Préservation de la fertilité chez les patientes atteintes d'affections hématologiques

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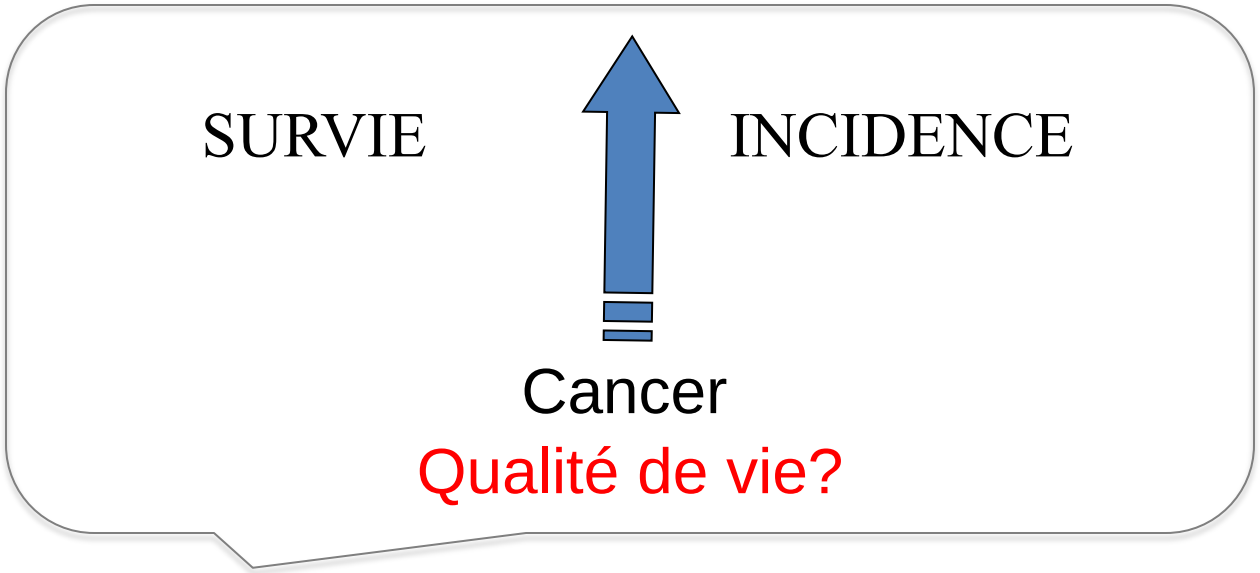
BHS nursing day-Ghent-25 january 2013



American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients

Stephanie J. Lee, Leslie R. Schover, Ann H. Partridge, Pasquale Patrizio, W. Hamish Wallace, Karen Hagerty, Lindsay N. Beck, Lawrence V. Brennan, and Kutluk Oktay

JCO-2006

FERTILITY PRESERVATION

Recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer

ISFP Practice Committee · S. Samuel Kim · Jacques Donnez · Pedro Barri · Antonio Pellicer · Pasquale Patrizio · Zev Rosenwaks · Peter Nagy · Tommaso Falcone · Claus Andersen · Outi Hovatta · Hamish Wallace · Dror Meirow · Debra Gook · Seok H Kim · Chii-Ruey Tzeng · Shuetu Suzuki · Bunpei Ishizuka · Marie-Madeleine Dolmans

J Assist Reprod Genet (2012)

Qui est concerné par une préservation de la fertilité?

- La probabilité d'avoir un enfant est réduite de **50% chez les femmes** et **30–57% chez les hommes** ayant eu un cancer (Madanat et al. 2008, Schover 2008).

