

NAVN:

CPR:

R+ Bendamustine (Control arm) 6 x 4 week cycles

Patientnummer _____

BEHANDLINGS- OG UNDERSØGELSESSKEMA

Visit code	Screening	Cycle 1	Cycle 2	Cycle 3	Mid-treatment assessment	Cycle 4	Cycle 5	Cycle 6	EOT eval.
Week no	-28 days	T=0	4w	8w	12w +/- 2w	12w	16w	20w	24w
Informeret samtykke	X								
Medical history	X								
Objektiv undersøgelse	X	X	X	X		X	X	X	X
ECOG	X	X	X	X		X	X	X	x
Højde	X								
Vægt	X	X	X	X		X	X	X	X
Puls, BT, tp, RF	X								
EKG	X								
Knoglemarv	X ⁵				X ^{1, 4}				X ^{1, 4}
Hæmatologi / Diff	X	X ³	X ³	X ³		X ³	X ³	X ³	X ³
Biokemi ²	X	X ³	X ³	X ³		X ³	X ³	X ³	X ³
Hepatitis B & C, HIV	X								
CT scan	X ⁵				X ⁴				X ⁴
MRD prøver		X			X				X
Adverse events (special skema)		X	X	X		X	X	X	X
Concomitant medication	X	X	X	X		X	X	X	X
Randomisering	X ⁷								
Rituximab 375 mg/m ² I.V		X	X	X		X	X ⁶	X ⁶	
Bendamustine 90mg/m ² I.V		Dag 1+2	Dag 1+2	Dag 1+2		Dag 1+2	Dag 1+2 ⁶	Dag 1+2 ⁶	
EORTC-QLQ-C30 questionnaire		X			X				X

¹ Kun hvis KM involvering v/baseline² ALT, LDH, bas.fosfatase, total bilirubin, kreatinin clearance, natrium, CRP³ kan tages indenfor 4 dage før dag1 i en given cycle.⁴ Udføres indenfor +/- 2 uger. Mid-treatment assessment: Hvis CR, CRu, PR fortsæt behandling – hvis SD eller PD stop behandling → Follow up⁵ Udføres indenfor 42 dage før cycle 1 dag 1 (6 uger)⁶ R-Bendamustin kan udelades hvis komplet remission efter cycle 4 (12w)⁶ R-Ibrutinib kan udelades hvis komplet remission efter cycle5 (12w)⁷ Patienterne randomiseres til behandling med enten Rituximab + Ibrutinib eller Rituximab + Bendamustine

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R+ Bendamustine (Control
arm) 6 x 4 week cycles

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BEHANDLINGS- OG UNDERSØGELSESSKEMA

12.4.1 Rituximab

There will be no protocol defined dose reductions for rituximab. Particular attention should be paid to the warnings and precautions section of the product label. Rituximab administration and dose modifications for infusion reactions must follow the product label.

Rituximab can be withheld for a maximum of 28 consecutive days; a hold greater than 28 days must be reviewed and approved by the Chief Investigator.

Rituximab should be permanently discontinued if it cannot be restarted within a further 28 days due to toxicity or in the opinion of the Chief Investigator. If rituximab is discontinued for toxicity; treatment with bendamustine may continue.

12.4.2 Bendamustine

Bendamustine may be withheld for a maximum of 28 consecutive days; a hold greater than 28 days must be reviewed and approved by the Chief Investigator.

Bendamustine should be permanently discontinued if it cannot be restarted within a further 28 days due to toxicity.

If bendamustine is discontinued for toxicity, treatment with rituximab may continue.

Table 4:

Bendamustine dose delays	
Event	Action
Bendamustine-related Grade 4 haematological toxicity	Hold until blood counts have improved (ANC $\geq 1 \times 10^9/L$; platelets $\geq 75 \times 10^9/L$). May be reinitiated at the discretion of the chief investigator.
Clinically significant Grade ≥ 2 nonhaematological toxicity	Hold until recovery to Grade ≤ 1 . May be reinitiated at the discretion of the chief investigator.

