Extranodal NK/T-cell lymphoma: the French experience

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JF. Benoist, P. Gaulard , O. Hermine

Limoges, Versailles, Creteil, Paris

Disclosures

- Celgene : research funding and honoraria
- Janssen: research funding and honoraria
- Sanofi: honoraria

None

More frequent in Asia (3 to 9 % of all NHL) than in Western countries

VOLUME 26 · NUMBER 25 · SEPTEMBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes

International T-Cell Lymphoma Project

Table 1. Major Lymphoma Subtypes by Geographic Region

Subtype	%		
	North America	Europe	Asia
PTCL-NOS	34.4	34.3	22.4
Angioimmunoblastic	16.0	28.7	17.9
ALCL, ALK positive	16.0	6.4	3.2
ALCL, ALK negative	7.8	3.4	2.6
NKTCL	5.1	4.3	22.4
ATLL	2.0	1.0	25.0
Enteropathy-type	5.8	9.1	1.9
Hepatosplenic	3.0	2.3	0.2
Primary cutaneous ALCL	5.4	0.8	0.7
Subcutaneous panniculitis-like	1.3	0.5	1.3
Unclassifiable T-cell	2.3	3.3	2.4

NHL in Europe: 85 % B-cell origin

Percentage of all T/NK-cell lymphoma

NK/T-cell lymphoma = 4,3% of 15% = **0,6% of all lymphomas**

In France : 40 new cases / year

Clinical presentation in Western Europe

223 patients from 38 centres in France, 1 in Belgium and 1 in Switzerland treated between 1986 and 2018, 68 women and 155 men (sex ratio: 2,28)

- Median age : 51 years (16-85)
- European origin: 69%
  - From Asia: 4%
  - From Africa: 23%

- Stage I/II : 59%,
- Stage III/IV: 41 %

International T-cell project

Nasal and extra-nasal ENKTL cases by region	Europe	USA	South America	Asia
ENKTL, nasal [n=70, 50%]	19 (46)	11 (46)	11 (42)	29 (59)
ENKTL, extra-nasal [n=70, 50%]	22 (54)	13 (54)	15 (58)	20 (41)
Total	41	24	26	49

Prognosis

The Lancet Oncology mars 2016

A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis

Seok Jin Kim, Dok Hyun Yoon, Arnaud Jaccard, Wee Joo Chng, Soon Thye Lim, Huangming Hong, Yong Park, Kian Meng Chang, Yoshinobu Maeda, Fumihiro Ishida, Dong-Yeop Shin, Jin Seok Kim, Seong Hyun Jeong, Deok-Hwan Yang, Jae-Cheol Jo, Gyeong-Won Lee, Chul Won Choi, Won-Sik Lee, Tsai-Yun Chen, Kiyeun Kim, Sin-Ho Jung, Tohru Murayama, Yasuhiro Oki, Ranjana Advani, Francesco d'Amore, Norbert Schmitz, Cheolwon Suh, Ritsuro Suzuki, Yok Lam Kwong, Tong-Yu Lin, Won Seog Kim

