Potential applications of FDG-PET in Mantle Cell Lymphoma

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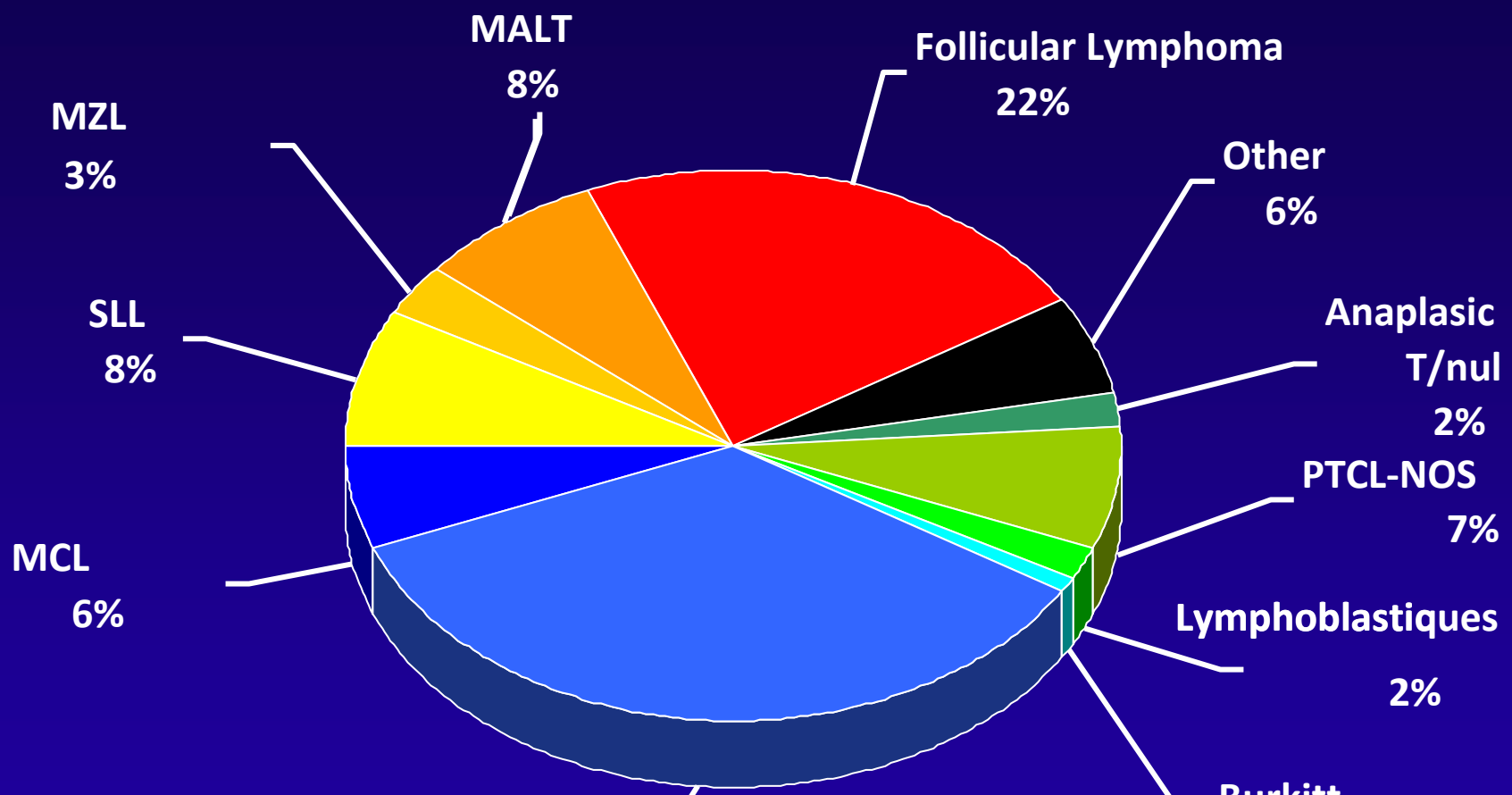
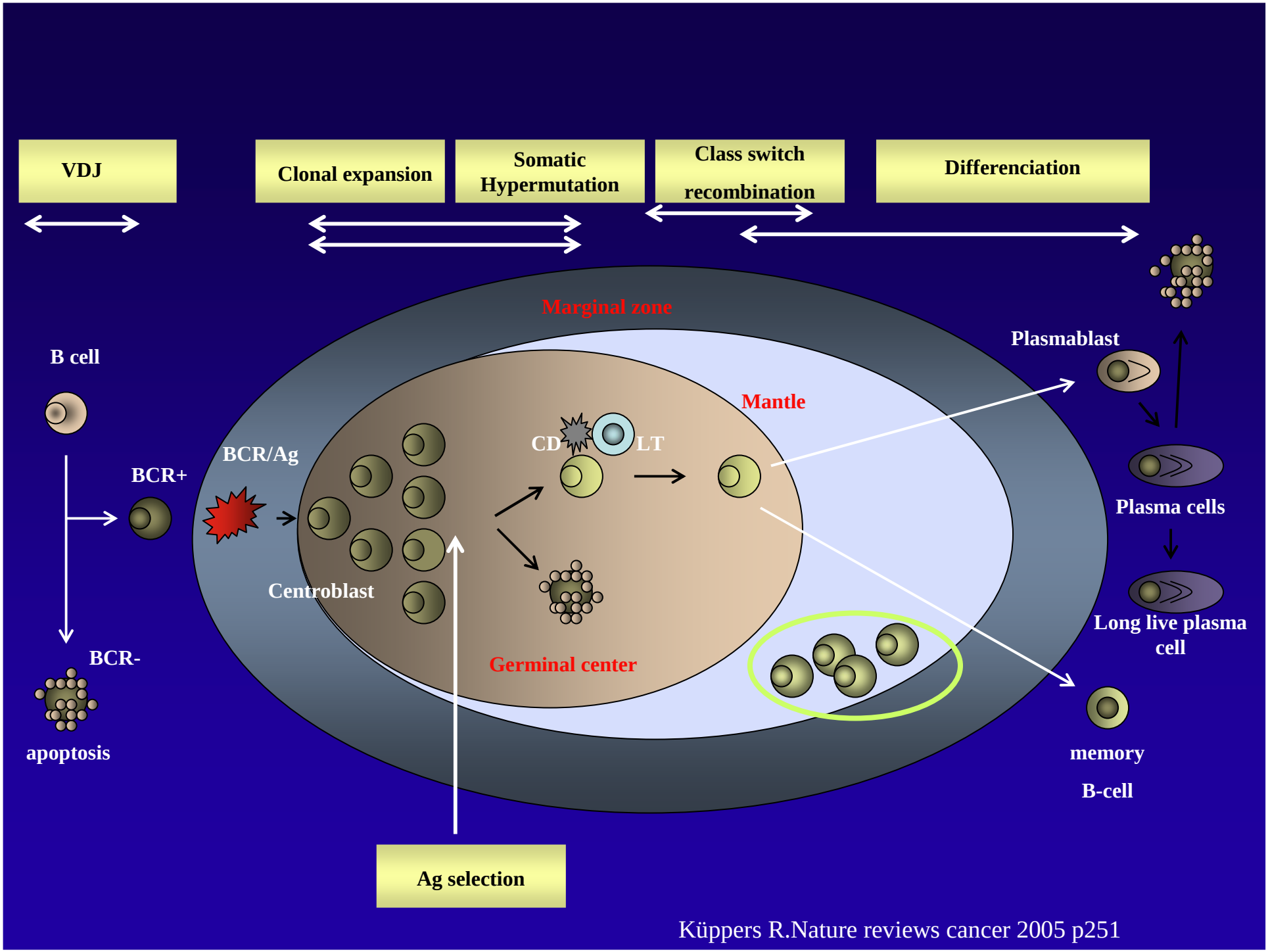
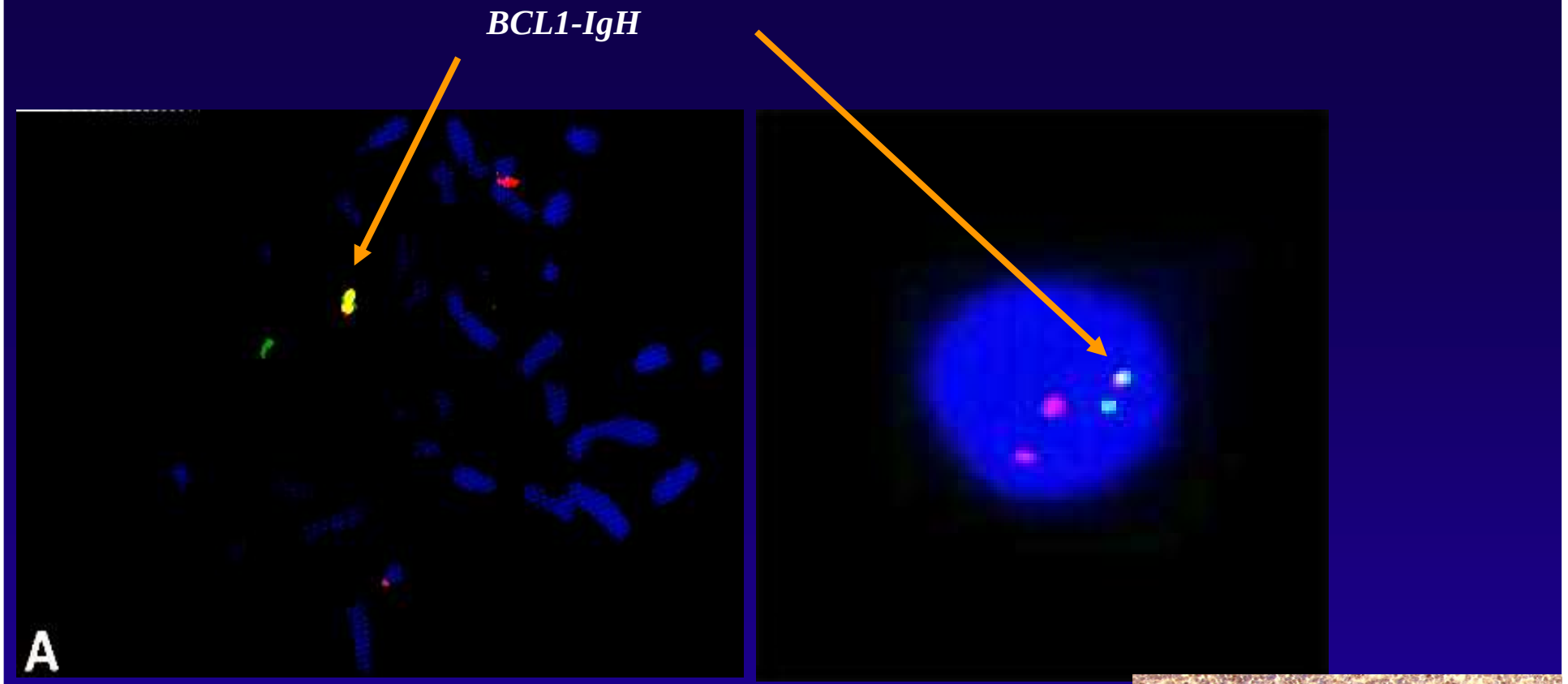
NHLs