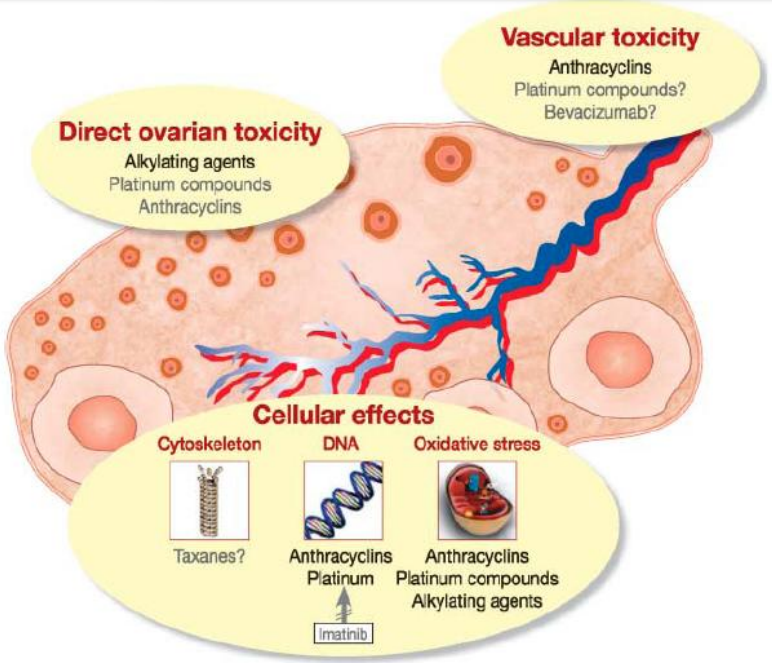
- Pour les patients atteints de Hodgkin, le **risque d'infertilité lié aux alkylants augmente** (van der Kaaij, 2010).

- Une étude norvégienne, avec un **follow-up de 20 ans**, montre que les femmes de moins de 30 ans ont un risque similaire de Prédéfaillance Ovarienne Prématurée (POF) comparé aux femmes de plus de 30 ans mais dans un intervalle différent. Risque cumulatif ~ 38%: Les **femmes de 25-29 ans** développent **une POF en moyenne 6 ans** après le diagnostic tandis que **les femmes de 30-40 ans** développent une **POF en moyenne 2 ans** après le diagnostic. (Haukvik UKH 2006.)

Risque		
Haut > 80%	Irradiation > 6Gy chez adulte	différents cancers
	Irradiation > 15Gy chez les filles prépubères Irradiation >10Gy chez les ado.	différents cancers
	Cy > 5g/m2 chez les + 40ans	différents cancers
	Cy > 7.5g/m2 chez les – 20 ans	NHL, ALL
	Conditionnement greffe moelle avec alkylant/TBI	BMT/SCT
	Protocoles contenant **procarbazine + 30 ans**: MOPP, MVPP, COPP, ChIVPP, ChIVPP/EVA, BEACOPP, MOPP/ABVD, COPP/ABVD	HL
Intermédiaire 30-70%	Irradiation moelle >25Gy	ALL, NHL
	Protocols containing **procarbazine – de 30 ans**: MOPP, MVPP, COPP, ChIVPP, ChIVPP/EVA, BEACOPP, MOPP/ABVD, COPP/ABVD	HL
Faible <20%	**Nonalkylan**t: ABVD, CHOP, COP Anthracycline cytarabine Multiagent therapies	AML, Hodgkin's lymphoma, NHL ALL

