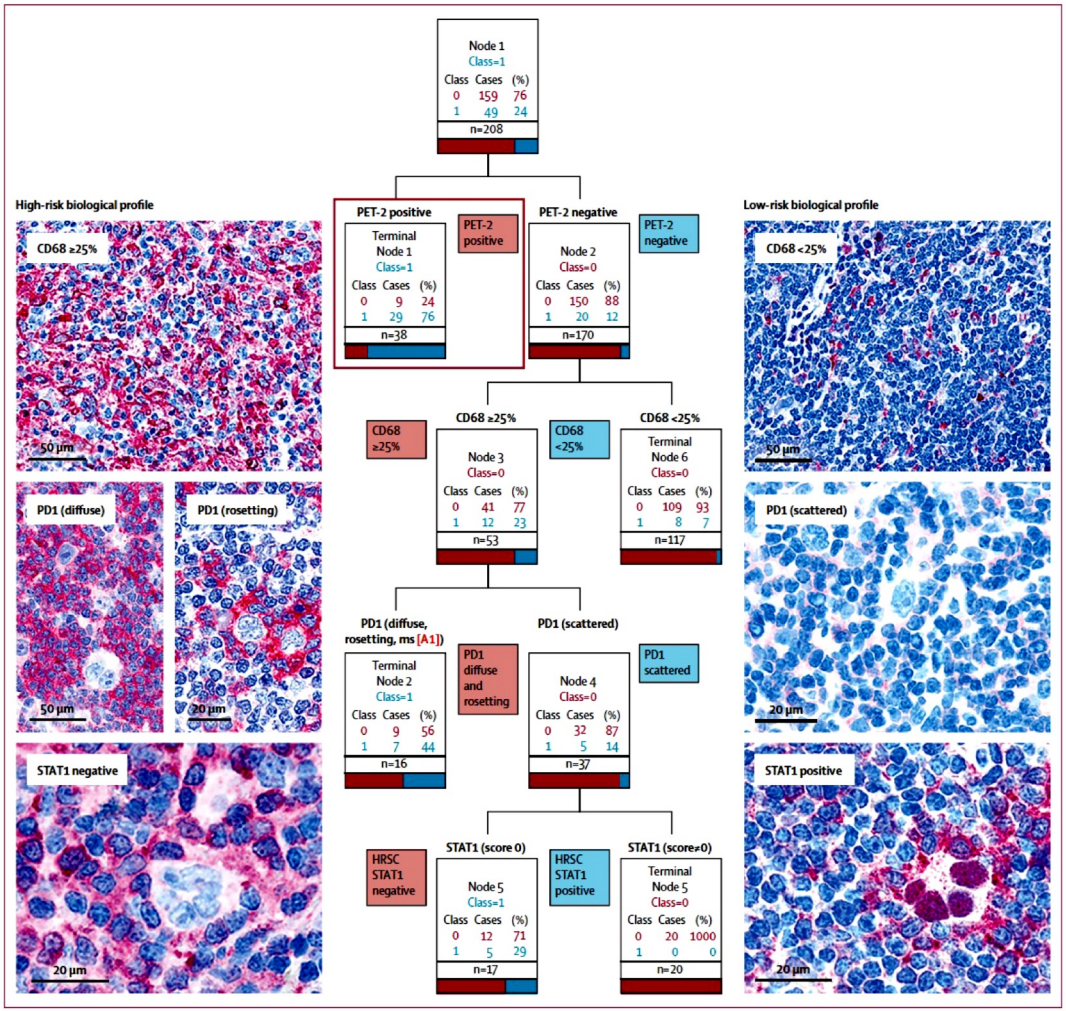
Increased tumor-associated macrophages (TAMs) are reported to be associated with poor prognosis in classic Hodgkin lymphoma (CHL). We investigated the prognostic significance of TAMs in the E2496 Intergroup trial, a multicenter phase 3 randomized controlled trial comparing ABVD and Stanford V chemotherapy in locally extensive and advanced stage CHL. Tissue microarrays were constructed from formalin-fixed, paraffin-embedded tumor tissue and included 287 patients. Patients were randomly assigned into training (n = 143) and validation (n = 144) cohorts. Immunohistochemistry for CD68 and CD163, and in situ hybridization for EBV-encoded RNA were performed. CD68 and CD163 IHC were analyzed by computer image analysis; optimum thresholds for overall survival (OS) were determined in the training cohort and tested in the independent validation cohort. Increased CD68 and CD163 expression was significantly associated with inferior failure-free survival and OS in the validation cohort. Increased CD68 and CD163 expression was associated with increased age, EBV-encoded RNA positivity, and mixed cellularity subtype of CHL. Multivariate analysis in the validation cohort showed increased CD68 or CD163 expression to be significant independent predictors of inferior failure-free survival and OS. We demonstrate the prognostic significance of TAMs in locally extensive and advanced-stage CHL in a multicenter phase 3 randomized controlled clinical trial. (*Blood*. 2012;120(16):3280-3287)


