Pixantrone

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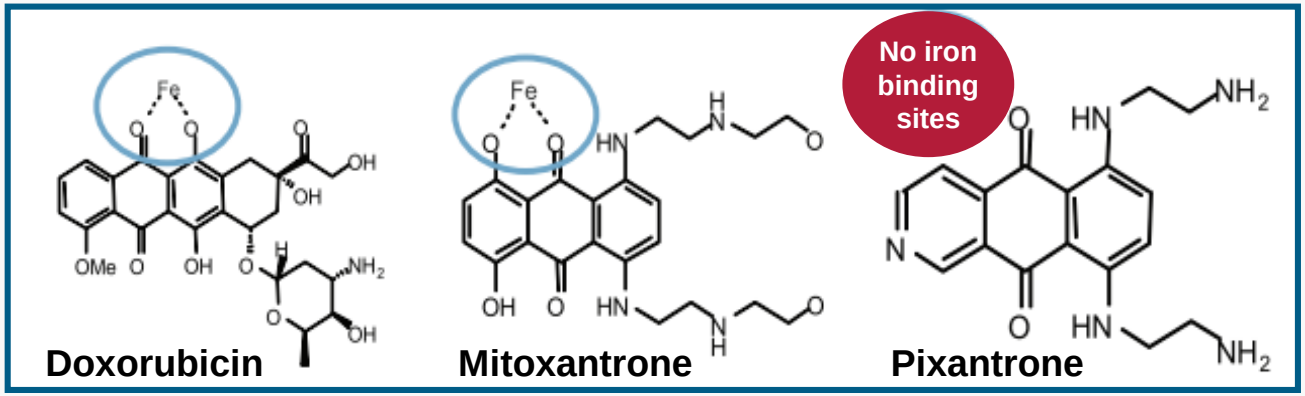
The chemical structure of pixantrone

