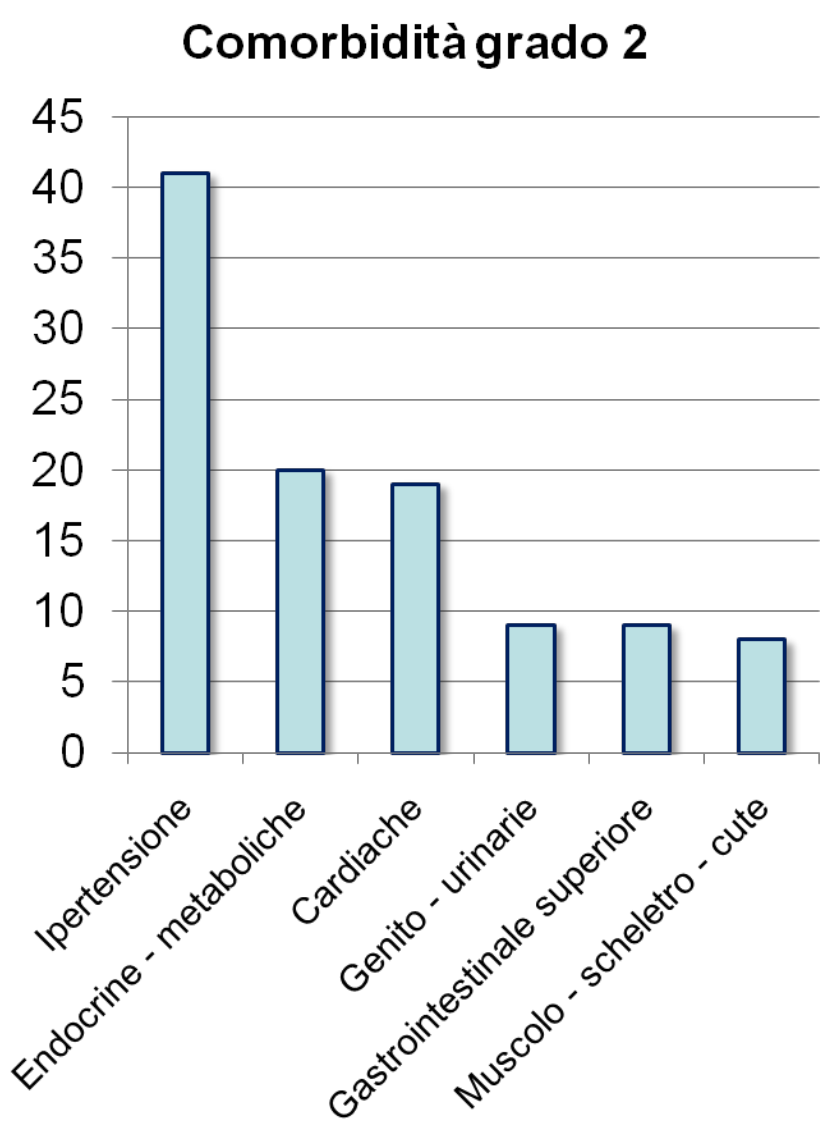
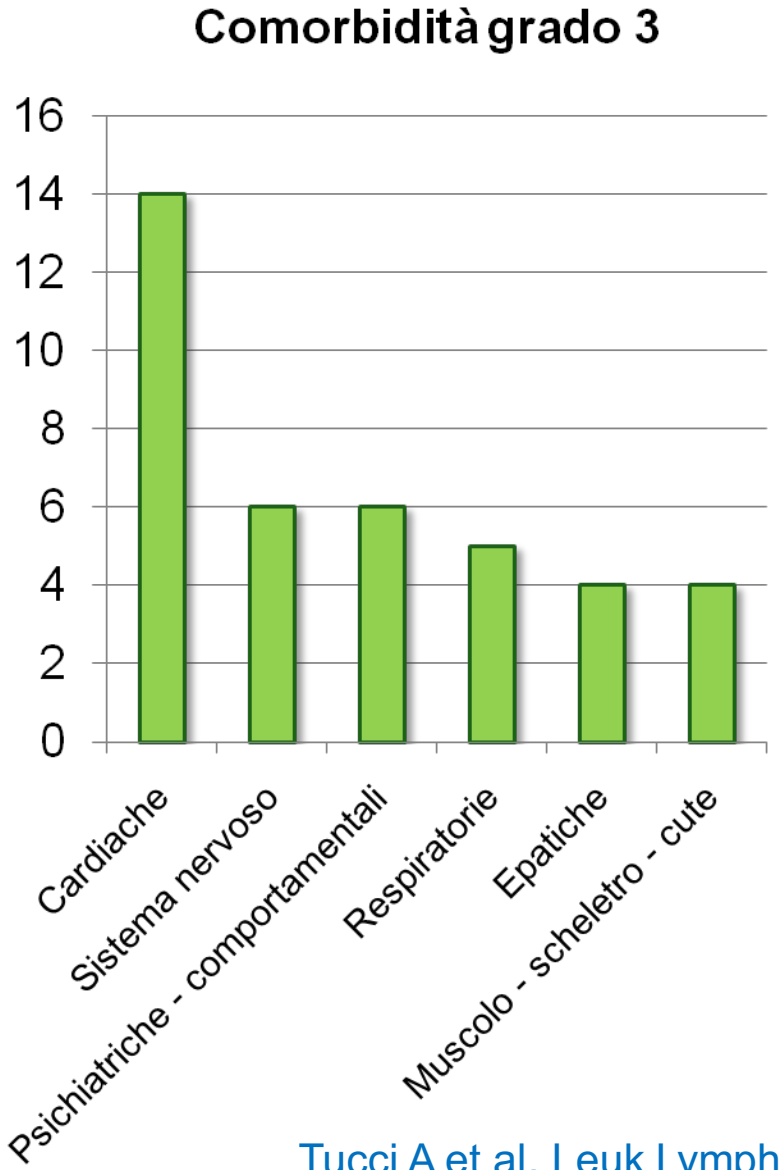
Torino, 17 maggio 2016

