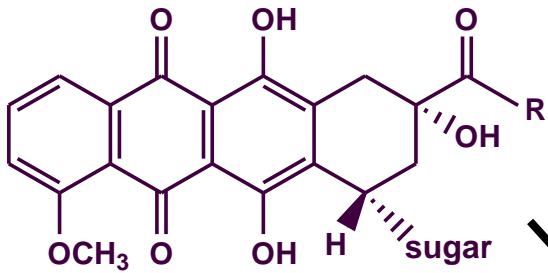


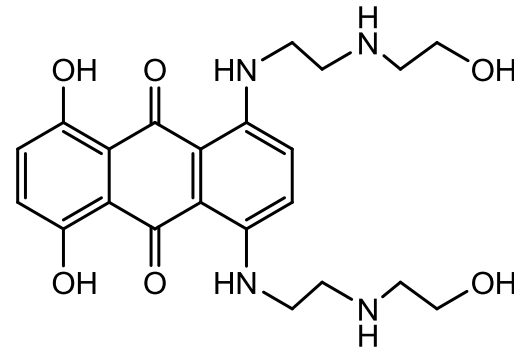
Pixantrone in relapsed and refractory NHL

Ruth Pettengell

St George's University of London



DOX



MITOX

topo II α
inhibition

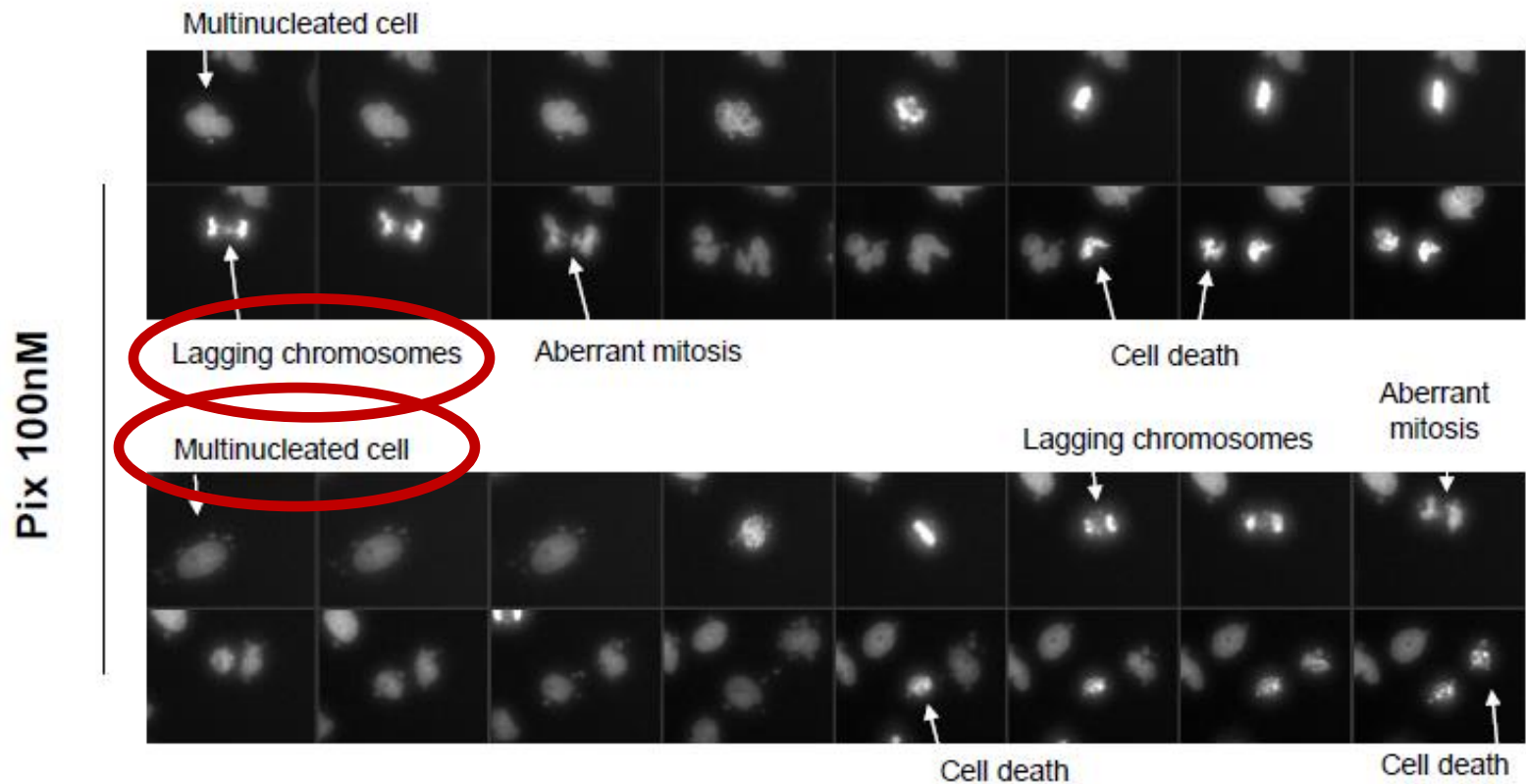
p53

APOPTOSIS

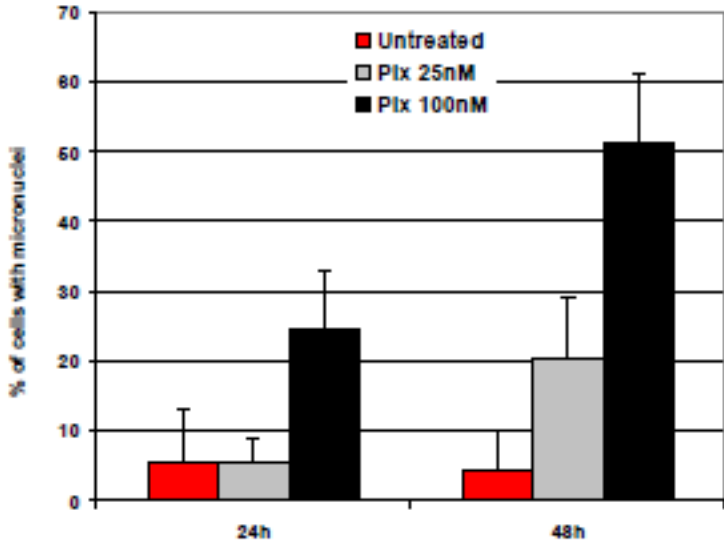
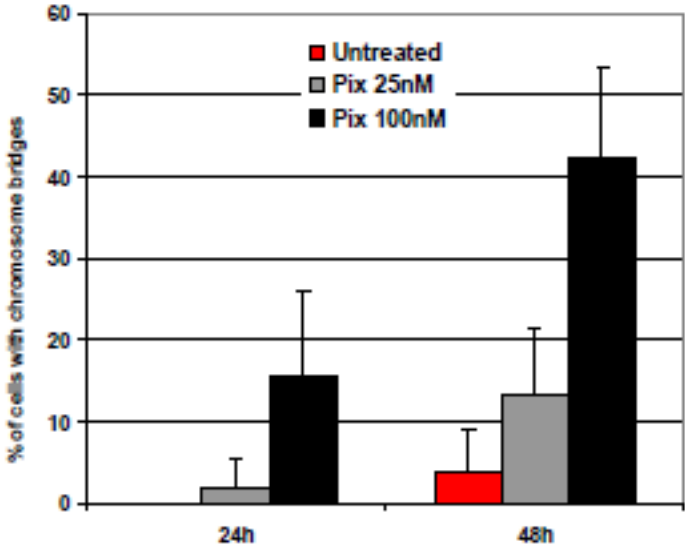
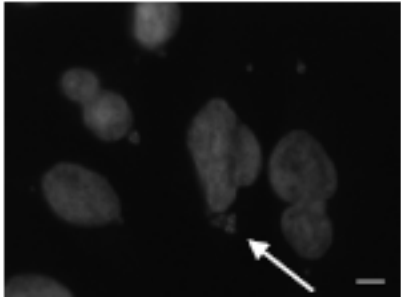
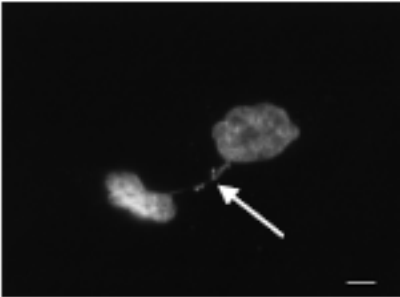
cell cycle-dependent