PINK

Stage III/IV

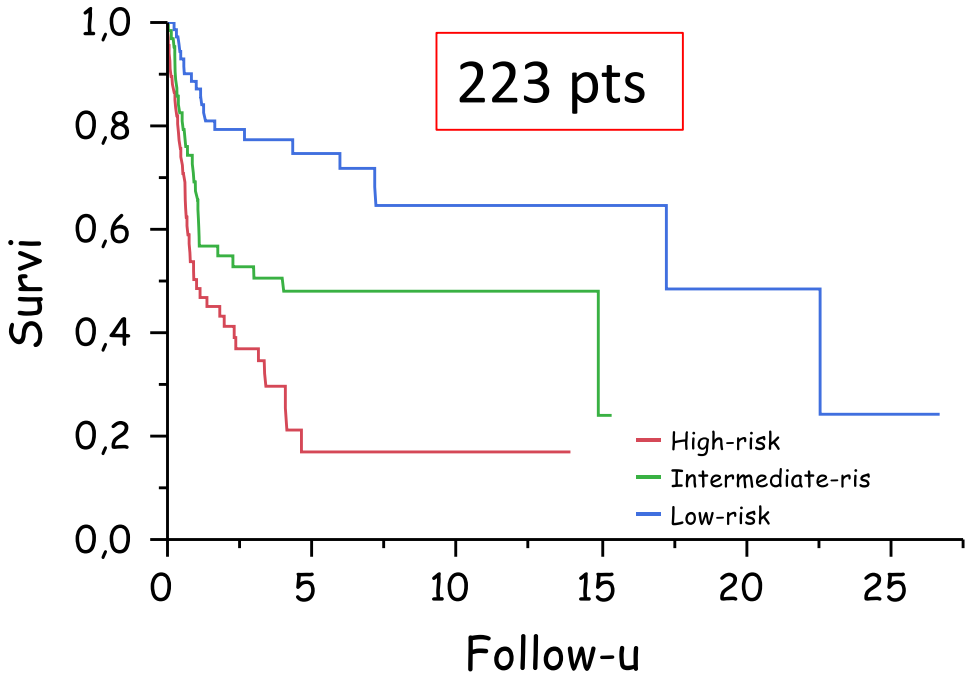
Age > 60

Distant lymph nodes

Extra-nasal type

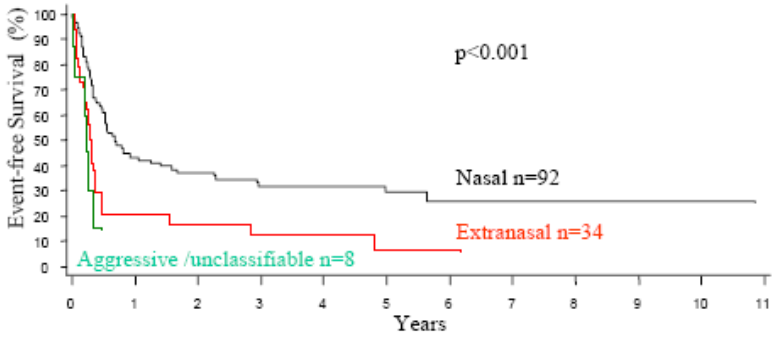
PINK-E

+/- EBV in the blood

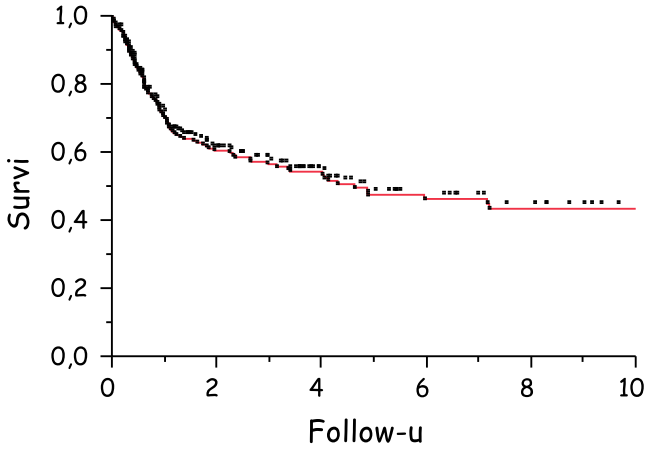


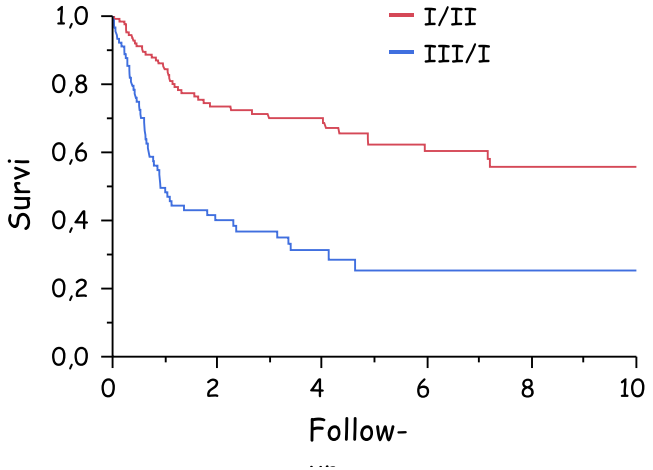
Treatment and survival: 223 pts

- Non-anthracycline with L-asparaginase :
  - First line : 62%
  - At anytime : 78%



The International T-cell Project. Blood 2008
Non-anthracycline with L-asparaginase: 35%





Living patienst: follow-up: 3,38 [0,16-26,69] years

5 year-survival 47%

I/II : 63 %

III/IV : 25 %

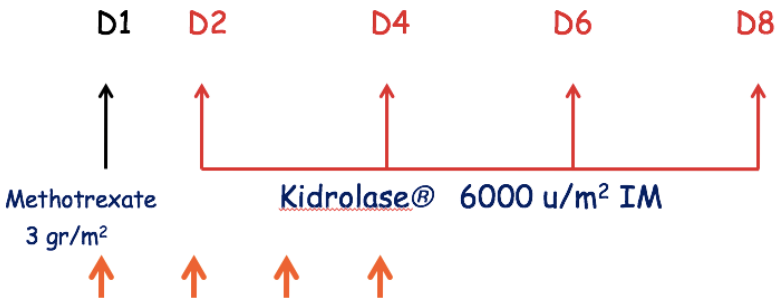
blood

2011 117: 1834-1839
Prepublished online December 1, 2010;
doi:10.1182/blood-2010-09-307454

Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study

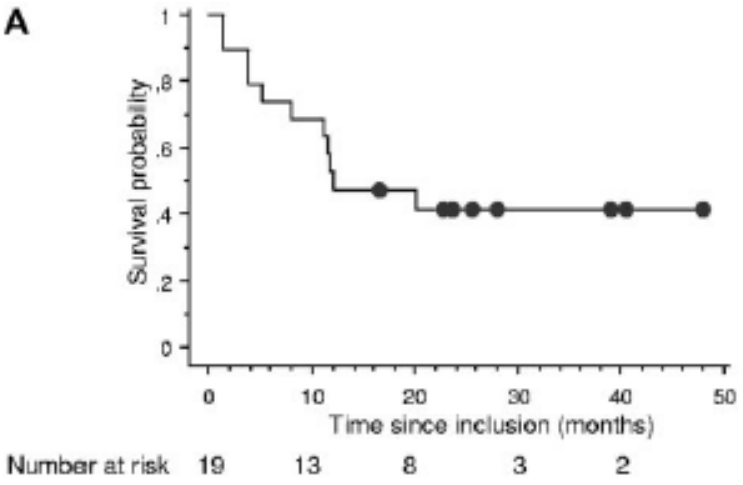
Arnaud Jaccard, Nathalie Gachard, Benoit Marin, Sylvie Rogez, Marie Audrain, Felipe Suarez, Hervé Tilly, Franck Morschhauser, Catherine Thieblemont, Loic Ysebaert, Alain Devidas, Barbara Petit, Laurence de Leval, Philippe Gaulard, Jean Feuillard, Dominique Bordessoule, Olivier Hermine and for the GELA and GOELAMS Intergroup

3 cycles with a 21 days interval and irradiation or 4 cycles plus ASCT or 6 cycles

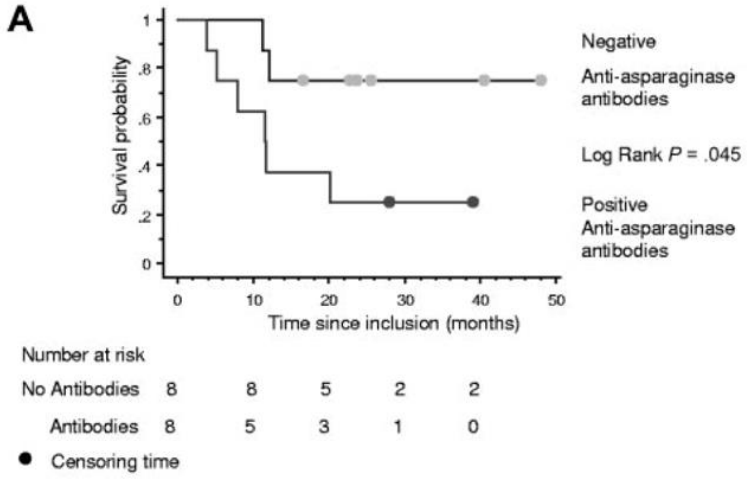


if > 70 years :
Methotrexate : 2 gr/m²
Dexamethasone : 20 mg

Overall survival



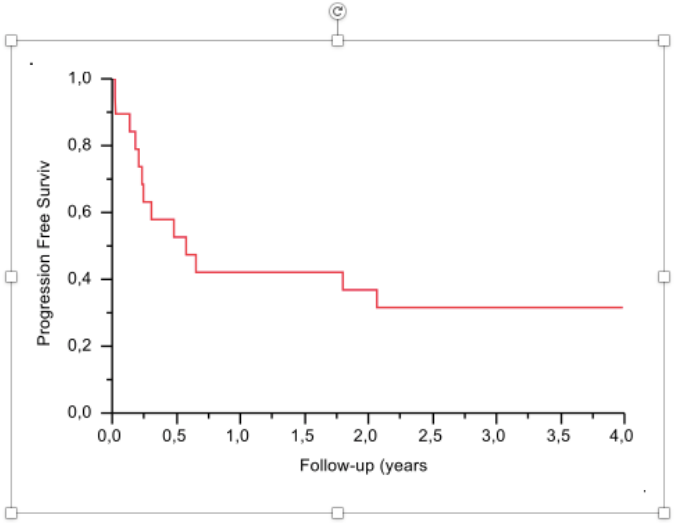
Anti-aspa antibodies



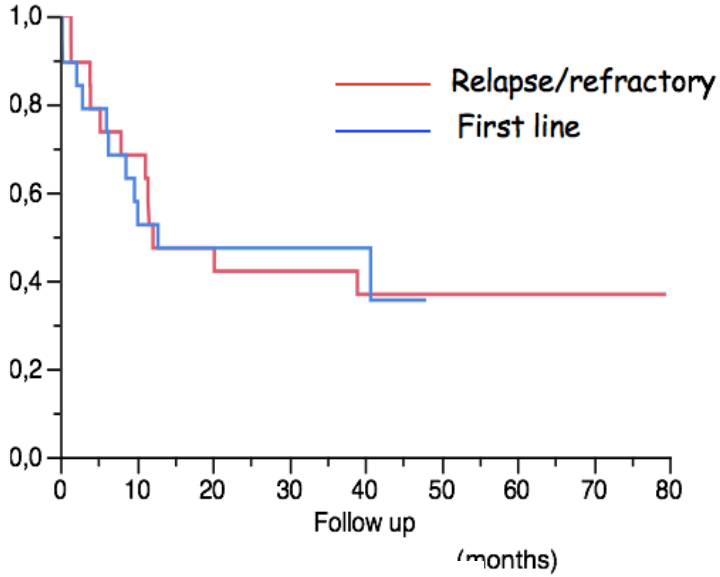
Second series with 19 naive patients

5 relapses (at 6, 7, 8, 22 and 24 months)

PFS



Overall survival



Anti-asparaginase antibodies ??