FFS
Training
Cumulative survival
CD68low (n=89)
CD68high (n=54)
Time (years)
FFS
Validation
CD68low (n=89)
CD68high (n=55)
p=0.04
Time (years)
OS
Training
CD68low (n=89)
CD68high (n=54)
Time (years)
OS
Validation
CD68low (n=89)
CD68high (n=55)
p<0.01
Time (years)


FFS
Training
Cumulative survival
CD163low (n=90)
CD163high (n=53)
Time (years)
FFS
Validation
CD163low (n=78)
CD163high (n=66)
p<0.01
Time (years)
OS
Training
CD163low (n=90)
CD163high (n=53)
Time (years)
OS
Validation
CD163low (n=78)
CD163high (n=66)
p<0.01
Time (years)

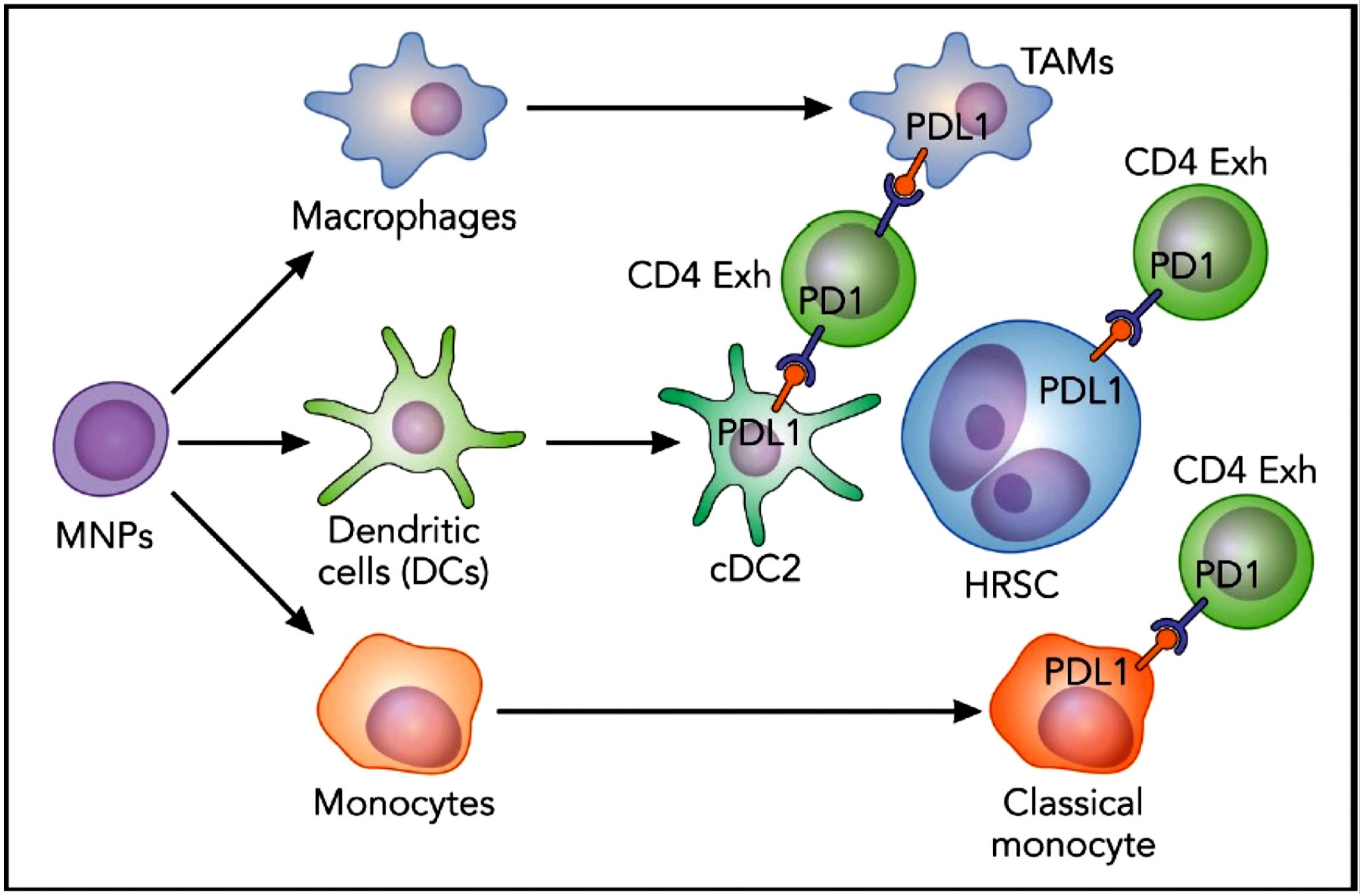


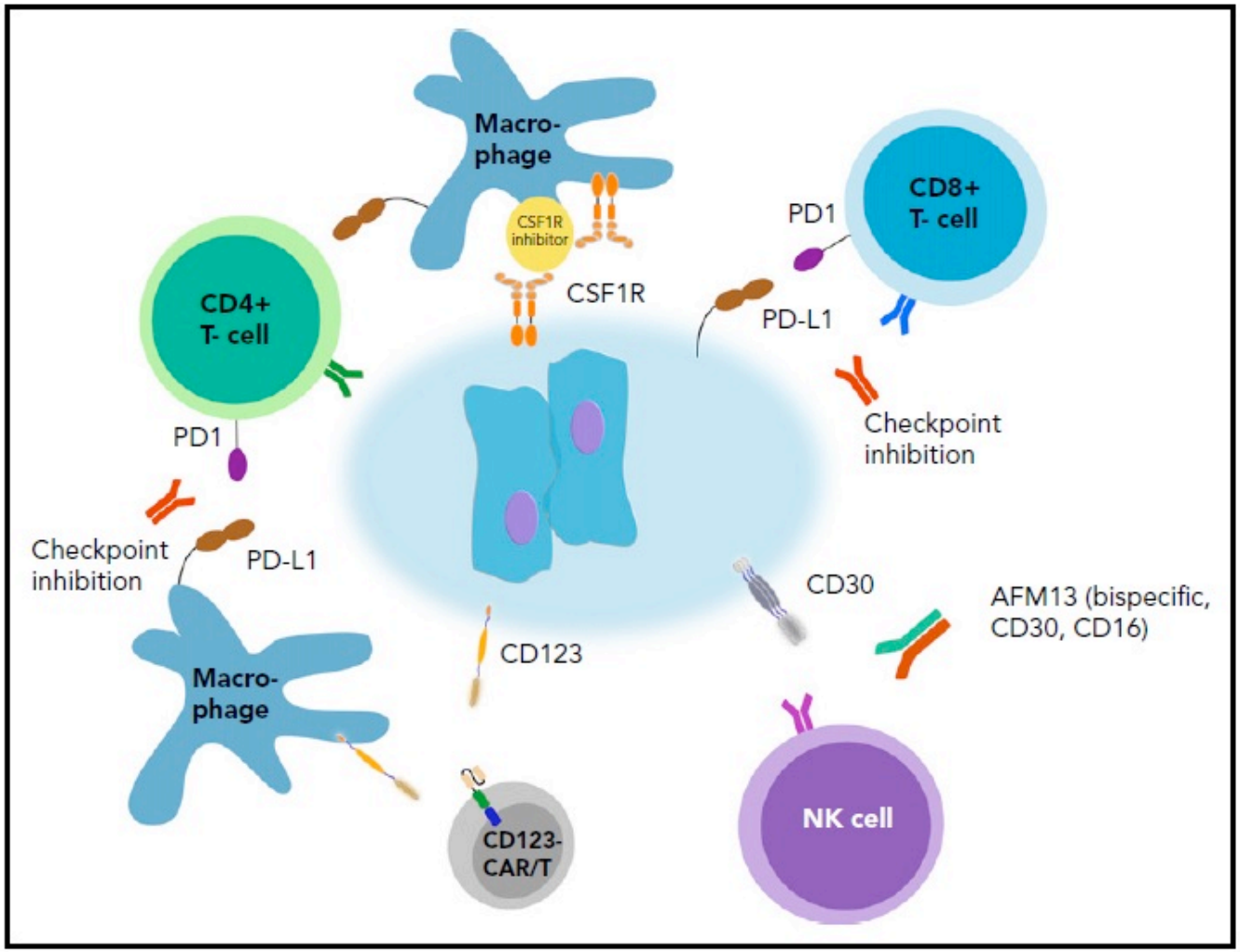
Carey CD et al. Blood 2017; 130:2420-30.