PIX works by different mechanisms

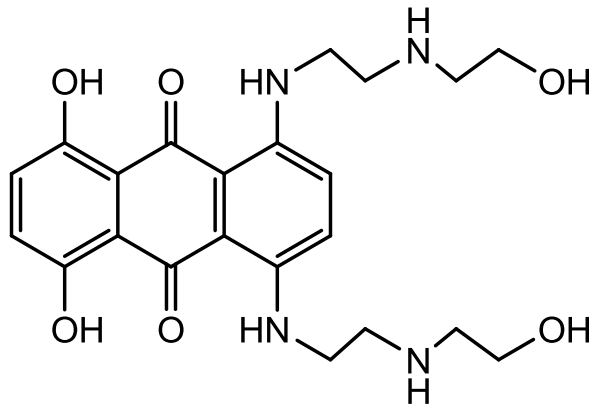
6. Cell death by pixantrone as a result of multiple aberrant cell divisions.



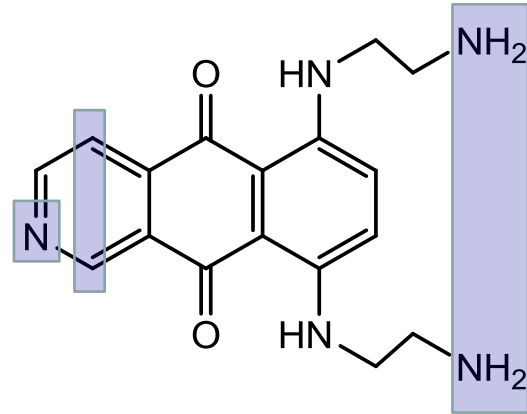
Pixantrone induced chromosome bridges and micro- and multi-nucleation



Beeharry *et al.*
2013-2015



MITOX



PIX

Lack of juxtaposed quinone-hydroquinone may be a factor of reduced interactions with topoisomerase 2 α

Highlighted Papers

1521-0103/344/2/467-478\$25.00

THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

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<http://dx.doi.org/10.1124/jpet.112.200568>

J Pharmacol Exp Ther 344:467-478, February 2013

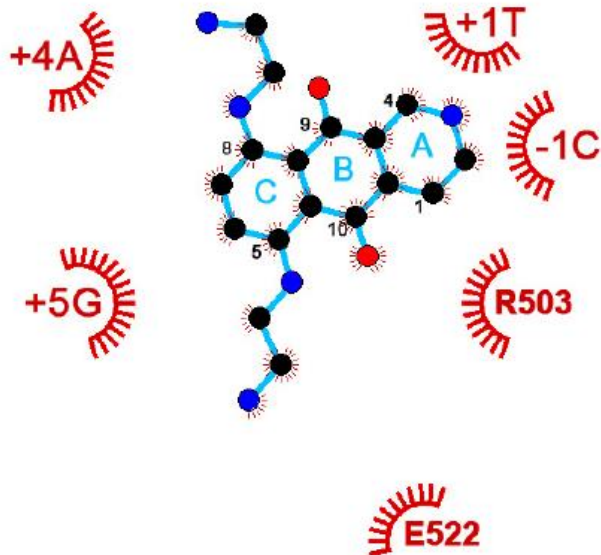
The Novel Anthracenedione, Pixantrone, Lacks Redox Activity and Inhibits Doxorubicinol Formation in Human Myocardium: Insight to Explain the Cardiac Safety of Pixantrone in Doxorubicin-Treated Patients

Emanuela Salvatorelli, Pierantonio Menna, Odalys Gonzalez Paz, Massimo Chello, Elvio Covino, Jack W. Singer, and Giorgio Minotti

Drug Sciences (E.S., P.M., O.G.P., G.M.) and Cardiac Surgery (M.C., E.C.), Center for Integrated Research, University Campus Bio-Medico, Rome, Italy; and Cell Therapeutics Inc., Seattle, Washington (J.W.S.)

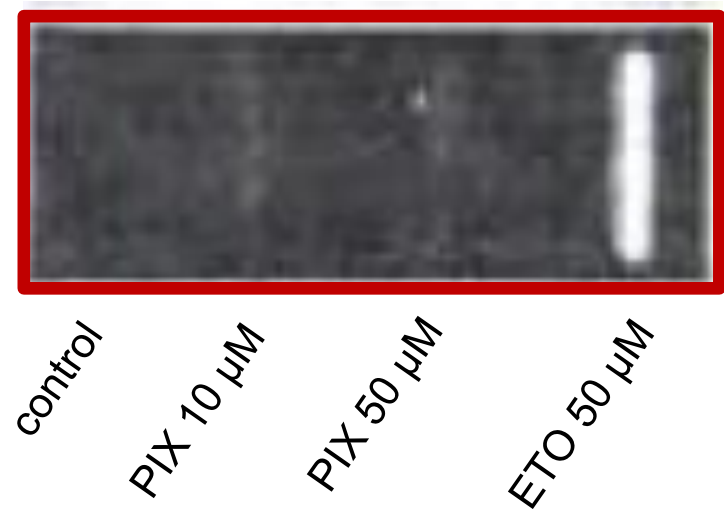
PIX does not target newly identified target, top2 β