Chemioterapia e Cardiotossicità In Ematologia

Annalisa Chiappella, Patrizia Pregno

Comprehensive geriatric assessment is an essential tool to support treatment decisions in elderly patients with diffuse large B-cell lymphoma: a prospective multicenter evaluation in 173 patients by the Lymphoma Italian Foundation (FIL)





Tucci A et al. Leuk Lymph 2014

Chemioterapia e Cardiotossicità

ANTRACICLINE: daunorubicina, doxorubicina

Si intercalano tra le catene del DNA compromettendone la funzionalità e provocandone la rottura.
Sono in grado di formare forme attivate dell'Ossigeno (ROS)

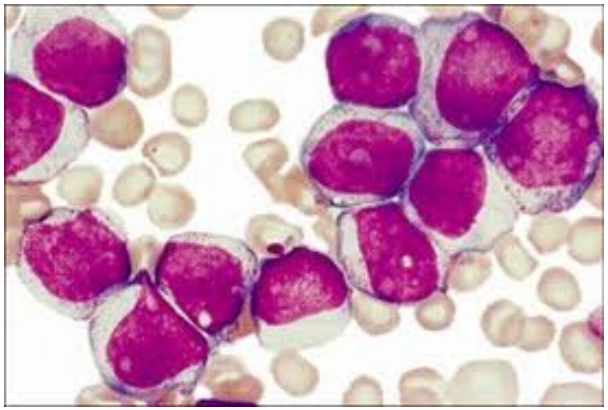
Effetti tossici:

Mielosoppressione, reazioni anafilattiche, alopecia, disturbi gastrointestinali
Potenziale mutagenicità/carcinogenicità

