

NAVN:
CPR:

Patientnummer: _____

	Screening besøg dato: -28 dage	Sign:
Informeret samtykke	Udført dato:	
In- eksklusionskriterier ¹⁾	Udført dato: Fit patient <input type="checkbox"/> frail patient <input type="checkbox"/>	
Medical history inkl. B-symptomer	Udført dato:	
Ann Arbor Klassifikation ²⁾	Udført dato:	
Diagnose	Udført dato:	
Medicin status ³⁾	Udført dato:	
Objektiv undersøgelse	Udført dato:	
Performancestats ⁴⁾	Udført dato:	
IPI ⁵⁾	Udført dato:	
Vitale Værdier	Udført dato:	
	BT / P.	
	Tp. Øre/ mund	
	Højde Vægt	
Labka pakke: Lymfombehandl.	Udført dato:	
Blodprøver: IgA, IgG og IgM	Udført dato:	
Blodprøver: Urat, bilirubin, basisk fosfatase, albumin, troponin	Udført dato:	
Blodprøver: EBV PCR + CMV PCR	Udført dato:	
Graviditetstest beta-hcg	Udført dato: NA	
Projekt prøver ⁶⁾ :	Udført dato:	
Flow cytometry af perifert blod	Udført dato:	
MUGA	Udført dato:	
EKG	Udført dato:	
Knoglemarv Marvsinvolvering ja _____ nej _____	Udført dato:	
Lymfeknudebiopsi ⁷⁾	Udført dato:	
PET-CT (hals, thorax, abdomen og pelvis)	Udført dato:	

NAVN:
CPR:

Fit patient
Fase 2

Patientnummer: _____

Dato:												
Cyklus (1 cyklus er 21 dage)	Cyklus 1				Cyklus 2				Cyklus 3			
Dag	1	2	8	15	1	2	8	15	1	2	8	15
I.v. Rituximab 375mg/m2 Gives som nummer nr. 1 efter afdl. skema/procedure ¹⁾	0											
s.c. Rituximab 1400 mg ¹⁾ Gives som nummer nr. 1 efter afdl. skema/procedure					0				0			
I.v. Pixantrone 50 mg/m2 Gives som nummer nr. 2 over 1 time ²⁺⁵⁾	0		0		0		0		0		0	
I.v. Etoposid 100mg/m2 Gives som nummer nr. 3 over 1 time ²⁺⁵⁾	0				0				0			
I.v. Bendamustin 90mg/m2 Gives som nummer nr. 4 over 30 min. ²⁺³⁾	0				0				0			
Antimetika iflg. SP	0				0				0			
Medicinstatus ⁴⁾	0				0				0			
Objektiv undersøgelse	0				0				0			
ECOC Performancestatus ⁵⁾	0				0				0			
BT, P og Tp.	0				0				0			
AE version 4.0 ⁶⁾	0				0				0			
Projektspl.	0		0		0		0		0		0	
Blodprøver (i SP): HB, LEU, DIFFMAS, THROM, CRP,	0		0	0	0		0	0	0		0	0
ALAT,BASP, LDH, GLU, CREA, DIFFBERE, Urat, billirubin, albumin	0				0				0			
Projektprøve (10ml. blod i EDTA før start og efter C2+6)									0			
MUGA								0				
EKG									0			
Knoglemarv 10ml. aspirat ⁷⁾							0					
PET-CT (hals, thorax, abdomen og pelvis) ⁸⁾								0				

NAVN:
CPR:

Fit patient
Fase 2

Patientnummer: _____

Dato:														
Cyklus (1 cyklus er 21 dage)	Cyklus 4				Cyklus 5				Cyklus 6				Eval	
Dag	1	2	8	15	1	2	8	15	1	2	8	15	30-35	
s.c. Rituximab 1400 mg ¹⁺²⁾ Gives som nummer nr. 1 efter afdl. skema/procedure	0				0				0					
I.v. Pixantrone 50 mg/m ² Gives som nummer nr. 2 over 1 time ²⁺⁵⁾	0		0		0		0		0		0			
I.v. Etoposid 100mg/m ² Gives som nummer nr. 3 over 1 time ²⁺⁵⁾	0				0				0					
I.v. Bendamustin 90mg/m ² Gives som nummer nr. 4 over 30 min. ²⁺³⁾	0				0				0					
Antimetika iflg. SP	0				0				0					
Medicinstatus ⁴⁾	0				0				0					
Objektiv undersøgelse	0				0				0					
ECOC Performancestatus ⁵⁾	0				0				0					
BT, P og Tp.	0				0				0					
AE version 4.0 ⁶⁾	0				0				0				0	
Projektspl.	0		0		0		0		0		0		0	
Blodprøver (i SP): HB, LEU, DIFFMAS, THROM, CRP,	0		0	0	0		0	0	0		0	0	0	
ALAT,BASP, LDH, GLU, CREA, DIFFBERE, Urat, billirubin, albumin	0				0				0				0	
Projektprøve (10ml. blod i EDTA før start og efter C2+6)													0	
MUGA													0	
EKG													0	
Knoglemarv 10ml. aspirat ⁷⁾													0	
PET-CT (hals, thorax, abdomen og pelvis) ⁸⁾													0	

