NIVEAU

Etude de phase II/ III, randomisée, comparant un traitement standard composé de rituximab, gemcitabine et oxaliplatine associé ou non à du nivolumab chez des patients ayant un lymphome non-hodgkinien agressif en première rechute ou réfractaires primaires, non éligibles à une greffe hématopoïétique

Phase : II, III

Type d'essai : Interventionnel

Thème spécifique : Sujets Agés

Etat de l'essai : Ouvert

Objectif principal

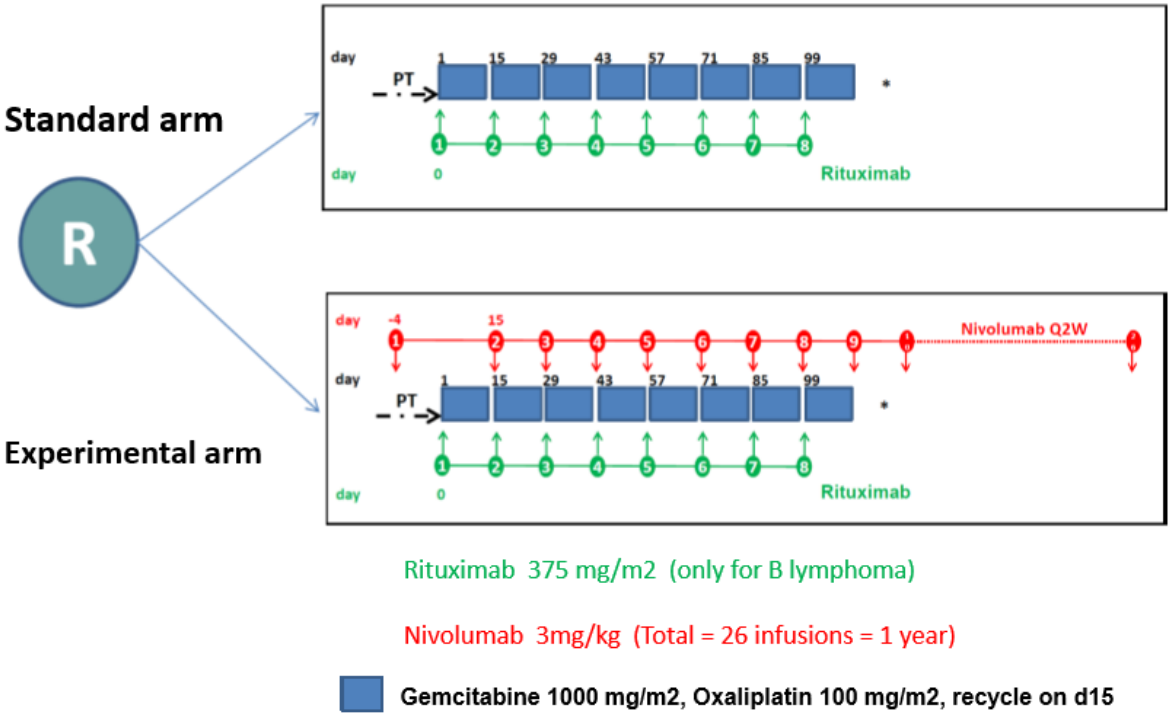
Improvement of 1-year PFS of (R)-GemOx in patients with progressed or relapsed aggressive NHLs not eligible for autologous nor allogeneic stem cell transplantation by nivolumab followed by nivolumab consolidation.

Objectifs secondaires

Complete response rate after eight cycles of (R)-GemOx.
Partial response rate after eight cycles of (R)-GemOx.
Overall response rate after eight cycles of (R)-GemOx.
Duration of response.
Progression rate.
Rate of treatment-related deaths.
Relapse rate.
Event-free survival.
Overall survival.
Toxicity.
Protocol adherence.
Quality of life as assessed by the EQ-5D-5L.
Outcome according to PD-L1 and PD-1 expression, cell of origin, 9p24.1 alterations.

Résumé / Schéma de l'étude

Bras standard (patients recevant uniquement la chimiothérapie) : 16 semaines (traitement d'induction) soient 8 cycles de (R)-GemOx.
Bras expérimental (patients recevant en plus le Nivolumab (Opdivo®)) : 16 semaines (traitement d'induction) soit 8 cycles de Nivolumab + (R)-GemOx + 36 semaines de Nivolumab seul (traitement de maintenance) soient 18 cycles.



Critères d'inclusion

1 Age : all patient > 65 years of age or older than 18 years if HCT-CI score > 2.

2 Ineligibility for neither autologous nor allogeneic stem cell transplantation as defined as : > 65 years of age or older than 18 years if HCT-CI score > 2.

3 Risk group : All risk groups (IPI 0 to 5).

4 Histology : Diagnosis of aggressive Non-Hodgkin's lymphoma, based on an excisional biopsy of a lymph node or on an appropriate sample of a lymph node or of an extranodal involvement at initial diagnosis or relapse or progression. It will be possible to treat the following entities in this study as defined by the 2016 revision of WHO classification of lymphoid neoplasms :

1. B-NHL :
    1. Follicular lymphoma grade IIIb.
    2. DLBCL, not otherwise specified (NOS).
    3. T-cell/histiocyte-rich large B-cell lymphoma.
    4. Primary cutaneous DLBCL, leg type.
    5. EBV-positive DLBCL, NOS.
    6. DLBCL associated with chronic inflammation.
    7. Primary mediastinal (thymic) large B-cell lymphoma.
    8. Intravascular large B-cell lymphoma.
    9. ALK-positive large B-cell lymphoma.
    10. Plasmablastic lymphoma primary effusion lymphoma.
    11. High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements.
    12. High-grade B-cell lymphoma, NOS.