Adapted from R Gressin



Küppers R.Nature reviews cancer 2005 p251

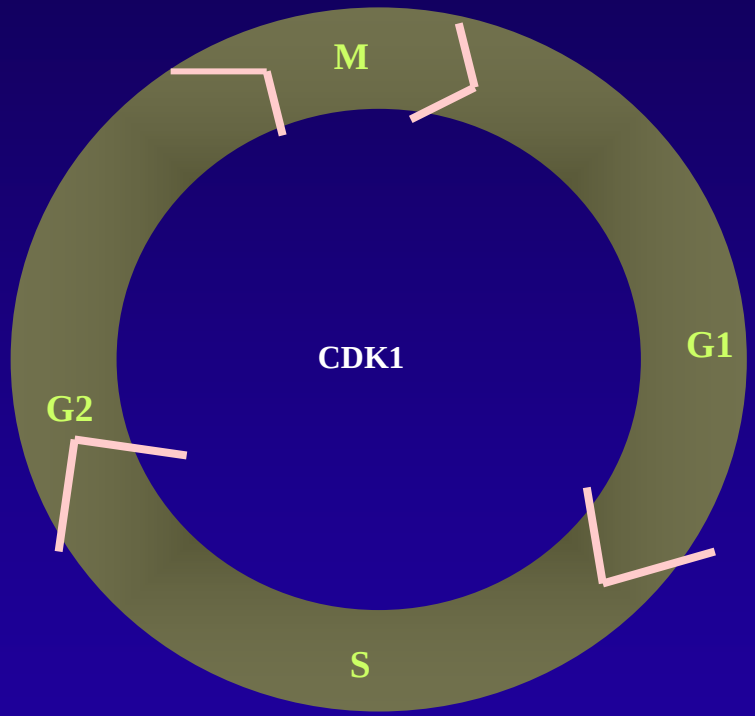


FISH

Immunochemestry

Overexpression of cycline D1 (CCND1)

Dysregulation of cell cycle in MCL cells



Abnormal mitotic signals ← t(11;14)

Lost of « checkpoints » of cell cycle ← Tumor suppressor genes

Lost or mutation in key regulator gnes

Dysregulation of proliferation

Chromosomic instability

Genomic instability

Adapted from Malumbres et al. Nature reviews cancer 2009 p153

CHALLENGES IN MCL DURING THE LAST DECADE:

- How to improve response rates ?
- How to reach long term CR ?