PIX - top2 β
crystallization



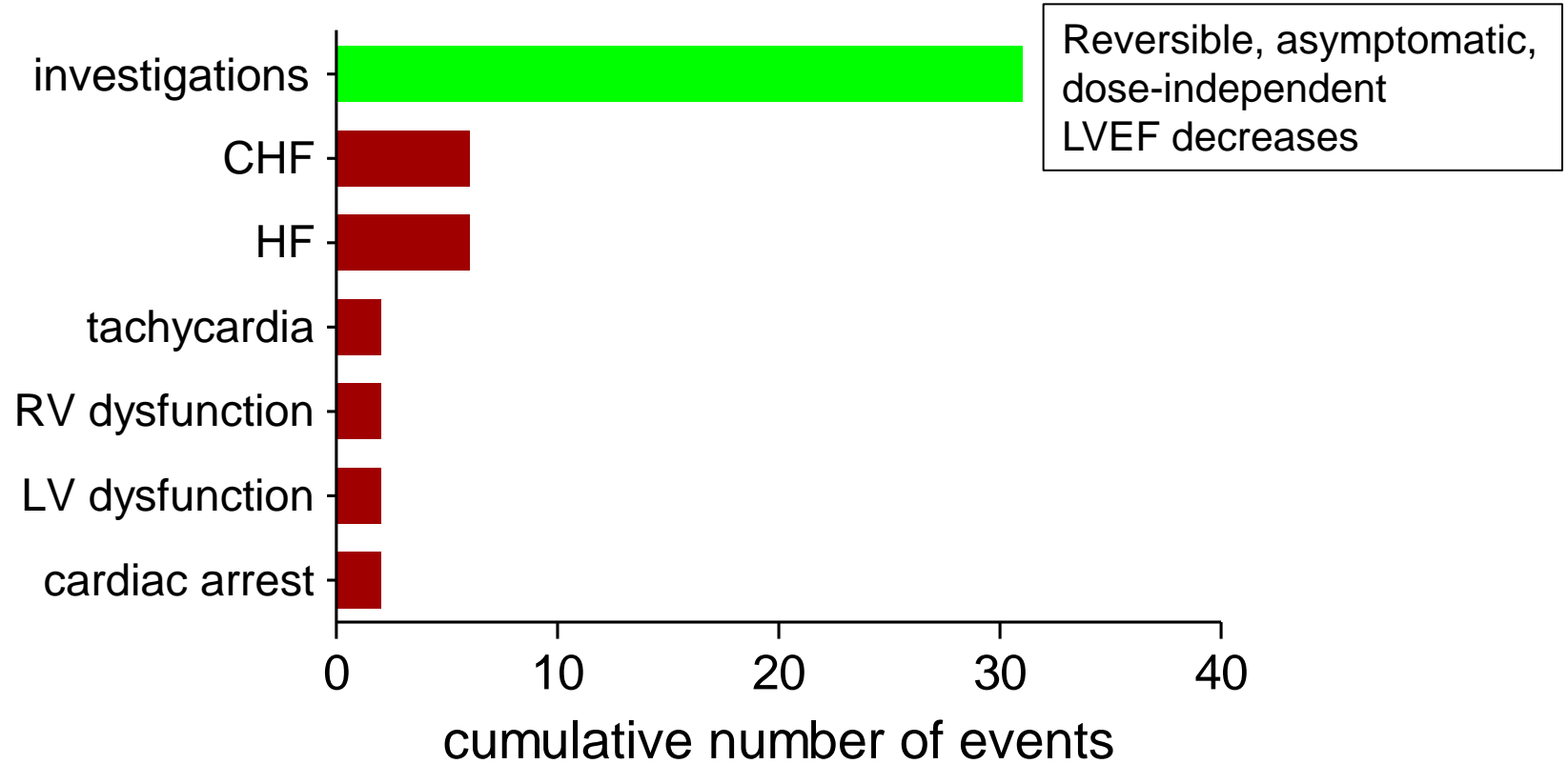
CTI data on file

PIX - top2 β
ICE assay




B. Hasinoff, AACR 2015

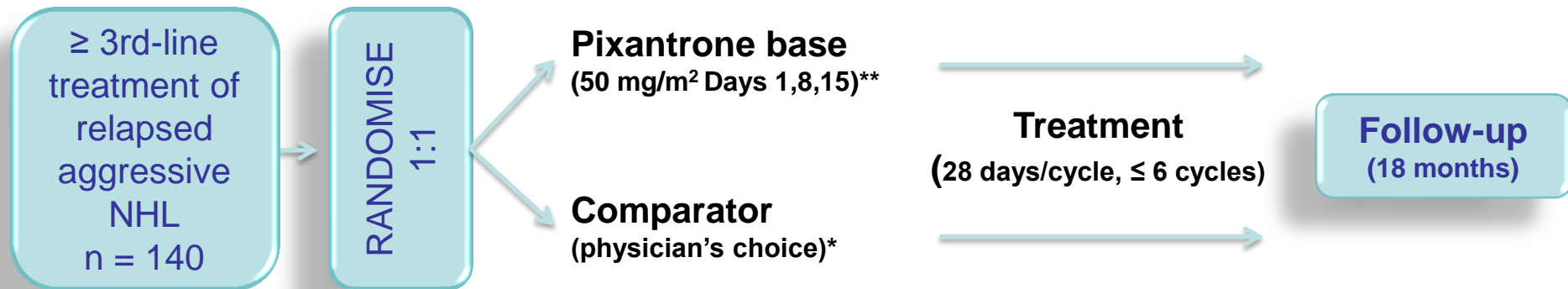
PSUR submitted in January 2015



Data from R-CPOP vs R-CHOP

| | CPOP-R n = 59 | CHOP-R n = 63 | P Value |
|--|--------------------------|--------------------------|----------------|
| Clinical CHF | 0 | 5 (7.9%) | 0.03 |
| LVEF decline >20% | 1 (1.7%) | 8 (12.7%) | 0.03 |
|  Troponin T Elevation | 2/42 (4.8%) | 15/46 (32.6%) | 0.002 |
| Mean Decline in LVEF at 12 months | -1.1% | -7.0%; | 0.002 |