Node 1
Class=1
Class Cases (%)
0 159 76
1 49 24
n=208
High-risk biological profile
PET-2 positive
PET-2 positive
Terminal
Node 1
Class=1
Class Cases (%)
0 9 24
1 29 76
n=38
PET-2 negative
PET-2 negative
Node 2
Class=0
Class Cases (%)
0 150 88
1 20 12
n=170
Low-risk biological profile
CD68 ≥25%
50 µm
CD68 <25%
50 µm
CD68 ≥25%
CD68 ≥25%
Node 3
Class=0
Class Cases (%)
0 41 77
1 12 23
n=53
CD68 <25%
CD68 <25%
Terminal
Node 6
Class=0
Class Cases (%)
0 109 93
1 8 7
n=117
PD1 (diffuse)
50 µm
PD1 (rosetting)
20 µm
PD1 (scattered)
20 µm
PD1 (diffuse, rosetting, ms [A1])
PD1 (diffuse, rosetting, ms [A1])
Terminal
Node 2
Class=1
Class Cases (%)
0 9 56
1 7 44
n=16
PD1 diffuse and rosetting
PD1 (scattered)
PD1 (scattered)
Node 4
Class=0
Class Cases (%)
0 32 87
1 5 14
n=37
PD1 scattered
STAT1 negative
20 µm
STAT1 positive
20 µm
HRSC STAT1 negative
STAT1 (score 0)
STAT1 (score 0)
Node 5
Class=1
Class Cases (%)
0 12 71
1 5 29
n=17
HRSC STAT1 positive
STAT1 (score≠0)
STAT1 (score≠0)
Terminal
Node 5
Class=0
Class Cases (%)
0 20 1000
1 0 0
n=20

Increasing microenvironment complexity in HL

Paola Chabay | Hospital de Niños Ricardo Gutiérrez




Macro-
phage
CSF1R
inhibitor
CSF1R
CD4+
T- cell
PD1
Checkpoint
inhibition
PD-L1
Macro-
phage
CD123
CD123-
CAR/T
PD1
CD8+
T- cell
PD-L1
Checkpoint
inhibition
CD30
AFM13 (bispecific,
CD30, CD16)
NK cell

LYMPHOID NEOPLASIA

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Spatial and molecular profiling of the mononuclear phagocyte network in classic Hodgkin lymphoma

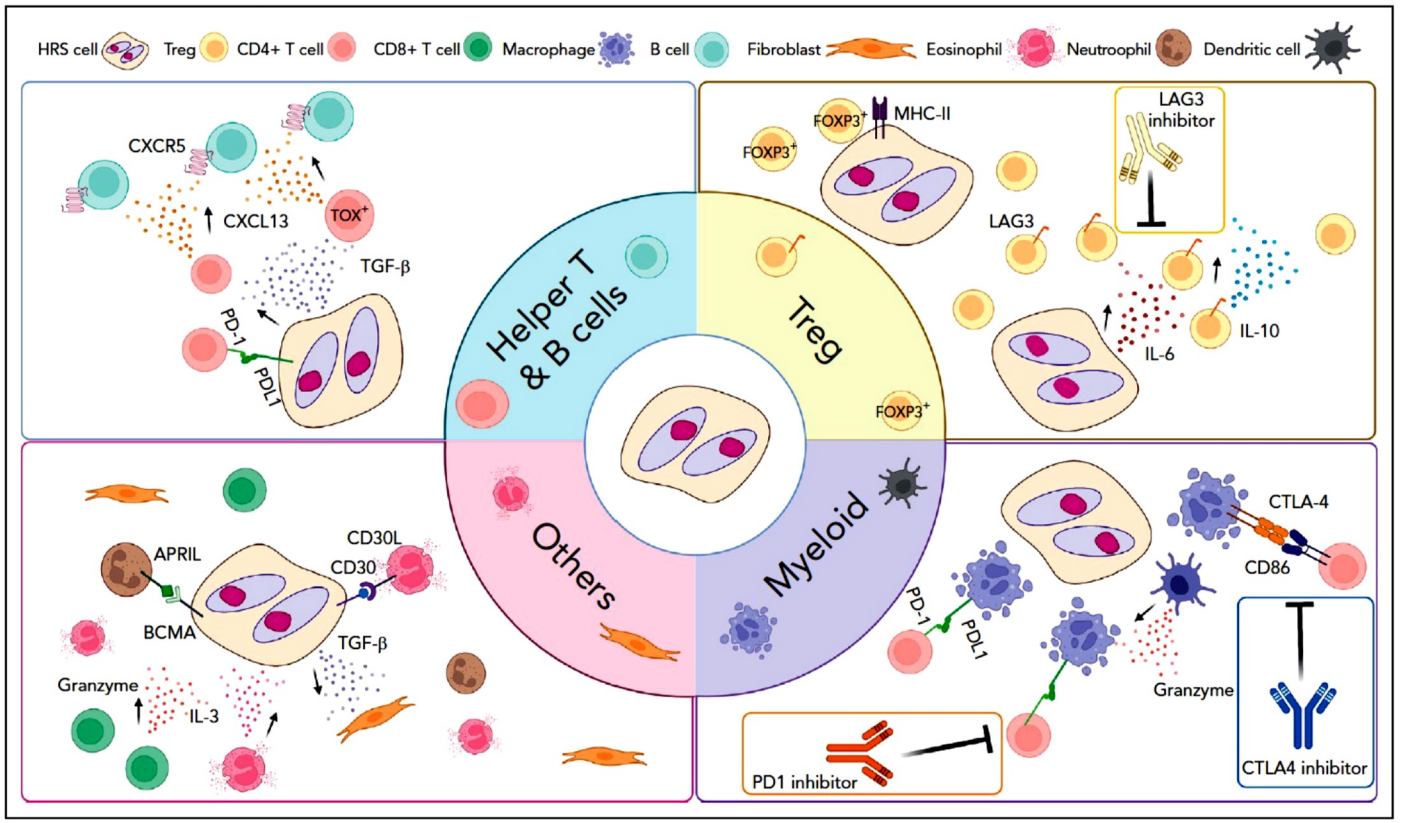
Benjamin J. Stewart,[1-3] Martin Fergie,[4] Matthew D. Young,[2] Claire Jones,[5] Ashwin Sachdeva,[6,7] Alex Blain,[8-10] Chris M. Bacon,[5,11] Vikki Rand,[9,10] John R. Ferdinand,[1] Kylie R. James,[12] Krishnaa T. Mahbubani,[13] Liz Hook,[3,14] Nicolaas Jonas,[3] Nicholas Coleman,[3,14] Kourosh Saeb-Parsy,[13] Matthew Collin,[11] Menna R. Clatworthy,[1-3] Sam Behjati,[2,3,15] and Christopher D. Carey[5,11]