MCL younger: Randomization and Treatment

4 x R-CHOP

2 x R-CHOP

PR, CR

(2+1) x R-CHOP/R-DHAP alternating

stem cell mobilization after course 6

DexaBEAM
(stem cell mobilization)

PR, CR

Cyclo 120mg/kg
+ TBI 12 Gray

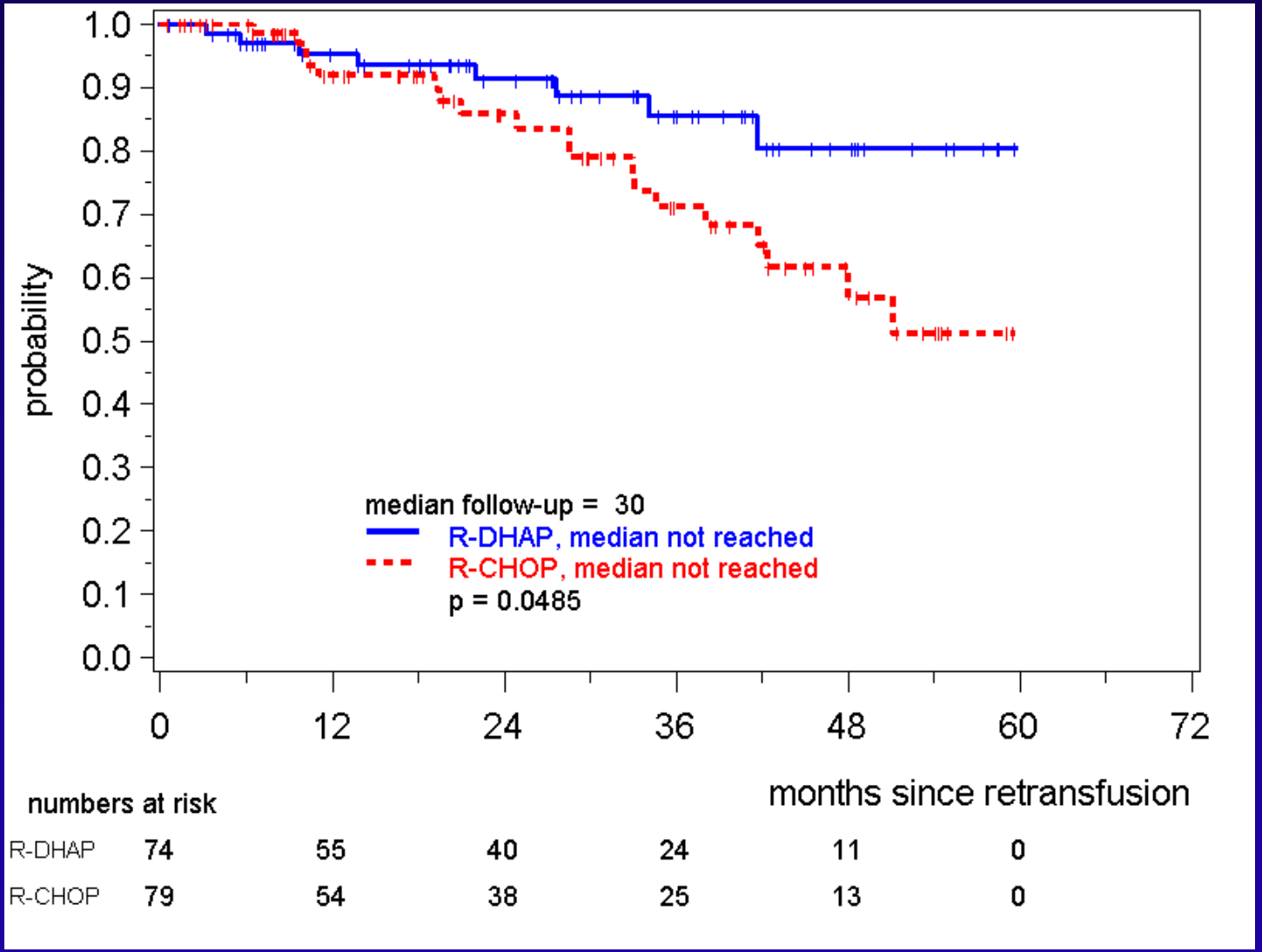
PBSCT

TBI 10 Gray
Ara-C 4x1.5 g/m2
Melphalan 140 mg/m2

PBSCT

Adapted from O Hermine ASH 2010 Abstract 110

MCL Younger: Duration of CR after ASCT



First RCT for MCL Elderly

8 countries, n = 560 (Jan 2004-Oct 2010)

Newly diagnosed, >60-65 yr; performance 0-2, Stages II-IV, central PA review

8 x R-CHOP

6 x R-FC

CR, CRu, PR

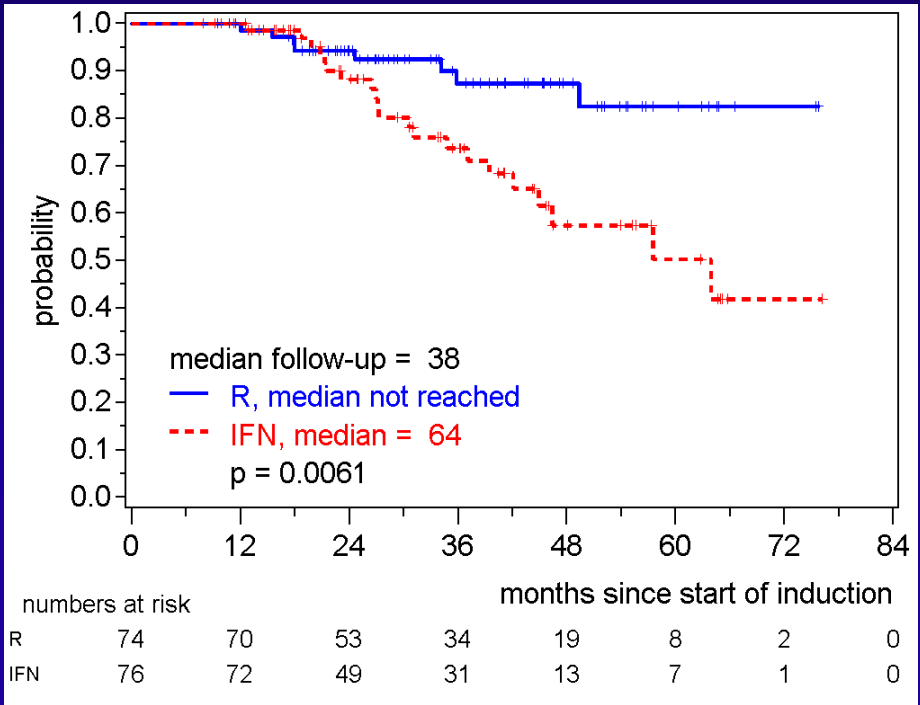
IFN-α maintenance
(3 x 3 M IU/week)
or Peg-IFN
(1ug/kg week)