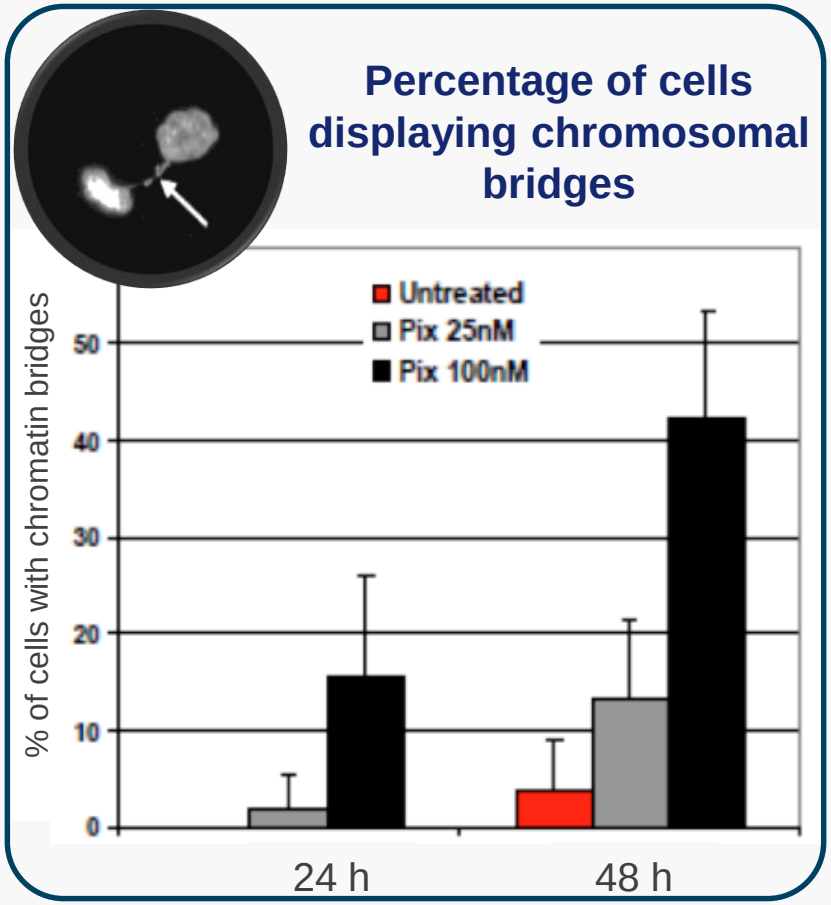


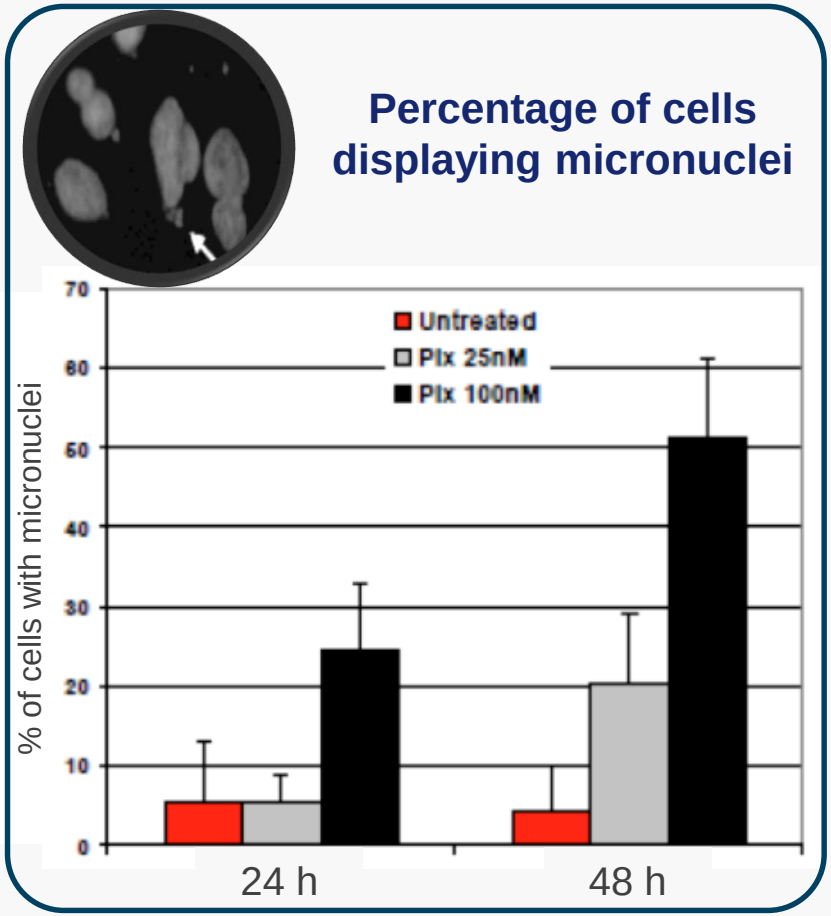
- DNA intercalator that inhibits Topo2α with additional activity through DNA crosslinkage[1]
- Compared with anthracyclines:
  - Pixantrone lacks an iron-binding site[1,2] and does not form toxic drug–metal complexes[2] which confers a limited potential to produce reactive oxygen species[1,3]
  - Cardiac myocyte predominantly express Topo2B
- Pixantrone lacks redox activity and inhibits doxorubicinol formation in human myocardium[4]