- All patients (except 2 patients who died early) have detectable antibodies at day 22 or day 44
- 1 patient/2 in relapse/refractory setting
- Allergy in less than half patients with antibodies

- 2 second CR with Erwiniase containing regimens

Aspa-Met-Dex

- Major component: **asparaginase**
- 20 % of patients are primary refractory to asparaginase
- AspaMedDex easy to deliver, even in older patients, very efficient in relapsing patients but efficacy limited by antibodies, especially in naive young patients

  Metho + dex clearly not enough if antibodies are present

Strategies to avoid asparaginase inactivation

- Use first pegylated form of asparaginase
  - Less antibodies (1/15% vs 25/75%) compared to native form in ALL

    Stock W et al. Leuk Lymphoma. 2011;52(12):2237–2253.

    Douer D et al. Leukemia. 2012;26(11):2303–2309

- Switch to Erwinia asparaginase if antibodies appear

Should be confirmed

LEUKEMIA & LYMPHOMA, 2017
https://doi.org/10.1080/10428194.2017.1393672

Taylor & Francis
Taylor & Francis Group

Check for updates

ORIGINAL ARTICLE: CLINICAL

Pegasparaginase silent inactivation during therapy for NK/T cell lymphoma

Deeter R. Neumann[a], Bernard L. Marini[a], Tycel J. Phillips[b], Ryan A. Wilcox[b], Tera L. Mayer[b], Anna Brown[a] and Anthony J. Perissinotti[a]

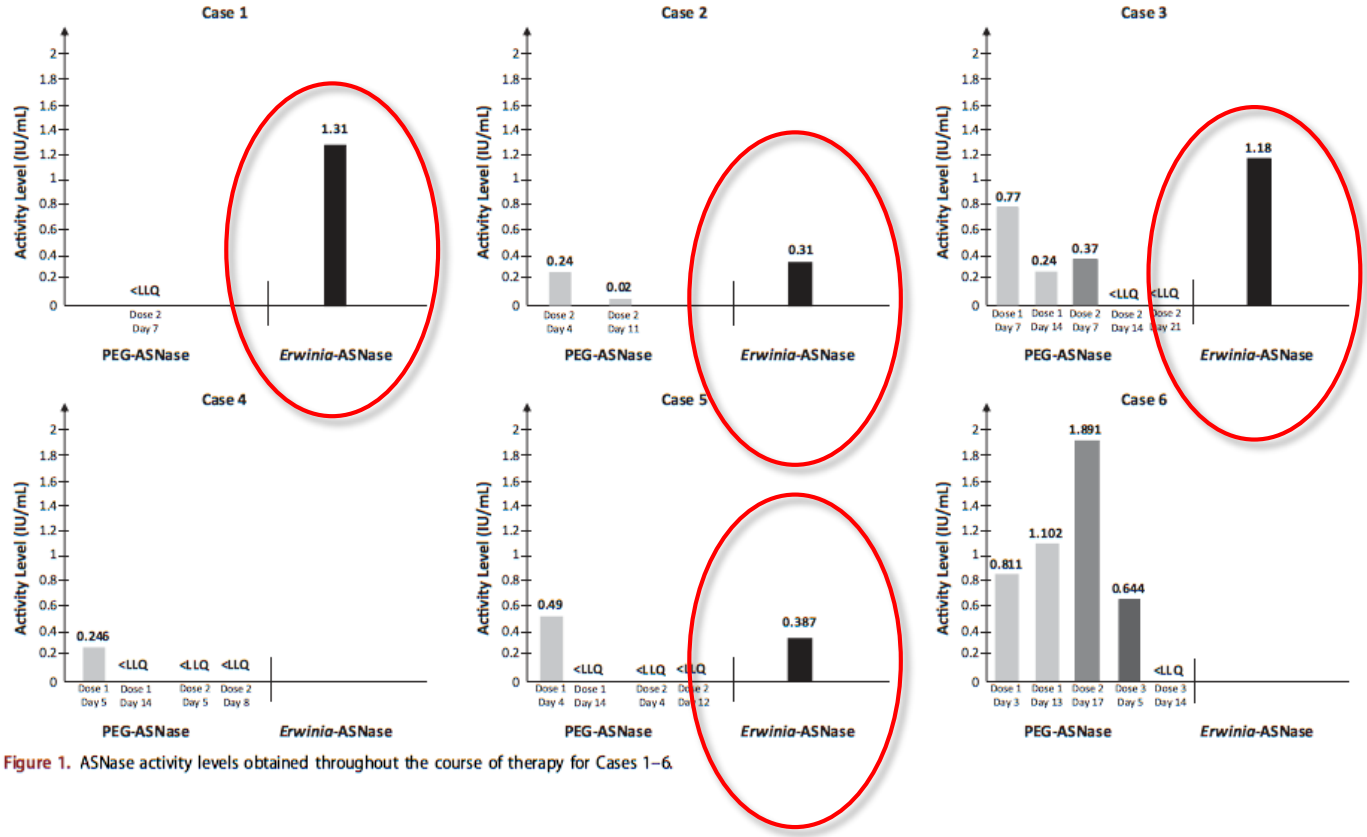


Figure 1. ASNase activity levels obtained throughout the course of therapy for Cases 1–6.