Rituximab
maintenance
(all 2 months)

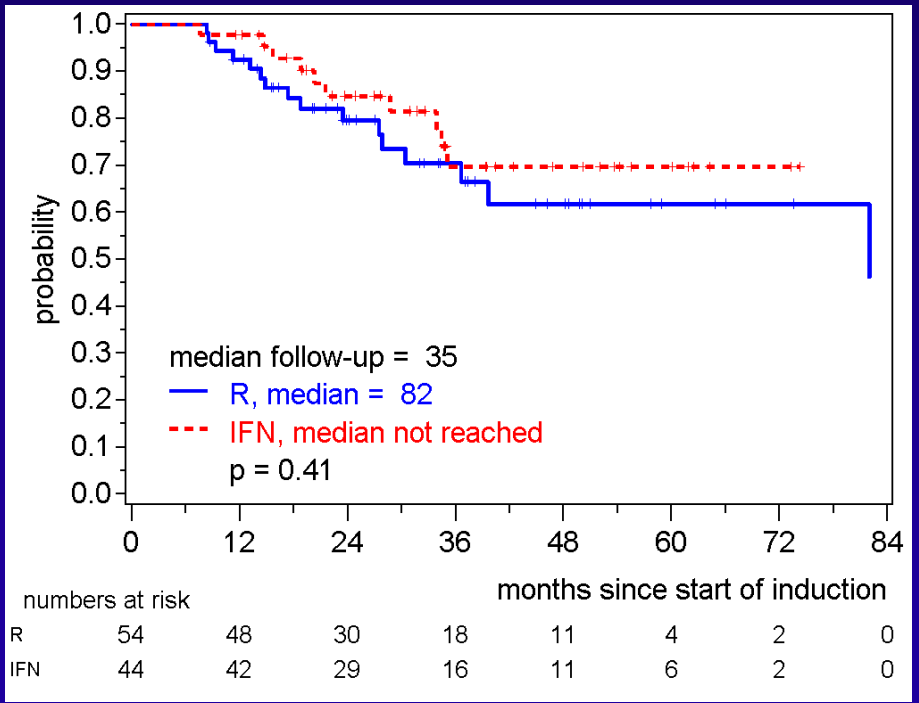
KLUIN-NELEMANS ET AL NEJM

MCL Elderly: overall survival related to induction regimen

After R-CHOP



After R-FC



p=0.055 for interaction of induction and maintenance

CHALLENGES OF THE LAST DECADES IN MCL:

- How to improve response rates ?
  - By the Use of high-dose aracytine upfront for young patients
- How to reach long term CR ?
  - By the use of Rituximab maintenance for elderly patients

WHAT NEXT ? …. New molecules: velcade, temsirolimus, lenalidomide, GA-101, BTK inhibitors ..

NEW CHALLENGES IN MCL:
How to identify high- or low-risk patients in order to built a risk-tailored therapy?

- Biomarkers at time of diagnosis (MIPI, Ki67, cytogenetic abnormalities, epigenetic dysregulations …)
- How to use MRD ?
- How to use FDG-PET?

STATE OF ART .....

Table 1. Recommended Timing of PET (PET/CT) Scans in Lymphoma Clinical Trials

Histology	Pretreatment	Mid-Treatment	Response Assessment	Post-Treatment Surveillance
Routinely FDG avid				
DLBCL	Yes*	Clinical trial	Yes	No
HL	Yes*	Clinical trial	Yes	No
Follicular NHL	Not	Clinical trial	Not	No
MCL	Not	Clinical trial	Not	No
Variably FDG avid				
Other aggressive NHLs	Not	Clinical trial	Not‡	No
Other indolent NHLs	Not	Clinical trial	Not‡	No

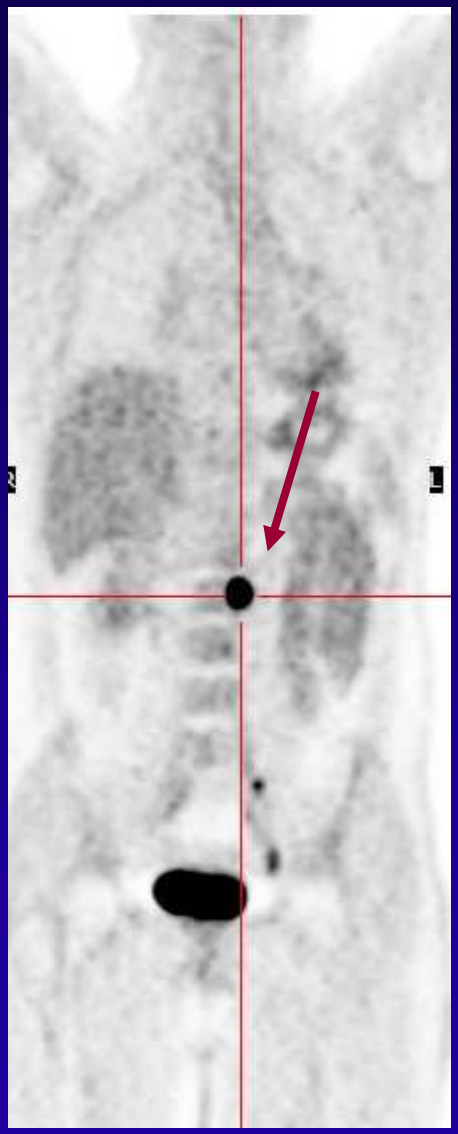
Abbreviations: PET, positron emission tomography; CT, computed tomography; FDG, [^{18}F]fluorodeoxyglucose; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; MCL, mantle-cell lymphoma; ORR, overall response rate; CR, complete remission.
*Recommended but not required pretreatment.
†Recommended only if ORR/CR is a primary study end point.
‡Recommended only if PET is positive pretreatment.