PIX301: Study design



Inclusion criteria

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

Exclusion criteria

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

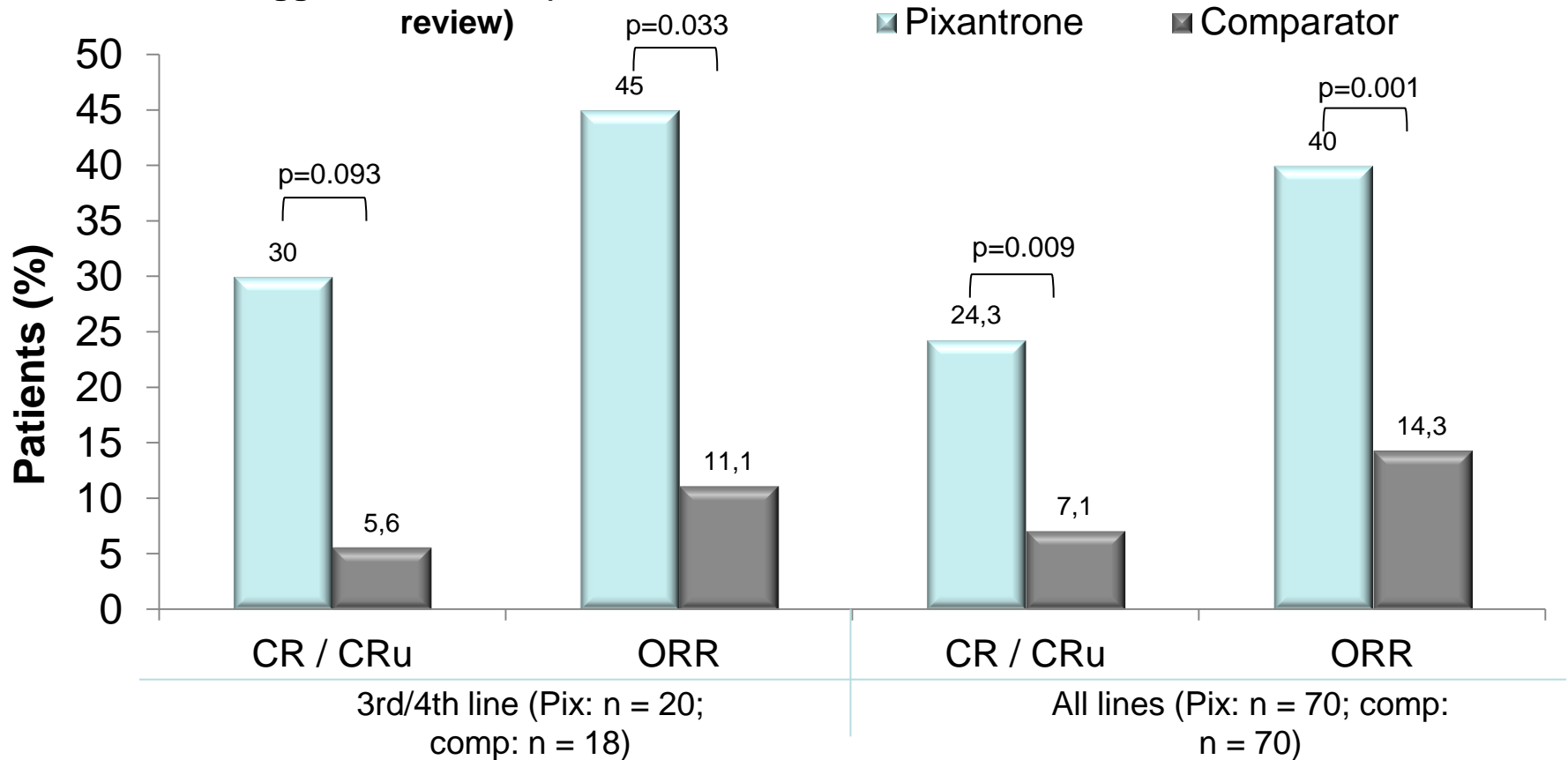
*Choice of comparators included vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine or rituximab

**Clinical trials were based on pixantrone dimaleate 85 mg/m², equivalent to 50 mg/m² pixantrone base, the EU approved dose

Phase III PIX301: response in histologically confirmed aggressive B-cell (+ prior rituximab)

Post-hoc analysis: RR at EOS in prior Rituximab treated aggressive B NHL (central review)

Primary analysis: RR at EOS (central review)



PIX301 Responders by Response to Last Therapy

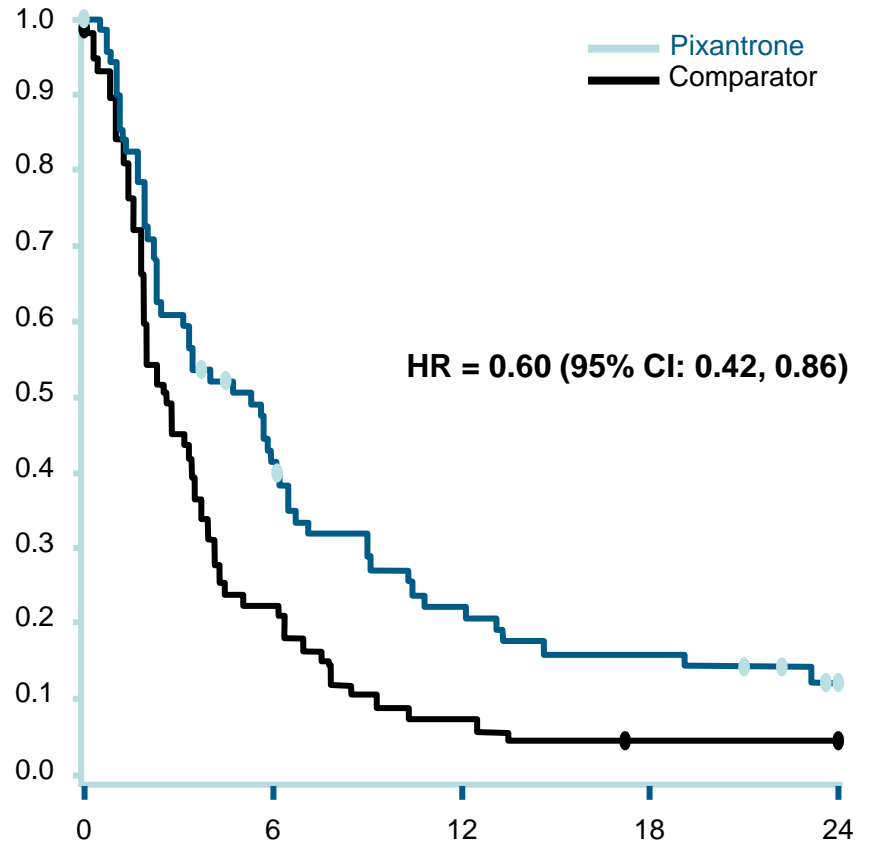
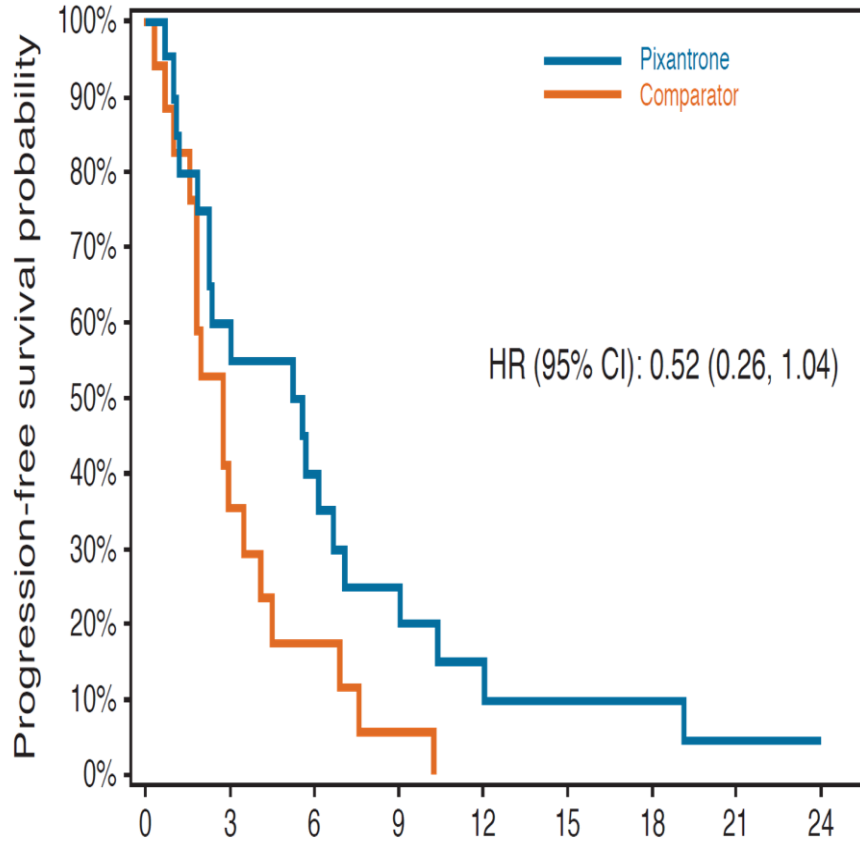
| Patients with CR/CRu During PIX301 | |
|------------------------------------|---------------------------------|
| Response to last Chemotherapy | Response to pixantrone (n = 17) |
| CR/CRu | 3 (4.3%) |
| PR | 8 (11.4%) |
| SD | 3 (4.3%) |
| PD | 3 (4.3%) |