[1]Pixantrone Summary of Product Characteristics 2017; [2]Thorn CF, et al, Pharmacogenet Genomics 2011;21:440–446;
[3]Pettengell R, et al. Lancet Oncology 2012;13:696–706; [4]Salvatorelli E, et al. J Pharmacol Exp Ther 2013;344:467–478.

Pixantrone is a novel aza-anthracenedione with unique MoA

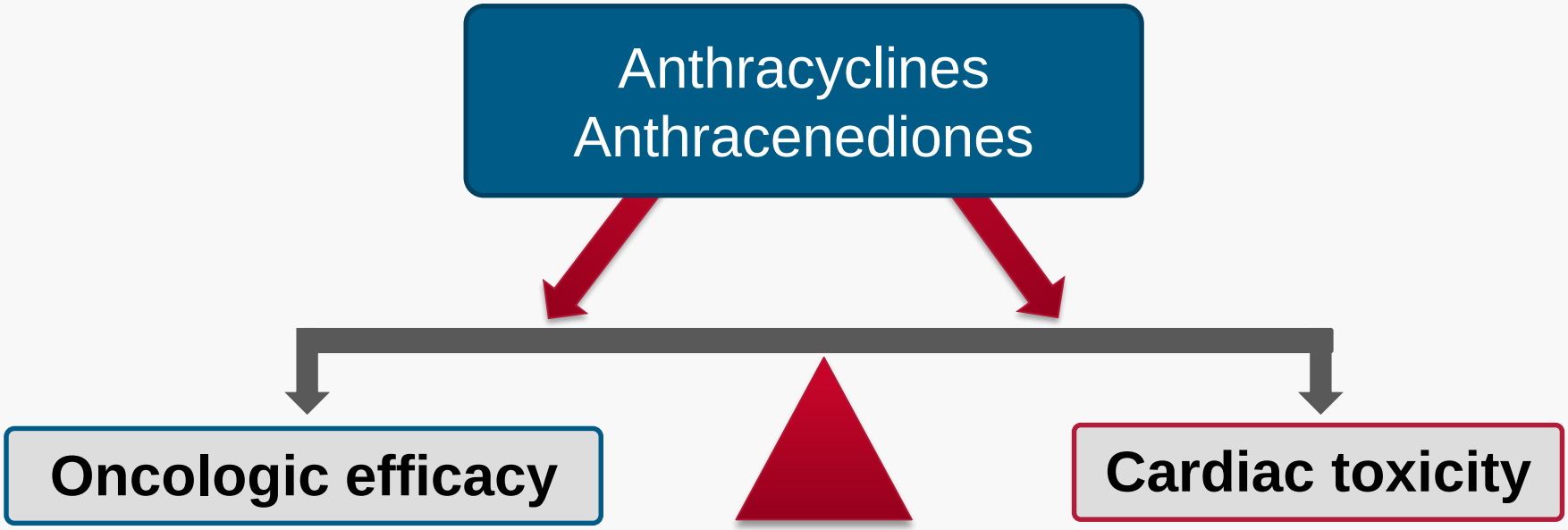
- Cell death by pixantrone results from multiple aberrant cell divisions
- Pixantrone induces chromosome bridges and micro- and multi-nucleation