Table 5:

Bendamustine dose modifications	
Event	Action
Grade 4 haematological toxicity	<ul style="list-style-type: none"> Reduce the dose to 70 mg/m² on day 1 and day 2 of each cycle. If grade 4 toxicity recurs, the dose may be reduced to 45 mg/m² on day 1 and day 2 of each cycle.
Grade ≥ 3 nonhaematological toxicity	<ul style="list-style-type: none"> Reduce the dose to 70 mg/m² on day 1 and day 2 of each cycle. If grade 3 or greater toxicity recurs, the dose should be reduced to 45 mg/m² on day 1 and day 2 of each cycle.

Dose re-escalation of bendamustine is **not** permitted.

NAVN:

CPR:

R+ CHOP21 (Control
arm) 8 x 3 week cycle

Patientnummer _____

BEHANDLINGS- OG UNDERSØGELSESSKEMA

Visit code	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Mid-treatment assessment	Cycle 5	Cycle 6	Cycle 7	Cycle 8	End of treatment
Week no	-28 days	T=0	3w	6w	9w	12w +/- 2w	12w	15w	18w	21w	24w
Informeret samtykke	X										
Medical history	X										
Objektiv undersøgelse	X	X	X	X	X		X	X	X	X	X
ECOG	X	X	X	X	X		X	X	X	X	x
Højde	X										
Vægt	X	X	X	X	X		X	X	X	X	X
Puls, BT, tp, RF	X										
EKG	X										
Knoglemarv	X ⁵					X ^{1, 4}					X ^{1, 4}
Hæmatologi / Diff	X	X ³	X ³	X ³	X ³		X ³				
Biokemi ²	X	X ³	X ³	X ³	X ³		X ³				
Hepatitis B & C, HIV	X										
CT scan	X ⁵					X ⁴					X ⁴
MRD prøver		X				X					X
Adverse events (special skema)		X	X	X	X		X	X	X	X	X
Concomitant medication	X	X	X	X	X		X	X	X	X	X
Randomisering	X ⁷										
Rituximab 375 mg/m ² I.V		X	X	X	X		X	X	X	X	
Cyclophosphamid 750 mg/m ²		X	X	X	X		X	X	X	x	
Doxorubicin 50 mg/m ²		X	X	X	X		X	X	X	x	
Vincristin 1,4 mg/m ²		X	X	X	X		X	X	X	x	
Prednisolon 50 mg dag 2-5		X	X	X	X		X	X	X	x	
EORTC-QLQ-C30 questionnaire		X				X					X

Godkendt af: Martin Hutching dato:

NAVN:

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R+ CHOP21 (Control
arm) 8 x 3 week cyclePatientnummer _____
BEHANDLINGS- OG UNDERSØGELSESSKEMA¹ Kun hvis KM involvering v/baseline² ALT, LDH, bas.fosfatase, total bilirubin, kreatinin clearance, natrium, CRP³ kan tages indenfor 4 dage før dag1 i en given cycle.⁴ Udføres indenfor +/- 2 uger. Mid-treatment assessment: Hvis CR, CRu, PR, SD fortsæt behandling – hvis PD stop behandling → Follow up⁵ Udføres indenfor 42 dage før cycle 1 dag 1(6 uger)⁷ Patienterne randomiseres til behandling med enten Rituximab + Ibrutinib (intervention arm) eller Rituximab + Bendamustin (control arm)

Rituximab

There will be no protocol defined dose reductions for rituximab. Particular attention should be paid to the warnings and precautions section of the product label.

Rituximab administration and dose modifications for infusion reactions must follow the product label.

Rituximab can be withheld for a maximum of 28 consecutive days; a hold greater than 28 days must be reviewed and approved by the Chief Investigator.

Rituximab should be permanently discontinued if it cannot be restarted within a further 28 days due to toxicity or in the opinion of the Chief Investigator.

If rituximab is discontinued for toxicity; treatment with CHOP may continue.

CHOP combination chemotherapy

Haematological Toxicity: Neutropenia

Event Action

Neutrophils <1.0x10 ⁹ /L on proposed day 1 of cycle	Delay therapy until neutrophils ≥1.0x10 ⁹ /L. If not recovered after 14 days, discontinue study treatment. GCSF permissible as secondary prophylaxis, must discuss with Chief Investigator.
Grade 4 neutropenia or any febrile neutropenia following any cycle of R-CHOP	All subsequent cycles of CHOP may be given with GCSF support according to local policy, must discuss with Chief Investigator.
Grade 4 neutropenia leading to infection despite GCSF support	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles.
Grade 4 neutropenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Discuss with Chief Investigator.

