6th International Workshop on PET in Lymphoma
Palais de l'Europe. Menton, France
September 20 -21, 2016

Trials with central review in NHL

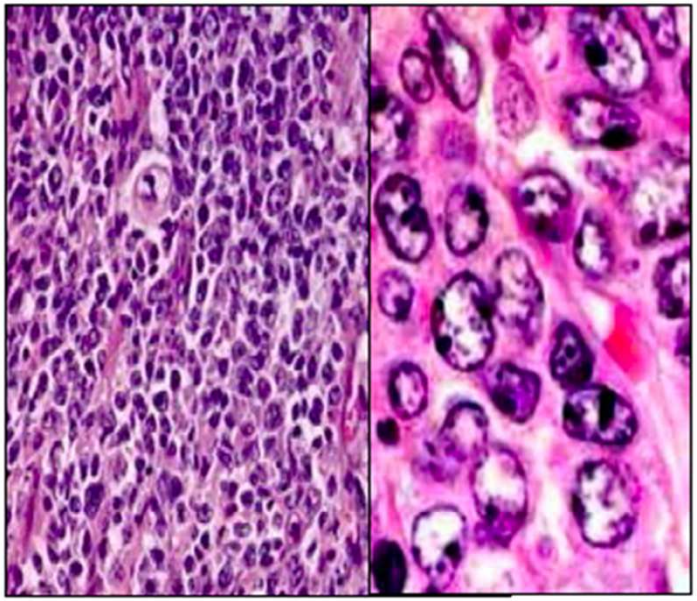
Dolores Caballero and Monica Coronado

Diffuse Large B-cell Lymphoma

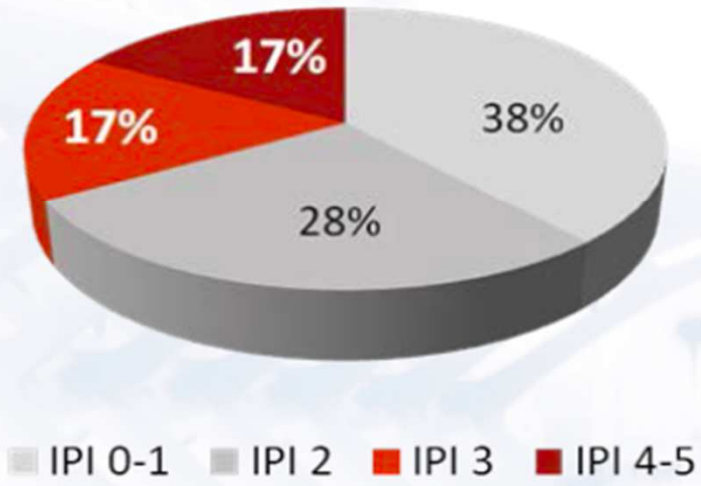
DLBCL:

- is the most common NHL: 40%
- peak incidence in the sixth decade
- incidence increased by 50-90% depending on race, gender
- Clinical outcomes and molecular features highly heterogeneous
- Median survival: weeks to months if not treated

Michallet AS et al. Blood Rev. 2009.



Distribution by IPI score: 34% of patients are IPI 3-5



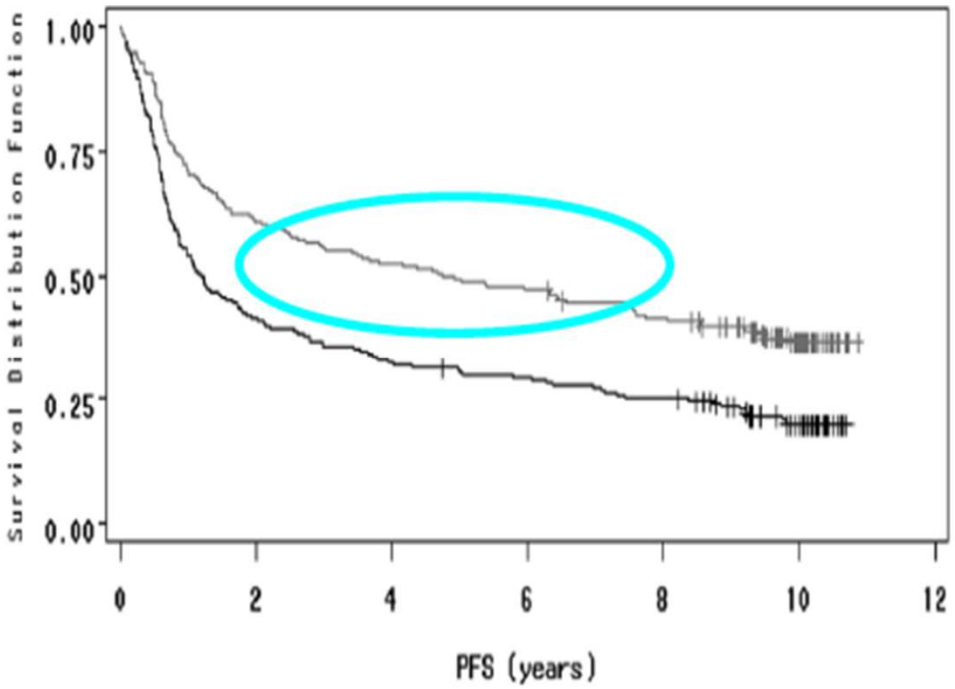
Shipp M et al, Blood 1994.

International Prognostic Index

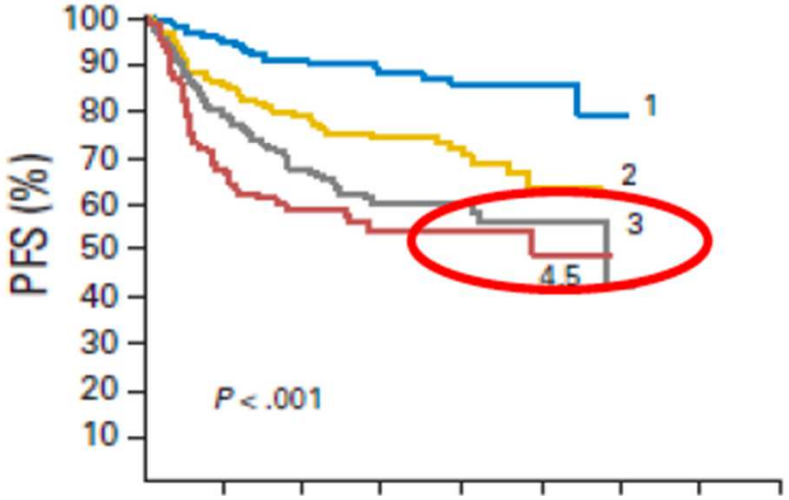
	No. of risk factors	% of pts.	Complete response rate	5-yr survival rate
Low	0,1	35 %	87 %	73 %
Low intermediate	2	27 %	67 %	51 %
High intermediate	3	22 %	55 %	43 %
High	4,5	16 %	44 %	26 %

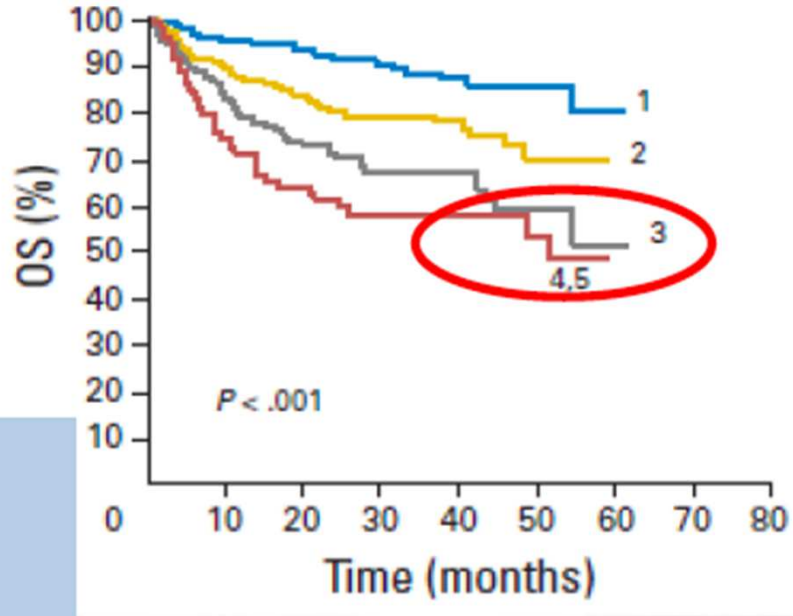
Diffuse Large B-cell Lymphoma

CHOP21 vs. R-CHOP21



Coiffier B et al, NEJM 2002. Coiffier B et al, Blood 2010.

