Actualités in Hématologie

Imagerie fonctionnelle et hémopathie du sujet âgé

Pr. Andrea Gallamini
Département de recherche, innovation médicale et statistique
Hôpital A. Lacassagne. Nice (France).

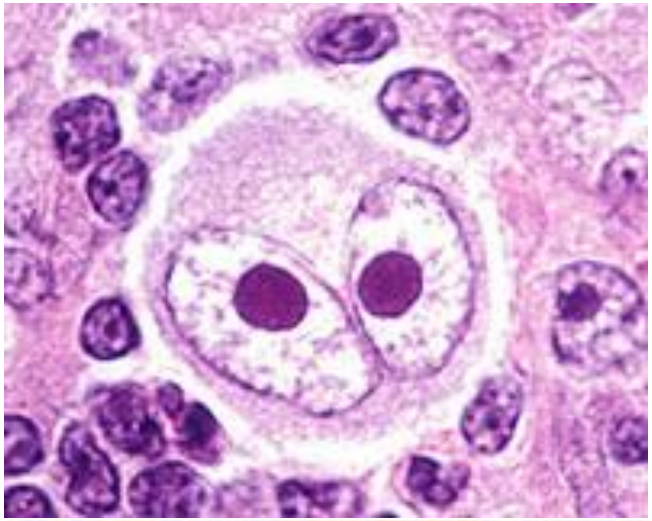
PET as a biomarker of tumor glycolysis:
(Warburg effect)

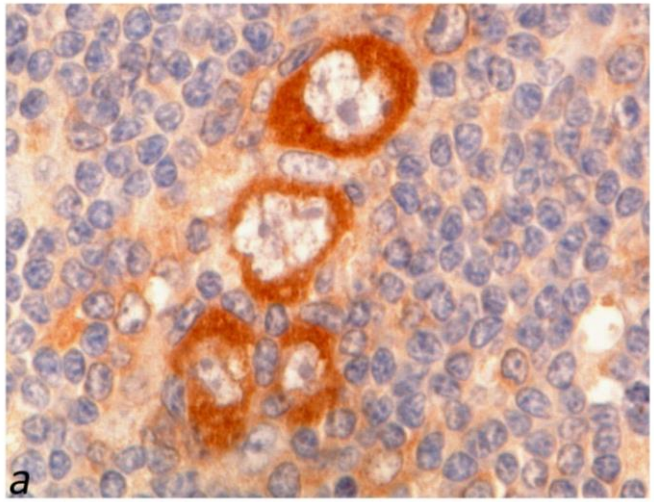
- FDG-PET selectively images tissues with accelerated glycolytic activity such as brain and heart.
- Neoplastic cell demonstrate an accelerated glycolysis compared to healthy tissues (> 200x) (Warburg effect)[1].
- This could be explained by the up-regulation of the trans-membrane glucose transporter protein GLUT-1 in tumors
- Chemotherapy switches off the metabolic activity of neoplastic cells along with its FDG uptake.

Otto Heinrich Warburg 1883-1970

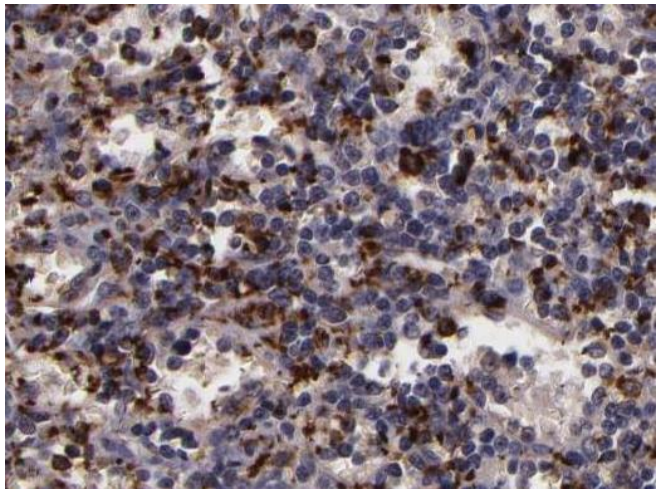
[1]Warburg O.: Uber den Stoffwechsel der tumoren. Berlin Dahlen, Springer Berlin 1926

Warburg effect exceptions in lymphoma. ME cells - I





In Hodgkin Lymphoma neoplastic and ME cells accounts for 1-5% and 95% of the total cells in tissue sample, respectively. CT is able to "switch-off" the metabolic activity of ME cells. These play a specific role in HL imaging: they act as an "amplifier" of ^{18}F-FDG signal and increase the detection ability of PET scan.



Glut-1 expression: HRS cells

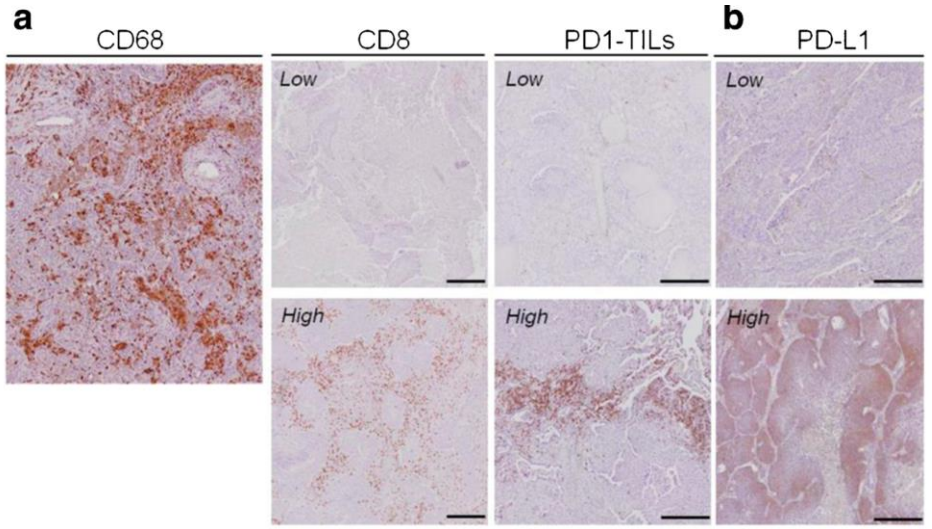
Glut-3 and Glut-6: ME cells

Hartman s: BMC Cancer. 2012 Dec 10;12:586.

Warburg effect exception in NSCLC-II

Correlation of metabolic information on FDG-PET with tissue expression of immune markers in patients with non-small cell lung cancer (NSCLC) who are candidates for upfront surgery

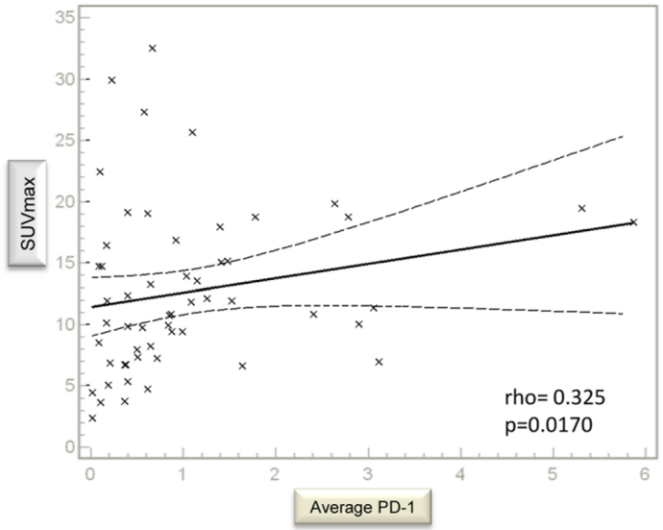
Egesta Lopci[1] · Luca Toschi[2] · Fabio Grizzi[3] · Daoud Rahal[4] · Laura Olivari[1] · Giovanni Francesco Castino[3] · Silvia Marchetti[2] · Nina Cortese[3] · Dorina Qehajaj[3] · Daniela Pistillo[2] · Marco Alloisio[5] · Massimo Roncalli[4,6] · Paola Allavena[6] · Armando Santoro[2,6] · Federica Marchesi[3,7] · Arturo Chiti[1,6]