Beeharry N, et al. Cancer Biol Ther 2015;16:1397–1406

A balance is required between treating disease and minimising toxicity



Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

Daniela Cardinale, MD, PhD, FESC; Alessandro Colombo, MD; Giulia Bacchiani, MD; Ines Tedeschi, MSc; Carlo A. Meroni, MD; Fabrizio Veglia, PhD; Maurizio Civelli, MD Giuseppina Lamantia, MD; Nicola Colombo, MD; Giuseppe Curigliano, MD, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

Real world prevalence
~9% LV dysfunction at 12 months

Cardinale et al, DOI: 10.1161/CIRCULATIONAHA.114.013777

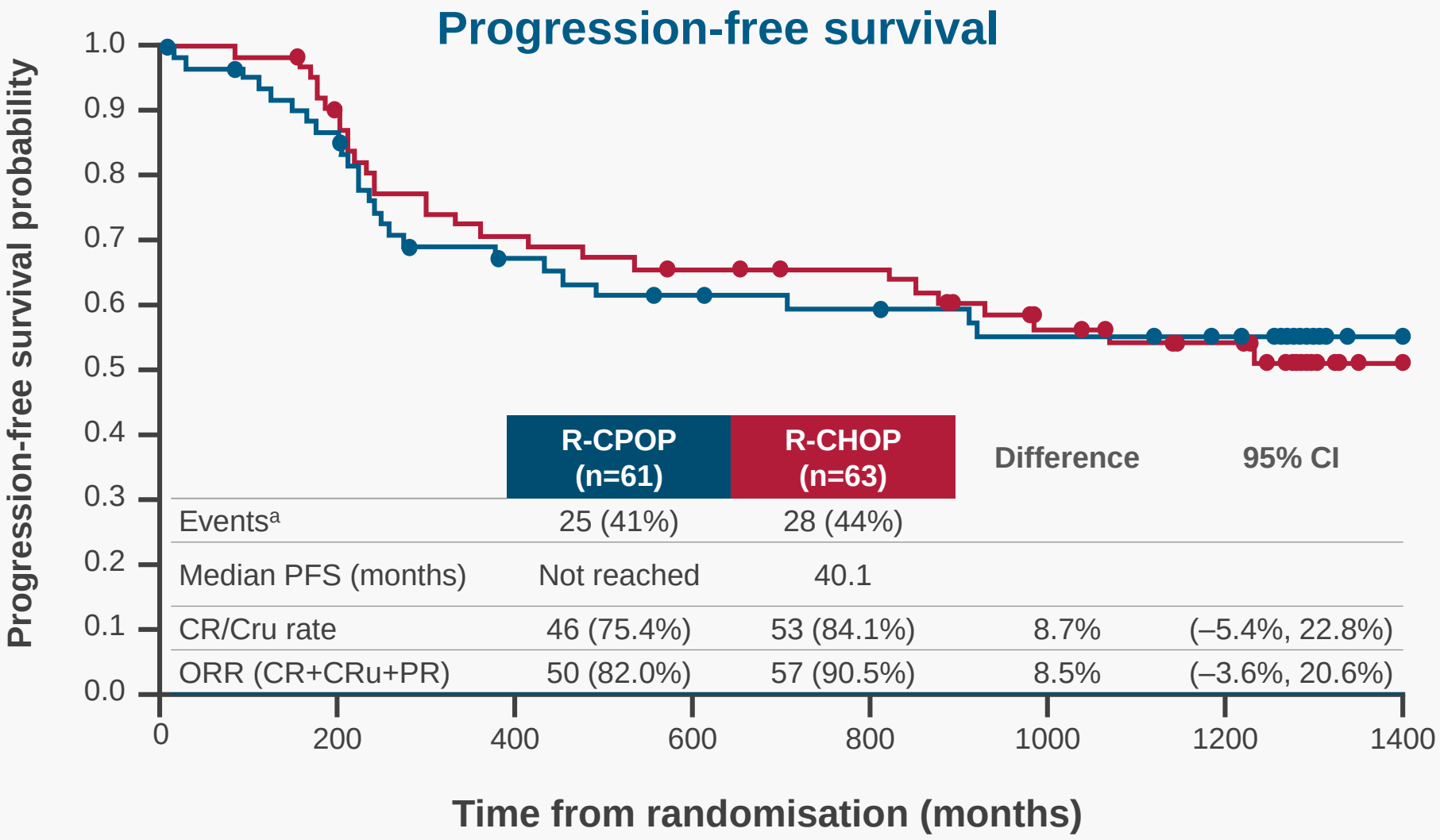
Comorbidities in NHL

Population-based study in The Netherlands

Comorbidity (%)	≤60 years n=559	>60 years n=690
No comorbidity	67	34
Cardiovascular	3	22
Hypertension	7	20
Other malignancy	14	17
Diabetes	3	11
COPD	4	9
Other/unknown	3	13

van Spronsen DJ, et al. Eur J Cancer 2005;41:1051–57
Sawyer DB. N Engl J Med. 2013;368:1154-6.

R-CHOP versus R-CPOP
Progression-free survival



	R-CPOP (n=61)	R-CHOP (n=63)	Difference	95% CI
Events[a]	25 (41%)	28 (44%)		
Median PFS (months)	Not reached	40.1		
CR/Cru rate	46 (75.4%)	53 (84.1%)	8.7%	(–5.4%, 22.8%)
ORR (CR+CRu+PR)	50 (82.0%)	57 (90.5%)	8.5%	(–3.6%, 20.6%)

[a]Events include PD or death or subsequent therapy without PD.

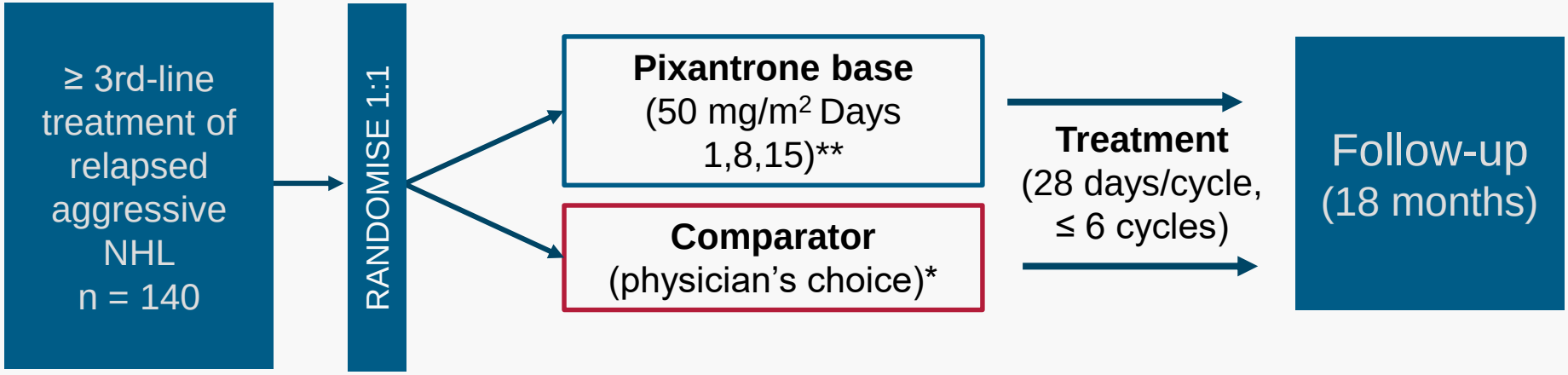
Herbrecht et al. Ann Oncol 2013;24:2618–23

R-CHOP versus R-CPOP
Adverse events (CV)