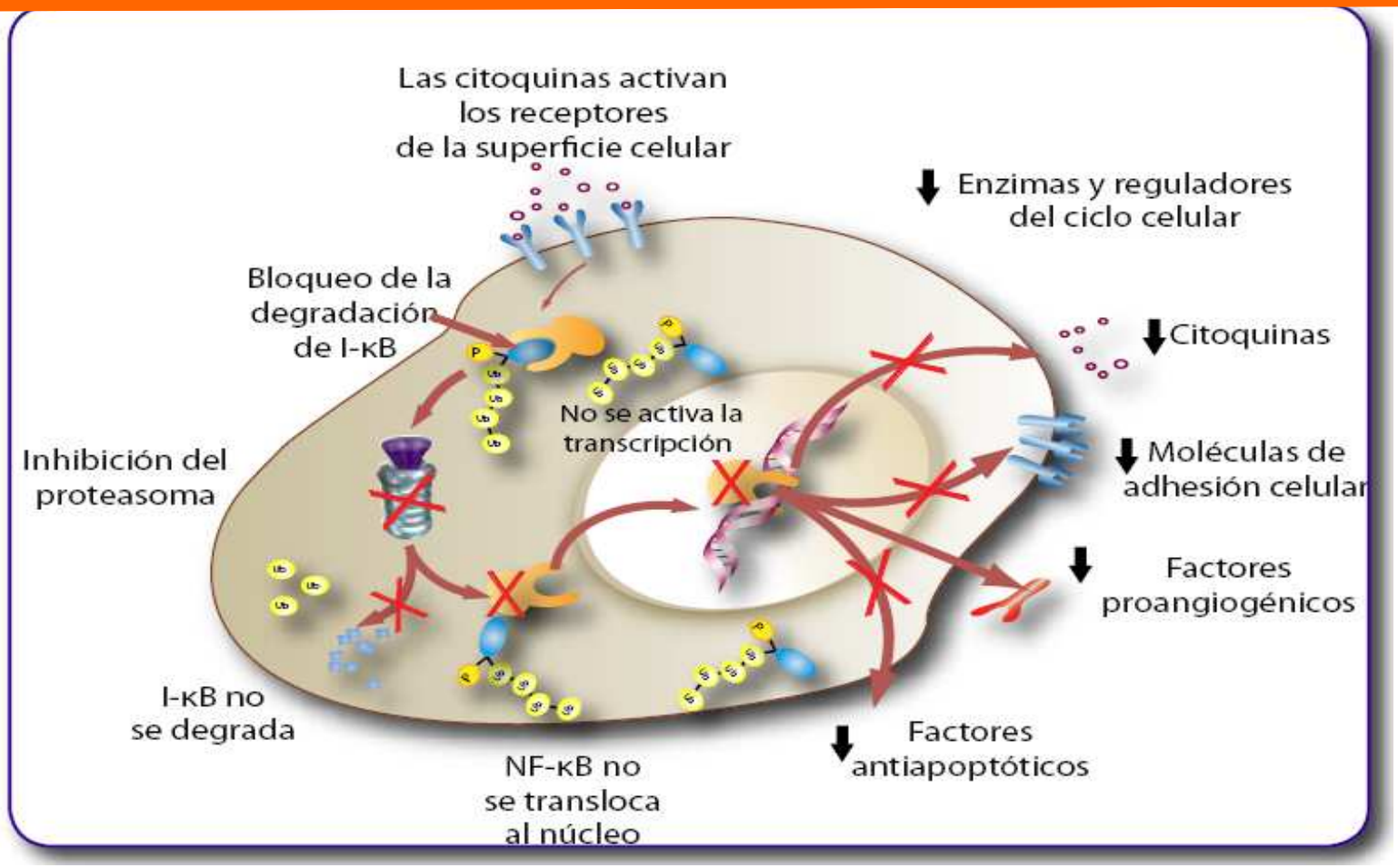




Ziepert M et al, J Clin Oncol 2010.

Do we need to improve R-CHOP results in DLBCL?

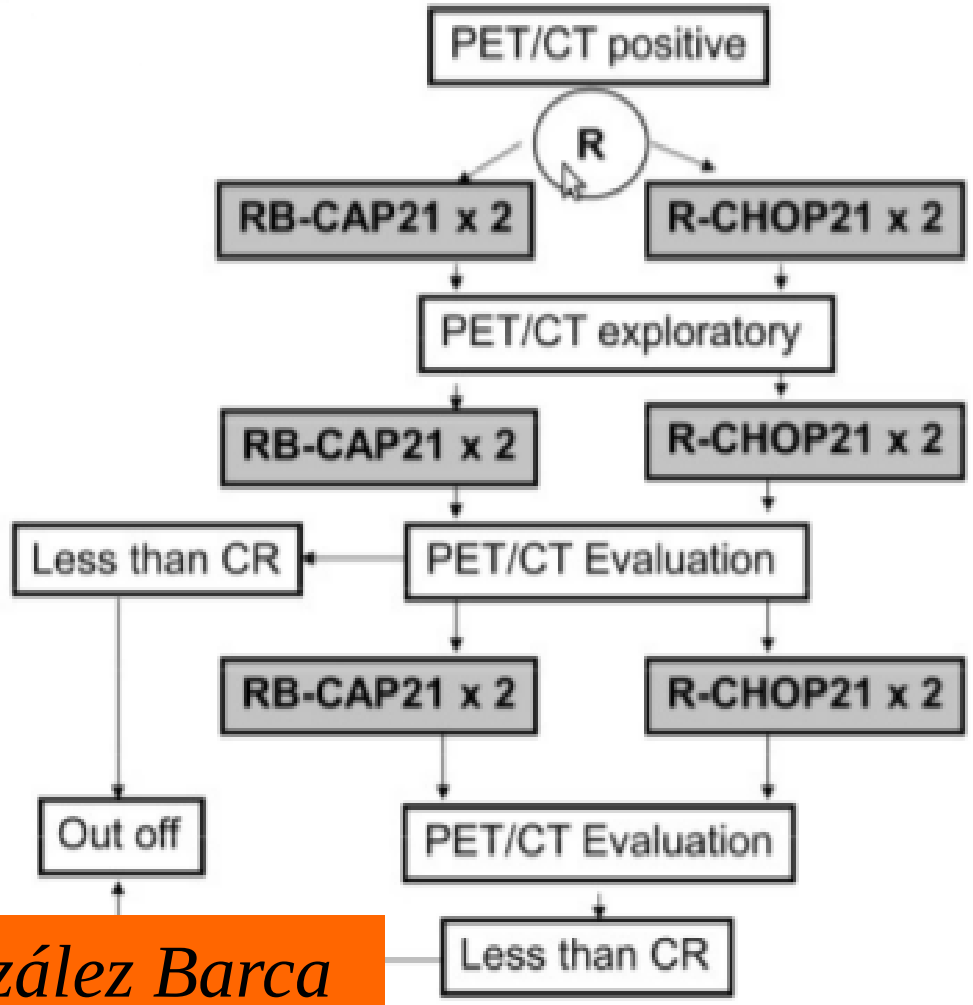
NFkB pathway blocked by Bortezomib



PHASE 2 RANDOMIZED TRIAL COMPARING 6 CYCLES OF STANDARD RCHOP CHEMOTHERAPY VS 6 CYCLES OF BRCAP (BORTEZOMIB, RITUXIMAB, CYCLOPHOSPHAMIDE, ADRIAMYCIN AND PREDNISONE) AS FIRST LINE TREATMENT IN YOUNG PATIENTS WITH POOR PROGNOSIS DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): INTERIM ANALYSIS.