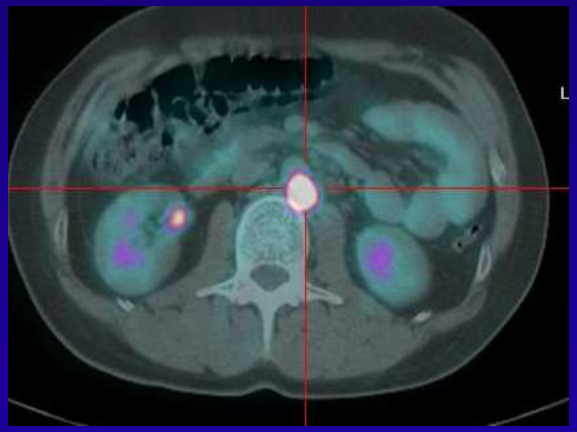
Cheson, J Clin Oncol, 2007

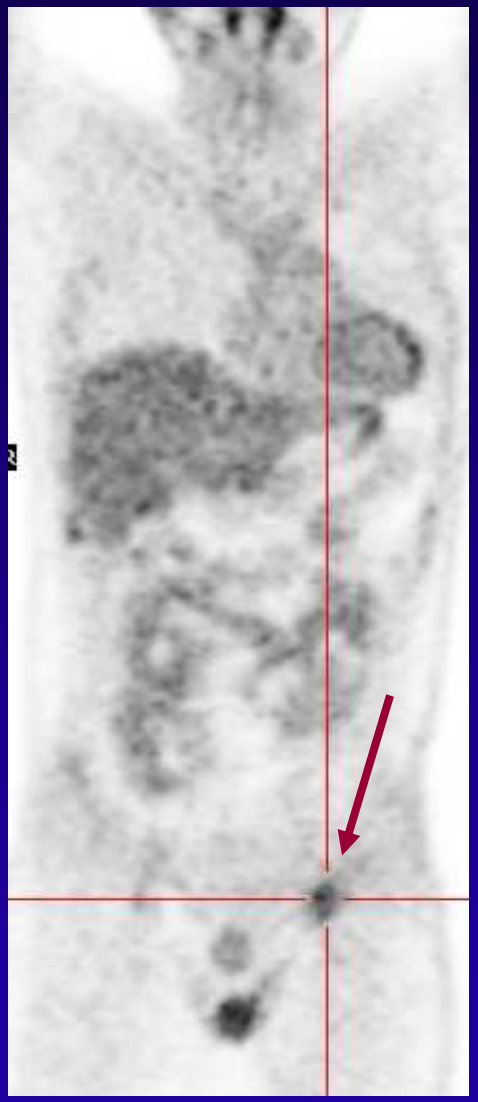
However, FDG-PET is moving forward in MCL:

- STEP 1: FDG-PET at diagnosis ?
- STEP 2: FDG-PET for response assessment at end of therapy ?
- STEP 3: FDG-PET for mid-treatment response assessment ?

STEP 1







STEP 1: FDG-PET at diagnosis

Study	N	Sensitivity	SUVmax range
Elstrom Blood 2003	7	100%	Not performed
Brepoels Leukemia & lymphoma 2008	37	100%	~1.8-19
Karam Nuclear medicine communications 2009	81	100%	< ou = 5: n=20
Gill Clinical Lymphoma & Myeloma 2008	28	100%	Not performed
Schaffel Blood (ASH Annual Meeting Abstracts) 2009	75	95%	Not performed
Bodet-milin Eur journal of nuclear medicine 2010	44	100%	1.7-18.8
Alavi Clinical Lymphoma & Myeloma 2011	19	100%	Not performed
Hosein Am journal of hematology 2011	34	94%	1.6-14
Mato Cancer 2012	53	92%	2.5-36.7

- High sensitivity for nodes and spleen.
- Insufficient sensitivity for bone marrow and gastrointestinal involvement.
- Heterogeneous Suvmax

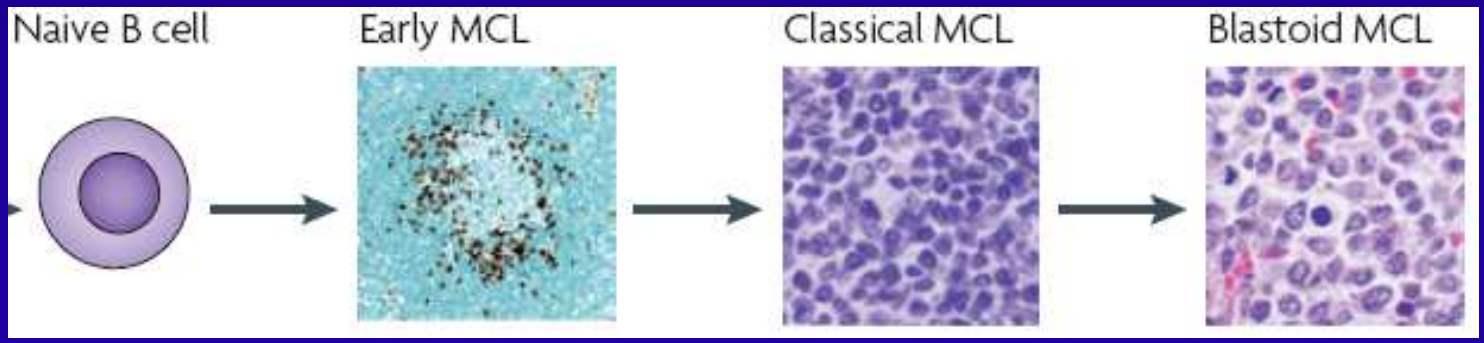
STEP 1

SUV max value

KI67 + cells

t(11:14)

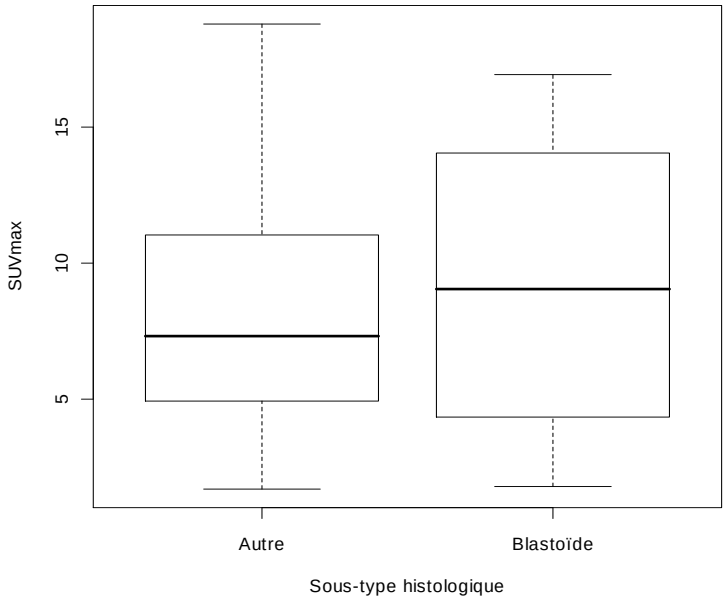
ONCOGENIC events (P53, MYC, ATM, BCL-2…)