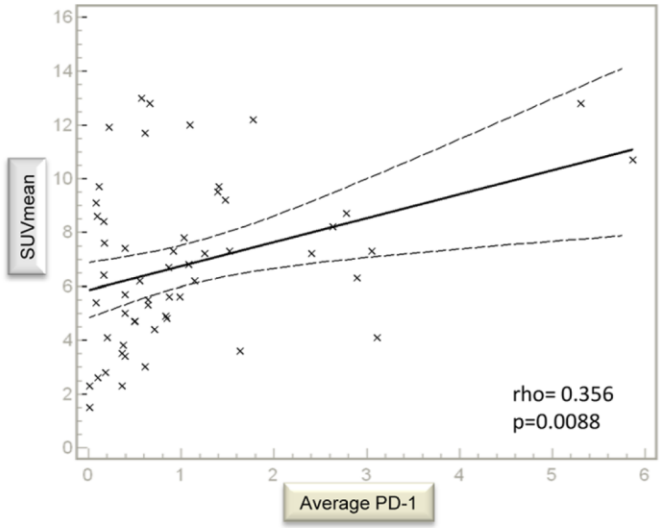


- 55 patients affected by lung tumor (36 adK., 15 SCC)
- Median SUV_{max} 11.3 (2.3-32), and SUV_{mean} 6.4 (1.5-13)
- Both significantly higher in SCC compared to other subtype (p=0.007 and 0.04, respectively)
- **Statistical correlation** between of SUVmax and SUV mean with
  - CD8 TILS (rho= 0.31; p=0.027)
  - PD-1 TILS (rho=0.33; p= 0.017)
- SUVmax, SUVmean and stage correlated with DFS (p=0.002, p=0.004 and <0.001)

Lopci S; JNMMI 2016; 43 (Oct): 1954-61

Correlation between SUVmax, SUVmean and PD-1 and between PD-1 and CD8-TILs





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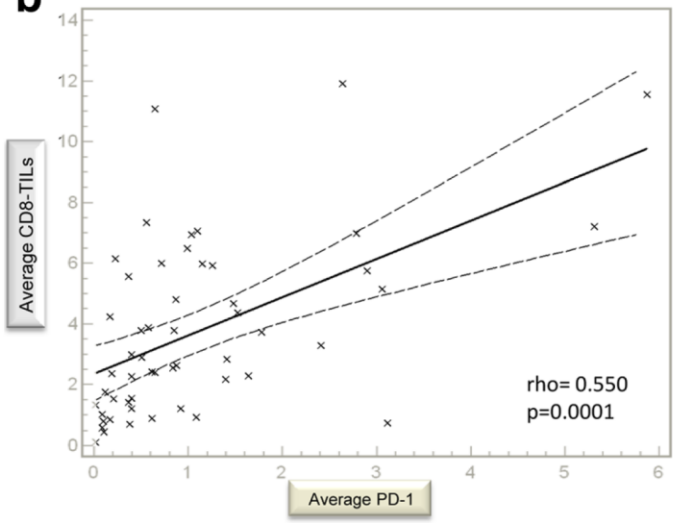
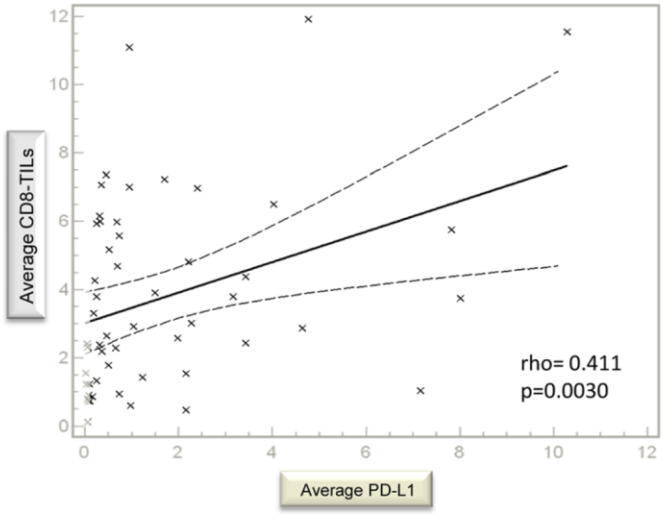
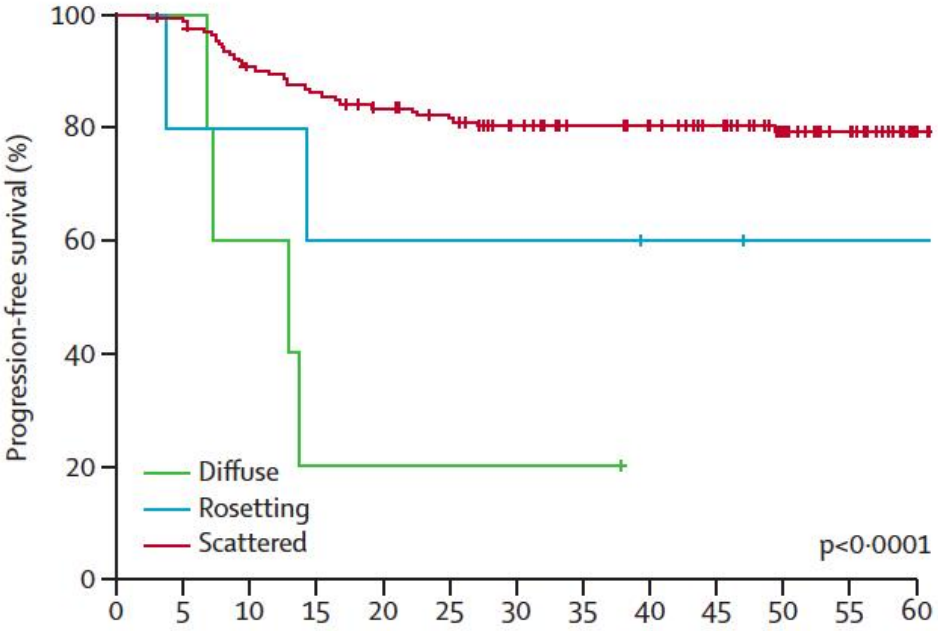
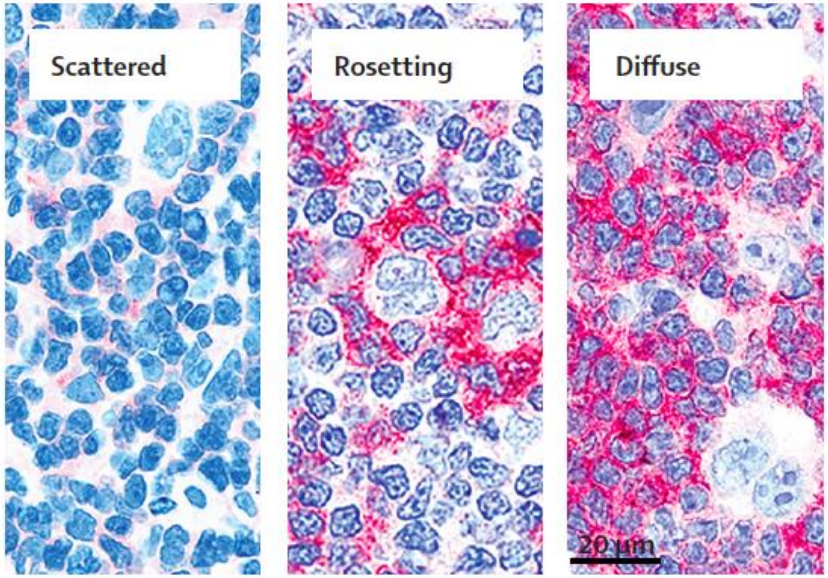