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

SD = Stable Disease
 PD = Progressive Disease

- 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

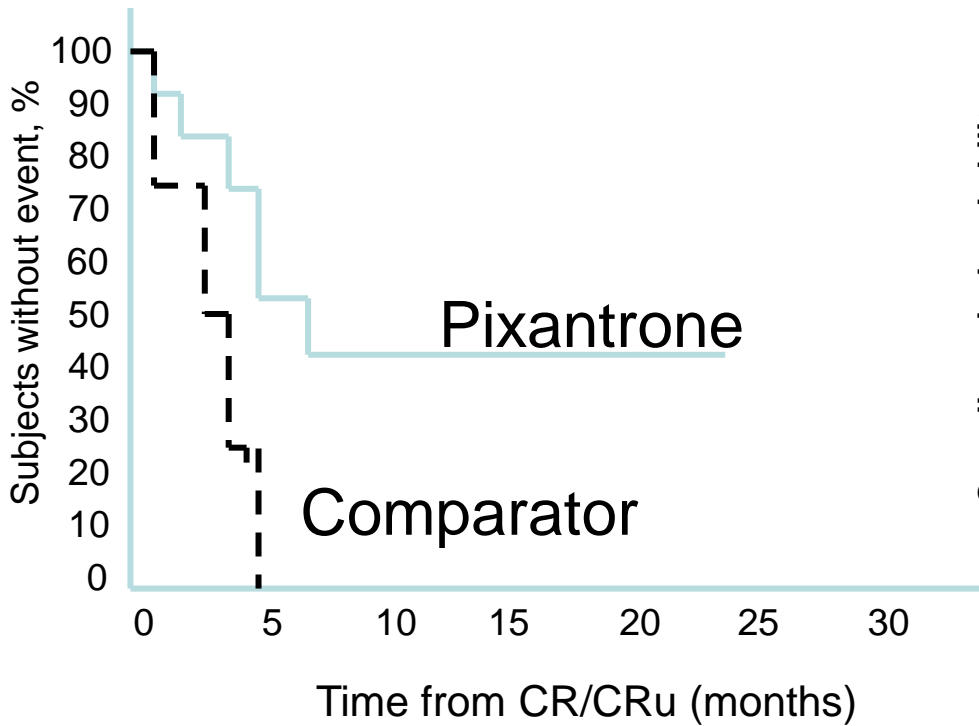
Phase III PIX301: PFS in histologically confirmed aggressive B-cell (3rd/4th line, + prior rituximab)



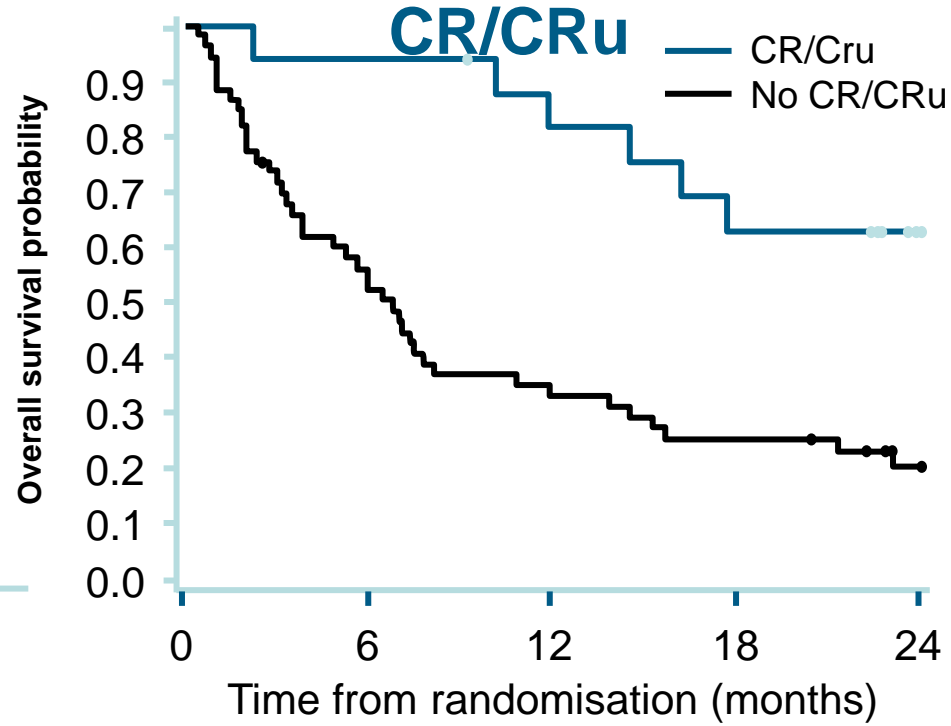
Time from randomisation (months)

Phase III PIX301: significance of CR / CRu

Duration of CR/CRu (months)



OS in patients with and without a CR/CRu



CR/CRu was a significant predictor of survival (HR = 0.35, 95% CI 0.18–0.68)