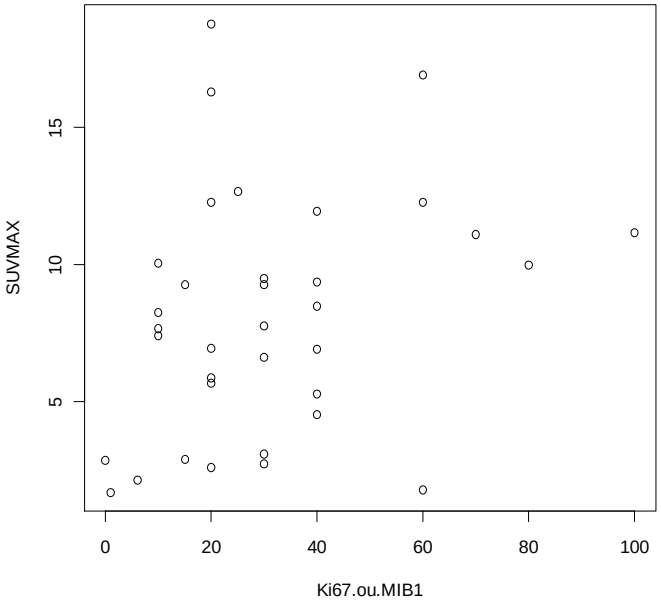
STEP 1

QUESTION

No link between
SUVmax and histologic subtype



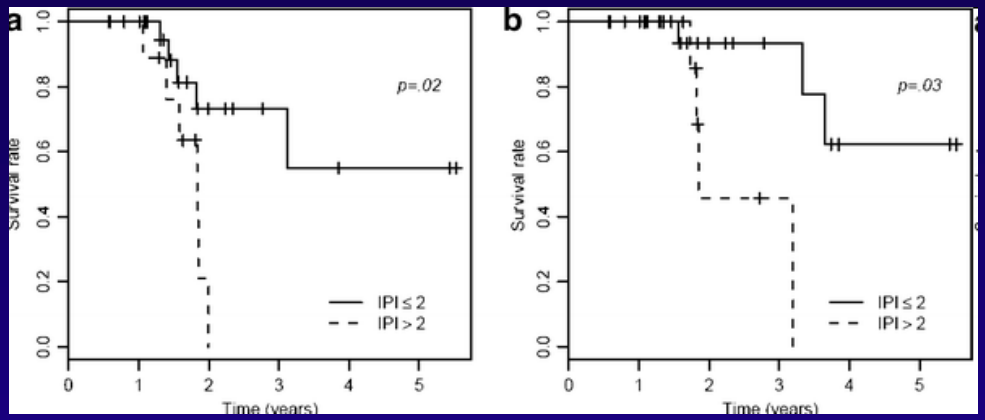
No link between
SUVmax and proliferation

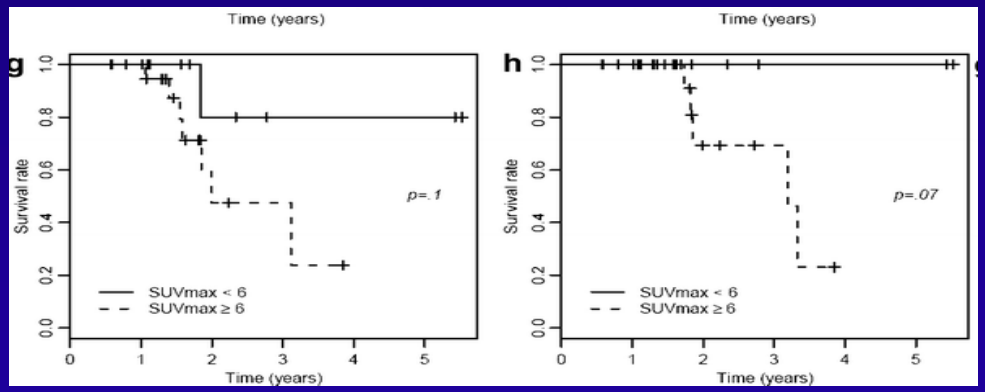


Bodet-milin et al (Eur journal of nuclear medicine 2010)

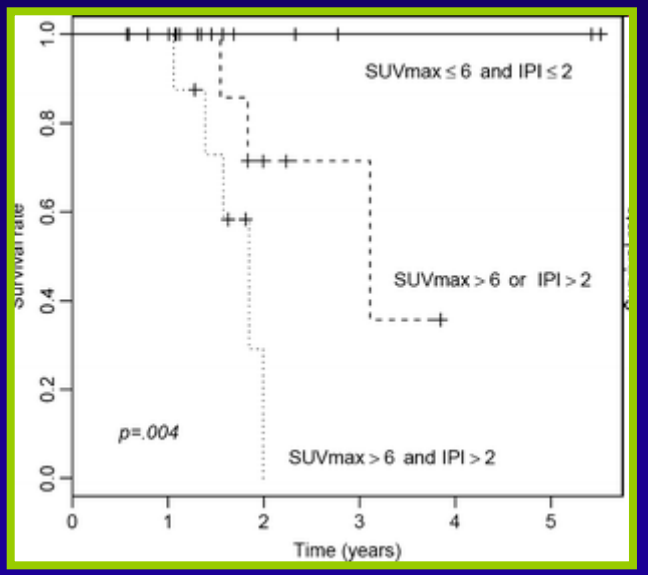
STEP 1

Prognosis Index?





Prognosis index



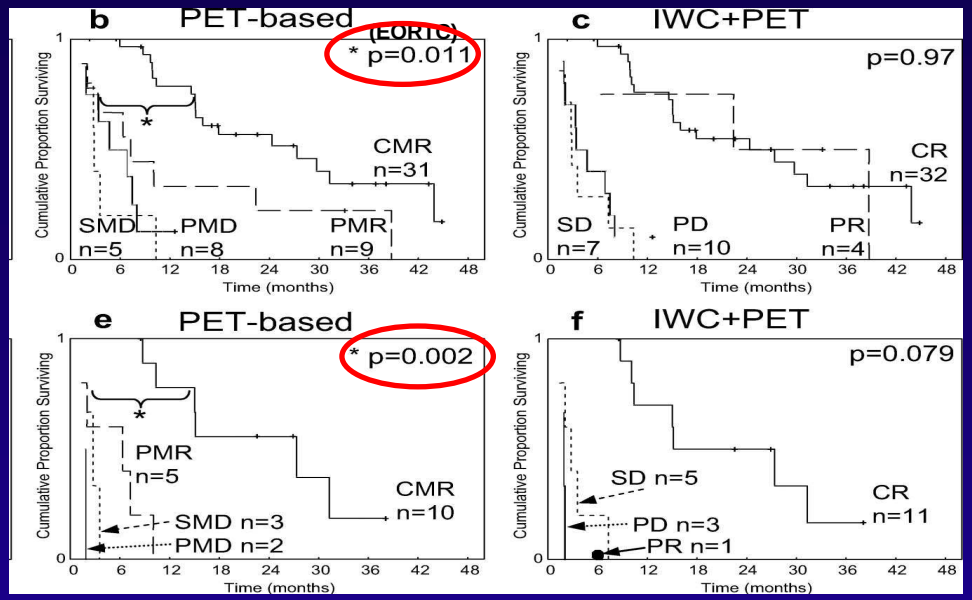
Bodet-milin et al (Eur journal of nuclear medicine 2010)

- STEP 1: FDG-PET at diagnosis OK
- STEP 2: FDG-PET for response assessment at end of therapy
- STEP 3: FDG-PET for mid-treatment response assessment