NAVN:
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Fit patient
Fase 2

Patientnummer: _____

- 1) Rituximab gives kun ved CD20-positive tumorer. 375 mg/m² i.v. dag 1, serie 1-6, **eller** 375 mg/m² i.v. dag 1, serie 1 + 1400 mg s.c. dag 1, serie 2-6
- 2) **Dosis** for pixantrone og bendamustin er i flg. amendment 2 fastlagt af resultater for MTD/Maximal tolerabel dosis i studiets fase 1 del til: Etoposide: MTD = 100 mg/m² i.v. dag 1. Bendamustine: MTD = 90 mg/m² i.v. dag 1
- 3) **Dosis modifikationer**
Dose modifications will not apply to the first course of chemotherapy. During the following courses modifications of the treatment schedule will only apply in case of:
 - a) **Myelosuppression not due to lymphoma involvement of the bone marrow**
If a patient has grade 3/ 4 neutropenia or thrombocytopenia on day 1 of any cycle, then drug should not be restarted until recovered to grade 2. If recovery occurs within 7 days then restart at same dose after the first episode. However, if it reoccurs in a subsequent cycle or if recovery takes longer than 7 days, then study drug will be restarted with the dose reductions listed in Table 4. If recovery does not occur within 14 days then the patient will go off protocol treatment. If a patient has grade 3/ 4 neutropenia or thrombocytopenia on day 8 of any cycle, then pixantrone should not be administered until recovered to grade 2. If recovery does not occur within 7 days the day 8 dose of pixantrone should be omitted.
 - b) **Cardiotoxicity**
In cases of documented cardiomyopathy developed during treatment, LVEF should be repeated. In case of a reduction of LVEF value by > 15% and a resulting absolute value of <35% (e.g. from 50% to < 35%) the patient goes off protocol treatment.
 - c) **Other toxicities**
If a patient develops a grade 3 non-hematologic toxicity presumed secondary to study drug, at any time during a cycle, with the exception of febrile neutropenia and alopecia, then the next cycle should be dose reduced as below. Any patient with any grade 4 non-hematologic toxicity should go off protocol treatment.

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Fit patient
Fase 2

Patientnummer: _____

Table 4	Dose Reduction
	Dose Reduction #1
Bendamustine	Reduce dose by 30 mg/m ²
Pixantrone	Reduce dose by 25 mg/m ² *
Etoposide	No dose reduction
Rituximab	No dose reduction

Table 4: Dose reduction. Minimum allowable dose of pixantrone is 25 mg/m². Minimal dose of bendamustine is 60 mg/m². If Dose falls below that level then the subject will go off protocol treatment.

- 4) **Medicin:** Der er tilladt at være i steroid behandling i max 2 uger forud for 1. behandling
- 5) **ECOG performancestatus:**
Grade 0: fully functional, no symptoms
Grade 1: ambulatory patient with symptoms, able to carry out light work
Grade 2: patient with symptoms, less than 50% of daytime in bed, self-sufficient
Grade 3: patient with symptoms, more than 50% of daytime in bed, requires some help from others
- 6) **AE indsamling:**
AE'er samt SAE'er skal indrapporteres fra første behandling til 6 måneder efter sidste behandling. SAE'er skal indrapporteres på Serious Adverse Event Report Forms og faxes til +45 78467597 se TMF/ p-drevet for yderligere info
- 7) Kun hvis positiv ved baseline
- 8) **Evaluerig:**
Der laves evalueringer efter cyklus 2 og cyklus 6, medmindre at patienten ikke planlægges til at skulle have alle 6 cykler. Stopper patienten fx efter cyklus 5 skal der således lave evaluering der. Knoglemarvs undersøgelse skal kun tages, hvis der ved indgang til studiet var marvsinvolvering.
Det er tilladt efter 4 cykler at lade patienten gå direkte til ASCT (allogen transp.), hvis patienten allerede efter 2 cyklus er i tilfredsstillende remission og opfylder kriterierne for ASCT samt opfylder "primary" og "secondary" end-point.