Lopci S; JNMMI 2016; 43 (Oct): 1954-61

PD1 in ME cells and Outcome in cHL

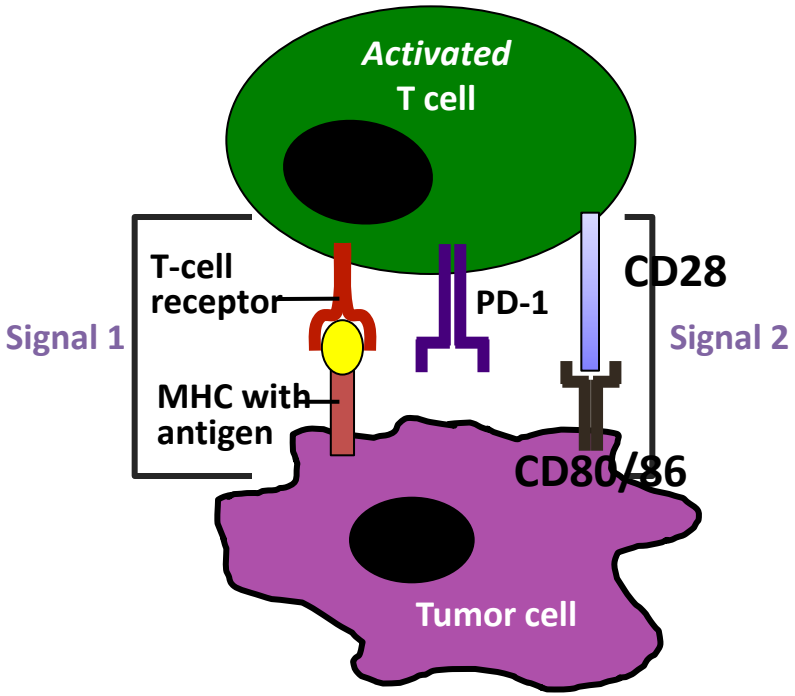




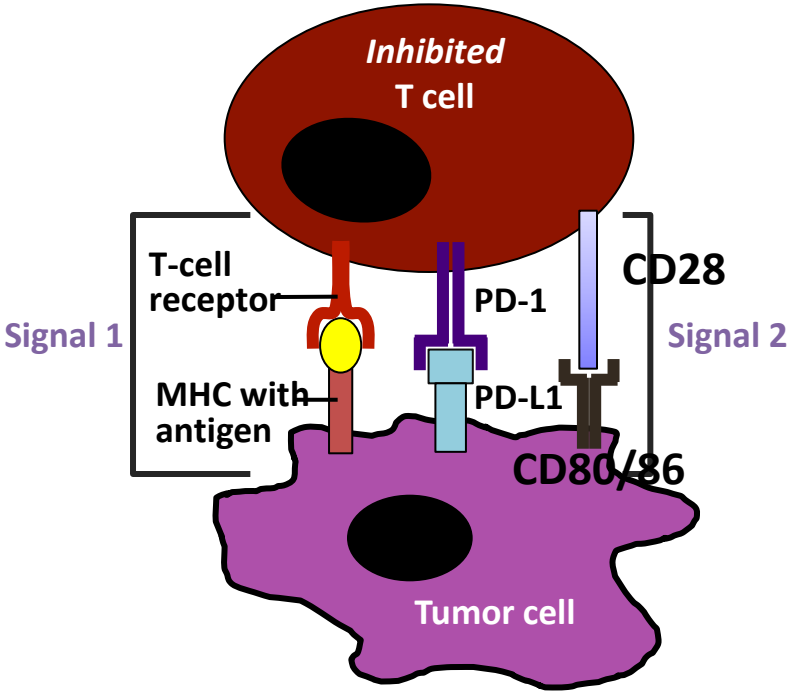
Agostinelli C, Gallamini A et al, Lancet Haematol 2016 e-pub on line

PD-1/PD-L1 in the Immune Response

Binding of activated T-cell to Tumor cell via TCR-MHC antigen induces cell lysis



Binding of PD-L1 to PD-1 receptor downregulates T-cell effector functions

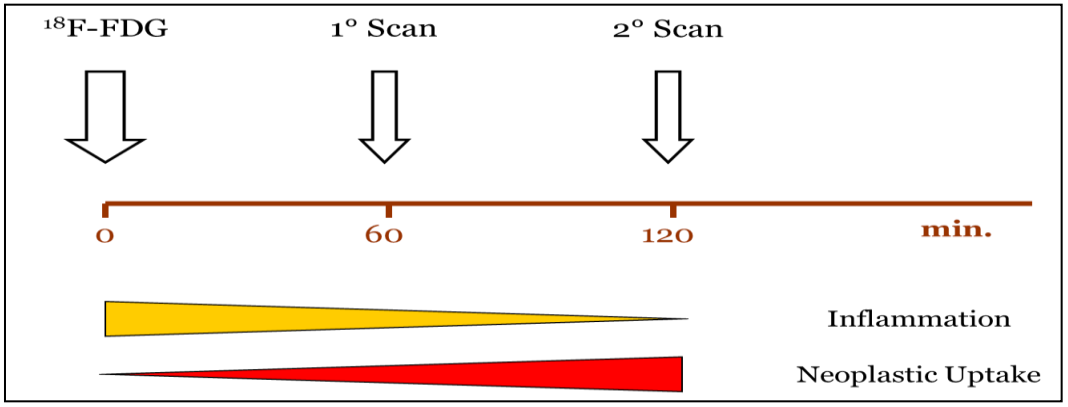


Sznol M, Chen L. *Clin Cancer Res.* 2013;19:1021-1034.

Relationship between aging and inflammation

Kinetics of ^{18}FDG uptake

- **Neoplastic cell:** ↑ GLUT1= ↑FDG uptake, ↑ hexokinase/glucose-6-phosphatase ratio = ↑↑ ^{18}FDG trapping[1,2,3].
- **Microenvironment cell:** ↑GLUT3 = ↑ FDG uptake , but ↓ hexokinase/glucose-6-phosphatase ratio = ↑^{18}FDG trapping, with some spontaneous eluition[2,3].
- Several reports confirmed that the FDG uptake kinetics over time could contribute to differentiate neoplastic from inflammatory tissue[4,5].