Phase III PIX301: adverse events $\geq 5\%$

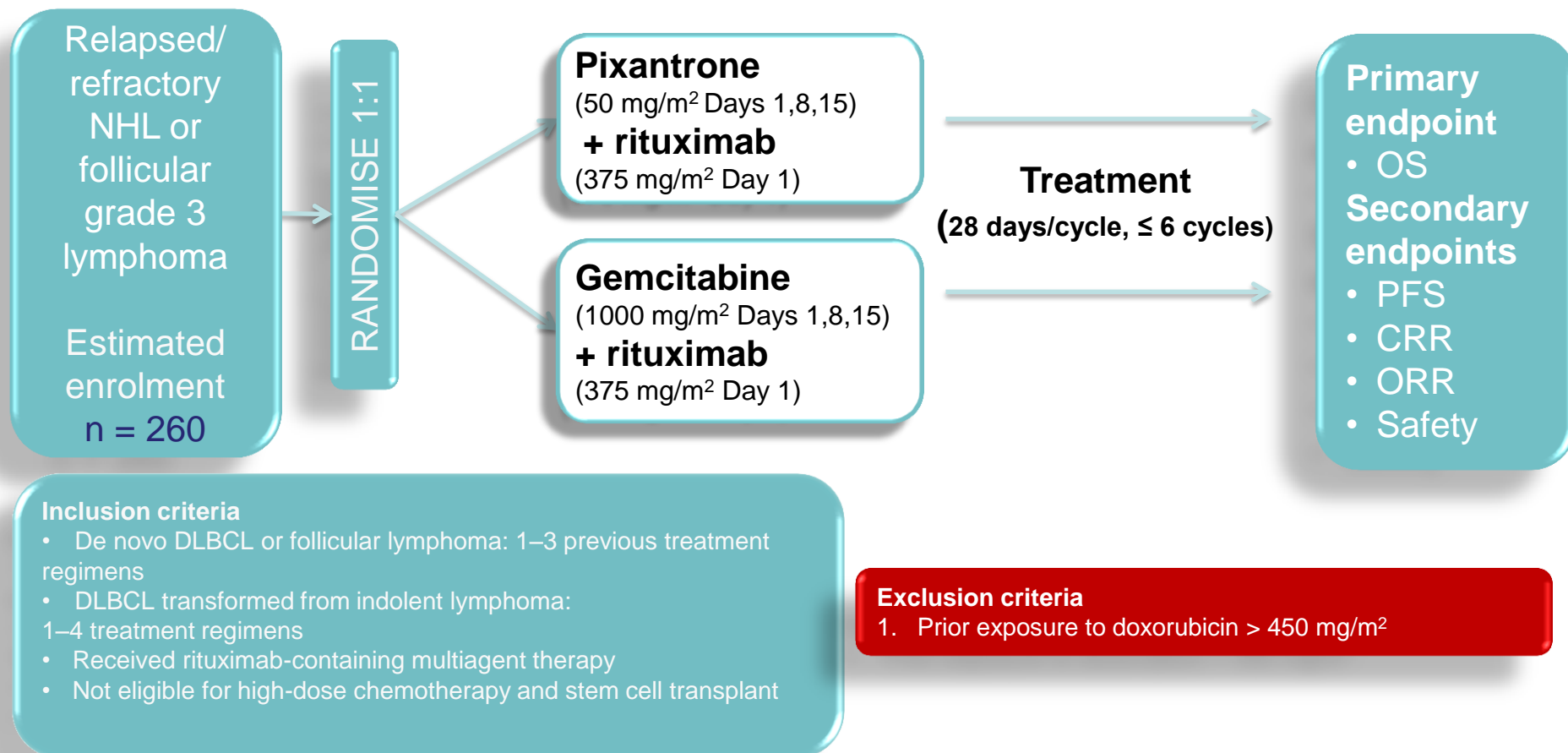
| | Grades 3 or 4 | |
|---------------------------|---------------------------------|---------------------------------|
| | Pixantrone (n = 68) n (%) | Comparator (n = 67) n (%) |
| Haematological | | |
| Anaemia | 4 (5.9) | 9 (13.4) |
| Neutropenia | 28 (41.2) | 13 (19.4) |
| Febrile neutropenia | 5 (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) |
| Dyspnea | 4 (5.9) | 3 (4.5) |

Activity of single agents in R/R DLBCL

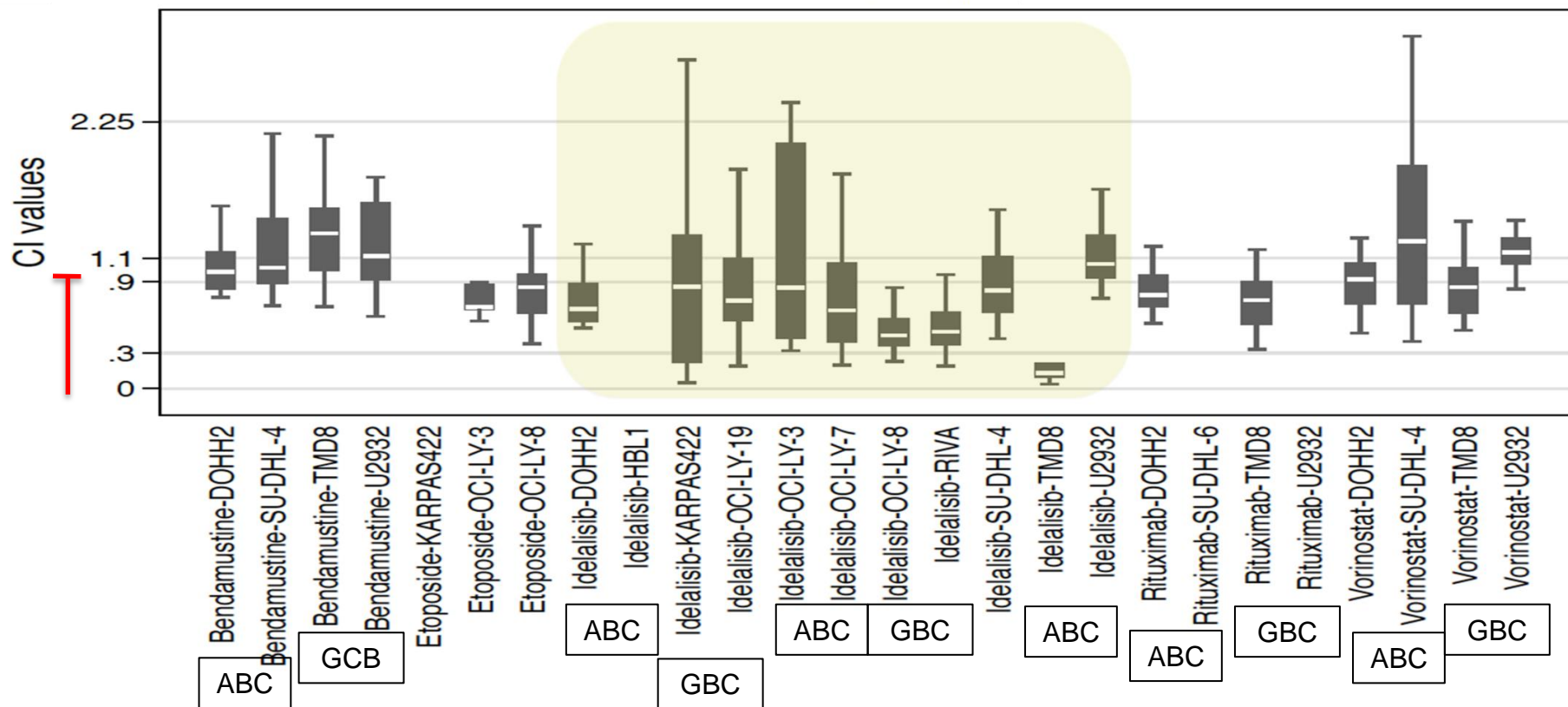
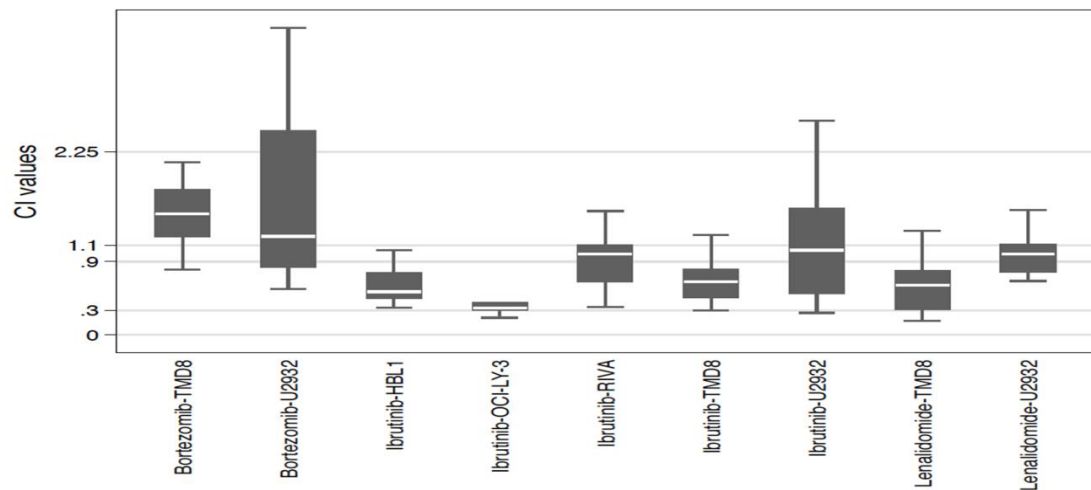
| | n | Number of prior chemo regimens | RR (CR) |
|------------------------------|-----|--------------------------------|-----------|
| Vincristine ¹ | 15 | ≥ 1 | 40% |
| Etoposide ¹ | 10 | ≥ 1 | 50% |
| Gemcitabine ² | 30 | 1-3 | 20% (5%) |
| Rituximab ³ | 21 | ≥ 1 | 38% |
| Inotuzumab ⁴ | 10 | | 90% |
| Lenalidomide ⁵ | 108 | 4 (median) | 27% (7%) |
| Bendamustine ⁶ | 18 | ≥ 1 | 44% (17%) |
| Ibrutinib (ABC) ⁷ | 29 | 3 | 32% (6%) |
| Pixantrone ⁸ | 70 | 3 | 45% (30%) |