- New diagnosed patients with DLBCL
- Up to 70 years old
- Poor prognosis defined as age adjusted IPI 2,3 or IPI 1 + high beta2m
- Primary objective: 2 years PFS
- Secondary: safety, Overall survival , impact of treatments depending on ABC or GCB subtypes

Trial Design .Phase II trial



PI: Dr Eva González Barca
ICO.Barcelona.

NCT01848132

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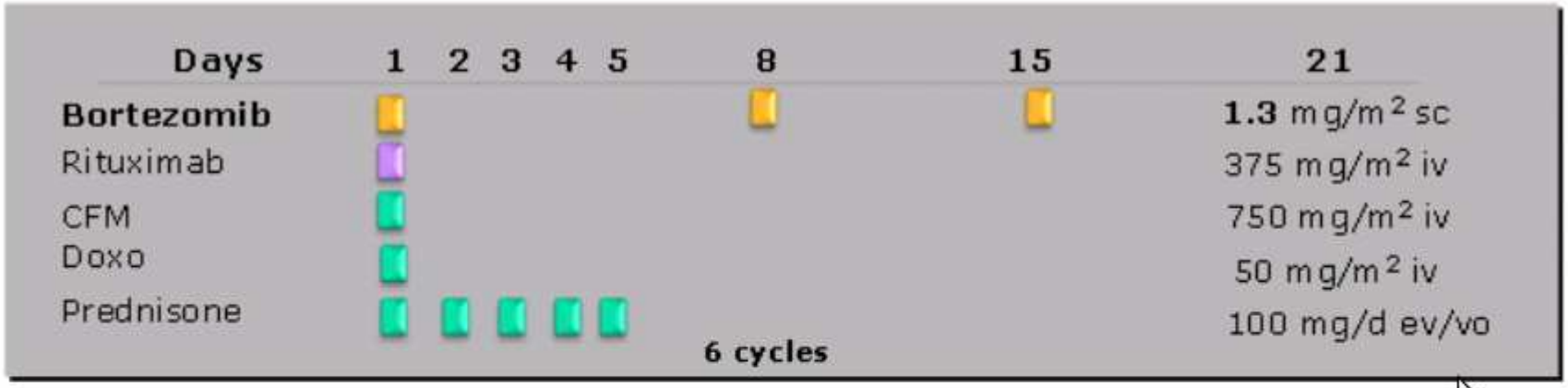
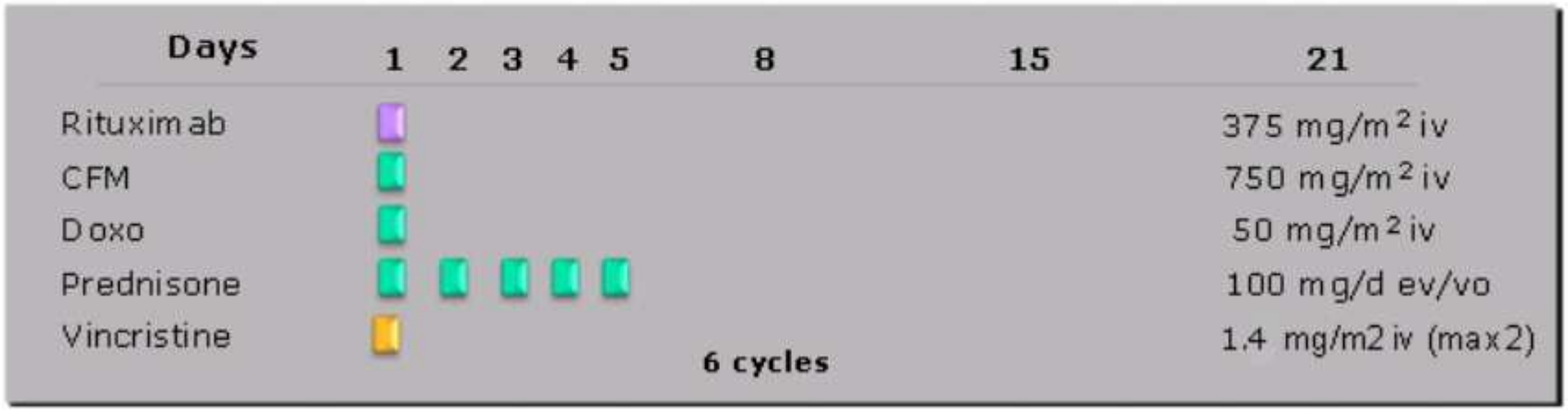
R-B-CAP21



R-CHOP21



Interim PET after 2 versus 4 cycles of immunotherapy in a Phase 2 randomized trial in diffuse large B-cell lymphoma (DLBCL) patients.

Mónica Coronado[1], Marc Simó[2], Pilar Sarandeses[3], Montserrat Cortés[4], Ana Cristina Hernández[3], Amanda Rotger [5], Eva González-Barça[6], Carlos García Grande[3], Dolores Caballero [7], Xavier Setoain [8]

Methods

A blinded, prospective, centralized review in real time of PET/CT images was realized by the GELTAMO PET network. For each patient, images of basal (PET0), iPET after 2 and 4 cycles (iPET2 and iPET4) and final PET after completion of chemotherapy (PET 6) were centrally reviewed.