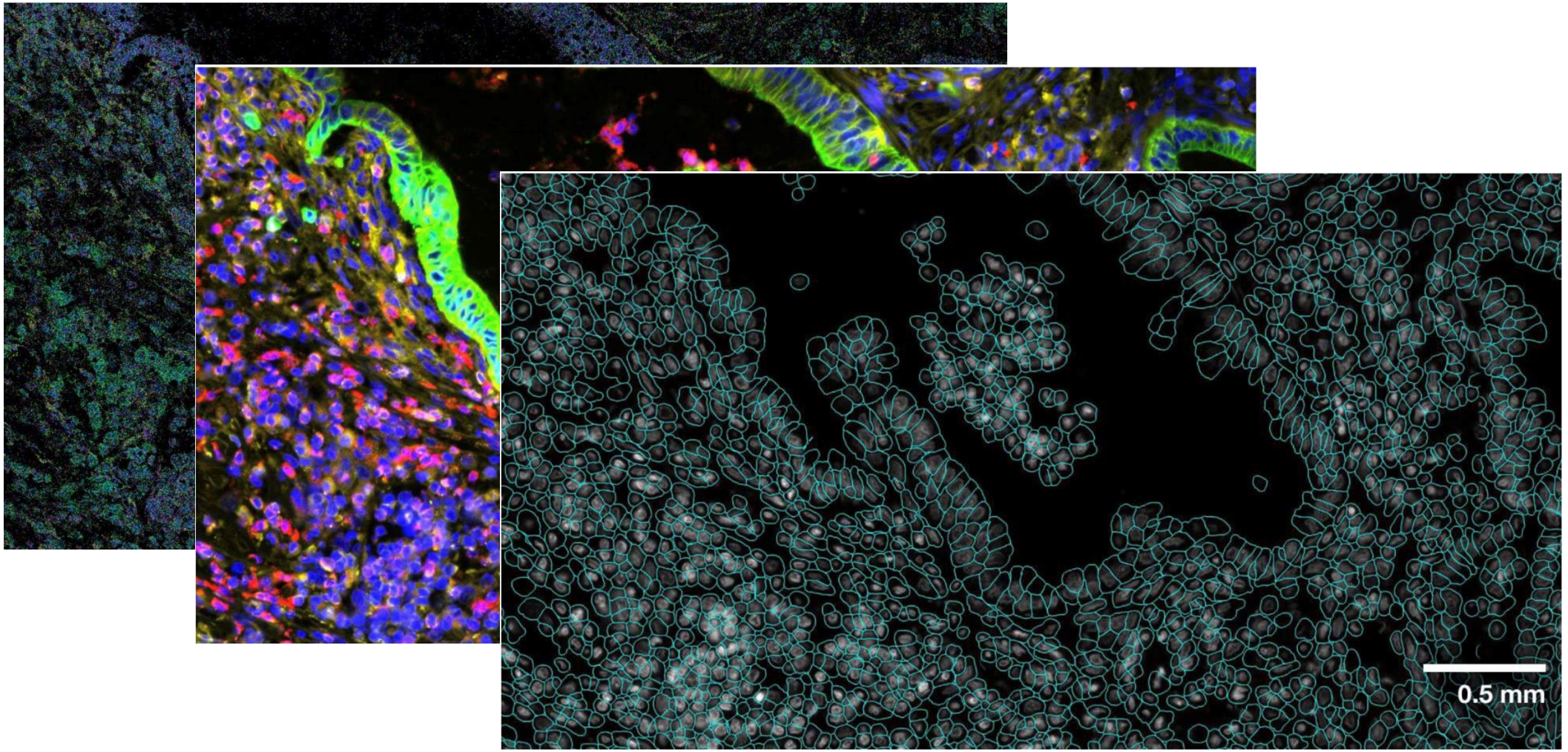
Novel insights into Hodgkin lymphoma biology by single-cell analysis