1. Webb et al. Leukemia Lymphoma 2002;43, 975 2. Fossa et al. J Clin Oncol 1999;17:3786. 3. Rothe et al. Haematologica. 004;2004;89:875-6
4. Fayad et al. J Clin Oncol 2013;31:573. 5. Witzig et al. Ann Oncol 2011;22 (7):1622. 6. Weidmann et al. Ann Oncol 2002;13:1285
7. Wilson et al. ASH 2012. Abs 686. 8. Pettengell et al. Lancet Oncol 2012;13:696

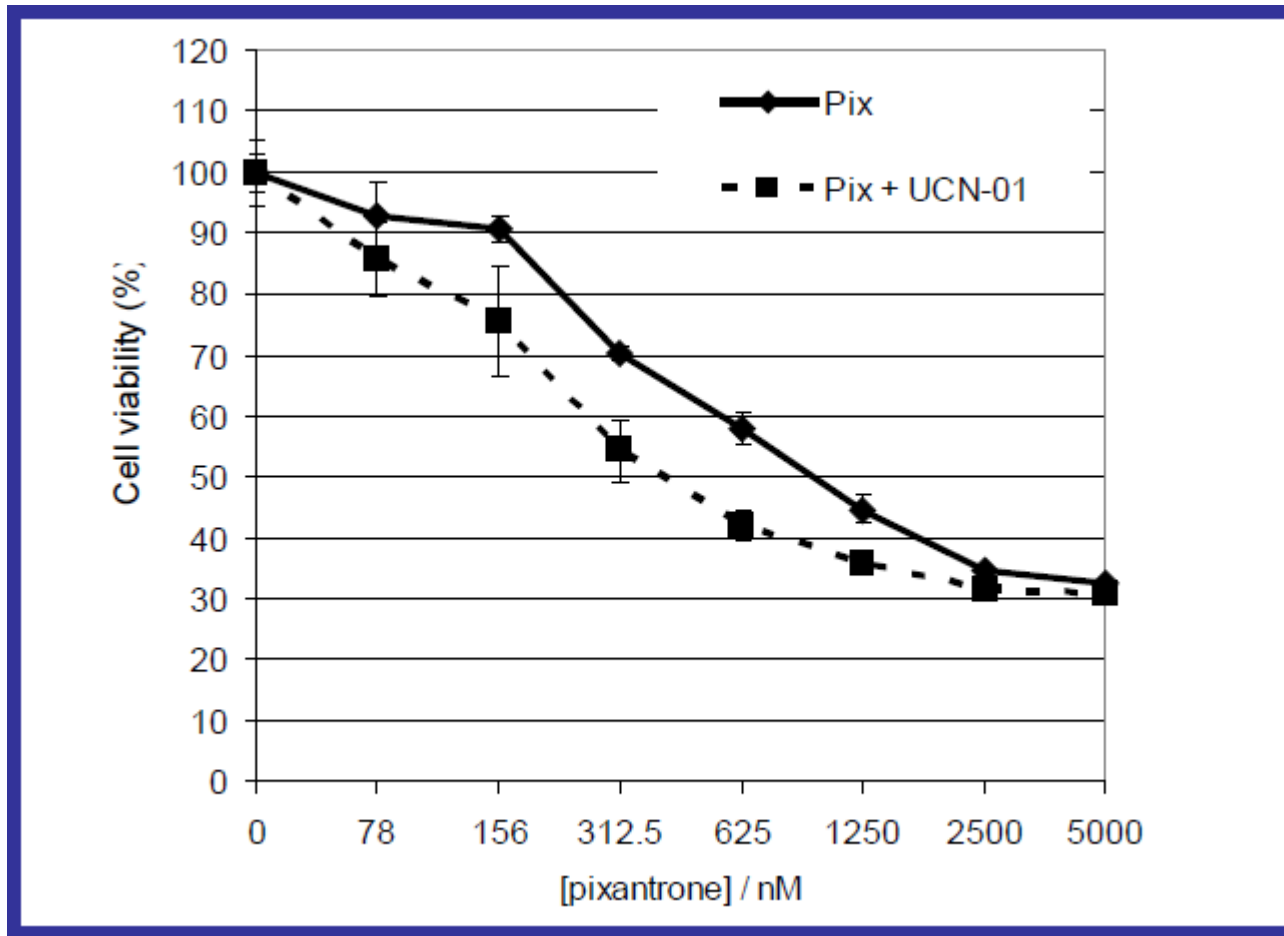
PIX306 (PIX-R): phase III trial in R/R aggressive B-cell NHL non-SCT eligible