Central iPET evaluation

Deauville score 4/5 defined (+) iPET

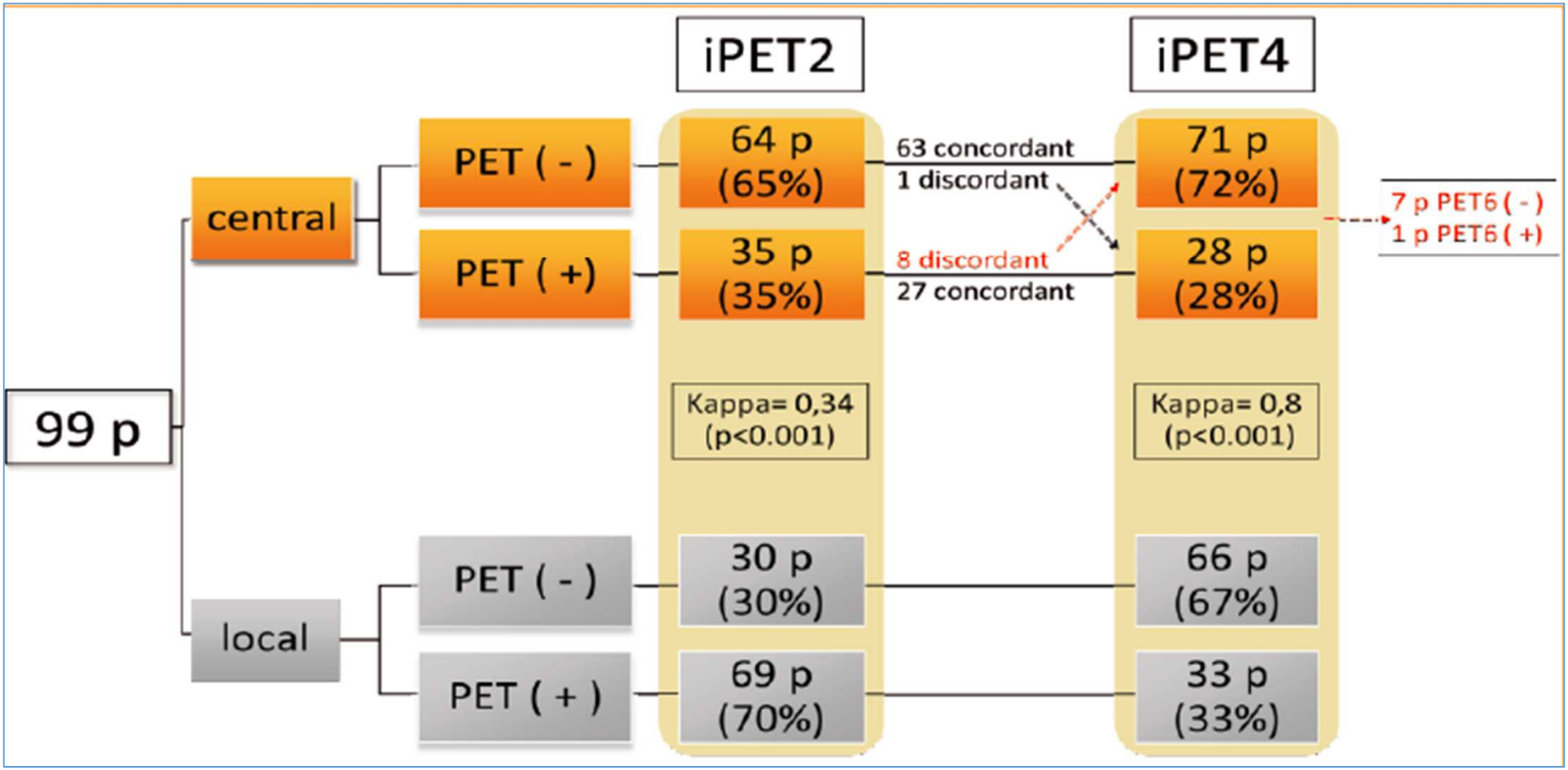
ΔSUVmax≤66% defined (+) iPET2
ΔSUVmax≤70% defined (+) iPET4

Central PET6 evaluation
Deauville score 4-5 defined (+) PET6

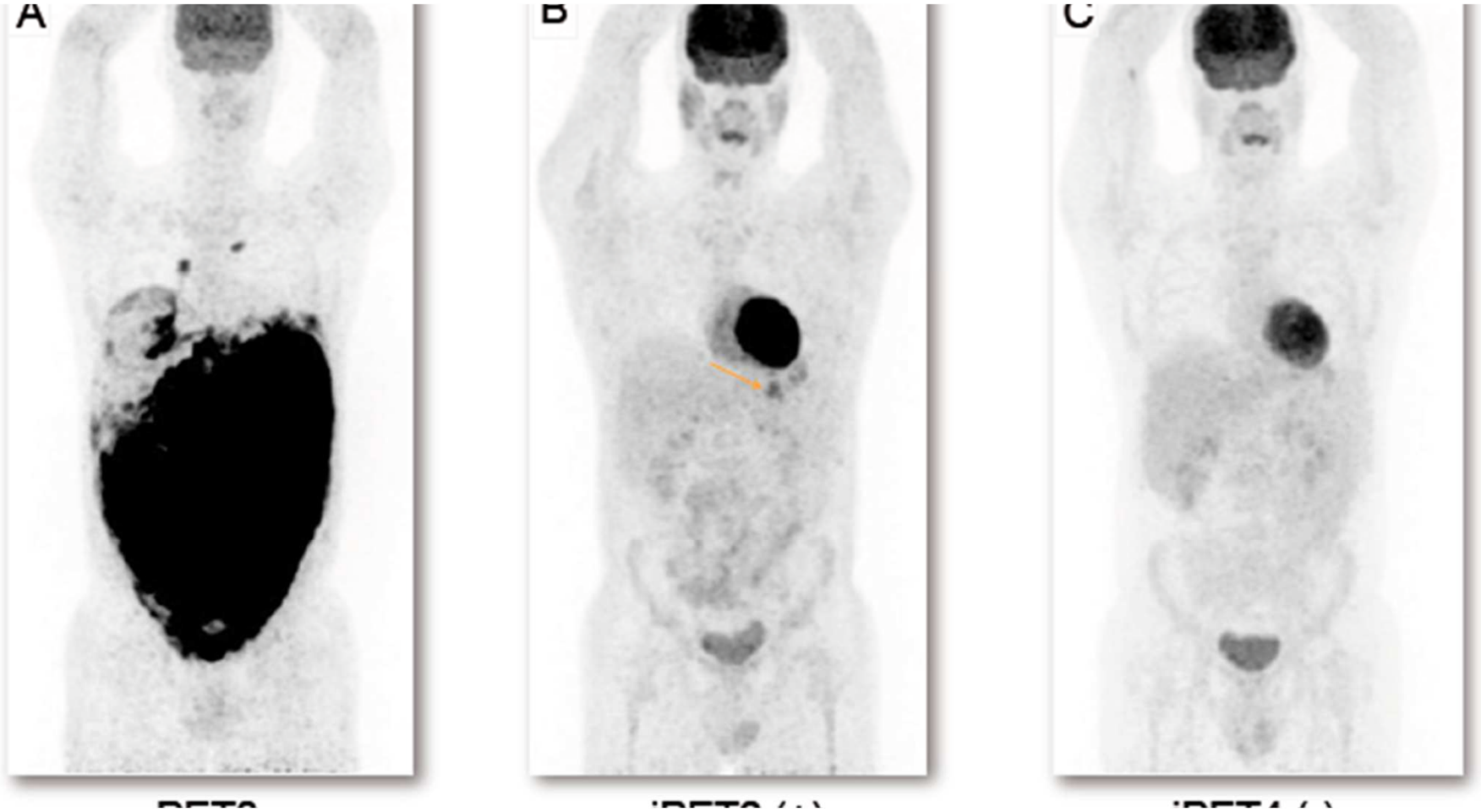
Semiquantitative analysis determined final (+) or (-) iPET result.
A (+) PET4 result determined dropped out from trial.

- iPET2 ability to predict iPET4 result was analyzed.
- Concordance between central and local iPET evaluation was analyzed.