Asparaginase activity

- Simple way to check if antibodies are present
  - Using a quantitative enzyme assay
    - To measure serum asparaginase activity during therapy as a surrogate parameter for antibodies against asparaginase
    - To detect any silent inactivation
    - To provide a rational basis for deciding whether to change to a different asparaginase preparation
  - 48 hours after native asparaginase injection
  - Up to 14 days after the pegylated asparaginase injection
- It must be done at each cycle and if activity is low asparaginase molecule must be switched

Rational for NK/T-cell lymphoma treatment in France

- Early radiotherapy if localized disease (20% refractory): 50 grays or 40 grays + cisplatyl
- Asparaginase and gemcitabine containing regimen
- Peg-asparaginase not allowed first line but monitoring of asparaginase activity and asparaginase switch

Actual treatment in France (waiting for Peg-aspa)

- Localized diseases: MGAD
  - Gemcitabine + Metho + Dex + e-coli aspa
  - Irradiation
  - Gemcitabine + Metho+ Dex + aspa ?

Depending on asparaginase activity 48 hours after the last asparaginase injection

if good : E-coli-asparaginase

if not : Erwinia asparaginase

Asparaginase activity

Service de biochimie hormonologie
Hôpital Robert Debré - 48 bd Sérurier - 75935 Paris Cedex 19

Responsable du dosage :
Dr Jean-François Benoist
Tél : 01 40 03 40 42 ; Mail : jean-francois.benoist@aphp.fr

FICHE DE LIAISON
DOSAGE DE L'ACTIVITE ASPARAGINASE RESIDUELLE

Identification du patient

Nom : ..... Prénom : .....
Date de naissance : ..... Sexe : ☐ Masculin ☐ Féminin

Type d'Asparaginase

☐ Kidrolase ☐ Erwinase ☐ PEG-Asparaginase

Posologie (en UI/m²) : .....

Prélèvement

Conditions du prélèvement	*Horaires d'administration / prélèvement*
Dosage de l'activité à la vallée (**activité résiduelle**) Prélever **juste avant l'administration de l'asparaginase suivante** (habituellement 48h après Kidrolase ou Erwinase ou 14 jours après PEG-Asparaginase) Prélèvement sanguin de 1 à 5 mL sur **tube hépariné** (héparinate de lithium, si possible avec gel séparateur). Envoyer le sang à température ambiante dans les 24h (détails au verso).	**Dernière administration d'asparaginase** Date : ...../...../20.... Heure de début d'administration : ..... **Prélèvement :** Date par rapport au cycle (ex : J18) J.... Date : ...../...../20.... Heure : .....

Renseignements cliniques

Service : ..... Hôpital : ..... Ville : .....
Médecin prescripteur : ..... e-mail : .....
Tel : ..... Fax : .....
Autre contact e-mail (médecin, ARC, IDE...) : .....

Contexte clinique :
Pathologie : ..... Protocole : .....
Groupe de risque (ex : VHR, VLR, A1, B1, T1...) .....
Phase du traitement :
☐ Induction
☐ Consolidation
☐ VANDA
☐ Réinduction/ Intensification n°1
☐ Réinduction/ Intensification n°2
☐ Autres – Préciser : .....

Commentaires

Service de biochimie hormonologie :

Tél : réception +33 (0)1 40 03 20 00, poste : 33 65 ou secrétariat +33 (0)1 40 03 33 63 ; Fax : +33 (0)1 40 03 47 90

RECOMMANDATIONS DE PRELEVEMENT

Principe du dosage

- Le dosage de l'activité Asparaginase résiduelle (activité à la vallée) se fait juste avant l'administration suivante de l'asparaginase. Ce timing de prélèvement dépend de l'Asparaginase utilisée. Il se fait généralement 48h après l'injection d'Asparaginase native d'E. coli ou d'Erwinase et 14 jours après l'injection de l'Asparaginase E. coli Pégylée.
- **Impératif : noter la date et l'heure de début de la dernière asparaginase pour valider le résultat rendu.**

Préparation du prélèvement

Prélèvement sanguin de 1 à 5 mL sur tube hépariné (tube à ionogramme - héparinate de lithium avec ou sans gel séparateur). En cas de contrainte, le volume de prélèvement peut être réduit à 0,5 mL.

- **Du lundi au jeudi :**

Envoyer le prélèvement à température ambiante dans les 24 heures *via* DHL **avec la fiche de liaison**.

- **Du vendredi au dimanche :**
  - ✓ Stocker le prélèvement au frigo ou à défaut à température ambiante.
  - ✓ Envoyer le prélèvement **dès le lundi** à température ambiante dans les 24h via DHL **avec la fiche de liaison.**

NB : La conservation du prélèvement à température ambiante est de 4 jours maximum. Si un délai supérieur ne peut être évité il faut, juste après le prélèvement, centrifuger le tube à 4°C (ou par défaut à température ambiante), à une vitesse de 1500 g (3 à 4000 t/mn) pendant 8 mn puis :

- *Si le tube hépariné est **avec** gel séparateur, placer le tube au réfrigérateur jusqu'à l'envoi,*
- *Si le tube hépariné est **sans** gel séparateur : pipetter le plasma, le mettre dans un tube à hémolyse, boucher et placer au réfrigérateur jusqu'à l'envoi.*

Envoi par DHL

✓ Contacter le service client DHL pour demander l'enlèvement. **Tel. : 0825 1000 80**

- Il s'agit d'un serveur automatique. Sélectionner : « *autre demande* » puis « *conseiller en ligne* » et demander l'enlèvement.
- Vous pouvez demander à DHL de vous apporter des **flyers (enveloppe plastifiée et bordereau vierge)** si vous n'en avez pas à disposition. Attention, certaines agences n'en ont pas forcément en stock.