Tomohiro Aoki[1,2] and Christian Steidl[1,2]

blood® 13 APRIL 2023 | VOLUME 141, NUMBER 15 1791

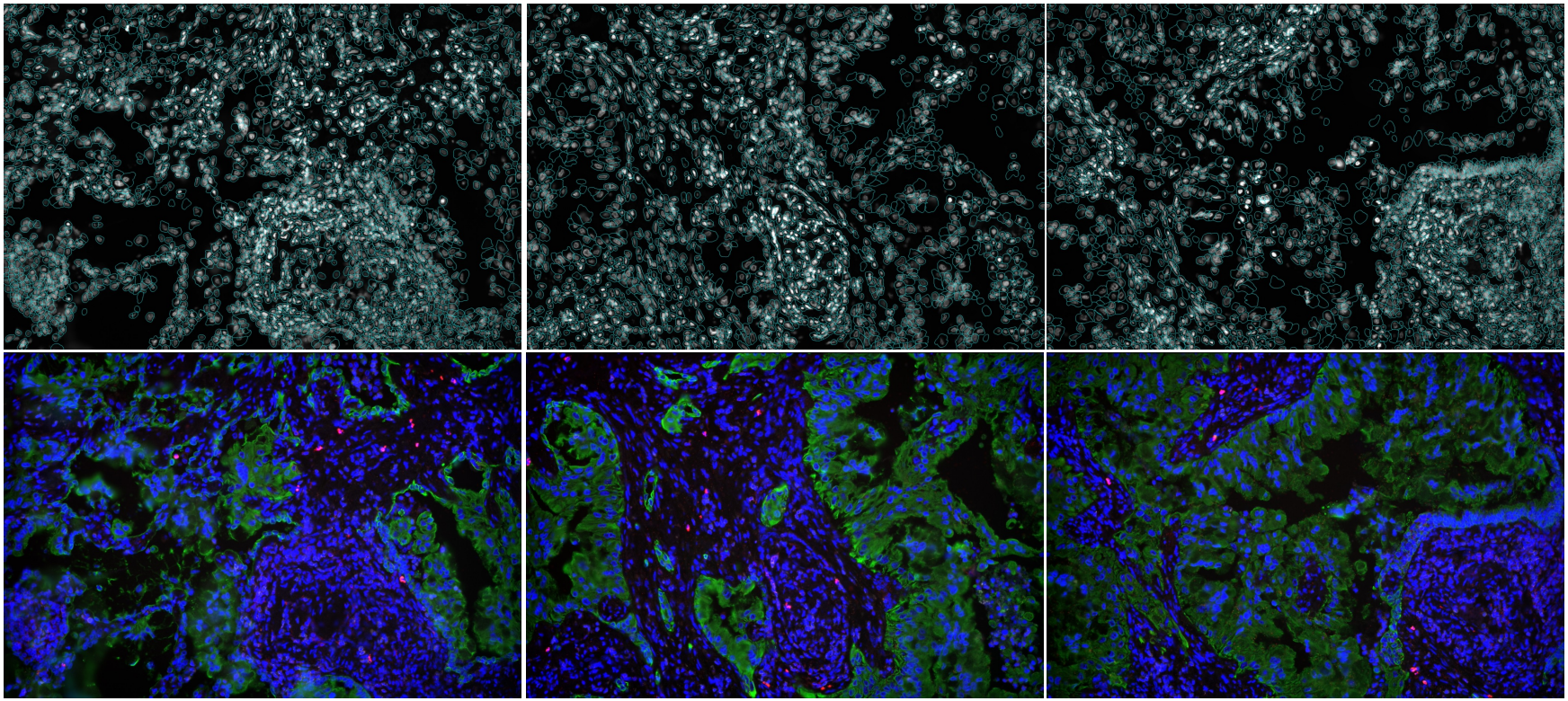
6K gene release



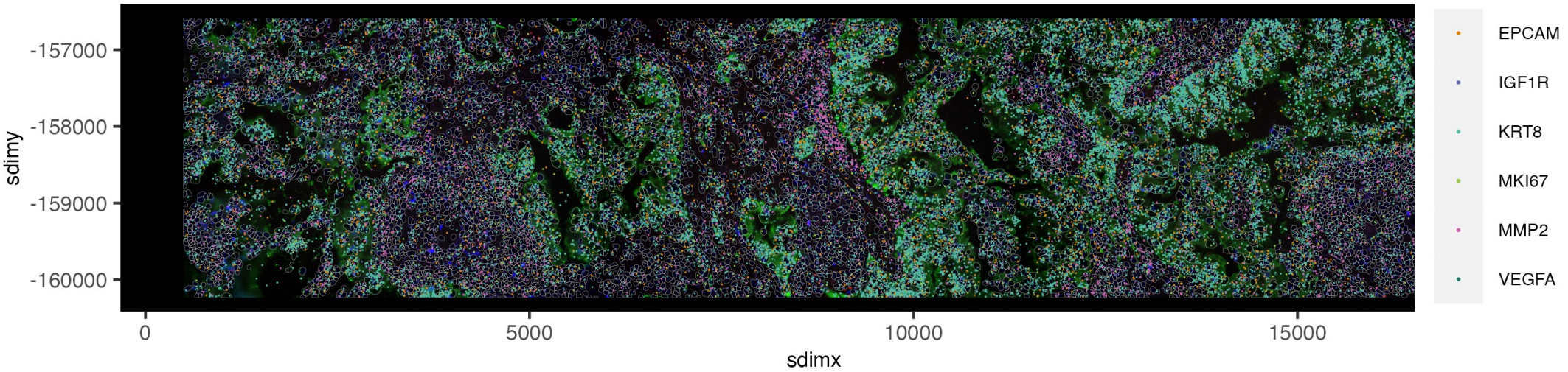

0.5 mm

Visualize cells and genes of interest on a spatial location

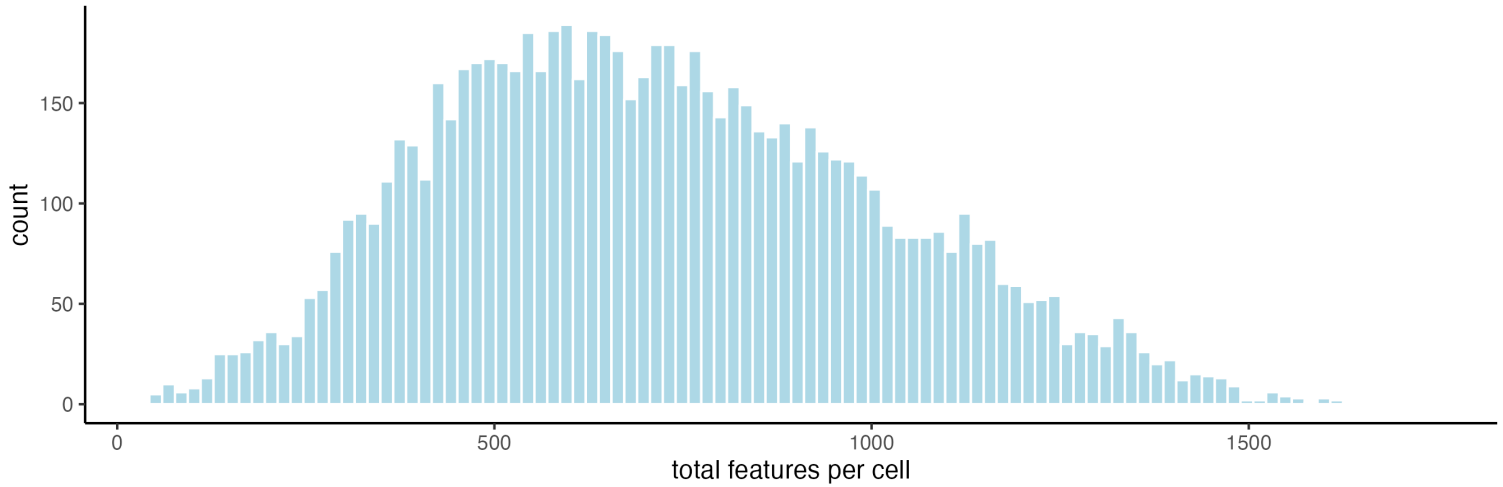
FOV 2 FOV 3 FOV 4



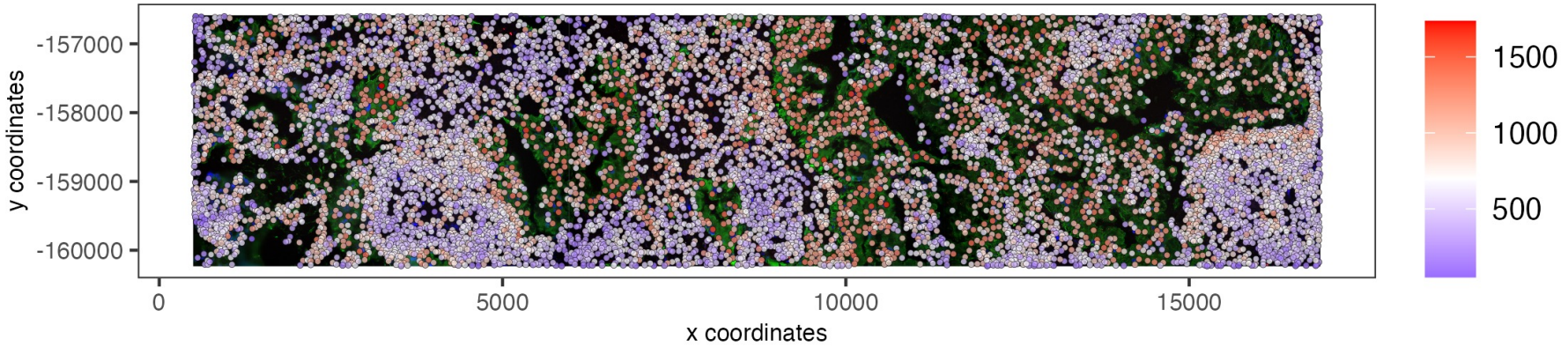
Visualize cells and genes of interest on a spatial location