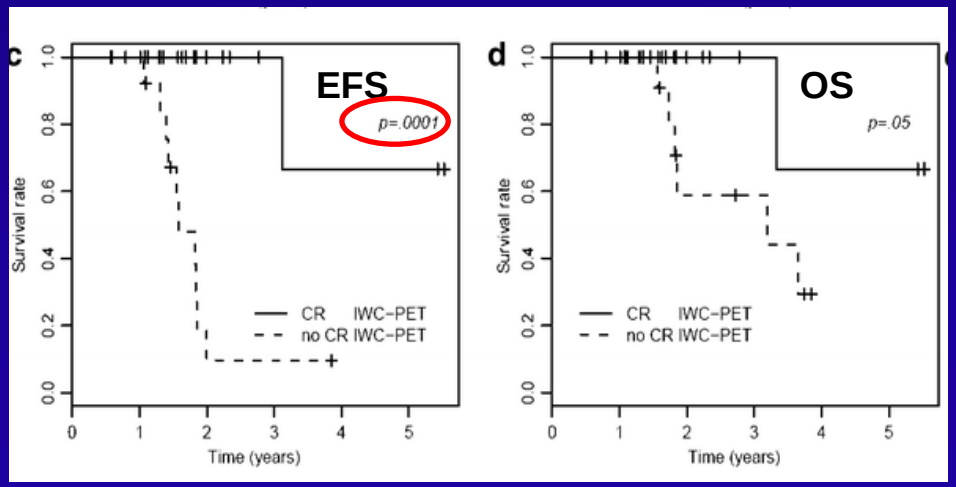
Steps 2 : Response assessment by PET

Study	N	Treatment	Interim PETevaluation	End treatment PET evaluation
Brepoels Leukemia & lymphoma 2008	37 Frontline	Heterogeneous	Eortc + IHP criteria	Eortc + IHP criteria
Schaffel Blood (ASH Annual Meeting Abstracts) 2009	75 Frontline	4 RCHOP 14 2-3 RICE + ASCT	IHP criteria	Not performed
Bodet-milin Eur journal of nuclear medicine 2010	44 Frontline	Heterogeneous	Not performed	IHP criteria
Hosein Am journal of hematology 2011	34 Frontline	Heterogeneous	IHP criteria	IHP criteria
Mato Cancer 2012	53 Frontline	R-HyperCVAD	IHP criteria	IHP criteria

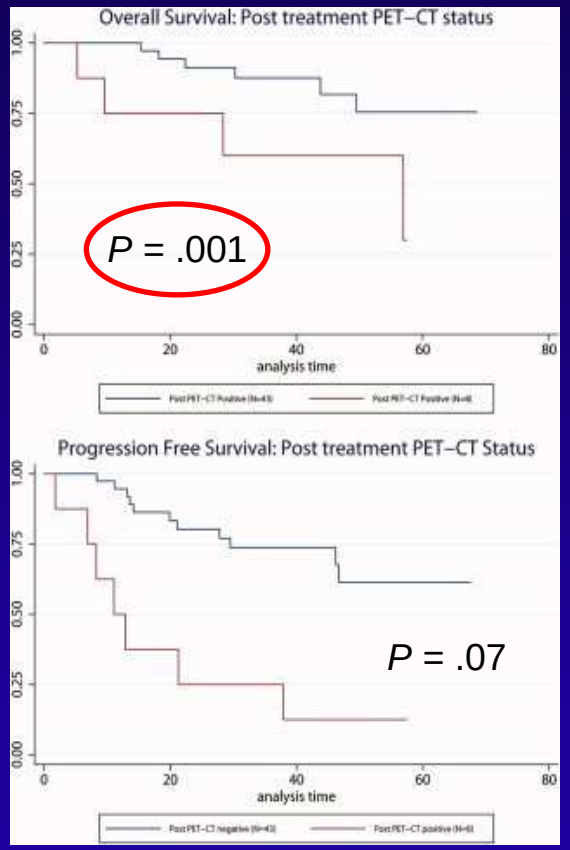
STEP 2: FDG-PET for response assessment at end of therapy



Brepoels, leukemia and lymphoma 2008



Bodet-Milin et al. Eur journal of nuclear medicine 2010



Mato et al. Cancer 2012

- STEP 1: FDG-PET at diagnosis OK
- STEP 2: FDG-PET for response assessment at end of therapy Probably yes but need to be validated
- STEP 3: FDG-PET for mid-treatment response assessment

STEP 3: FDG-PET for mid-treatment response assessment

Study	N	Treatment	Interim PETevaluation	End treatment PET evaluation
Brepoels Leukemia & lymphoma 2008	37 Frontline	Heterogeneous	Eortc + IHP criteria	Eortc + IHP criteria
Schaffel Blood (ASH Annual Meeting Abstracts) 2009	75 Frontline	4 RCHOP 14 2-3 RICE + ASCT	IHP criteria	Not performed
Hosein Am journal of hematology 2011	34 Frontline	Heterogeneous	IHP criteria	IHP criteria
Mato Cancer 2012	53 Frontline	R-HyperCVAD	IHP criteria	IHP criteria

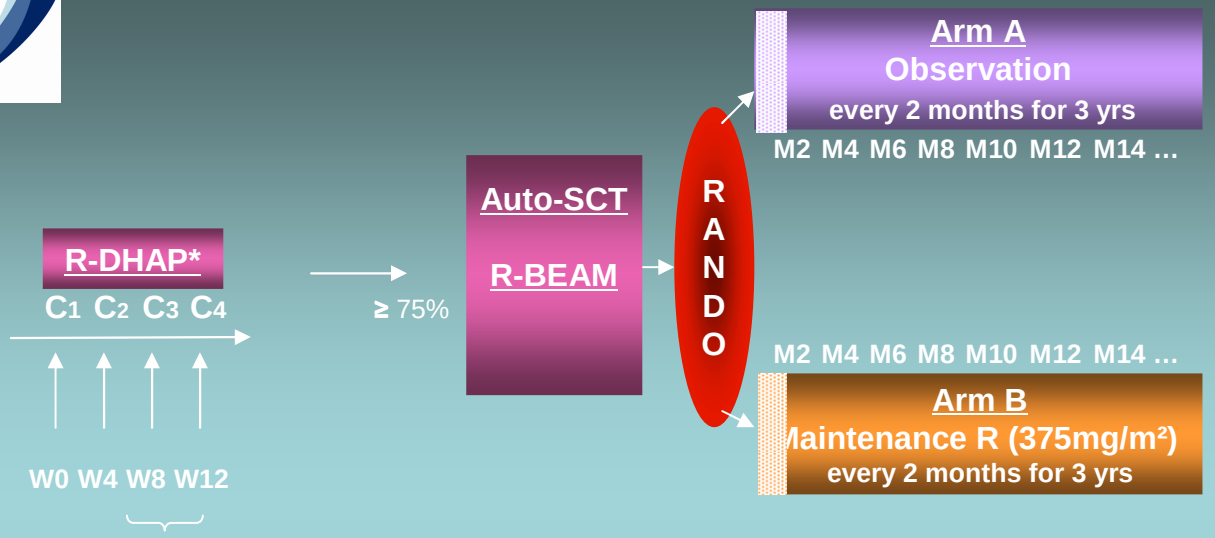
- In all studies, PET seems to be able to identify non responders after 2 or 3 cycles of chemotherapy, especially in patients considered as responders on CT