13. B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma.

2. T-NHL :

1. Aggressive NK cell leukemia.
2. Enteropathy-associated T-cell lymphoma.
3. Hepatosplenic T-cell lymphoma.
4. Primary cutaneous gamma-delta T-cell lymphoma.
5. Peripheral T-cell lymphoma, NOS.
6. Angioimmunoblastic T-cell lymphoma.
7. Anaplastic large cell lymphoma, ALK-positive.
8. Anaplastic large cell lymphoma, ALK-negative.
9. Peripheral T-cell lymphoma with TFH phenotype.
10. Monomorphic epitheliotropic intestinal T-cell lymphoma.
11. Subcutaneous panniculitis-like T-cell lymphoma.

5 Performance status : Performance status ECOG 0 – 2. Also patients with performance status 0 – 2 are eligible when assessed after prephase treatment. The performance status of each patient should be assessed before the initiation and after the end of prephase treatment which, as experience has shown, can result in its significant improvement.

6 Previous therapy : Patients must have only one prior chemotherapy regimen including an anthracycline. The last cytotoxic drug must be given at least four weeks before entering the study. Rituximab must be part of the firstline regimen in case of B-cell lymphoma. Patients may have received prior radiation therapy as part of their first-line therapy.

7 Men who are sexually active with women of childbearing potential (WOCBP) must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 12 months after the last dose of investigational product. Women who are not of childbearing potential ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception. A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level higher than 40 mIU/mL.

8 Written informed consent of the patient.

9 Patient must be covered by social security system.

Critères de non-inclusion

1 Already initiated lymphoma therapy after first relapse or progression (except for the prephase).

2 Serious accompanying disorder or impaired organ function (except when due to lymphoma involvement), in particular :

1. Heart : angina pectoris CCS >2, cardiac failure e.g. NYHA > 2.
2. Liver : total bilirubin > 1.5 times the upper reference limit (except subjects with Gilbert Syndrome, who can have total bilirubin < 51 µmol/l), aspartate transaminase (AST) or alanine transaminase (ALT) > 3 x institutional upper reference limit.
3. Kidney : creatinine clearance < 30 ml/min.

3 WBC < 2.5 G/l, Neutrophils < 2 G/l, Platelets < 100 G/l (does not apply if cytopenia is caused by lymphoma).

4 Prolongation of QTc interval > 450 ms, demonstrated in at least two electrocardiograms.

5 Family history for Long QT-syndrome.

6 Patients with an active, known or suspected autoimmune disease. Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

7 There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration (except for treatment of lymphoma).

8 Chronic active hepatitis B or C as defined either HBs Ag positive or HBc Ac positive with detectable viral DNA or hepatitis C virus ribonucleic acid positive.

9 HIV-infection.

10 Poor patient compliance.

11 Prior chemo or radiotherapy, long-term use of corticosteroids or anti-neoplastic drugs for previous disorder (except for first-line therapy of lymphoma).

12 Previous therapy with Gemcitabine or Oxaliplatin.

13 Patients with a “currently active” second malignancy other than non-melanoma skin cancer. Patients are not considered to have a “currently active” malignancy if they have completed therapy since 6 months and are considered by their physician to be less than 30% risk of relapse within one year.

14 CNS involvement of lymphoma (intracerebral, meningeal, intraspinal intradural) or primary CNS lymphoma.

15 Persistent neuropathy grade > 2 (NCI CTC-AE v4.03) (unless due to lymphoma involvement).

16 Pregnancy or breast-feeding women.

17 Women of childbearing potential (WOCBP). A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level higher than 40 mIU/mL.

18 Active serious infections not controlled by oral and/or intravenous antibiotics or antifungal medication.

19 Any medical condition which in the opinion of the investigator places the subject at an unacceptably high risk for toxicities.

20 Lymphomas other than those listed in the inclusion criteria notably indolent lymphoma, Mantle cell lymphoma, Burkitt lymphoma.

21 Persons not able to understand the impact, nature, risks and consequences of the trial (including language barrier).

22 Persons not agreeing to the transmission of their pseudonymous data.

23 Persons depending on sponsor or investigator.

24 Persons from highly protected groups.

25 Allergies and Adverse Drug Reaction History to study drug components.

26 Participation in another clinical trial with drug intervention within 4 weeks prior to start of the first cycle and during the study. However, participation in a clinical trial of firstline therapy of lymphoma is allowed.

Calendrier prévisionnel

Lancement de l'étude : Avril 2018
Fin estimée des inclusions : Décembre 2022
Nombre de patienst à inclure : 388 monde / 108 France

Etablissement(s) participant(s)

> Institut Paoli-Calmettes (IPC)

(13) BOUCHES-DU-RHÔNE

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