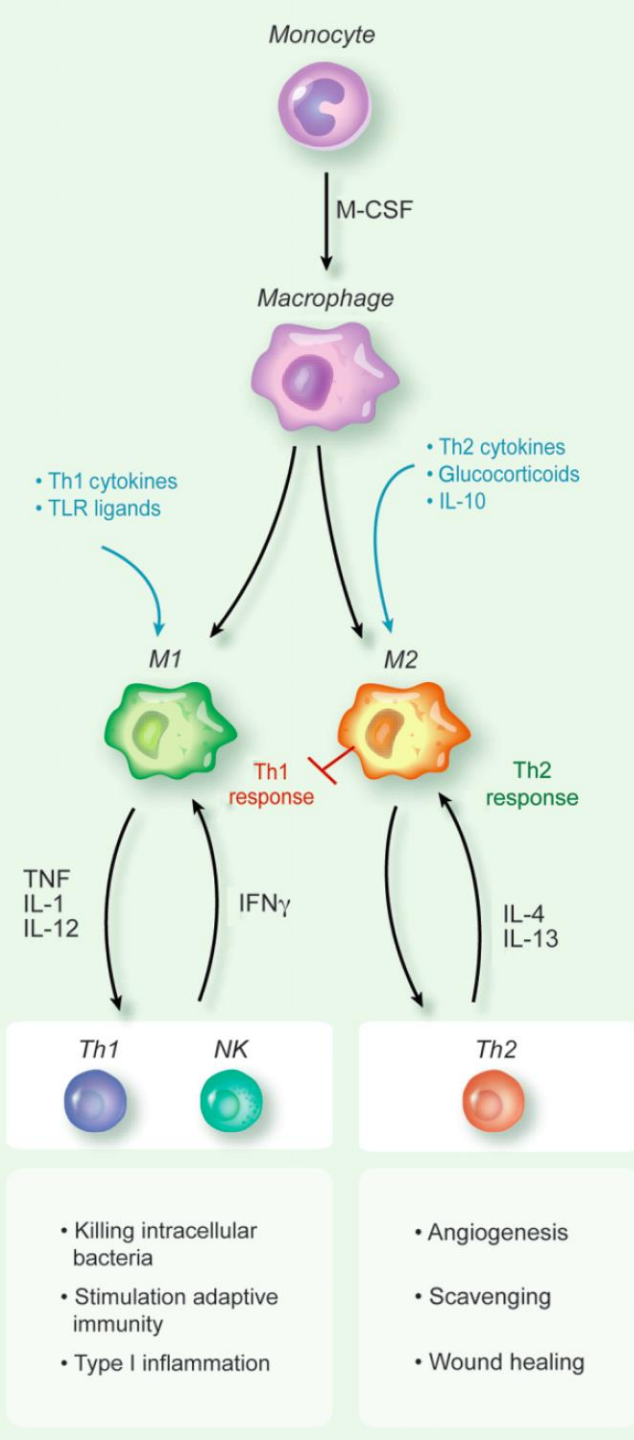


[1]Pauwels, E.K., et al.,. Nucl Med Biol, 1998. 25(4): p. 317-22.
[2]Zhuang, H., et al.,. J Nucl Med, 2001. 42(9): p. 1412-7.
[3]Hartmann et al. BMC Cancer 2012, 12:586
[4]Barger, R.L.,. Acad Radiol, 2012. 19(2): p. 153-8.
[5]Zhang, L., Acta Radiol, 2013 Sep 1;54(7):770-7

What is “Immunosenescence”?

Immunosenescence in elderly patients (>65 yrs.):

- depleted population of naïve T cells
- Shrinking repertoire of T cell clone
- Increasing number of T-reg. (CD4+ Foxp3+) downregulating T cell response
- A low-grade pro-inflammatory status
- Macrophage polarization: M_1 ➔ M_2 and
- Increased number of MDSC
- Macrophage polarization promotes cancer-related inflammation through cytokine (IL-6, TNF) and chemokine (CCL2, CXCL8, CXCL 12) production



Interactions between immune challenges and cancer cells proliferation: timing does matter!

EVOLUTION, MEDICINE, & PUBLIC HEALTH

Allavena P: Clin Exper. Immunology 2012; 167:195-205.
Camille J.: Evolution, Medicine and public health 2016; p299-311

Antoine Lacassagne
CENTRE DE LUTTE CONTRE LE CANCER DE NICE

Eudract Number : 2014-003320-51

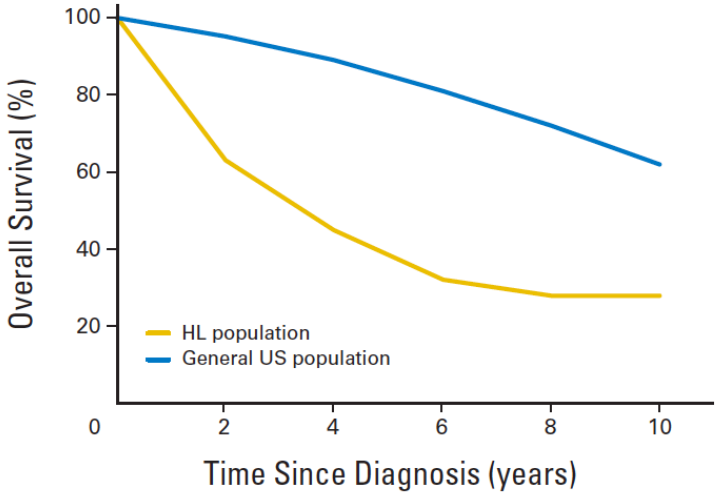
A phase 1/2 clinical trial to assess safety and efficacy of a new treatment for Hodgkin lymphoma's disease combining Adcetris® and Levact® in Old patients

HALO

Hodgkin lymphoma treatment with Adcetris and Levact in the Old patient

Report from the 2nd interim analysis (28.02.2017)

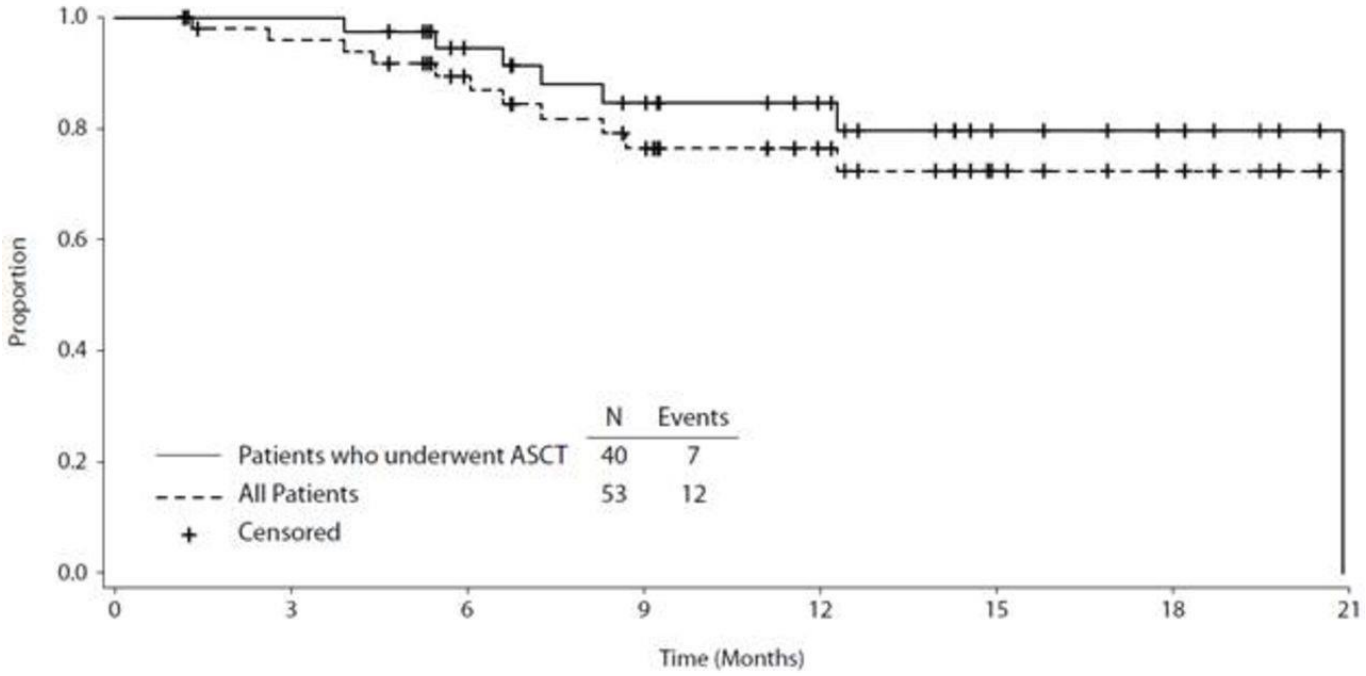
HL in the elderly



- Age > 60 Y.; 15%-35% of the whole HL population
- Different disease:
  - MC 31%-50%; EBV+ > 34%
  - Advanced or infra-diaphragmatic disease.
- 5-Y EFS 30-40%; 5-Y OS 40-50%.
- ABVD often used, but not considered standard of care
- Bleomycin lung toxicity (BLT) prohibitive, increased by G-CSF
- BLT rate: 18%
- TRM: 9% Vs. 0.3% (<60 y.).
- Role of co-morbidity
- Reduced RDI