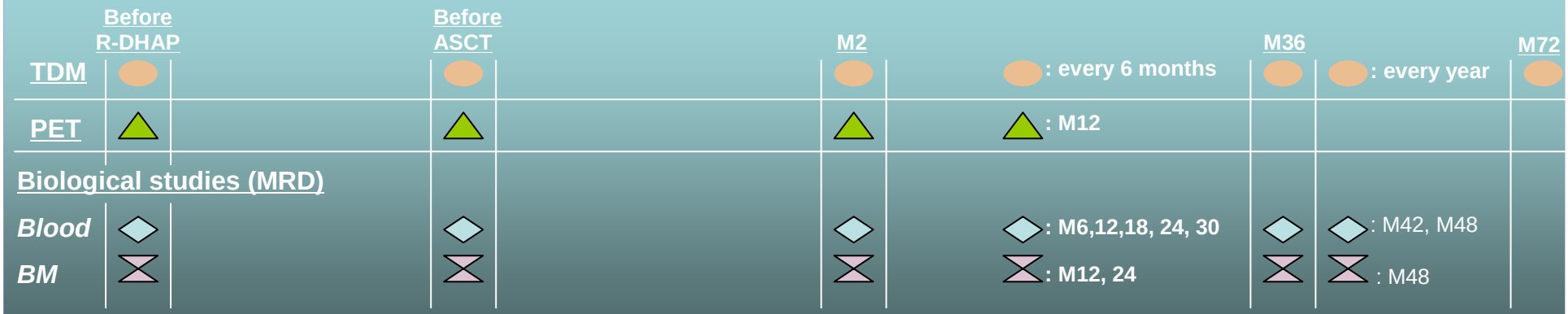
- **But** Negative interim PET is associated with better PFS (84% vs 40%) and OS (94%vs 70%) in only ¼ study (Schaffel et al.)

However, Art is moving forward !

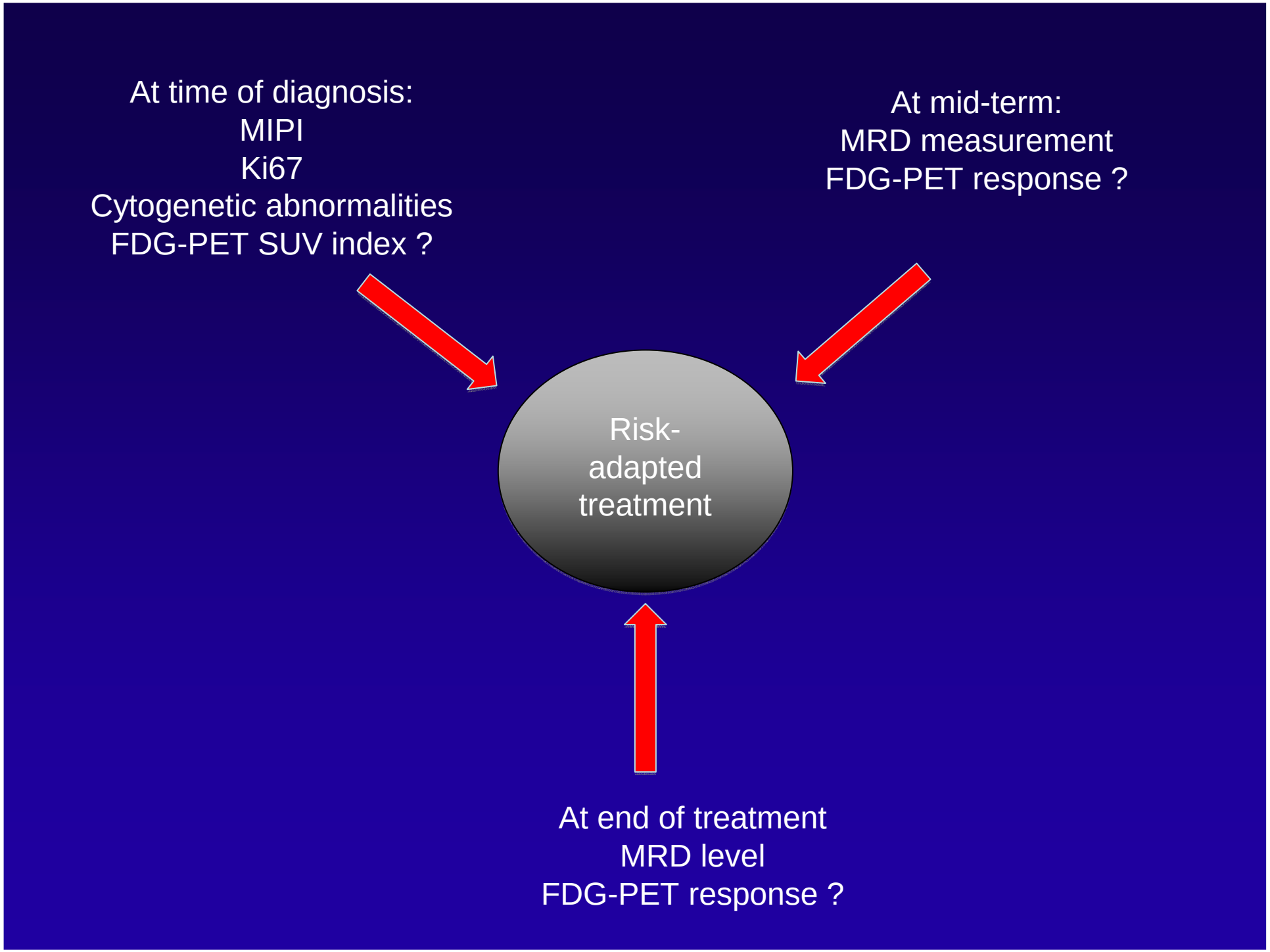
- STEP 1: FDG-PET at diagnosis OK
- STEP 2: FDG-PET for response assessment at end of therapy Probably but need to be validated
- STEP 3: FDG-PET for mid-treatment response assessment Uncertain and need prospective studies

LyMa ttrial





R-DHAP or R-DHA-Carboplatin or R-DHA-Oxaliplatinum*


At time of diagnosis:
MIPI
Ki67
Cytogenetic abnormalities
FDG-PET SUV index ?
At mid-term:
MRD measurement
FDG-PET response ?
Risk-adapted treatment
At end of treatment
MRD level
FDG-PET response ?

THANKS / MERCI

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