	R-CPOP (n=59)	R-CHOP (n=63)	P value
LVEF decline vs baseline			
≥10% point decline and to <50%	9 (15.3%)	17 (27.0%)	0.127
≥15% point decline	10 (16.9%)	20 (31.7%)	0.063
≥20% point decline	1 (1.7%)	11 (17.5%)	0.004
	n=59	n=63	
Grade 3 CHF during treatment	**0 (0%)**	**4 (6.3%)**	**0.120**
	n=43	n=46	
Troponin T shifts to a higher toxicity grade from baseline to end of treatment	3 (7.0%)	15 (32.6%)	0.003

Adapted from: Herbrecht et al. Ann Oncol 2013;24:2618–23

PIX301: Study design



* Choice of comparators included vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine or rituximab

** Clinical trials were based on pixantrone dimaleate 85 mg/m^2, equivalent to 50 mg/m^2 pixantrone base, the EU approved dose

Inclusion criteria

- Histologically-confirmed aggressive NHL
- Response to anthracycline regimen≥ 24 weeks
- ECOG PS 0–2
- Baseline LVEF ≥ 50%
- No clinically significant CV abnormalities

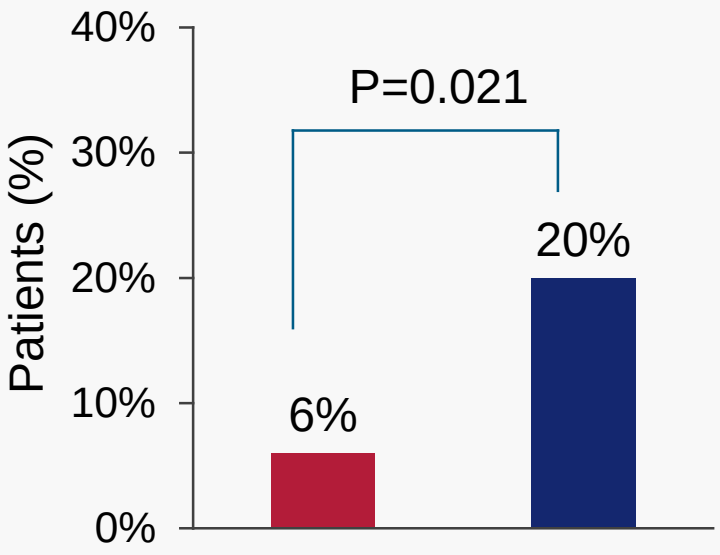
Exclusion criteria

- Prior exposure to doxorubicin > 450 mg/m2
- Myocardial infarction within previous 6 months

Pettengell et al. Lancet Oncol 2012;13:696.
Engert et al. Clin Lymphoma Myeloma 2006;7:152

Phase III PIX301 study: design and outcomes

Significant CR/CRu increase
End of treatment



	Pixantrone	Active Comparator
A longer median duration of CR/CRu (months)	9.6	4
	P=0.081 HR=0.32 (95% CI 0.09-1.23)	
Significant median PFS improvement (months)	5.3	2.6
	P=0.005 HR 0.60 (95% CI 0.42–0.86)	
A longer median OS (months)	10.2	7.6
	P=0.251	

Pettengell et al. Lancet Oncol 2012;13:696.
Engert et al. Clin Lymphoma Myeloma 2006;7:152.

PIX301: adverse events ≥5%

	Grades 3 or 4	
	Pixantrone (n=68) n (%)	Comparator (n=67) n (%)
Haematological		
Anaemia	4 (5.9)	9 (13.4)
Neutropenia	28 (41.2)	13 (19.4)
Febrile neutropenia	5 (7.4)	2 (3.0)
Leukopenia	16 (23.5)	5 (7.5)
Non-haematological		
Abdominal pain	5 (7.4)	3 (4.5)
Pyrexia	3 (4.4)	6 (9.0)
Pneumonia	4 (5.9)	3 (4.5)
Dyspnoea	4 (5.9)	3 (4.5)

Pettengell R, et al. Lancet Oncol 2012;13:696-706.