Evens e J Clin Oncol 2013
AJagadeesh D. Haematol Oncol 2013; 31(suppl 1), 69-75

BE-BV in relapsed/refractory HL

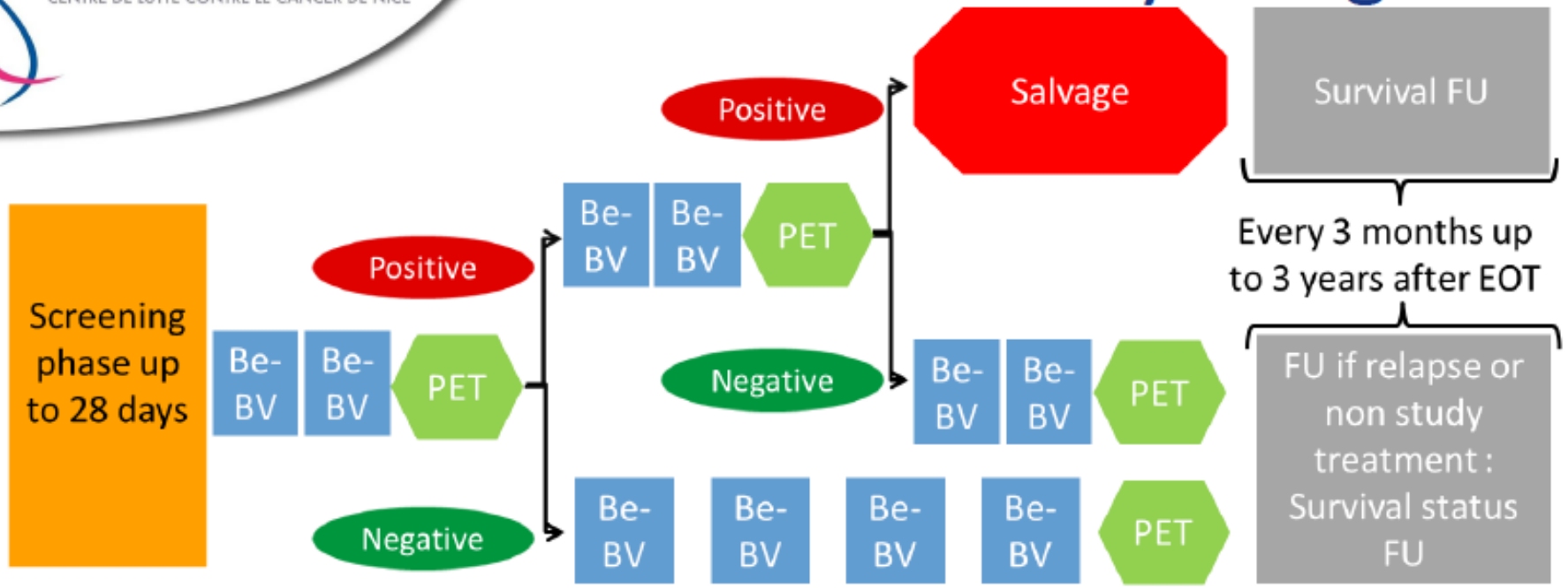


- 55 HL pts, 53 evaluable for response
- 51% had relapsed 49% refractory disease
- BV: 1.8 mg/Kg. q. 21 Days Be 90 mg/m^2 day 1° -2° q 21 days x 6 cycles
- Eligible patients underwent ASCT, followed by BV maintenance.
- CR 74% ORR (CR + PR): 93%
- The CR rate was 64% for for refractory and 84% for relapsed pts, respectively.
- Estimated 1-Y PFS 80%.

LaCasce AS Blood 2015; 126(23): 3982 [Abstr.].

Antoine Lacassagne
CENTRE DE LUTTE CONTRE LE CANCER DE NICE

Overall study design



- PET assessment following the Lugano criteria :

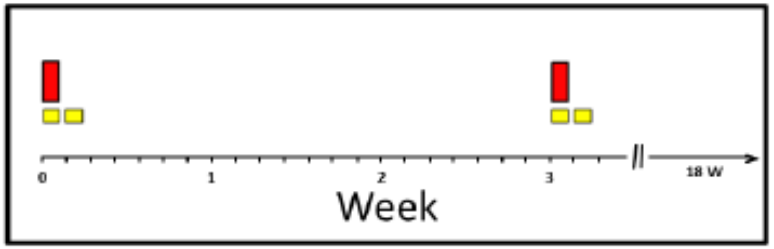
1-3 : Negative

4-5 : Positive

- Salvage therapy is out of study on investigator decision

1) Adcetris® (BV) : 1.2 mg/kg intravenously
- Infusion over 30 min

2) Levact® (Be): 90 mg/m²/day IV at D1 and D2
•30 min after Adcetris infusion, Infusion over 30-60 min



Antoine Lacassagne
CENTRE DE LUTTE CONTRE LE CANCER DE NICE

HALO Design :

- **Phase 1 (Toxicity)**

The phase is composed of two stages with only one dose of treatment (no escalation)

Stopping rules toxicities is defined as :

- Grade 2 neuropathy
- Grade 3 Neutropenia and thrombocytopenia

The inclusions will be not suspended between the two stages

Stage 1 :Inclusion of 6 patients

Patients with toxicity :

0, 1, 2 → OK — Go to stage 2, Addition of 6 patients

3 → STOP

Stage 2 : Inclusion of 12 patients

Patients with toxicity :

0, 1, 2, 3 → OK — Go to phase 2

4 → STOP

- **Phase 2 (Efficacy)**

Stage 1: Inclusion of 19 patients

Patients with CR :

≥ 13 → OK — Go to stage 2, Addition of 34 patients

< 13 → STOP

6 patients with toxicities (30%) → IDMC + STOP

Stage 2: Inclusion of 53 patients

Patients with CR :

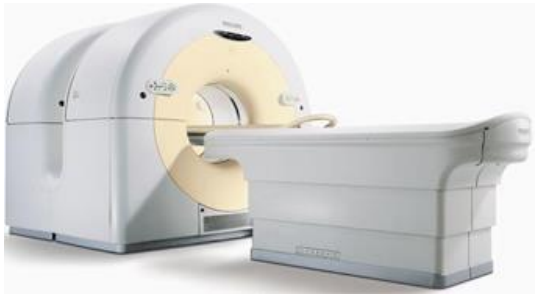
≥ 38 → Efficacy

< 38 → Inefficacy

Image Exchange for Blinded independent central review

WIDEN

SCANNERS OR WORKSTATIONS → WIDEN → LOCAL WORKSTATIONS OR WEB-VIEWER

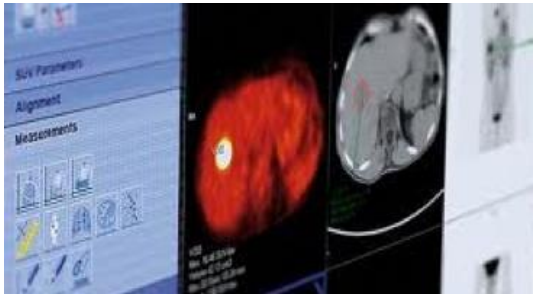


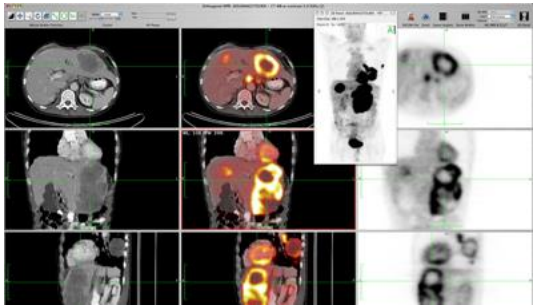
No hardware or software installation required for PET sites