Primary end-point of the phase 1 part of the trial

- MTD of pixantrone, bendamustine and etoposide in 'fit' rel aNHL pts

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Fit patient
Fase 2

Patientnummer: _____

Primary end-point of the phase 2 part of the trial

- ORR in both 'fit' and 'frail' rel aNHL pts

Secondary end-points of the phase 1 part of the trial

- ORR
- CRR
- Duration of response (DOR)

Secondary end-points of the phase 2 part of the trial

- Safety and tolerability of the P[R]EBEN combination regimen
- CRR
- DOR
- PFS
- OS
- Successful bridging to allogeneic transplantation

Lugano Classification are:

➤ Complete remission (CR)

Disappearance of all evidence of disease

- Nodal Masses: mass of any size permitted if PET negative.
- Bone marrow: Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative

➤ Partial remission (PR)

Regression of measurable disease and no new sites

- Nodal Masses: 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes.
- One or more PET positive at previously involved site
- Bone marrow: Irrelevant if positive prior to therapy

➤ Stable disease (SD)

Failure to attain CR/PR or PD

- Nodal Masses: PET positive at prior sites of disease and no new sites on CT or PET

➤ Progressive disease (PD)

- Any new lesion or increase by 50% of previously involved sites from nadir
- Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis
- Lesions PET positive

NAVN:
CPR:

Frail patient
Fase 2

Patientnummer: _____

Dato:														
Cyklus (1 cyklus er 21 dage)	Cyklus 1				Cyklus 2				Cyklus 3					
Dag	1	2	8	15	1	2	8	15	1	2	8	15		
I.v. Rituximab 375mg/m ² ¹⁺²⁾ Gives som nummer nr. 1 efter afdl. skema/procedure	0													
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I.v. Bendamustin 90mg/m ² ²⁾ Gives som nummer nr. 4 over 30 min.	0				0				0					
Antimetika iflg. SP	0				0				0					
Medicinstatus ²⁾	0				0				0					
Objektiv undersøgelse	0				0				0					
ECOC Performancestatus ⁴⁾	0				0				0					
BT, P og Tp.	0				0				0					
AE version 4.0 ⁵⁾	0				0				0					
Projektspl.	0		0		0		0		0		0			
Blodprøver (i SP): HB, LEU, DIFFMAS, THROM, CRP,	0		0	0	0		0	0	0		0	0		
ALAT,BASP, LDH, GLU, CREA, DIFFBERE, Urat, billirubin, albumin	0				0				0					
Projektprøve (10ml. blod i EDTA før start og efter C2+6)									0					
MUGA								0						
EKG									0					
Knoglemarv 10ml. aspirat ⁶⁾							0							
PET-CT (hals, thorax, abdomen og pelvis) ⁷⁾								0						

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Antimetika iflg. SP	0				0				0					
Medicinstatus ²⁾	0				0				0					
Objektiv undersøgelse	0				0				0					
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AE version 4.0 ⁵⁾	0				0				0				0	
Projektspl	0		0		0		0		0		0		0	
Blodprøver (i SP): HB, LEU, DIFFMAS, THROM, CRP,	0		0	0	0		0	0	0		0	0	0	
ALAT,BASP, LDH, GLU, , CREA, DIFFBERE, Urat, billirubin, albumin	0				0				0				0	
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b) Cardiotoxicity

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c) Other toxicities

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3) **Medicin:** Det er tilladt at være i steroid behandling i max 2 uger forud for 1. behandling.

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Frail patient
Fase 2

Patientnummer: _____

4) **ECOG performancestatus:**

Grade 0: fully functional, no symptoms

Grade 1: ambulatory patient with symptoms, able to carry out light work

Grade 2: patient with symptoms, less than 50% of daytime in bed, self-sufficient

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5) **AE indsamling:** AE'er samt SAE'er skal indrapporteres fra første behandling til 6 måneder efter sidste behandling. SAE'er skal indrapporteres på Serious Adverse Event Report Forms og faxes til +45 78467597 se TMF for yderligere info.

6) Kun hvis positiv ved baseline

7) **Evaluering:**

Der laves evalueringer efter cyklus 2 og cyklus 6, medmindre at patienten ikke planlægges til at skulle have alle 6 cykler. Stopper patienten fx efter cyklus 5 skal der således laves evaluering der. Knoglemarvs undersøgelse skal kun tages, hvis der ved indgang til studiet var marvsinvolvering.

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Primary end-point of the phase 1 part of the trial

- MTD of pixantrone, bendamustine and etoposide in 'fit' rel aNHL pts

Primary end-point of the phase 2 part of the trial

- ORR in both 'fit' and 'frail' rel aNHL pts

Secondary end-points of the phase 1 part of the trial

- ORR
- CRR
- Duration of response (DOR)

Secondary end-points of the phase 2 part of the trial

- Safety and tolerability of the P[R]EBEN combination regimen
- CRR
- DOR
- PFS

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Frail patient
Fase 2

Patientnummer: _____

- OS
- Successful bridging to allogeneic transplantation

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- Any new lesion or increase by 50% of previously involved sites from nadir
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- Lesions PET positive

NAVN:
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Follow-up

Patientnummer: _____

Dato:														
	FU år 1				FU år 2				FU år 3		FU år 4		FU år 5	
Måned:	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Objektiv undersøgelse	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ECOC Performancestatus ¹⁾	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CT-scan (hals, thorax, abdomen og pelvis)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Labka pakke: Lymfombehandl. Diffmas.	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urat, bilirubin og albumin	0	0	0	0	0	0	0	0	0	0	0	0	0	0

1) **ECOG performancestatus:**

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