PIX301: responders by response to last therapy

Patients with CR/CRu during PIX301	
Response to last Chemotherapy	Response to pixantrone (n=17)
CR/CRu	3 (4.3%)
PR	8 (11.4%)
SD	3 (4.3%)
PD	3 (4.3%)

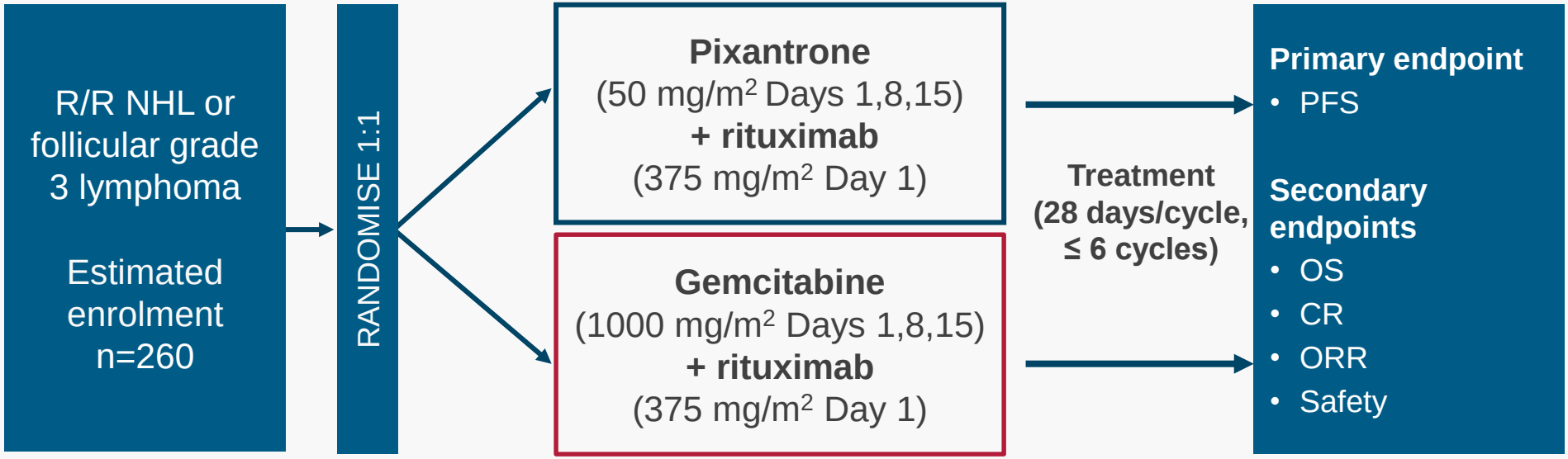
Last therapy regimens (n): +/- rituximab	
CHOP	(4)
ESHAP	(2)
CVP	(2)
DHAP	(3)
ICE	(2)
Other multi-agent regimens	(4)

- Single agent pixantrone achieved CR/CRu's in patients that had PR, SD, PD from prior intensive salvage therapies
- **82% (14 of 17)** of the pixantrone CR/CRu had a sub-optimal response to these prior therapies yet went on to achieve a CR with single agent pixantrone

SD, stable disease; PD, progressive disease

Pettengell R. *Clin Drug Invest.* 2018;38(6):527-533

PIX306: Phase III trial in R/R aggressive B-cell NHL non-SCT eligible



Inclusion criteria

- De novo DLBCL or follicular lymphoma: 1–3 previous treatment regimens
- DLBCL transformed from indolent lymphoma: 1–4 treatment regimens
- Received rituximab-containing multiagent therapy
- Not eligible for high-dose chemotherapy and stem cell transplant

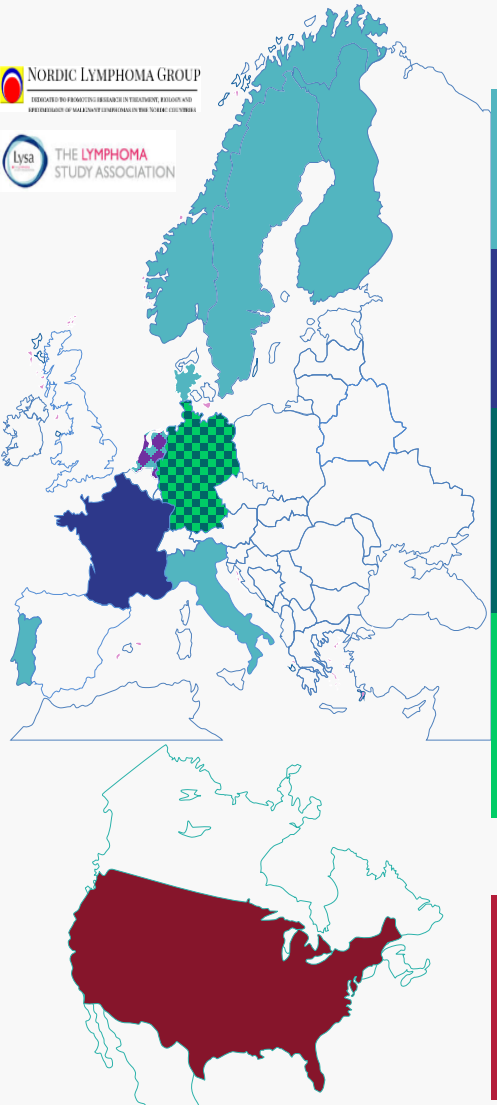
Exclusion criteria

- Prior exposure to doxorubicin > 450 mg/m^2

Belada D. et al. *Future Oncol*. 2016

clinicaltrials.gov/ct2/show/NCT01321541

Combination studies (investigator initiated studies)