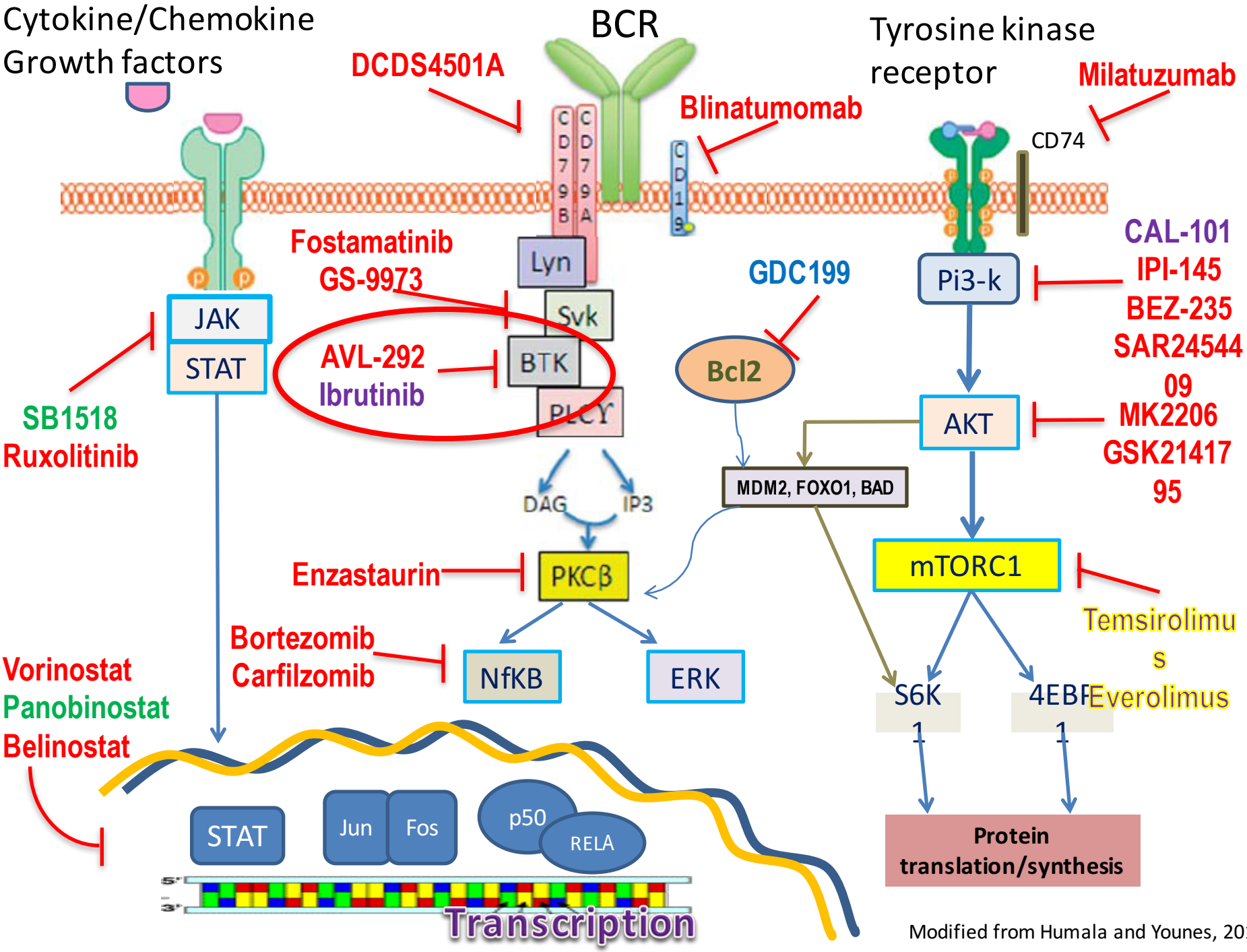
Cardiovascular toxicity of biologic agents for cancer therapy

Anti-HER2 therapy	
Trastuzumab	Left ventricular dysfunction, congestive heart failure, conduction abnormalities (including right and left bundle branch blocks), ECG changes (including T-wave inversions)
Pertuzumab	Left ventricular dysfunction
Lapatinib	Congestive heart failure
VEGF inhibitors	
Bevacizumab	Hypertension, arterial thromboembolic events, congestive heart failure
Sunitinib, sorafenib	Hypertension, intracranial hemorrhage, congestive heart failure
Other targeted agents	
Alemtuzumab	Hypertension, left ventricular dysfunction
Rituximab	Hypertension, cardiogenic shock
Cetuximab	Hypotension
Tyrosine kinase inhibitors	
Imatinib	Congestive heart failure, pericardial effusion
Dasatinib	QTc prolongation, left ventricular dysfunction, congestive heart failure
Nilotinib	QTc prolongation, arterial occlusive disease, myocardial ischemia
Ponatinib	Hypertension, arterial and venous thrombosis
Proteasome inhibitors	
Bortezomib	Congestive heart failure, cardiac ischemia
Carfilzomib	Congestive heart failure, cardiac arrest
Histone deacetylase inhibitors	
Vorinostat Romidepsin	Hypotension, pulmonary embolism, QTc prolongation, ECG changes (including nonspecific ST changes)
Immunomodulatory drugs	
Thalidomide	Sinus bradycardia
Lenalidomide	Sinus bradycardia
Pomalidomide	Venous thromboembolism

ECG = electrocardiogram; HER2 = human epidermal growth factor receptor 2; VEGF = vascular endothelial growth factor.