✓ Indiquer sur le bordereau DHL EXPRESS Export et France **le numéro : 958079022** (facturation Eusa Pharma)

⇨ Si besoin, DHL hotline informatique pour accompagner les démarches au : 0820 345 543.

Destinataire : **Dr Jean-François Benoist** Service de Biochimie Hormonologie Hôpital Robert Debré 48 boulevard Sérurier 75019 PARIS	**Email :** jean-francois.benoist@aphp.fr **Ligne directe :** +33 (0)1 40 03 40 42 **Réception - Tel :** +33 (0)1 40 03 20 00, poste : 33 65 **Secrétariat - Tél :** +33 (0)1 40 03 33 63 **Fax :** +33 (0)1 40 03 47 90

Rendu des résultats

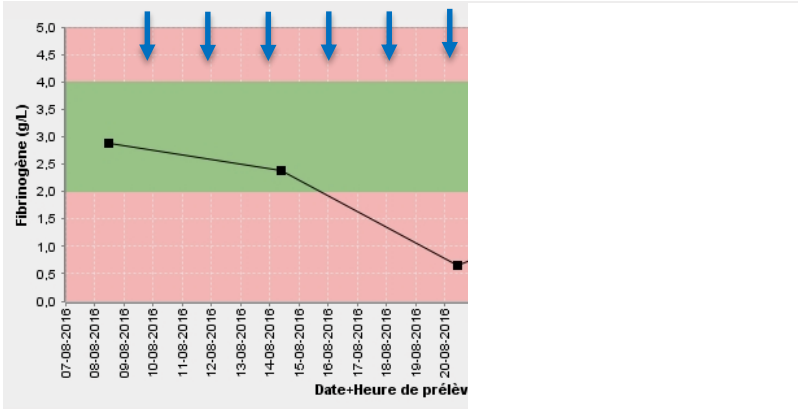
- Les résultats sont envoyés **par courrier systématiquement**

Aspa monitoring

- 17 tested patients , low activity at least once in 10 patients
- 9 patients in first line
  - Low activity at the end of the first cycle in 5 (55%)

- Example: 42 year-old patient, stage II (nasal cavity + cervical nodes), MGAD treatment, no clinical allergy

Asparaginase injections



Fibrinogen measurement

Date du prelevement 2608
SUIVI DU TRAITEMENT PAR ASPARAGINASE :
Spécialité de médicament: Kidrolase
Date dernière injection : 24/08/16
Date prélèvement J+ 2 jours
Activité Asparaginase 3 U/L
Activité recommandée >100 U/L
- J+48H pour les patients sous Kidrolase et Erwinase.
- J+14 jours pour les patients sous Oncaspar.

attention activité effondrée evoquant
l'apparition d'anticorps symptome clinique
lors de l'injection?

Résultats validés par :
Dr. RIGAL Odile

Actual treatment in France

- Disseminated diseases: MOGAD
  - Gemcitabine + oxaliplatin + Metho + Dex + e-coli aspa
    then
  - Gemcitabine + oxaliplatin + Metho + Dex + aspa ?

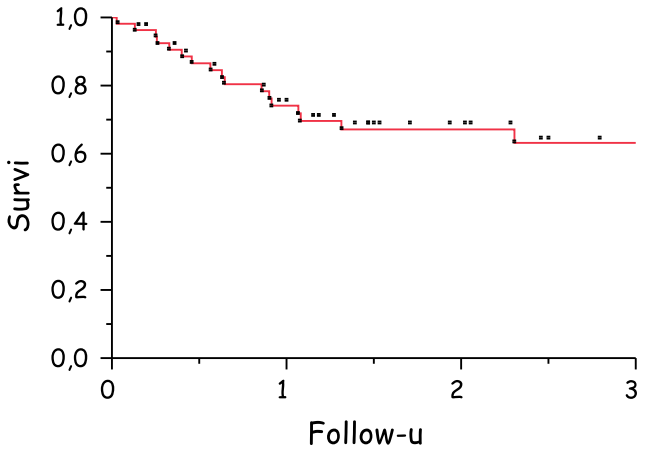
  Depending on asparaginase activity 48 hours after the last asparaginase injection