Study	Sponsor – PI	Treatments	Phase	Patient population
PREBEN*	Aahrus University F. d'Amore	Pixantrone Rituximab Etoposide Bendamustine	I/II single arm	B and T-cell RR NHL
PIVeR*	LYSARC LM. Fornecker	Rituximab Pixantrone Ifosfamide Etoposide	I/II single arm	RR NHL
GOAL	Johannes Gutenberg-Univ.Mainz / G. Hess	Pixantrone + Obinutuzumab	II single arm	RR NHL
R-CPOP	University of Freiburg / R. Marks	Rituximab Cyclophosphamide Pixantrone Vincristine Prednisone	II single arm	Elderly or with limited cardiac function
BuRP	University of North Carolina, USA / A Beaver	Bendamustine Rituximab Pixantrone	I single arm	RR NHL

PREBEN: EudraCT number: 2015-000758-39; PIVeR: NCT03458260; GOAL: NCT02499003; NCT02499003; BuRP: NCT01491841

PREBEN: a Phase I/II study in relapsed (non-refractory) aNHL

Drug	Day
Pixantrone 50 mg/m^2	d1+8
Rituximab 375 mg/m^2	D1
Etoposide 100 mg/m^2	D1
Bendamustine 90 mg/m^2	D1
q3 week (max 6 courses), outpatient regimen	

Patient characteristics	
Patients, n	30
Median number of previous regimens	3 (1–7)
Male, n (%)	19 (63)
Age (range), years	(49–81)
IPI score, n (%)	
Intermediate or high risk	30 (100)
Cancer type, n (%)	
DLBCL	17 (57)
Transformed indolent lymphoma	6 (20)
PTCL	7 (23)

- All patients were assessed for chemosensitivity with PET/CT, after cycle 1 or 2
- G-CSF support was applied and administered according to local practice

Clausen MR et al. Presented at ASH 2016

PREBEN: results

Well tolerated

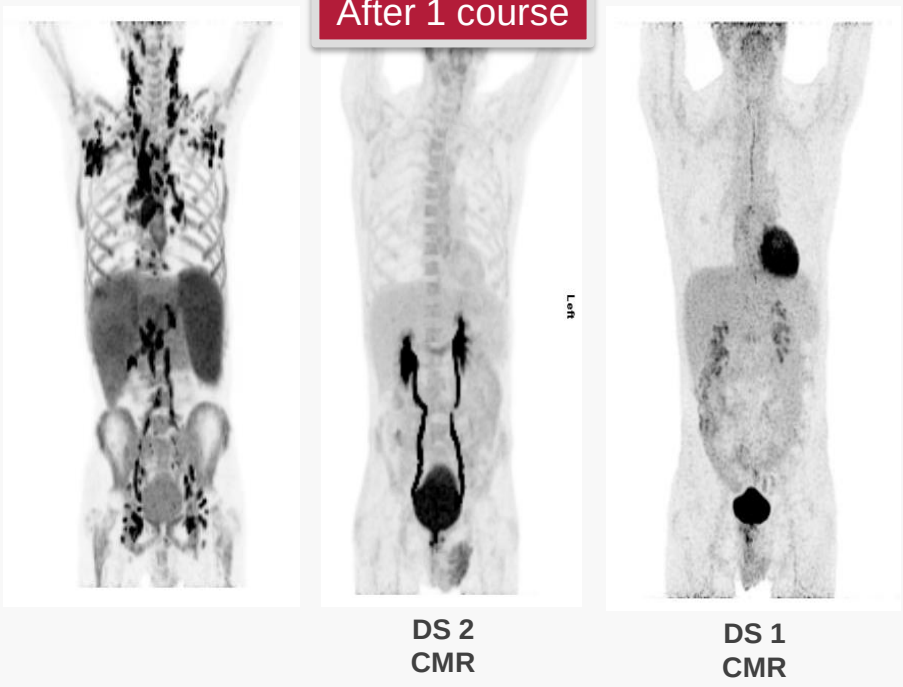
Early CRs not uncommon

Some durable responses

Sept 2013

Nov 2013

Feb 2014



DS 2 CMR

DS 1 CMR

Efficacy and feasibility	
Treated patients	30
ORR - DLBCL	53% (CR35%)
ORR - PTCL	57% (CR14%)
Response duration	2–23+ months
Gr 3-4 haematological	52%
Gr 3-4 infections	21%
Other toxicity	One patient with CHF, one patient with tMDS/AML (previous RIT)