Bhave M et al, Oncology, 2014;28(6):482-90.

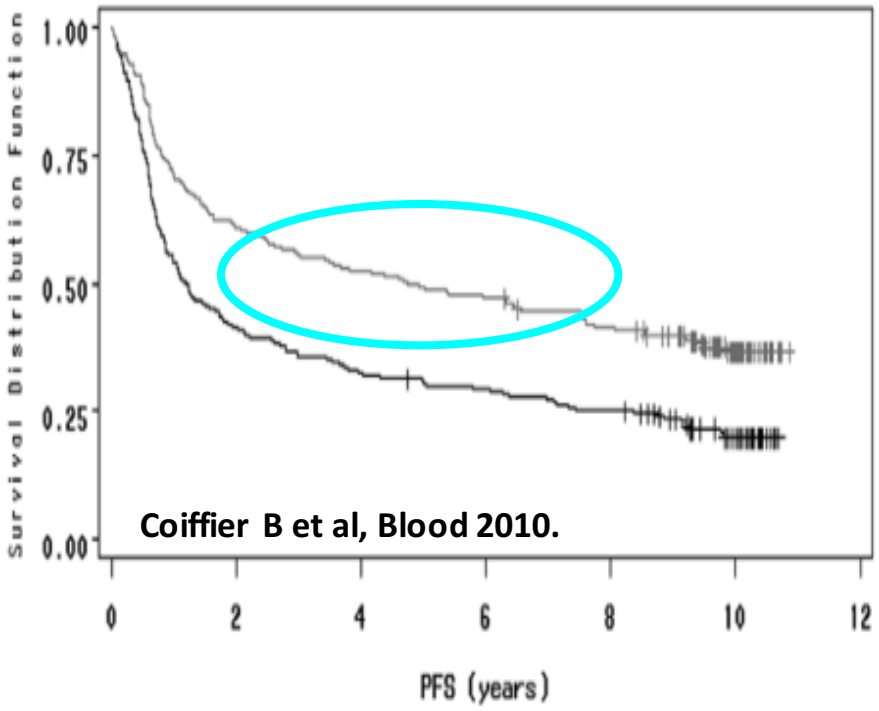


Modified from Humala and Younes, 2013

First line treatment, DLBCL: FIT patients

RCHOP (N = 202) vs CHOP (N = 197):
2-yr PFS 57% vs 38%
10-yrs PFS 37% vs 20%

CHOP21 vs. R-CHOP21



Coiffier B et al, Blood 2010.

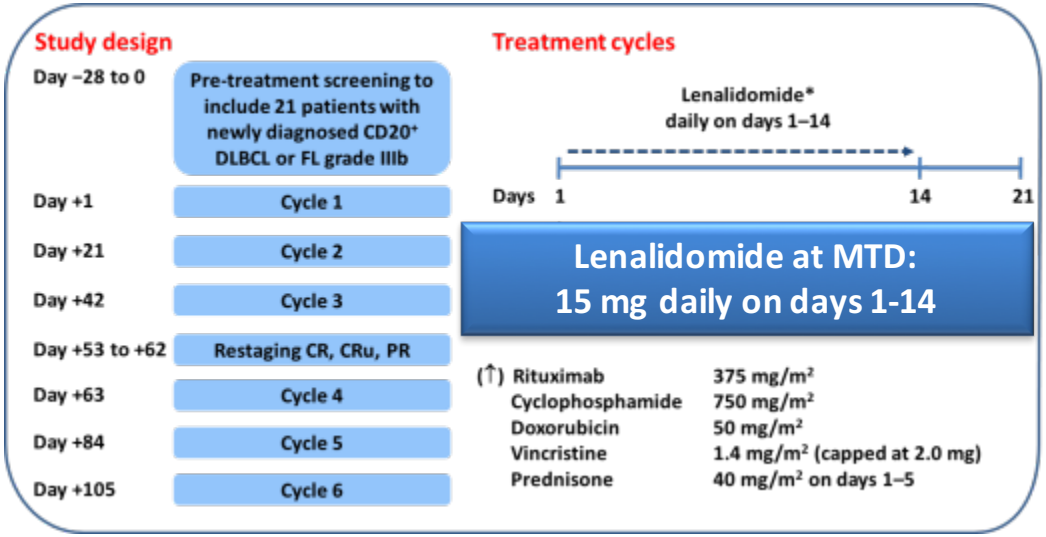
TABLE 4. NONHEMATOLOGIC ADVERSE EVENTS OBSERVED IN PATIENTS TREATED WITH CHOP PLUS RITUXIMAB OR CHOP ALONE.*