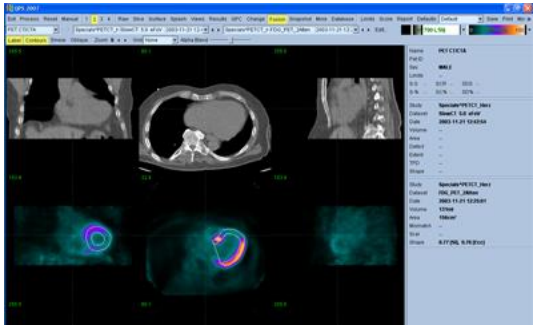
Exchange for all Image Modalities, including RT

DICOM interoperability

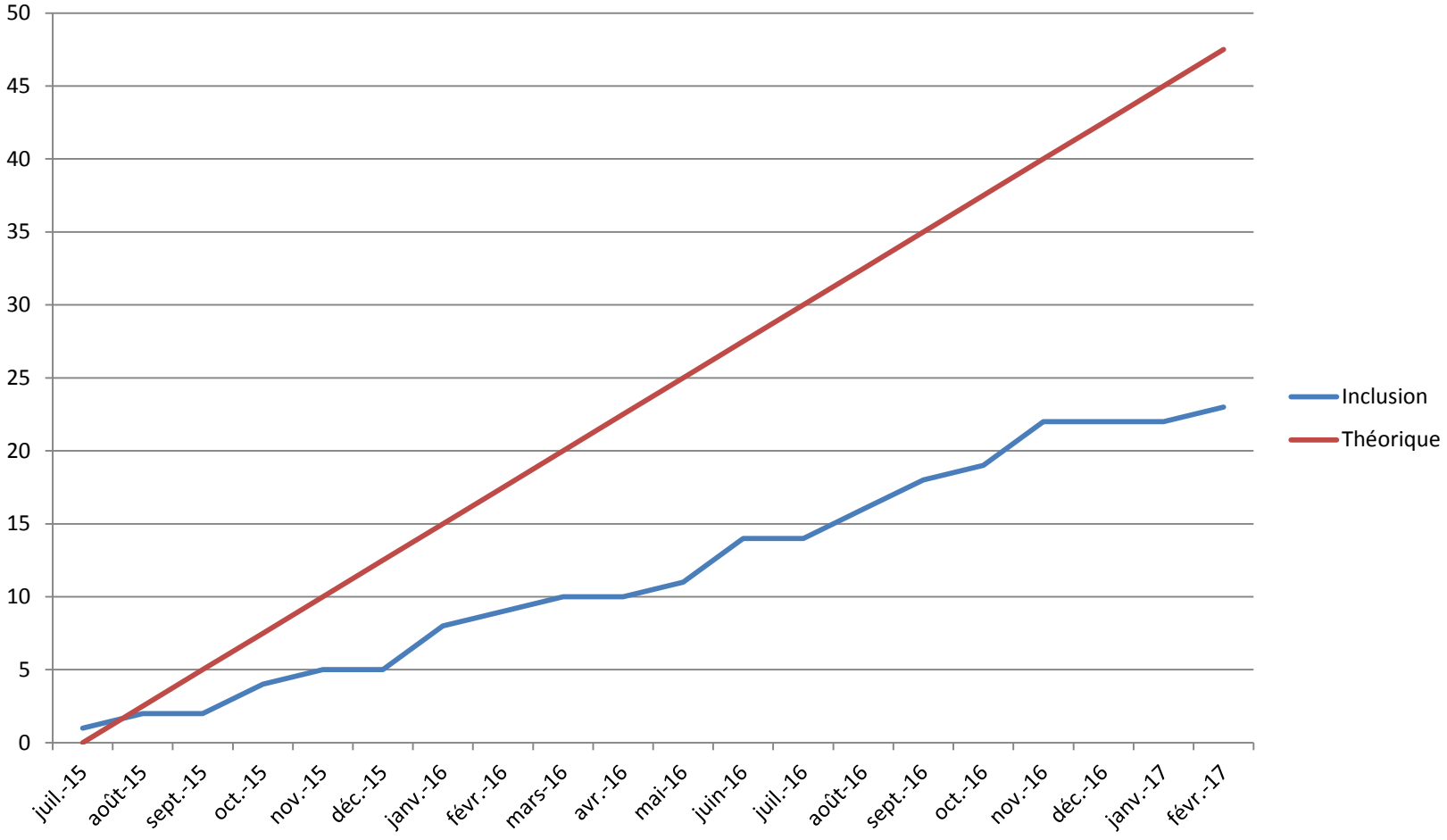
Patented ®



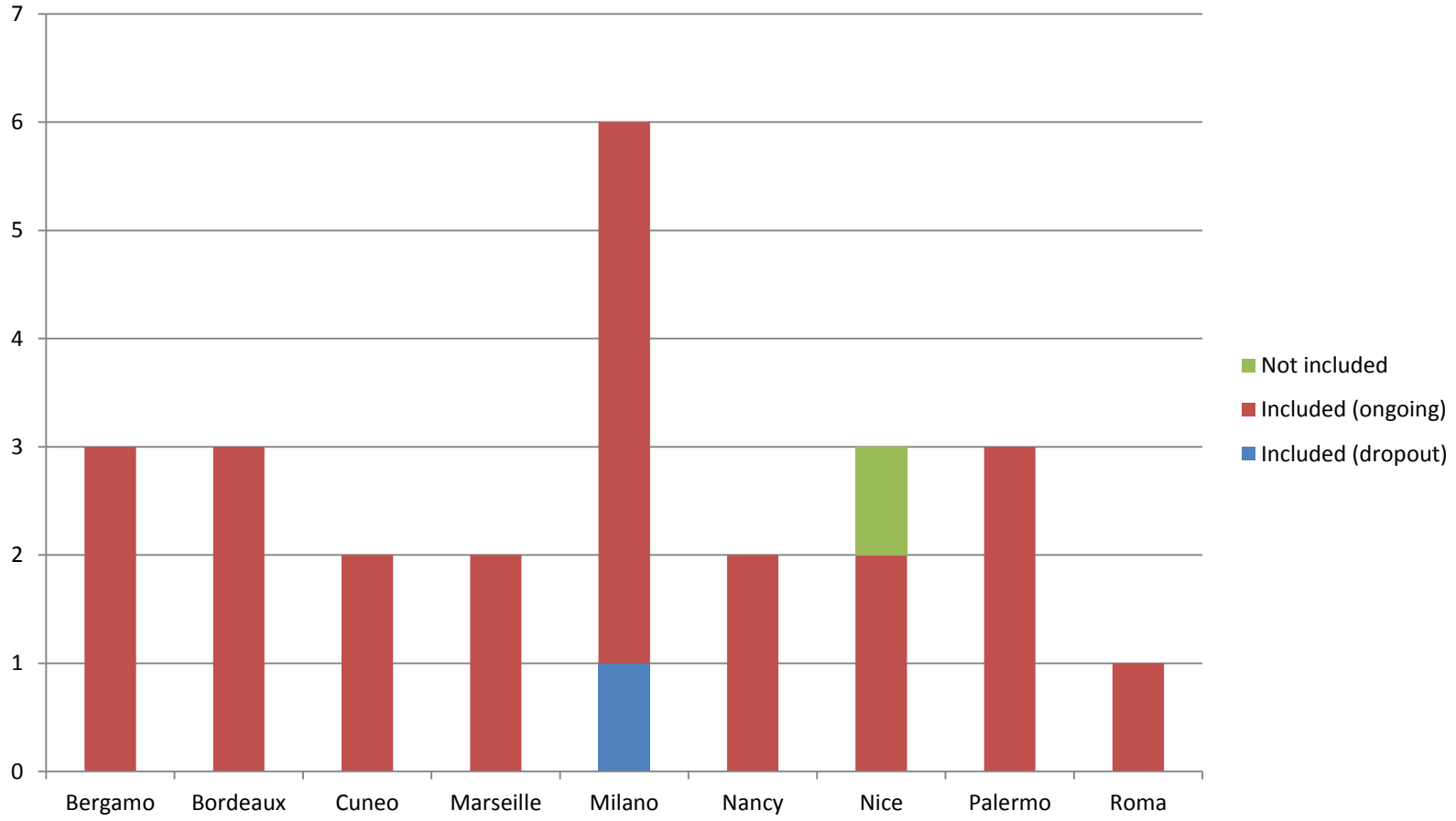




Inclusions at 28.02.2017



Inclusions for center at 28.02.2017



Demographics (N=22)