Activity and Synergism of PIX in both GC and ABC cell lines



Chk-1 inhibition enhances PIX activity



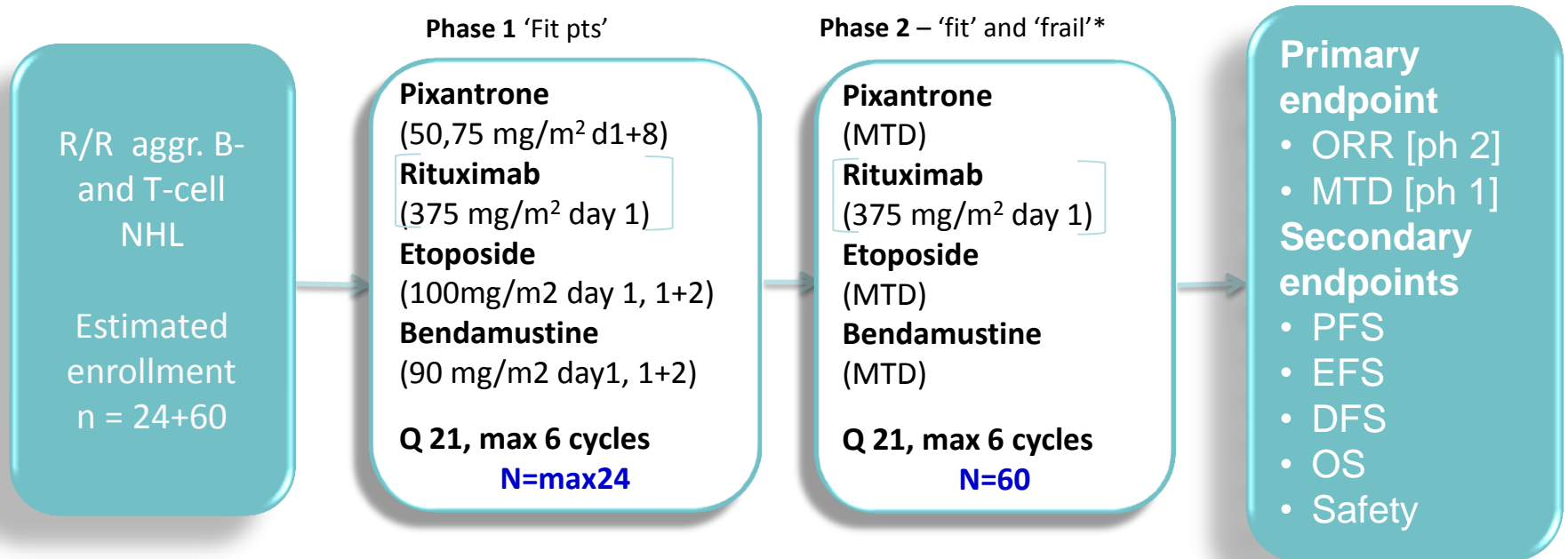
Beeharry *et al.*
AACR – EORTC 2013

Current Pixantrone Clinical IST Program

| PI | Site | Title | Disease | Treatment | Enrollment status | Comments |
|---------|----------------------------|---|----------------------------|---|--|--|
| Heß | Univ Mainz | Rescue Treatment With The Monoclonal Anti Cd20-antibody Obinotuzumab (GA101) In Combination With Pixantrone (Plus Dexamethasone) For The Treatment Of Patients With Relapsed Aggressive B-cell | Relapsed aNHL | Obinotuzumab (GA101) + PIX | 17/64 | In discussion for next agent: BCL2i |
| Marks | Univ Med Clinic Freiburg | R-CPOP as first line therapy for elderly patients with DLBCL and for patients with limited cardiac function with DLBCL | DLBCL | R-CPOP | 3/60 | |
| Raderer | Medical University Vienna | Lenalidomide plus pixantrone in patients with MALT lymphoma | MALT | Lenalidomide + PIX | 0/46 | (Not finalized) |
| d'Amore | Aarhus University Hospital | Pixantrone and bendamustine for relapsed non-Hodgkin lymphoma of B and T-cell phenotype. (PREBEN /Pix-Ben-Eto Trial) | Relapsed B/T-cell lymphoma | Bendamustine, etoposide, rituximab + PIX | 0/60 First patient not treated due to CNS lesions | Swedish insurance resolved. Additional country budget needed |
| Hübel | University clinic Cologne | A multicenter, open label, uncontrolled, phase II trial evaluating the safety and efficacy of pixantrone in combination with idelalisib and GA101 in previously treated patients with follicular lymphoma | Relapsed FL | Pixantrone GA101 Idelalisib (Gilead approved) | 0/30-40 | Not finalized |

Phase I/II trial of pixantrone, rituximab [only in CD20+ tumors], etoposide, bendamustine, in pts with relapsed aggressive NHL

NORDIC LYMPHOMA GROUP



*Frail pts enter directly the phase II part of the trial at baseline dose level

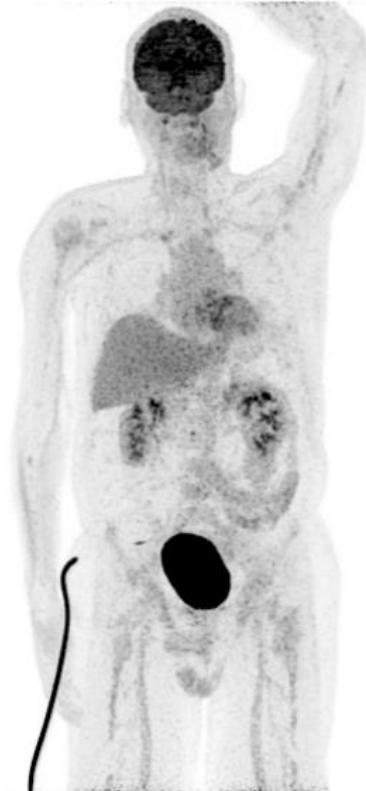
PREBen Regimen Series

- 19 evaluable pts (10 DLBCL, 4 PTCL, 5 tFL/Ind)
- Complete metabolic responses in DLBCL (CR 40%, PR 20%) and PTCL (CR 25%, PR 50%)
- Transf indolent and primary refr to DHAP/ICE had low response rates
- Responses detectable after the 1st course(no TLS observed)
 - Response durations are in the range 4- 17+ mo
 - Out-patient regimen
 - Grade 3-4 infections in 40% of pts

PREBen Patient Series

Pre RX

Post Rx



Pre RX

Post Rx



Conclusions

- ✓ **Pixantrone** shows unique MOAs in tumor and cardiac cells
- ✓ **Pixantrone is active and safe** in patients with refractory-relapsed NHL and can bridge to other modalities
- ✓ **Pixantrone** is amenable to combination with potentially numerous agents