EVENT	ANY GRADE		GRADE 3 OR 4	
	CHOP PLUS RITUXIMAB	CHOP	CHOP PLUS RITUXIMAB	CHOP
	percentage of patients with an event in at least 1 cycle			
Fever	64	59	2	5
Infection	65	65	12	20
Mucositis	27	31	3	2
Liver toxicity	46	46	3	5
Cardiac toxicity	47	35	8	8
Neurologic toxicity	51	54	5	9
Renal toxicity	11	14	1	2
Lung toxicity	33	30	8	11
Nausea or vomiting	42	48	4	8
Constipation	38	41	2	5
Alopecia	97	97	39	45
Other toxicities	84	80	20	25

Lancet Oncol 2014

Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial

Umberto Vitolo, Annalisa Chiappella, Silvia Franceschetti, Angelo Michele Carella, Ileana Baldi, Giorgio Inghirami, Michele Spina, Vincenzo Pavone, Marco Ladetto, Anna Marina Liberati, Anna Lia Molinari, Pierluigi Zinzani, Flavia Salvi, Pier Paolo Fattori, Alfonso Zaccaria, Martin Dreyling, Barbara Botto, Alessia Castellino, Angela Congiu, Marcello Gaudiano, Manuela Zanni, Giovannino Ciccone, Gianluca Gaidano, Giuseppe Rossi, on behalf of the Fondazione Italiana Linfomi



CNS prophylaxis according to Italian Society of Hematology guidelines
Pegfilgrastim or G-CSF as neutropenia prophylaxis
Low Molecular Weigh Heparin as DVT prophylaxis

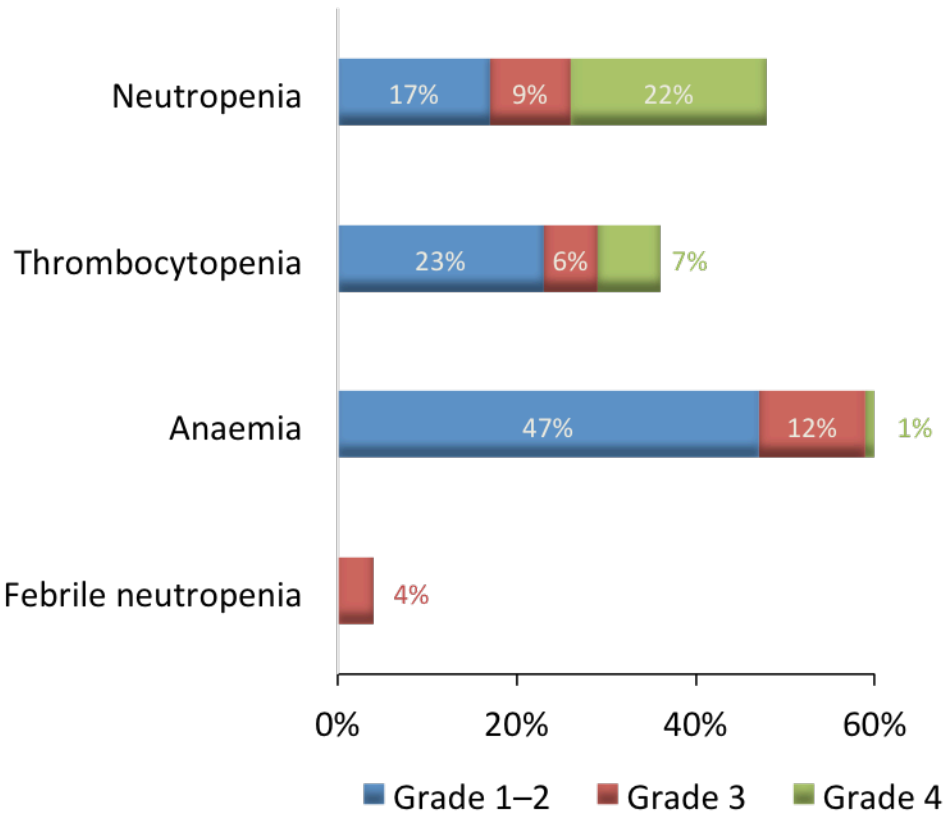
	Enrolled patients (n=49)
Age (years)	69 (64–71)
Sex	
Men	29 (59%)
Women	20 (41%)
Eastern Cooperative Oncology Group performance status	
0–1	42 (86%)
2	7 (14%)
Ann Arbor stage	
II	6 (12%)
III	8 (16%)
IV	35 (71%)
International Prognostic Index risk	
Low-intermediate risk	19 (39%)
High-intermediate or high risk	30 (61%)
Lymphoma type	
Diffuse large B-cell lymphoma	45 (92%)
Follicular lymphoma grade 3b	4 (8%)
Bone marrow involvement	17 (35%)
B symptoms	21 (43%)
Increased lactate dehydrogenase concentration*	22 (45%)
Increased β_2 microglobulin*	34 (69%)