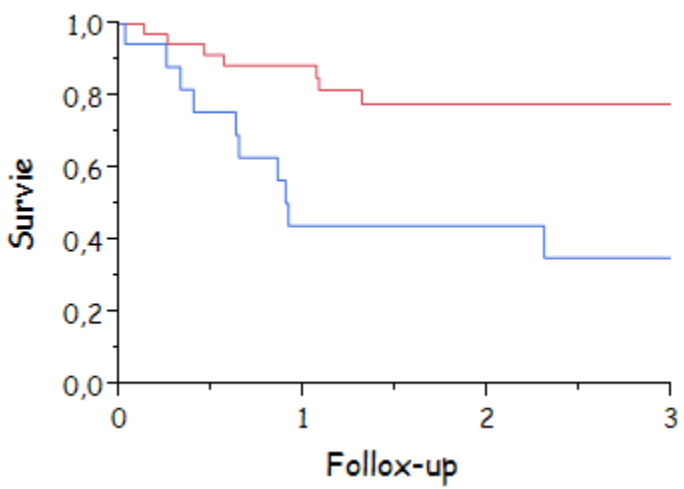
  - 3 to 4 cycles then ASCT if possible

  - Allograft ? ? Probably for patients in PR

Survival of naive patients treated with MGAD or MOGAD in 21 centres

- 54 patients, follow-up for living patients: 16 months (0-62)





36 pts

18 pts

Pink score

High-risk	10
Intermediate-risk	21
Low-risk	22

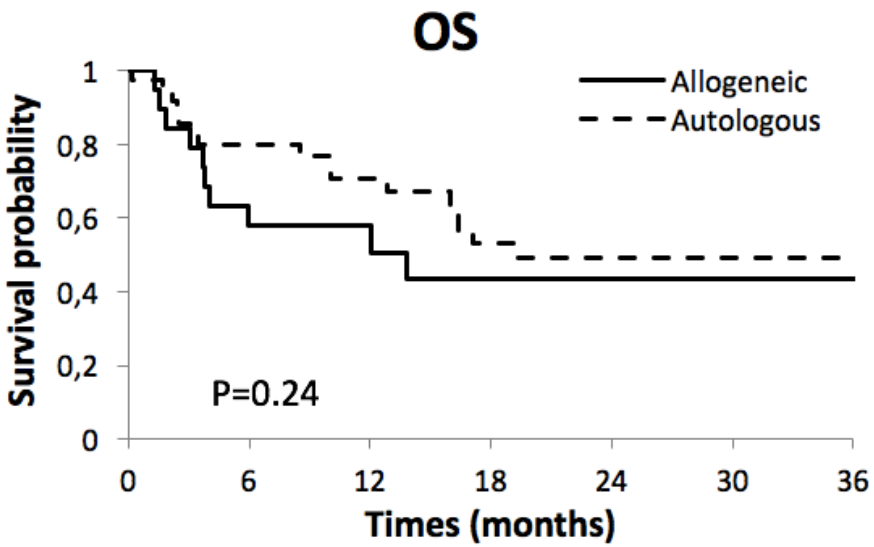
2 year-survival 67%

I/II : 78 %

III/IV : 44 %

High dose treatment : auto vs allo transplant

- Retrospective study on the behalf of the SFGMTC
- 57 patients, median age: 42 years, 33 (58%) with a disseminated disease
  - No significant difference in age, Ann Arbor stage, bone marrow involvement, IPI and PINK risk groups
  - Allo : 19 patients, 5 (26%) in first line
  - Auto : 38 patients, 18 (47%) in first line



PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing L-asparaginase

Yok-Lam Kwong,[1] Thomas S. Y. Chan,[1] Daryl Tan,[2,3] Seok Jin Kim,[4] Li-Mei Poon,[5] Benjamin Mow,[6] Pek-Lan Khong,[7] Florence Loong,[8] Rex Au-Yeung,[8] Jabed Iqbal,[9] Colin Phipps,[2,3] and Eric Tse[1]

BLOOD, 27 APRIL 2017 • VOLUME 129, NUMBER 17

In France

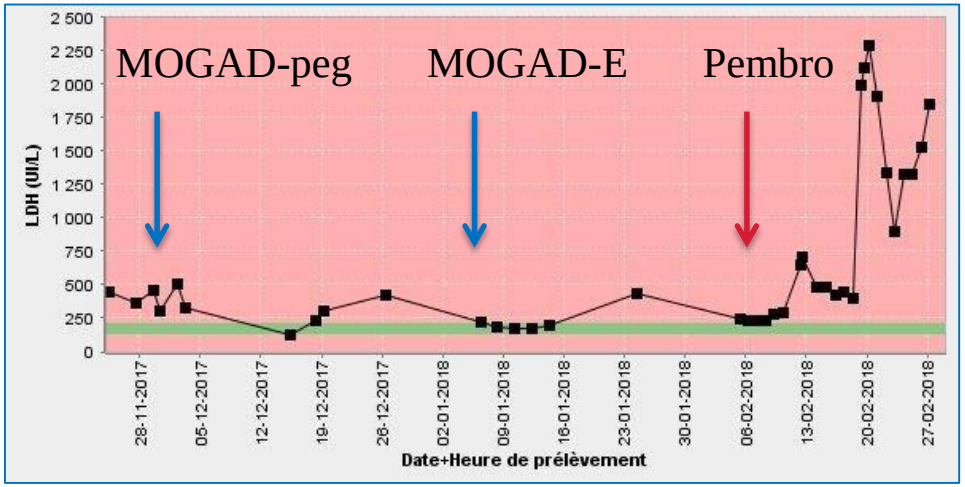
- 5 patients treated (4 with Pembro, 1 with Nivo) outside a formal protocol
  - All in relapse
  - All in stage IV
  - 2 with HLH
- 1 spectacular response but the patient died of cerebral bleeding after 1 cycle
- 1 progression after 9 injections
- 3 rapid deaths in very severe patients