Results in 99 patients. Total sample: 132



PET 2 pos/PET 4 neg



Conclusions:

1. iPET2 is predictive of iPET4 in DLBCL patients treated with standard/modified R-CHOP regimen.
2. In patients with discordant iPET result, iPET4 is preferable to define final metabolic response.
3. Concordance between on-site and central evaluation is better in iPET4 than in iPET2

Results

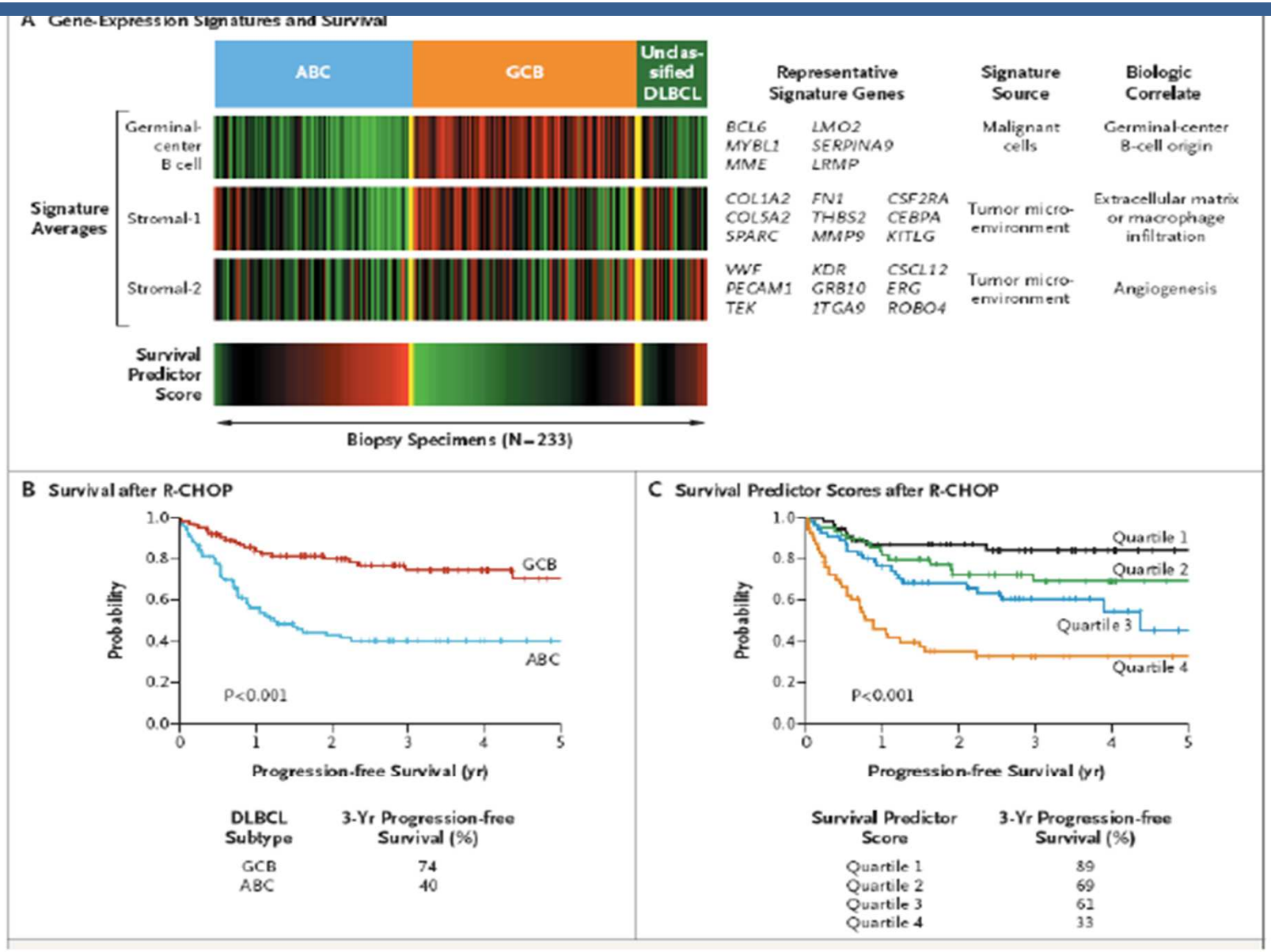
9% discordant iPET2 - iPET4 result

iPET2 was predictive of iPET4 ($p<0.001$).

On-site versus central review:

iPET2: 63% concordant and 37% discordant results.
Poor concordance, Kappa= 0,34 ($p<0.001$)

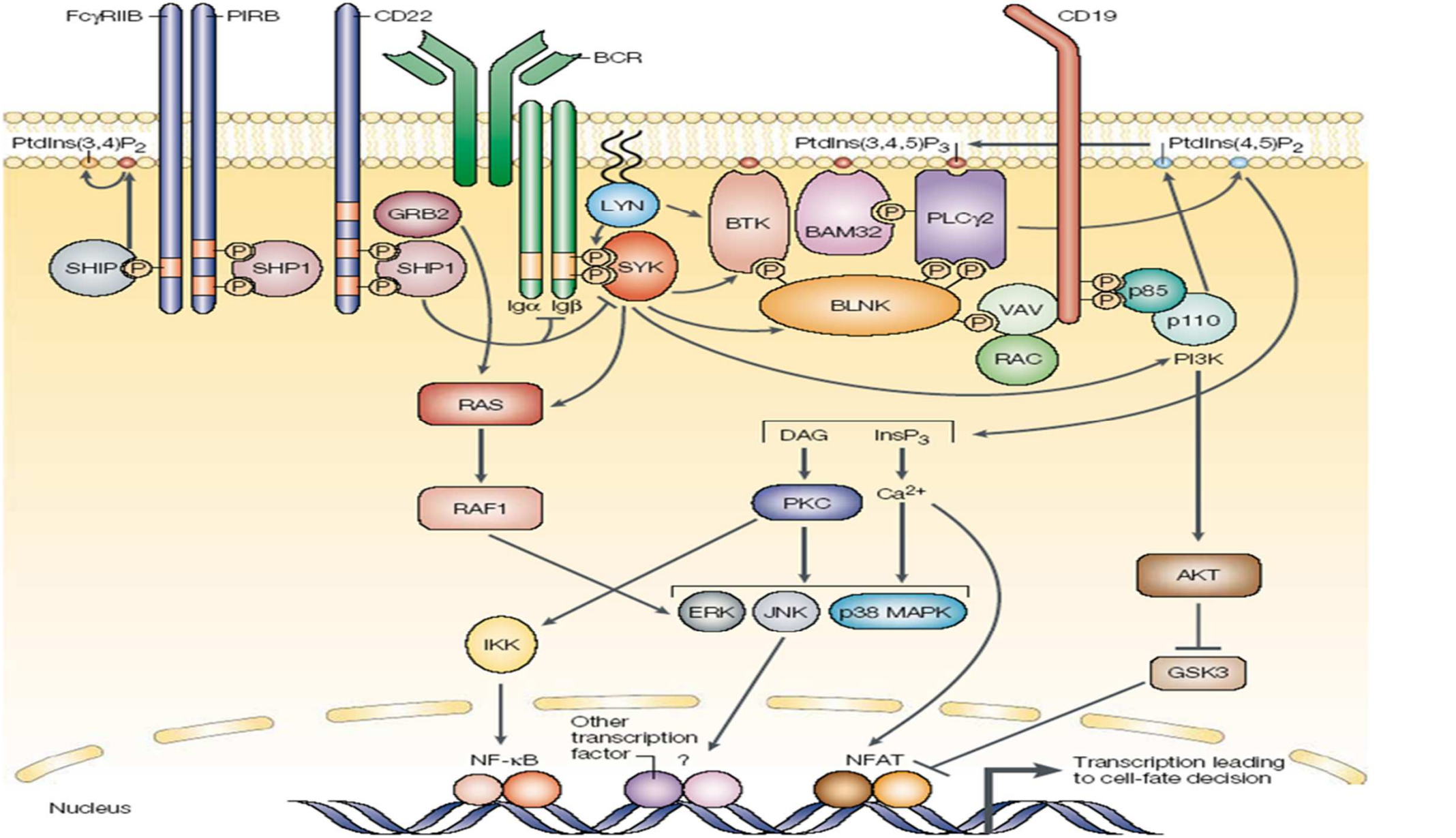
Influence of GEP on survival (ABC vs GCB)