Data are median (IQR) or n (%). *Higher than the upper limit of normal.

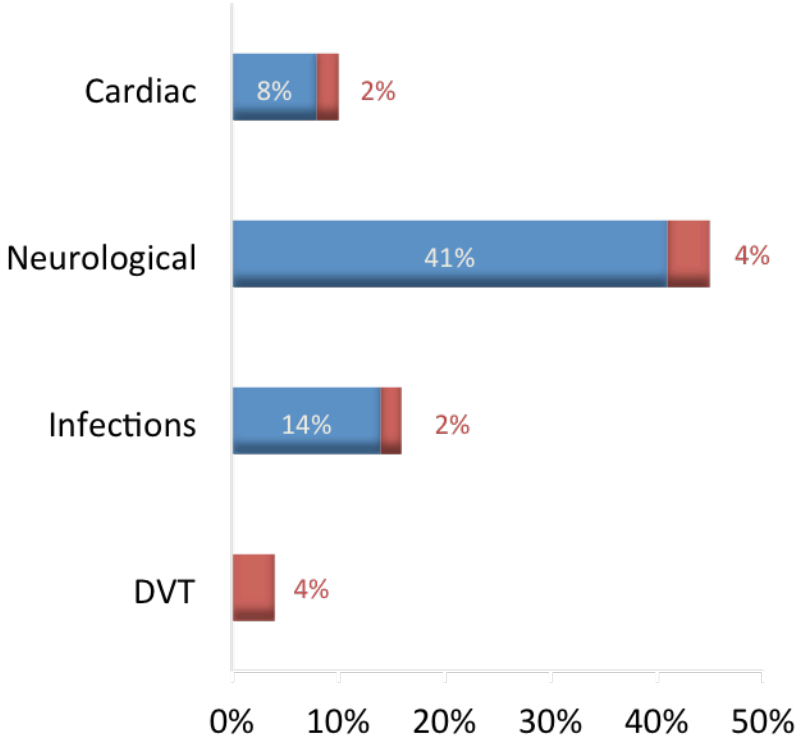
Table 1: **Baseline clinical characteristics**

REAL07 phase II R2-CHOP21 in elderly untreated DLBCL: safety data – all grades AEs

Haematological AEs by % of treatment cycles (n = 277)



Non-haematological AEs by % of patients (n = 49)



AEs, adverse events; DLBCL, diffuse large B-cell lymphoma; DVT, deep-vein thrombosis.

Vitolo U, et al. Lancet Oncol. 2014;15:730-7.

Heart - Tyrosine-Kinase Proteins

PDGF-R

- Regulation of interstitial fluid pressure
- Stressed cardiomyocyte repair by hemodinamic overload

→ *EDEMA*

SRC

- Vascular permeability
- Pleural space homeostasis

→ *PLEURAL EFFUSION*

ABL-ARG

- Response to DNA damage
- Protection to oxidative stress

→ *CARDIOMYOCYTE TOXICITY*

VEGF-R

- Angiogenesis,
- Cardiac homeostasis

→ *HYPERTENSION*
HEART FAILURE
THROMBOSIS
ARTERIAL OCCLUSION

Arterial Hypertension

- The European Guidelines for the management of hypertension identify as drugs of choice for the treatment of hypertension:
  - thiazide diuretics (TD)
  - angiotensin II receptor blockers (ARBs)
  - angiotensin-converting enzyme inhibitors (ACEIs),
  - b-blockers (BBs),
  - calcium channel blockers (CCBs)

Drug-drug interactions to occur with these treatments and second-generation TKIs should be carefully considered.