53 year-old woman

- First episode in 2003 ; bone marrow and liver involvement, refractory to CHOP, CR after asparaginase containing regimen and ASCT
- Her mother died from NK/T-cell lymphoma

- Relapse in Nov 2017 with a leukemic form with liver, spleen and bone involvement, 40 millions EBV copies
- No response after MOGAD with Peg-asparaginase and then Erwinia-asparaginase
- Treatment with pembrolizumab : 200mg/m^2, partial response on leukemic cells but at Day 14 cytokine release syndrome with:
  - 40° fever
  - LDH X 15
  - Fibrinogen 0,4 gr/l
- Remission with anti-Il6 antibodies but disease progression

LDH



UNICANCER Immunotherapy Group

Protocol n° UC-0105/1612

EudraCT n°: 2016-002260-14

Secured access to pembrolizumab for adult patients with selected rare cancer types

Abbreviated title: **AcSé Pembrolizumab**

Version n°2.0, September 12, 2017

1 PATIENT SELECTION

1.1 Inclusion Criteria

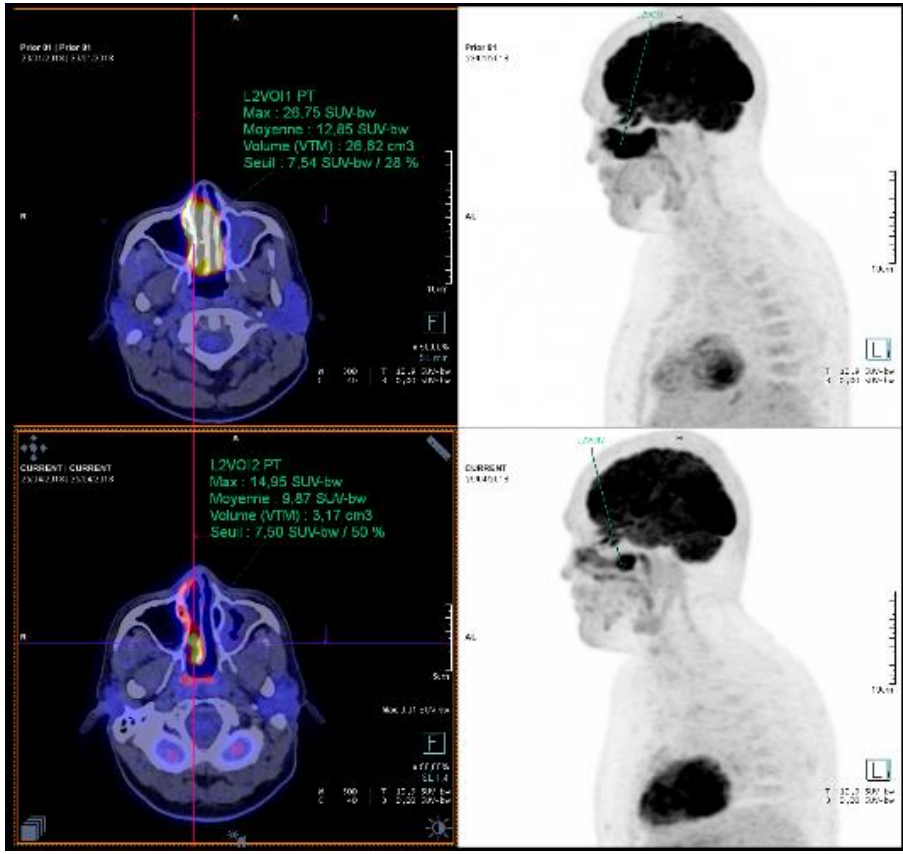
Patients must meet all of the following criteria to be included in the study:

1. Histologically confirmed diagnosis of a pathology corresponding to one of the following selected cancer types:
    - Natural killer T-cell lymphoma: extranodal NK/T-cell lymphoma regardless of localization that is resistant or refractory to prior L-asparaginase therapy.

AcSé Pembrolizumab

- 2 patients included
  - First one in Limoges, 43 year-old patient with the low asparaginase activity

    - At relapse, 18 months after initial treatment
      - Tumor volume : 26 cm3
    - After 4 injections of pembrolizumab
      - Tumor volume : 3 cm^3



Conclusion

In our view, treatment of NK/T-cell lymphoma :

- Rapid irradiation and a short course of chemotherapy for localized disease
- Asparaginase and gemcitabine containing regimen for all patients
- Monitoring of asparaginase treatment with asparaginase activity
- Autologous stem cell transplant for fit patients with a disseminated disease in CR
- Checkpoints inhibitors for patients in relapse

Questions ?

- Role of allogenic transplant ?
- Peg-asparaginase better than native forms ?
- Role of new treatments ?:
  - Anti-EBV CTL
  - Daratumumab
  - Jak, BCL2 and HDAC inhibitors,

ACKNOWLEDGMENTS

- LYSA and Tenomic groups
- All participating centres
- EUSA Pharma (JAZZ) for providing Erwiniase® for the prospective trials

November 2014. Congress of the Japanese Society of Hematology