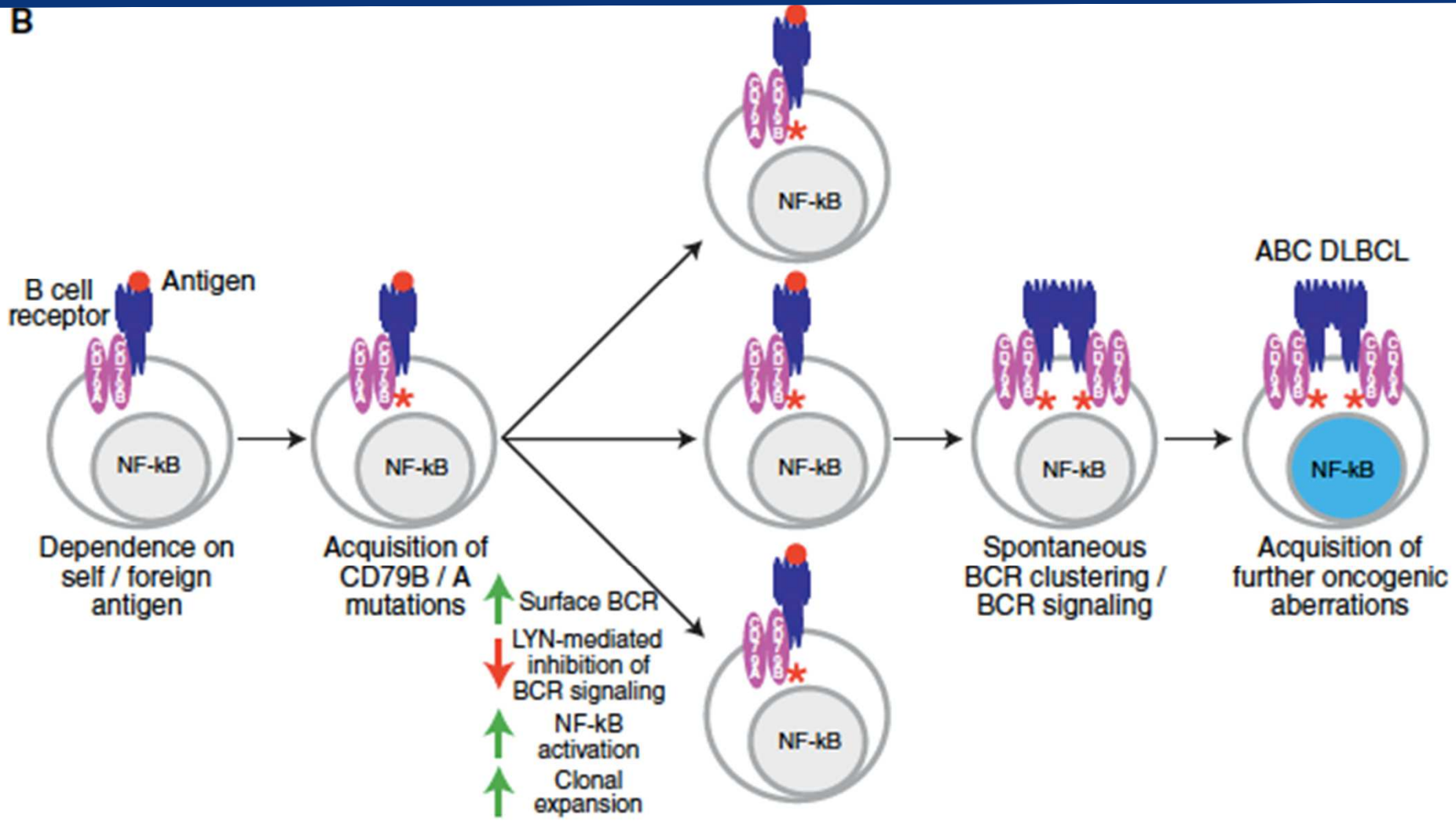
Georg Lenz, M.D., and Louis M. Staudt, M.D., Ph.D.