DS, Deauville score; CMR, complete metabolic response; CHF, congestive heart failure; AML, acute myeloid leukemia

d'Amore et.al. Presented at ASH 2014;
d'Amore et al. Presented at ICML 2015;
Clausen et al. Presented at ASH 2016

- The treatment schedule was feasible and most patients received it on an outpatient basis

BuRP Phase I study: novel combination in patients with R/R B-cell NHL

Drug	Day
Bendamustine 120 mg/m^2	D1
Rituximab 375 mg/m^2	D1
Pixantrone 55, 85 or 115 mg/m^2 (3 cohorts)	D1
21-day cycles (max 6 courses)	

Patient characteristics	
Patients, n	22
Median number of prior regimens	3 (1–6)
Male, n (%)	16 (73)
Median age (range), years	63 (34–84)
R-IPI score, n (%)	
1	1 (6)
2	8 (47)
3	5 (29)
4	3 (18)
Cancer type, n (%)	
DLBCL	11 (50)
Transformed lymphoma	6 (26)
Follicular lymphoma	3 (14)
PMBCL	1 (5)
SLL/CLL	1 (5)

Heyman B, et al. Clin Lymphoma Myeloma Leuk 2018;18:679–686.

BuRP Phase I study: novel combination in patients with R/R B-cell NHL

AEs occurring in >5% of patients*		
Event	All grades, %	Grade 3/4, %
Neutropenia	27	27
Thrombo-cytopenia	32	23
Anaemia	32	13
Febrile neutropenia	14	9
Diarrhoea	41	9
Fatigue	64	23
Oliguria	9	9

*One patient had a change in LVEF greater than 10% and died secondary to treatment-induced cardiomyopathy after the 6th cycle

Response	All patients (n=16), % (95% CI)	Pix 55 mg/m^2 (n=4), %	Pix 85 mg/m^2 (n=5), %	Pix 115 mg/m^2 (n=8), %
ORR	37.5 (15–65)	0	20	63
CR	12.5 (2–38)	0	0	25
PR	25 (7–52)	0	20	38
SD	25 (7–52)	50	20	25

Conclusion

"The favourable toxicity profile plus encouraging response rates warrant continued investigation of the highest dose"

- Heyman B, et al. Clin Lymphoma Myeloma Leuk 2018;18:679–686

Real world experience

UK-wide retrospective multi-centre audit of 92 R/R DLBCL who received pixantrone

Eyre T.A. et *al*, BJH published online 9 March 2016

Characteristics		(N=90)
N		90
Age, median		**66 (20-86)**
Sex (%)	Female	34
	Male	66
IPI (%)	0–1	6
	2	21
	3–5	**73**
Ann Arbor (%)	I/II	10
	III/IV	**90**
ECOG (%)	0–1	46
	≥ 2	**54**
Relapsed (%)		15
Refractory (%)		**86**

Prior lines	(N=90)
Median prior treatments	2 (range 1-6)
Prior rituximab	99%
Prior transplant	16%

Result	(N=90)
ORR (%)	**24**
CR (%)	**10**
PR (%)	14
SD (%)	6
DCR (%)	**30**
PFS (months)	2 months
OS (months)	3.4 months

PIX301 eligible patients = 7 pts; ORR 57%, PFS 4.6 mo

PIXA registry

Observational, retrospective, multicentre study, post authorisation

80 patients in Spain + Italy

Key inclusion criteria

Patient with multiply R/R aggressive B-NHL treated as per licensed indication

Pixantrone (50 mg/m^2)

days 1, 8, 15 every 28-days

(up to 6 cycles)

Endpoints

- **Primary endpoint:** PFS
- **Secondary endpoints:** CRR; ORR; time to response; DR; OS; Safety; number of cycles of pixantrone

Conclusions

Pixantrone:

- Unique MOAs in tumour and cardiac cells
- Active and safe in patients:
  - with R/R NHL
  - who exhausted the cumulative dose of doxorubicin
- Approved as monotherapy for adult patients with multiply R/R aggressive NHL
- Monotherapy has significantly greater efficacy than comparator agents (PIX301)
- Predictable and manageable safety profile[1]
- Amenable to combination with potentially numerous agents

[1]Pettengell R, et al. Lancet Oncol 2012;13:696-706.

Thank you