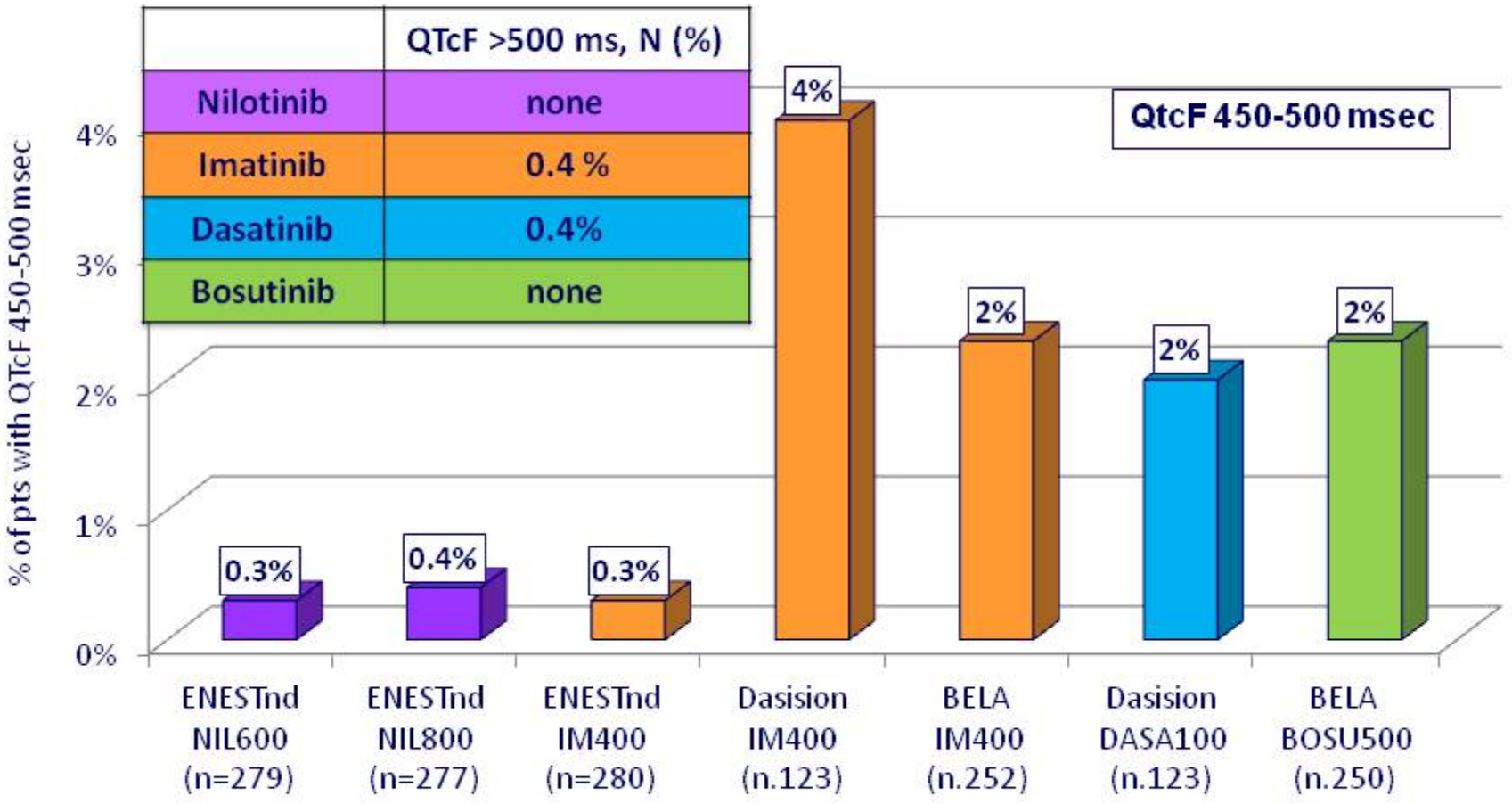
	TD	ARB (CYP2C9 substrates)	ACE	BB (CYP2D6 substrates)	CCB (CYP3A4 substrates)
NILOTINIB		X		X	X
DASATINIB					X