	Modality	
Age	Median (range)	69.6 (62-79)
Gender	M/F	14/8
Performance state	0-2	19
	>2	3
Stage	IIB	4
	III	9
	IV	9
B Symptoms	N/Y	8/14
LDH (U/l)	Median (range)	452 ± 209.09
Bulky	Y/N	2/22
Hemoglobin (gr./dl)	Median (range)	12.82 ± 1.96
Leukocytes (n° /µl)	Median (range)	9.09 ± 3.96
IPS	0-1	0
	2-3	15
	>3	7

Comorbidity

Comorbidity	Number	Frequency
Alcohol use	1	2.86%
Aortic valve insufficiency	1	2.86%
Atrial fibrillation	2	5.71%
Cardiac pacemaker insertion	1	2.86%
Carotid artery stenosis	1	2.86%
Chronic obstructive pulmonary disease (COPD)	1	2.86%
Colitis ulcerative	1	2.86%
Diabetes mellitus	2	5.71%
Diverticulitis	1	2.86%
Hypercholesterolemia	3	8.57%
Hypertension	10	28.57%
Hypothyroidism	1	2.86%
Retinal maculopathy	1	2.86%
Peripheral sensory neuropathy	1	2.86%
Phlebitis superficial	1	2.86%
Pulmonary hypertension	1	2.86%
Pyelonephritis	1	2.86%
Rheumatoid arthritis	1	2.86%
Thyroid disorder	1	2.86%
Urostomy	1	2.86%
Ventricular extra systoles	1	2.86%

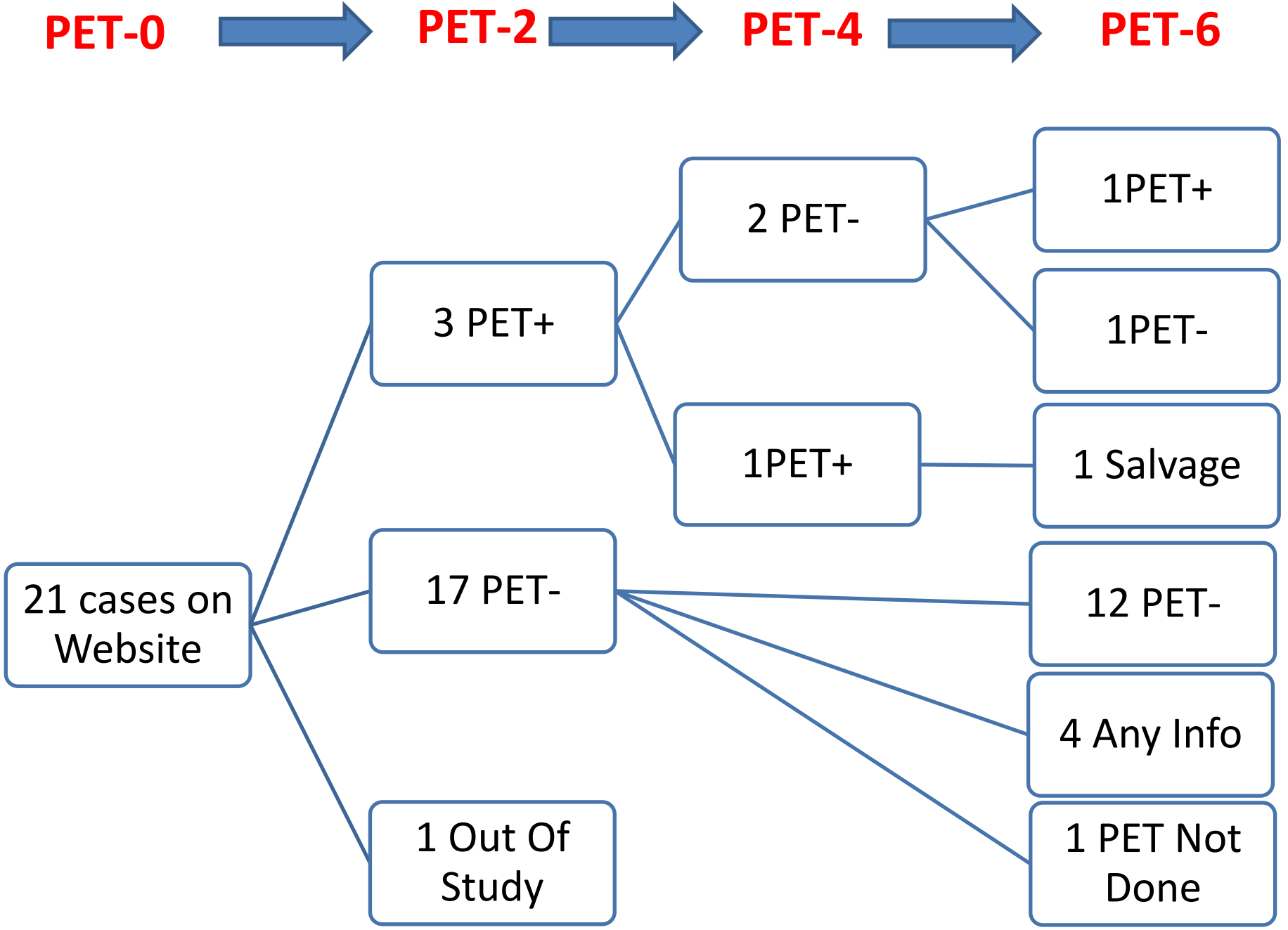
Toxicity grade 3-4 by cycle (N= 112)

Neutropenia	9
Thrombocytopenia	3
Anemia	0
Febrile neutropenia	0
CMV reactivation	1
Infection	0
Rash maculo-papular	1
Drug hypersensitivity	1
Liver toxicity	2
Pulmonary embolism	1
Stomatitis	2
Pyrexia	1
Other (Lympho-, Leukopenia, Leukocytosis, ↑INR)	89