Haematological Toxicity: Thrombocytopenia

Event Action

Platelets <100x10 ⁹ /L on proposed day 1 of cycle	Delay therapy until platelets ≥100x10 ⁹ /L. If not recovered after 14 days, withdraw participant from study.
Grade 4 thrombocytopenia following any cycle of R-CHOP	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles.
Grade 4 thrombocytopenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Withdraw participant from CHOP treatment.

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R+ CHOP21 (Control
arm) 8 x 3 week cycle

Patientnummer _____

BEHANDLINGS- OG UNDERSØGELSESSKEMA

Non-haematological Toxicity**Event Action**

Modification for neutropathic pain or peripheral neuropathy	<ul style="list-style-type: none"> If grade ≥ 2 motor or grade ≥ 3 sensory neurological toxicity to vincristine appears, the dose will be decreased to 1mg per cycle. If the neurological toxicity increases despite dose reduction, vincristine will be stopped.
Other non-haematological toxicity	<ul style="list-style-type: none"> Dose reduction of individual medications can be considered if other toxicities such as severe mucositis occur, as per usual local practice. Dose reductions for hepatic or renal impairment should be according to local policy.

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Vedligeholdelses behandling R + Ibrutinib

Patientnummer _____
BEHANDLINGS- OG UNDERSØGELSESSKEMA

Visit code	MV 1	MV2	MV3	MV4	MV5	MV6	MV7	MV8	MV9	MV10	MV11	MV12	EOM	FU1 etc
Week no	EOT+1m	+3m	+5m	+7m	+9m	+11m	+13m	+15m	+17m	+19m	+21m	+23m	+24m	EOM +3m
Objektiv undersøgelse	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vægt	X ³													
Puls, BT, tp, RF	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG														
Knoglemarv ¹			X ¹			X ¹			X ¹					X ¹
Hæmatologi / Diff	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biokemi ²	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT scan			X			X			X					X
MRD														X
SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rituximab 1400 mg S.C	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ibrutinib 560 mg dagligt	X ⁴													
Treatments beyond PD														X ⁵
EORTC-QLQ-C30 questionnaire													X	

¹Kun hvis KM involvering ved baseline² ALT, LDH, bas.fosfatase, total bilirubin, kreatinin clearance, natrium, CRP³Kun hvis klinisk indiceret af læge⁴Kun patienter fra intervention arm og indtil PD. OBS : Ibrutinib kan/skal forsættes udover vedligeholdelsesperioden på 24 mdr og indtil PD.⁵Behandlinger for MCL efter PD

Godkendt af: Martin Hutching dato:

NAVN:

CPR:

Vedligeholdelses behandling R + Ibrutinib

Patientnummer _____
BEHANDLINGS- OG UNDERSØGELSESSKEMA***Ibrutinib dose modifications and delays***

At each clinic visit, the participant will be evaluated for possible drug toxicities. These are graded in accordance with the NCI-CTCAE v4.03 (see section 17.2.2) and should be managed as described in table 3. Refer to section 13.3.3 for participants requiring the initiation of anticoagulants while receiving ibrutinib.

A maximum of two dose level reductions are permitted during the study. Once the ibrutinib dose is reduced, it cannot be re-escalated.

Possible drug toxicities:

- Grade 3 or greater neutropenia with infection or fever
- Grade 4 neutropenia (absolute neutrophil count $<0.5 \times 10^9/L$)
- Grade 3 thrombocytopenia (platelets $<50 \times 10^9/L$) in the presence of significant bleeding
- Grade 4 thrombocytopenia (platelets $<25 \times 10^9/L$)
- Grade 3 or greater non-haematological toxicity

Ibrutinib may be omitted for a maximum of 28 consecutive days. It should be permanently discontinued in the event of a toxicity lasting more than 28 days, unless agreement is sought from the Chief Investigator.