Risk of cardiovascular events

Risk of pleural effusion

E. Abruzzese, M. Breccia, R. Latagliata, BioDrugs 2013

TKIs and QTc prolongation



1. Saglio et al. N Engl J Med (2010) 362:2251-2259.

2. Kantarjian et al. N Engl J Med (2010) 362:2260-2270.

3. Cortes et al. J Clin Oncol (2012) 30:3486-3492.

Imatinib and cardiac failure

Incidence of cardiac failure in patients exposed to Imatinib compared with cardiac failure incidence in general population

Patients Exposed to Imatinib			Data From Framingham Heart Study		
Age, Yrs	(n/N)	Incidence of CHF,* %	Age, Yrs	CHF 5-Year Risk,* %	
				Male	Female
< 45	(0/409)	0	40	0.2	0.1
45-55	(1/322)	0.3	50	0.8	0.1
56-65	(6/291)	2.0	60	1.3	0.7
66-75	(5/211)	2.3	70	4.0	2.2
76-85	(4/43)	9.3	80	8.3	7.8

Atallah et al, *Blood* 2006;108(11):abs#2146.

Arterial Occlusive Events of Interest (Any Cause)

Adverse event	Dasatinib (n=259)				Imatinib (n=260)			
	Grade 1/2	Grade 3/4	Grade 5	Total n (%)	Grade 1/2	Grade 3/4	Grade 5	Total n (%)
Cardiac ischemia				10 (3.9%)				3[a] (1.2%)
Myocardial infarction[b]	1	2	2	5 (1.9%)	0	1	1	2 (0.8%)
Angina[c]	2	1	0	3 (1.2%)	1	0	0	1 (0.4%)
Coronary artery disease, myocardial ischemia	2	0	0	2 (0.8%)	1	0	0	1 (0.4%)
Peripheral arterial occlusive disease	0	0	0	0	0	0	0	0

- Patients with a history of cardiac disease were included in DASISION, except those who had angina within 3 months, myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation
- 9 of 10 dasatinib and 2 of 3 imatinib patients with cardiac ischemia had at least 1 baseline risk factor for cardiovascular disease (eg, diabetes, hypertension, hyperlipidemia, left ventricular dysfunction, coronary artery disease)

[a]4 events in 3 imatinib patients.
[b]MedDRA preferred terms: myocardial infarction, acute myocardial infarction, and silent myocardial infarction.
[c]MedDRA preferred terms: angina pectoris and unstable angina.

Protocol CC-122-cointaing regimen

12-lead Electrocardiograms

- Screening - must be performed ≥ 72 hours prior to Day 1
- **Cycle 1, Day 1 - predose** (0 hr; ≤ 1.5 hours prior to dosing) **and 1.5 hours postdose**
- Cycle 1, Day 8 - predose (within 1.5 hours prior to dosing)
- **Cycle 1, Day 15 - predose** (0 hr; ≤ 1.5 hours prior to dosing) **and 1.5 hours postdose**
- Cycle 1, Day 22 - predose (≤ 1.5 hours prior to dosing)
- **Day 1 of subsequent cycles - predose** (≤ 1.5 hours prior to dosing)
- **EOT**

ECHOCARDIO

- Screening
- Cycles 2, Day 1
- **Every 3 cycles** (C5D1, C8D1, etc..)
- EOT

Elevated BNP levels for pt 302_1003

Fluctuations of the BNP levels since screening.

At screening -	99ng/L,
C1D8	117ng/L,
C1D1	108ng/L,
C1D22	120ng/L,
C2D1-	194ng/L,
C4D1-	138ng/L,
C5D1 -	222ng/L,
C6D1-	107ng/L,
C7D1 -	144ng/L

Open questions: novel drugs…

- ✓ CC122: monitoraggio BNP
- ✓ iBTK: rischio di FA e sanguinamento
- ✓ Romidepsina & iHDAC: allungamento QTc

Work in progress

- ✓ Chiappella, Pregno, Fava, Giorgi: stesura manuale pratico farmaci e cardiotossicità