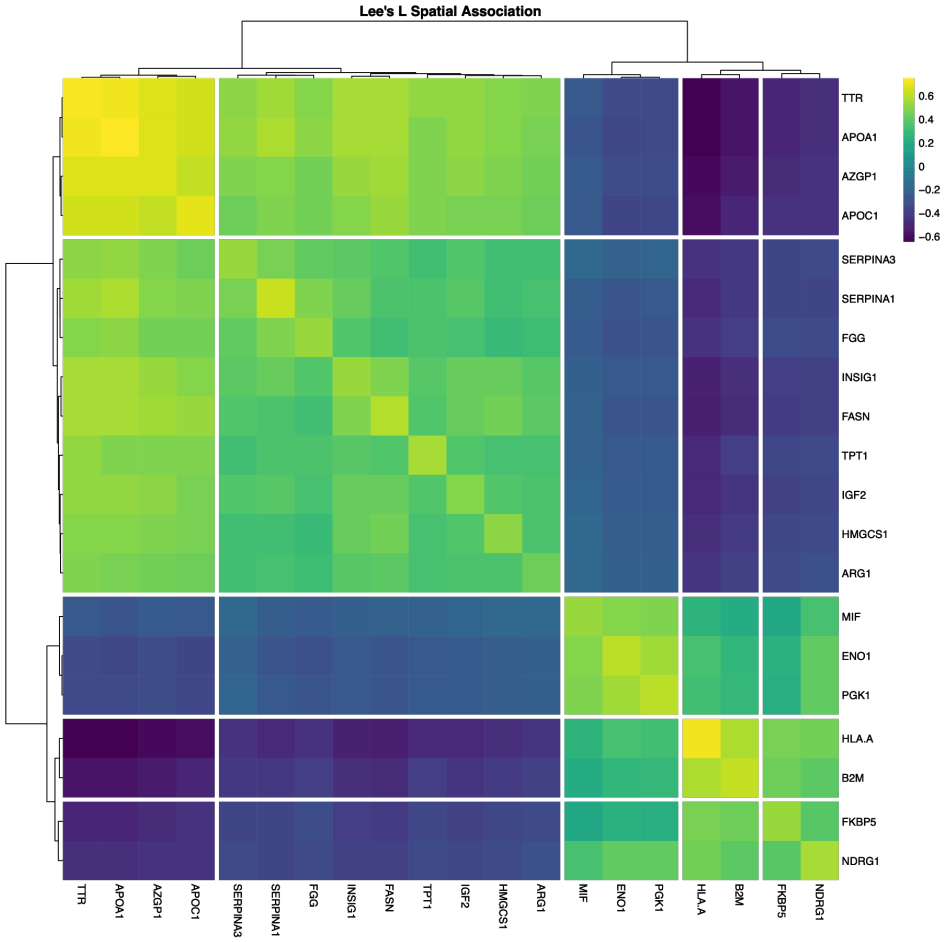
Transcript Total Expression Distribution (Histogram)



Transcript Total Expression Distribution (Spatial location)



Spatial co-expression analysis




thank you
danke
謝謝
ngiyabonga
teşekkür ederim
gracias
merci
obrigado
bedankt
dziękuję
sukriya
kop khun krap
go raibh maith agat
mochchakkeram
tapadh leat
спасибо
Баярлалаа
рахмат
spas
mersi
barka
welalin
tack
dank je
misaotra
matondo
paldies
grazzi
mahalo
faafetai lava
vinaka
blagodaram
kiitos
dankie
dhanyavad
nanni
nandri
hvala
maururu
koszonom
bayarlalaa
gracie
enkosi
хвала
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rahmet
grazie
dhanyavadagalu
shukriya
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kam sah hamnida
rahmat
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