N ENGL J MED 362;15 NEJM.ORG APRIL 15, 2010

B cell receptor signaling pathway

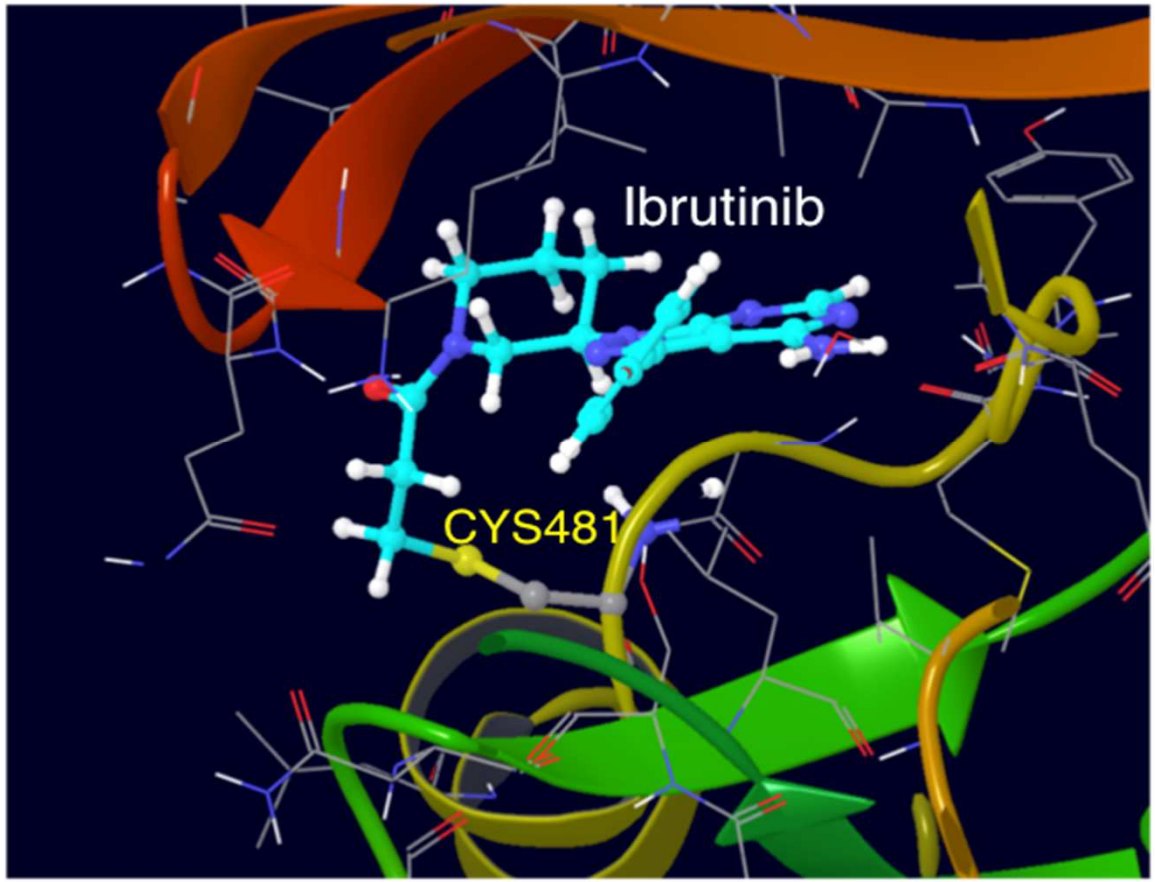


Chronic BCR signaling activation in the pathogenesis of ABC DLBCL



Louis M. Staudt
Cold Spring Harb Perspect Biol 2010

Ibrutinib: A First-in-Class Inhibitor of BTK



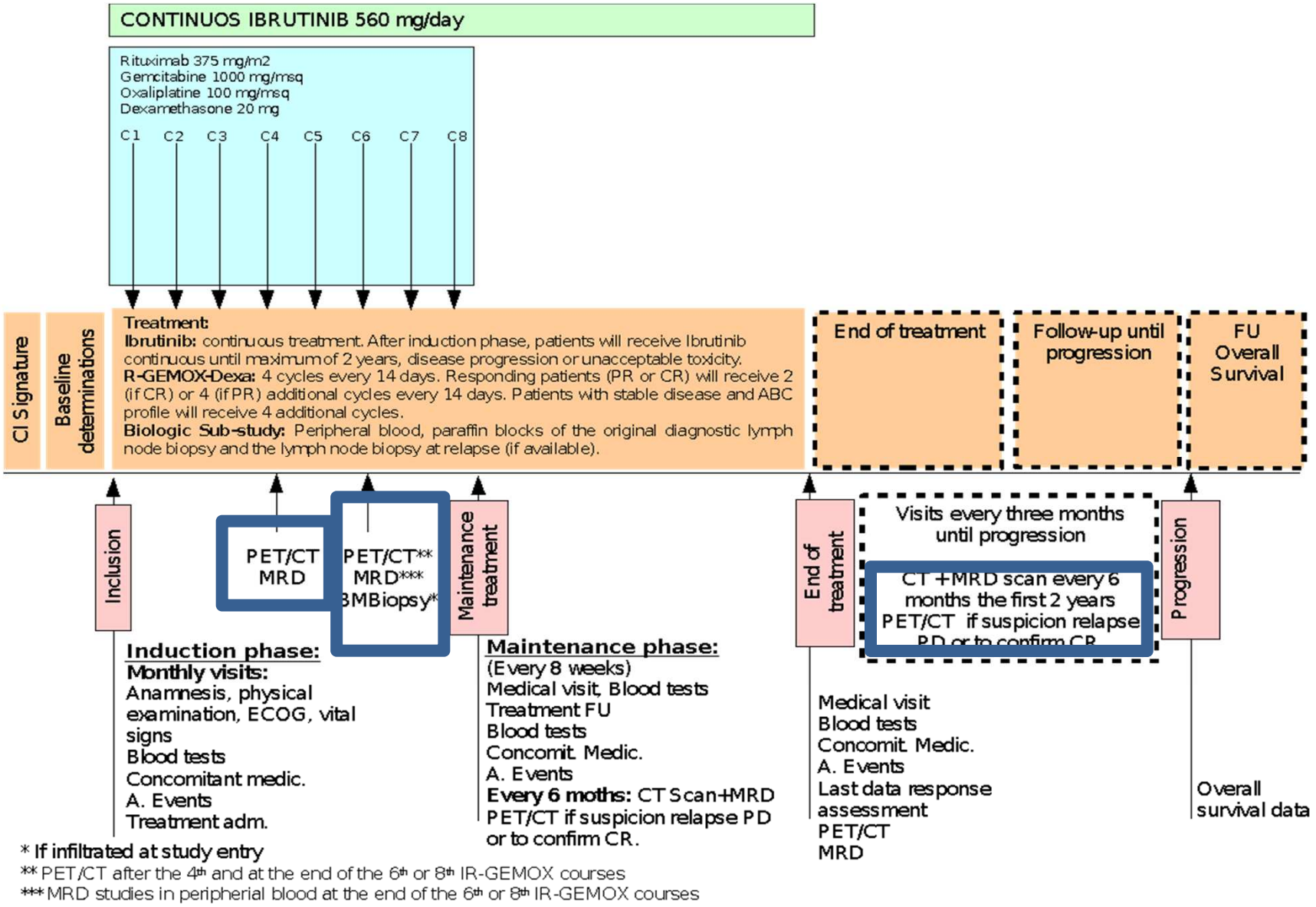
- Forms covalent bond with cysteine-481 in BTK
- High BTK specificity
- IC_{50} = 0.5 nM
- Daily oral dosing produces 24-hr BTK inhibition
- Blocks NF-κB activation in ABC-DLBCL cell lines[1,2]

[1]*Staudt et al, Blood 2011; 118:2716*
[2]*Balasubramanian et al, Blood 2011;118: 4969*

IDLB-GELTAMO-2015
Rituximab – Gemcitabine/oxaliplatin/dexametasone and Ibrutinib followed by ibrutinib maintenance in patients with refractory/relapse Non Germinal center DLBCL. A phase II Trial

PI: Dolores Caballero
Alejandro Martín

Salvage therapy with Ibrutinib+gemcitabin plus oxaliplatin
in patients with Non GCB DLBCL patients non candidates to ASCT



Ibrutinib and Rituximab as first line therapy in patients with indolent Mantle cell lymphoma.A phase II trial

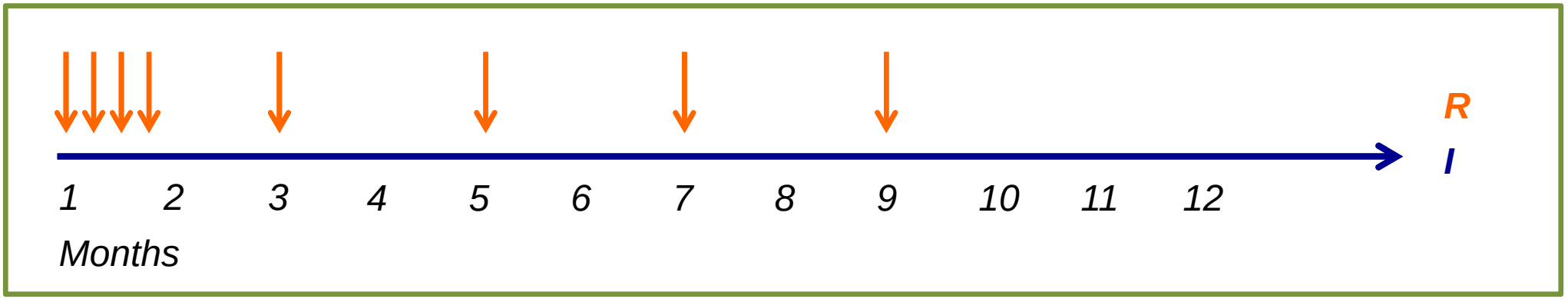
- A chemo free combination in indolent MCL

PI: Dr Eva Gine

Hospital Clinic.Barcelona

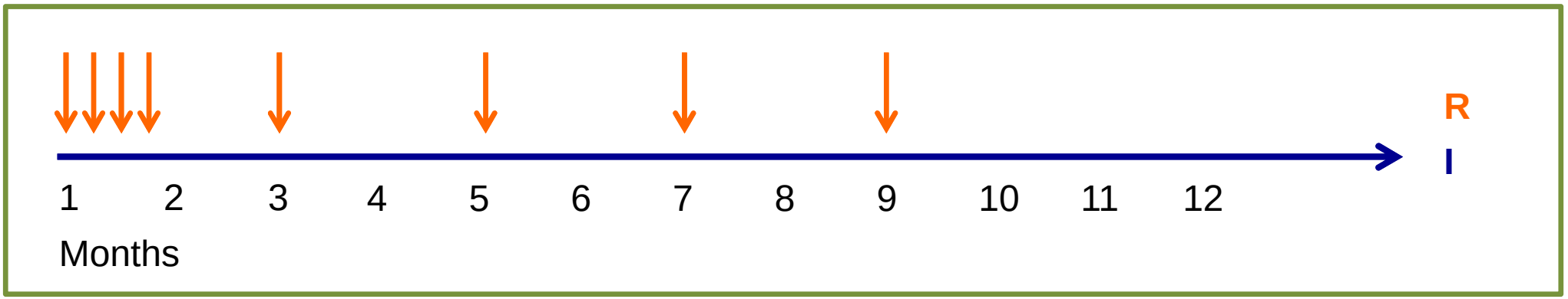
Nº Eudra CT: *2015004158 17*

GELTAMO-IMCL-2015



- *Ibrutinib 560 mg/24h vo , up 2 years if CR by MRD. If not CR until toxicity or progression*
- *Rituximab 375 mg/m2 iv*