Ibrutinib Dose Modifications

Occurrence	Action
First	Hold ibrutinib until recovery to Grade ≤1; may restart at original dose level
Second	Hold ibrutinib until recovery to Grade ≤1; restart at 1 dose level lower (420mg daily)
Third	Hold ibrutinib until recovery to Grade ≤1; restart at 1 dose level lower (280mg daily)
Fourth	Discontinue ibrutinib

Prohibitions and restrictions

The following guidance should be applied during the perioperative period for participants who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be withheld for at least seven days prior to the procedure and for at least seven days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be withheld for at least three days prior to the procedure and should not be restarted for at least three days after the procedure. It is not necessary to withhold ibrutinib for bone marrow biopsy.
- For emergency procedures, ibrutinib should be withheld after the procedure until the surgical site is reasonably healed, must be for at least seven days after the urgent surgical procedure.

Rituximab

There will be no protocol defined dose reductions for rituximab. Particular attention should be paid to the warnings and precautions section of the product label. Rituximab administration and dose modifications for infusion reactions must follow the product label.

Rituximab can be withheld for a maximum of 28 consecutive days; a hold greater than 28 days must be reviewed and approved by the Chief Investigator.

Rituximab should be permanently discontinued if it cannot be restarted within a further 28 days due to toxicity or in the opinion of the Chief Investigator.

NAVN:

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Vedligeholdelses behandling R + Ibrutinib

Patientnummer _____
BEHANDLINGS- OG UNDERSØGELSESSKEMA

If rituximab is discontinued for toxicity; treatment with ibrutinib may continue.

13.3 Concomitant therapy to be used with caution whilst receiving ibrutinib

13.3.1 CYP Inhibiting/inducing drugs

Concomitant use of strong CYP3A4/5 inhibitors (such as indinavir, nefinavir, ritonavir, saquinavir, clarithromycin, telithromycin, ketoconazole, itraconazole, and nefazodone) should be avoided while the participant is receiving treatment.

Moderate CYP3A4/5 inhibitors (aprepitant, erythromycin, fluconazole, verapamil, and diltiazem) should be used with caution. Grapefruit juice and Seville or dark blood oranges may also increase ibrutinib plasma concentrations and must be avoided for the duration of ibrutinib treatment.

If use of a strong CYP3A4/5 inhibitor is indicated, selection of an alternate concomitant medication with less potent enzyme inhibition potential is strongly recommended.

If ibrutinib must be administered with a strong or moderate CYP3A4/5 inhibitor, the Chief Investigator or delegated deputy should be consulted beforehand, and a dose reduction of ibrutinib to 140 mg daily or temporary withholding of ibrutinib should be considered.

Participants should be closely monitored for potential treatment-related toxicities.

Co-administration of ibrutinib with strong CYP3A4/5 inducers (such as carbamazepine and rifampin) may decrease ibrutinib plasma concentrations and should be avoided.

Strong inhibitors A strong inhibitor is one that causes a >5-fold increase in plasma AUC values or >80% decrease in clearance.	INDINAVIR; NELFINAVIR; RITONAVIR; CLARITHROMYCIN; ITRACONAZOLE; KETOCONAZOLE; NEFAZODONE; SAQUINAVIR; TELITHROMYCIN
Moderate inhibitors: A moderate inhibitor is one that causes a >2-fold increase in plasma AUC values or 50-80% decrease in clearance.	Aprepitant; erythromycin; diltiazem; fluconazole; grapefruit juice; Seville orange juice; Verapamil
Weak inhibitors: A weak inhibitor is one that causes a >1.25-fold but <2-fold increase in plasma AUC values or 20- 50% decrease in clearance.	Cimetidine
All other inhibitors:	Amiodarone; NOT azithromycin; Chloramphenicol; Boceprevir; Delavirdine; diethyl-dithiocarbamate; fluvoxamine; gestodene; imatinib; mibepradil; mifepristone; norfloxacin; norfluoxetine; star fruit; Telaprevir; Troleandomycin
Inducers of CYP3A4/5	Carbamazepine; Efavirenz; Nevirapine; Barbiturates; Carbamazepine; Glucocorticoids; Modafinil; Oxcarbazepine; Phenobarbital; Phenytoin; Pioglitazone; Rifabutin; Rifampin; St. John's Wort; Troglitazone

NAVN:

CPR:

Vedligeholdelses behandling R + Ibrutinib

Patientnummer _____
BEHANDLINGS- OG UNDERSØGELSESSKEMA**13.3.2 QT Prolonging Agents**

Any medications known to cause QT prolongation (see Appendix 4) should be used with caution; periodic monitoring with electrocardiograms (ECGs) and serum electrolytes should be considered. Use of these medications should first be discussed with the Chief Investigator or delegated deputy.