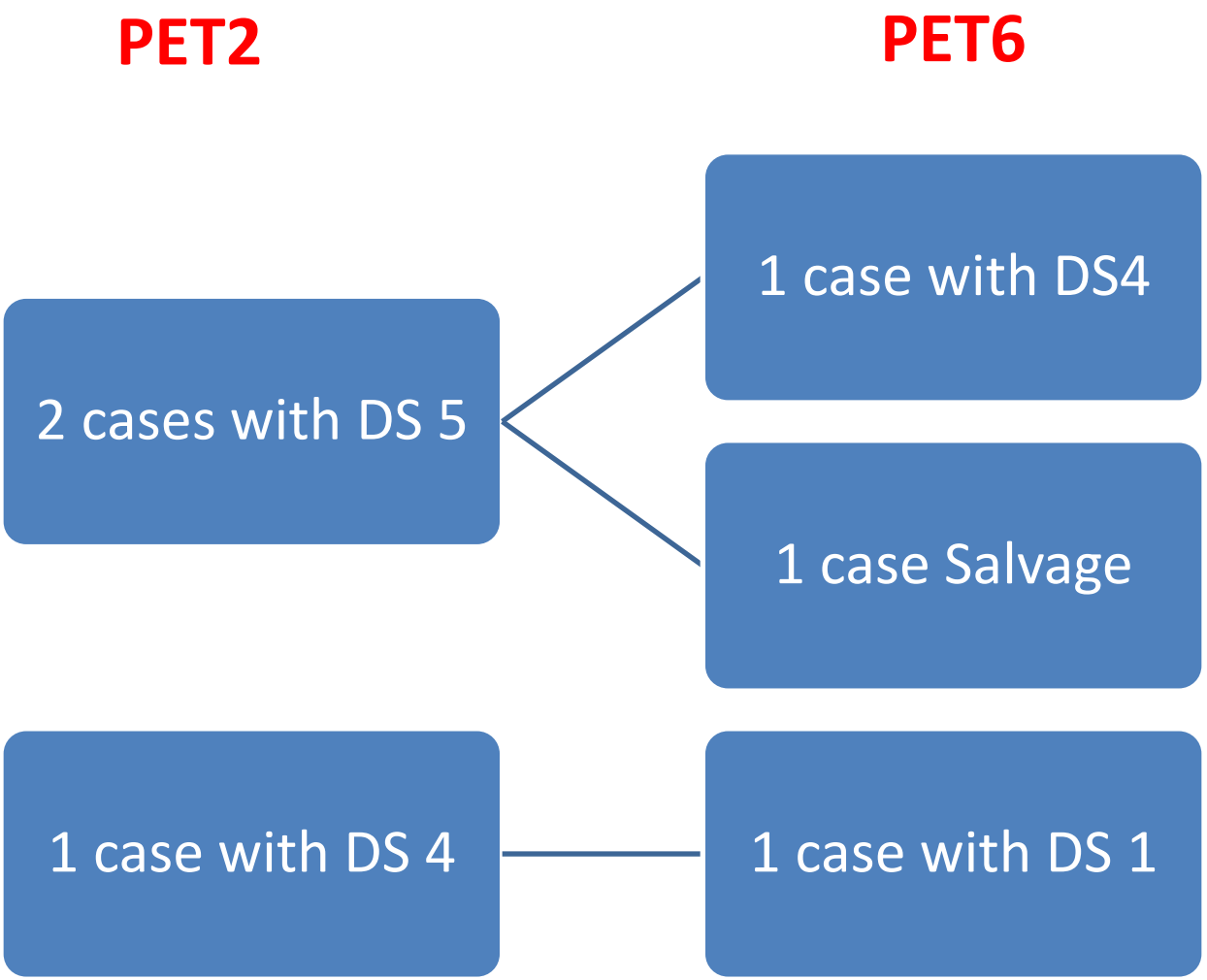
Treatment outcome (N=15)

Response (Clinical)	PET-2 score (N°)	Clinical Response C2	PET-6 score (N°)	Clinical Response C6
CR	1-3 (17)	15	1-3 (13)	14
PR	4(1), 5(1)	5	4(1)	0
SD-PRO	5(1)	1	4(1)	1
n.a.	2	1	7	7
Total	22	22	22	22

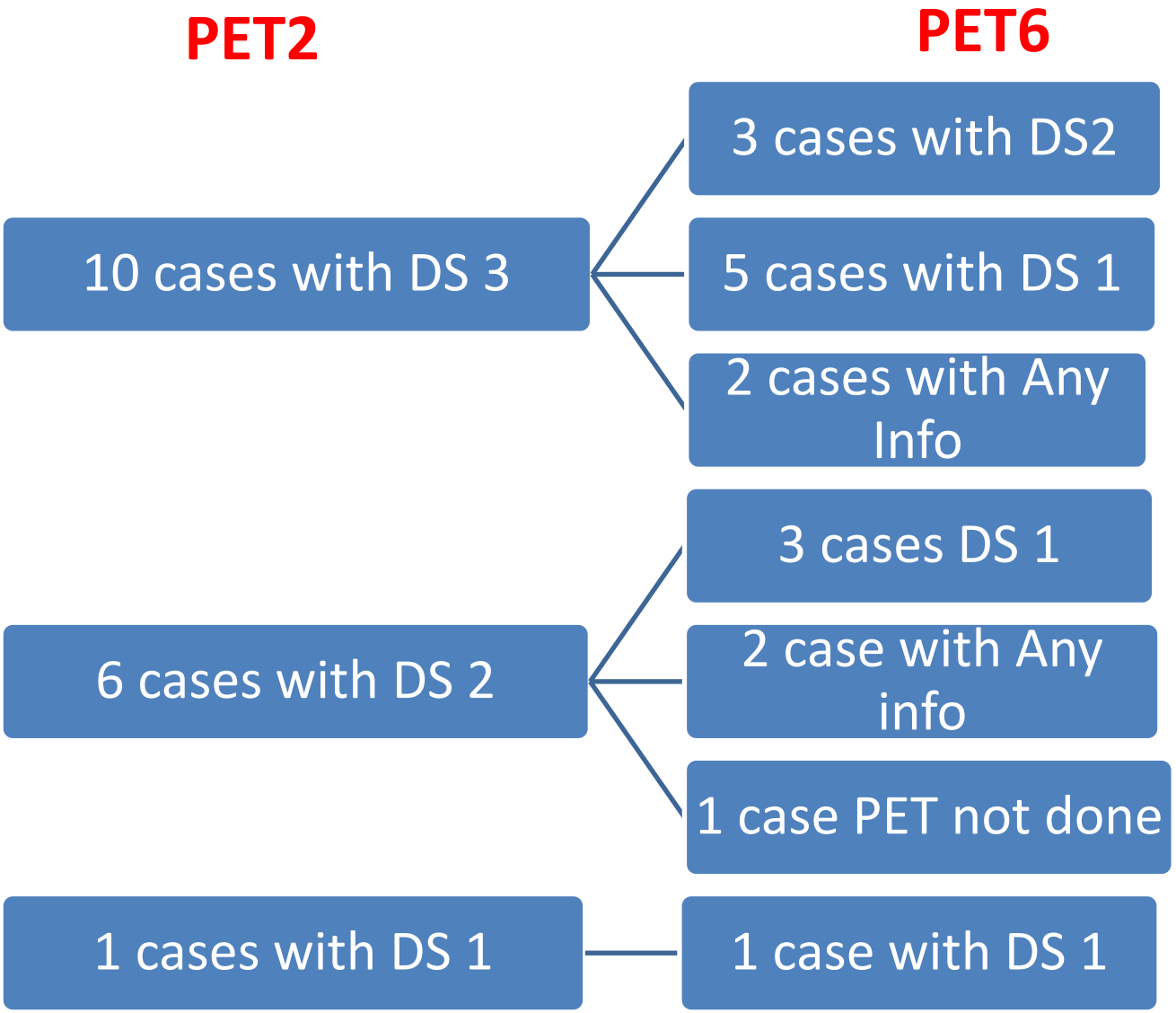
After a mean follow-up of 271 (135-445) days 10/15 are still in continuous CR: 5/15 showed disease relapse +154 days, + 280 days, +303 days, + 378 days and + 488 days, after registration.


PET-0
PET-2
PET-4
PET-6
21 cases on Website
3 PET+
17 PET-
1 Out Of Study
2 PET-
1PET+
1PET+
1PET-
1 Salvage
12 PET-
4 Any Info
1 PET Not Done

PET2 positive: 3 cases



PET2 negative: 17 cases



Merci à nos confrères…

Centre	Nice	Bordeaux	Nancy	Grenoble	Marseille	Cuneo	Rome	Milan	Bergamo	Palermo
Responsible	Thyss	Soubeyran	Bologna	Molina	Schiano de Colella	Grasso	Cantonetti	Viviani	Rambaldi	Patti

Thank you for the attention

Pr. Andrea Gallamini

Research, Innovation and Statistics.

A. Lacassagne Cancer Center, Nice - France

andreagallamini@gmail.com