Indolent MCL.Trial design



Screening:
- PET/CT
- BM
- gene sequencing and MRD in Peripheral blood
- Central review

6 months:
- CT
- MRD in blood

12 months*:
- PET/CT
- central review
- BM
- MRD in PB

* Response evaluation

Follow up:
- MRD in PB and CT every 4 months up 4 years

Value of PET/CT, compared to multiparametric flow cytometry and histology, for the detection of BM infiltration in patients with DLBCL

Coordinators:

Dr. Alejandro Martín and Dolores Caballero
Hematology Department
Hospital Universitario de Salamanca / IBSAL

Dr. Pilar Tamayo and Luis Díaz
Department of Nuclear Medicine
Hospital Universitario de Salamanca / IBSAL

Background

- BM biopsy , PET/CT or both at staging DLBCL???
- The role of Standardized high sensitivity flow cytometry[2] could be more sensitive than histology and PET/CT in detecting BM infiltration

[1]Cheson et al, J Clin Oncol 2014

[2]Van Dongen et al, Leukemia 2012

Objectives

- Primary objective
  - Assess the sensitivity of PET/CT, histology and flow cytometry in detecting BM infiltration baseline and after treatment in a series of 90 DLBCL patients included in a prospective clinical trial (GEL-R-COMP-2013)
- Secondary objectives
  - Assess the prognostic impact (response rates, PFS and OS) of BM infiltration according to each technique
  - Assess the prognostic impact of concordant and discordant BM infiltration

Patients and methods

- Patients included in the randomized phase 2 trial GEL-R-COMP-2013 (N=90), comparing R-CHOP vs R-COMP in untreated patients with DLBCL
- Methods:
  - Centralized high sensitivity flow cytometry analysis of BM samples (baseline and after treatment) has been performed in Hospital Universitario de Salamanca, according to EuroFlow protocols
  - Retrospective and centralized PET/CT review will be performed by means of the PET/CT GELTAMO platform
  - Retrospective and centralized BM histology review will be performed in Hospital Universitario Marqués de Valdecilla (Santander)

CRITERIOS DE INCLUSIÓN:

1- Diagnóstico histológico confirmado de LDCBG

2- ≥ 18 años

3- Subtipo LDCBG no centro germinal

4- Enfermedad recidivante o resistente al tratamiento después de:

- Al menos una línea previa de tratamiento, que incluye rituximab en combinación con quimioterapia;o,
- Después de un TACM previo; o,
- Después de un trasplante alogénico con acondicionamiento de intensidad reducida, a menos que el paciente esté recibiendo fármacos inmunosupresores o presencia de enfermedad injerto contra huésped en el momento de la inclusión en el estudio.

5- Puntuación en la escala funcional **ECOG ≤ 2.**

6- PET con FDG basal que demuestra lesiones positivas (Deauville 4 o 5) compatibles con las localizaciones tumorales anatómicas definidas en la TC.

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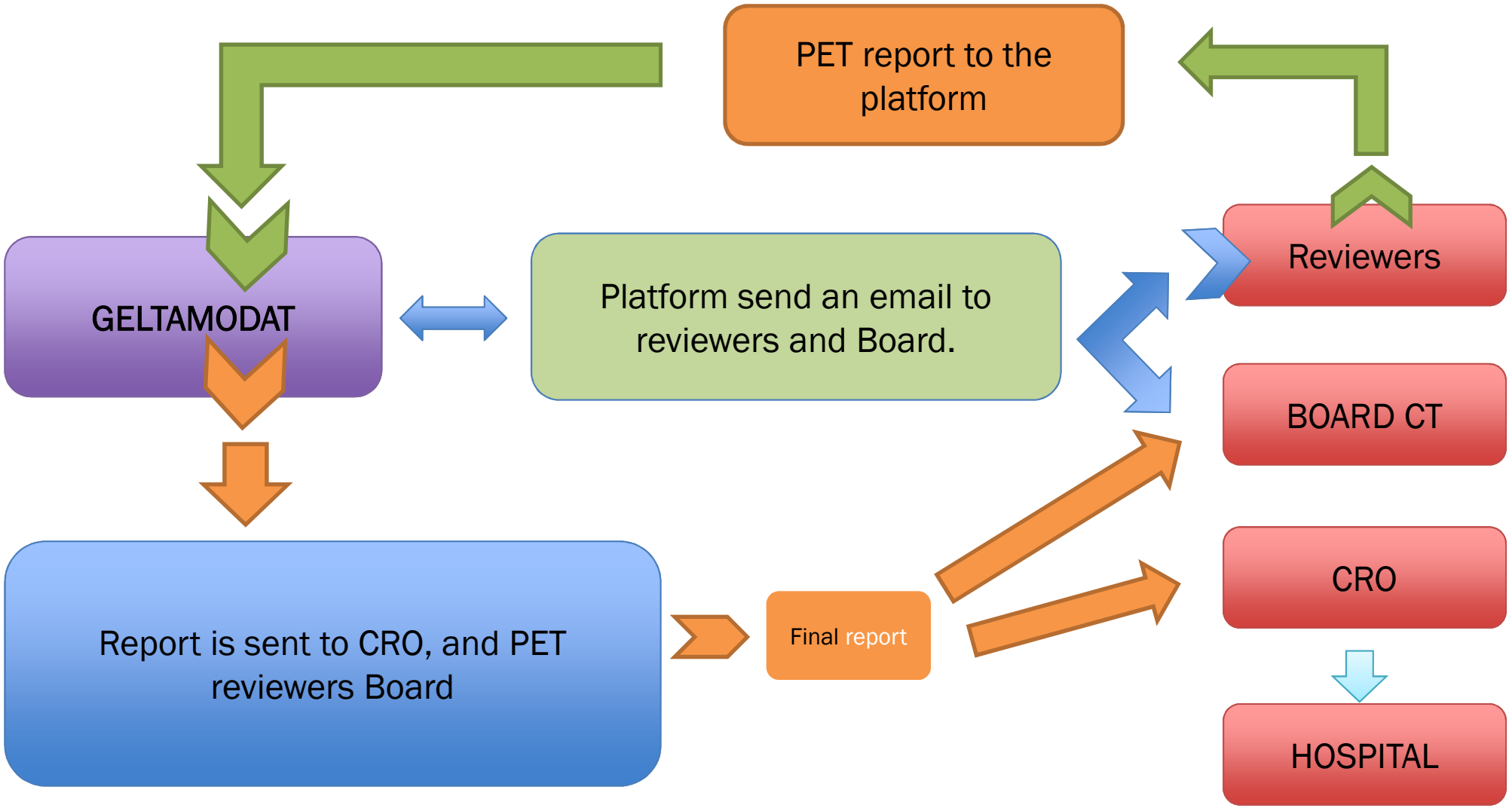
First PET educational meeting Madrid .May 2012

PET subcommittee integrated in the GELTAMO group since may 2015

PROCESS


PET report to the platform
GELTAMODAT
Platform send an email to reviewers and Board.
Reviewers
BOARD CT
Report is sent to CRO, and PET reviewers Board
Final report
CRO
HOSPITAL

Revisores del BR-CAP

>330 PET/CT revisados

Gracias¡¡¡¡¡¡¡