Substantial evidence supports the conclusion that the drugs listed below prolong the QT interval and have a risk of *torsade de pointes* when used as directed in labelling.

Appendix 4: QT prolonging agents

Amiodarone	Haloperidol
arsenic trioxide	Ibutilide
astemizole	Levomethadyl
bepridil	Mesoridazine
chloroquine	Methadone
chlorpromazine	Moxifloxacin
cisapride	Pentamidine
citalopram	Pimozide
clarithromycin	Probucol
disopyramide	Procainamide
dofetilide	Quinidine
domperidone	Sotalol
droperidol	Sparfloxacin
erythromycin	Terfenadine
flecainide	Thioridazine
halofantrine	Vandetanib

13.3.3 Anticoagulants and anti-platelet drugs

Warfarin, or equivalent vitamin K inhibitors, and anticoagulants should not be given concomitantly whilst the participant is receiving ibrutinib. For participants requiring anticoagulant therapy, LMW heparin should be considered instead. Anti-platelet drugs may be used with ibrutinib but can be associated with increased bruising and bleeding. Therefore participants on these agents should be monitored for any significant change in bruising or bleeding.

13.3.4 Live Vaccines

Use of live vaccinations is prohibited during the study and for three months after last dose of the IMP

NAVN:

CPR:

Vedligeholdelses behandling Rituximab

Patientnummer _____
BEHANDLINGS- OG UNDERSØGELSESSKEMA

Visit code	MV 1	MV2	MV3	MV4	MV5	MV6	MV7	MV8	MV9	MV10	MV11	MV12	EOM	FU1 etc
Week no	EOT+1m	+3m	+5m	+7m	+9m	+11m	+13m	+15m	+17m	+19m	+21m	+23m	+24m	EOM +3m
Objektiv undersøgelse	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vægt	X ³													
Puls, BT, tp, RF	X	X	X	X	X	X	X	X	X	X	X	X	X	x
EKG														
Knoglemarv ¹			X ¹			X ¹			X ¹					X ¹
Hæmatologi / Diff	X	X	X	X	X	X	X	X	X	X	X	X	X	x
Biokemi ²	X	X	X	X	X	X	X	X	X	X	X	X	X	x
CT scan			X			X			X					X
MRD														X
SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rituximab 1400 mg S.C	X	X	X	X	X	X	X	X	X	X	X	X	X	
Treatments beyond PD														X ⁵
EORTC-QLQ-C30 questionnaire														X

¹ Kun hvis KM involvering ved baseline² ALT, LDH, bas.fosfatase, total bilirubin, kreatinin clearance, natrium, CRP³ Kun hvis klinisk indiceret af læge⁵ Behandlinger for MCL efter PD

Godkendt af: Martin Hutching dato:

NAVN:

CPR:

Vedligeholdelses behandling Rituximab

Patientnummer _____
BEHANDLINGS- OG UNDERSØGELSESSKEMA**Rituximab**

There will be no protocol defined dose reductions for rituximab. Particular attention should be paid to the warnings and precautions section of the product label. Rituximab administration and dose modifications for infusion reactions must follow the product label.

Rituximab can be withheld for a maximum of 28 consecutive days; a hold greater than 28 days must be reviewed and approved by the Chief Investigator.

Rituximab should be permanently discontinued if it cannot be restarted within a further 28 days due to toxicity or in the opinion of the Chief Investigator.

If rituximab is discontinued for toxicity; treatment with ibrutinib may continue.

13.3 Concomitant therapy to be used with caution whilst receiving ibrutinib

13.3.1 CYP Inhibiting/inducing drugs

Concomitant use of strong CYP3A4/5 inhibitors (such as indinavir, nefinavir, ritonavir, saquinavir, clarithromycin, telithromycin, ketoconazole, itraconazole, and nefazodone) should be avoided while the participant is receiving treatment.

Moderate CYP3A4/5 inhibitors (aprepitant, erythromycin, fluconazole, verapamil, and diltiazem) should be used with caution. Grapefruit juice and Seville or dark blood oranges may also increase ibrutinib plasma concentrations and must be avoided for the duration of ibrutinib treatment.

If use of a strong CYP3A4/5 inhibitor is indicated, selection of an alternate concomitant medication with less potent enzyme inhibition potential is strongly recommended.

If ibrutinib must be administered with a strong or moderate CYP3A4/5 inhibitor, the Chief Investigator or delegated deputy should be consulted beforehand, and a dose reduction of ibrutinib to 140 mg daily or temporary withholding of ibrutinib should be considered.

Participants should be closely monitored for potential treatment-related toxicities.

Co-administration of ibrutinib with strong CYP3A4/5 inducers (such as carbamazepine and rifampin) may decrease ibrutinib plasma concentrations and should be avoided.

Strong inhibitors A strong inhibitor is one that causes a >5-fold increase in plasma AUC values or >80% decrease in clearance.	INDINAVIR; NELFINAVIR; RITONAVIR; CLARITHROMYCIN; ITRACONAZOLE; KETOCONAZOLE; NEFAZODONE; SAQUINAVIR; TELITHROMYCIN
Moderate inhibitors: A moderate inhibitor is one that causes a >2-fold increase in plasma AUC values or 50-80% decrease in clearance.	Aprepitant; erythromycin; diltiazem; fluconazole; grapefruit juice; Seville orange juice; Verapamil
Weak inhibitors: A weak inhibitor is one that causes a >1.25-fold but <2-fold increase in plasma AUC values or 20- 50% decrease in clearance.	Cimetidine
All other inhibitors:	Amiodarone; NOT azithromycin; Chloramphenicol; Boceprevir; Delavirdine; diethyl-dithiocarbamate; fluvoxamine; gestodene; imatinib; mibepradil; mifepristone; norfloxacin; norfluoxetine; star fruit; Telaprevir; Troleandomycin
Inducers of CYP3A4/5	Carbamazepine; Efavirenz; Nevirapine; Barbiturates; Carbamazepine; Glucocorticoids; Modafinil; Oxcarbazepine; Phenobarbital; Phenytoin; Pioglitazone; Rifabutin; Rifampin; St. John's Wort; Troglitazone

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Vedligeholdelses behandling Rituximab

Patientnummer _____
BEHANDLINGS- OG UNDERSØGELSESSKEMA**13.3.2 QT Prolonging Agents**

Any medications known to cause QT prolongation (see Appendix 4) should be used with caution; periodic monitoring with electrocardiograms (ECGs) and serum electrolytes should be considered. Use of these medications should first be discussed with the Chief Investigator or delegated deputy.

Substantial evidence supports the conclusion that the drugs listed below prolong the QT interval and have a risk of *torsade de pointes* when used as directed in labelling.

Appendix 4: QT prolonging agents

Amiodarone	Haloperidol
arsenic trioxide	Ibutilide
astemizole	Levomethadyl
bepridil	Mesoridazine
chloroquine	Methadone
chlorpromazine	Moxifloxacin
cisapride	Pentamidine
citalopram	Pimozone
clarithromycin	Probucol
disopyramide	Procainamide
dofetilide	Quinidine
domperidone	Sotalol
droperidol	Sparfloxacin
erythromycin	Terfenadine
flecainide	Thioridazine
halofantrine	Vandetanib

13.3.3 Anticoagulants and anti-platelet drugs

Warfarin, or equivalent vitamin K inhibitors, and anticoagulants should not be given concomitantly whilst the participant is receiving ibrutinib. For participants requiring anticoagulant therapy, LMW heparin should be considered instead. Anti-platelet drugs may be used with ibrutinib but can be associated with increased bruising and bleeding. Therefore participants on these agents should be monitored for any significant change in bruising or bleeding.

13.3.4 Live Vaccines

Use of live vaccinations is prohibited during the study and for three months after last dose of the IMP



NAVN:

CPR:

Vedligeholdelses behandling Rituximab

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BEHANDLINGS- OG UNDERSØGELSESSKEMA