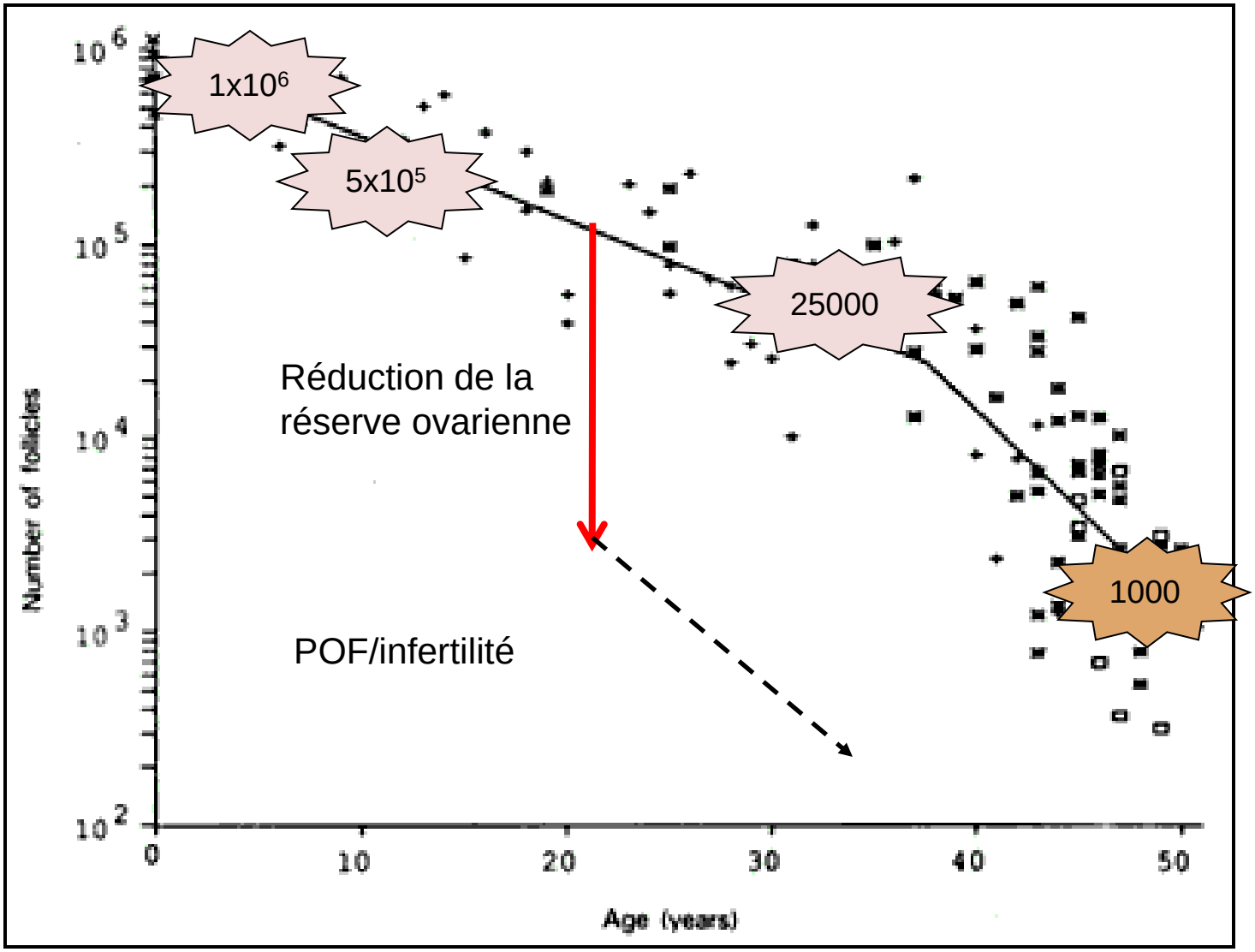
Authors	Treatment	n	Age (range)	Ovarian recovery (%)	Follow-up
Spinelli 1994	CT + TBI CT + TBI	14 60	<18 y >18 y	6 (43) 4 (6)	4-108 (48.8)
Sanders 1996	Cy **Bu/Cy** Cy +TBI	103 **73** 532	28 y (13-58) **38 y (14-57)** 28 y (11-58)	56 (54.3) **1 (1.3)** 53 (10)	12-204 months (median 36)
Sarafoglou 1997	Cy + TBI	16	Prepubertal	9 (56)	
Teinturier 1998	CT **CT /Bu**	11 **10**	5.8y (2-14.8) **12.7y (4.7-17.3)**	7 (73) **0 (0)**	14-156 months (median 84)
Thibaud 1998	CT CT + TBI	8 23	10.3 y (3.2-17.5)	3 (37.5) 3 (13)	14-138 months (median 72)
Bath 1999	CT + TBI	8	11.5y (5.9-15)	2 (25)	
Couto-silva 2001	CT+ TBI CT	22 5	7.3 y (1.5-13) 5.3 y (0.6-12.9)	3 (13.6) 2 (40)	
Tauchmanova 2002	**Bu/Cy**	**21**	**13-45 y**	**2 (5)**	12-62 months (median 38)

Effet gonadotoxique de la chimiothérapie



High risk	Intermediate risk	Low/no risk
Cyclophosphamide	Doxorubicin	Methotrexate
Busulfan	Cisplatin	Bleomycin
Melphalan	Carboplatin	5-Fluorouracil
Chlorambucil		Actinomycin-D
Dacarbazine		Mercaptopurine
Procarbazine		Vincristine
Ifosfamide		
Thiotepa		
Nitrogen mustard		

Effet sur la réserve ovarienne



Diagnosis

Contact fertility unit

Consulting

Fertility preservation

Type of disease
Previous chemotherapy
Other associated diseases
Time to treatment
State of health
Menstruation period

Procedure?

Oncological treatment

Follow-up

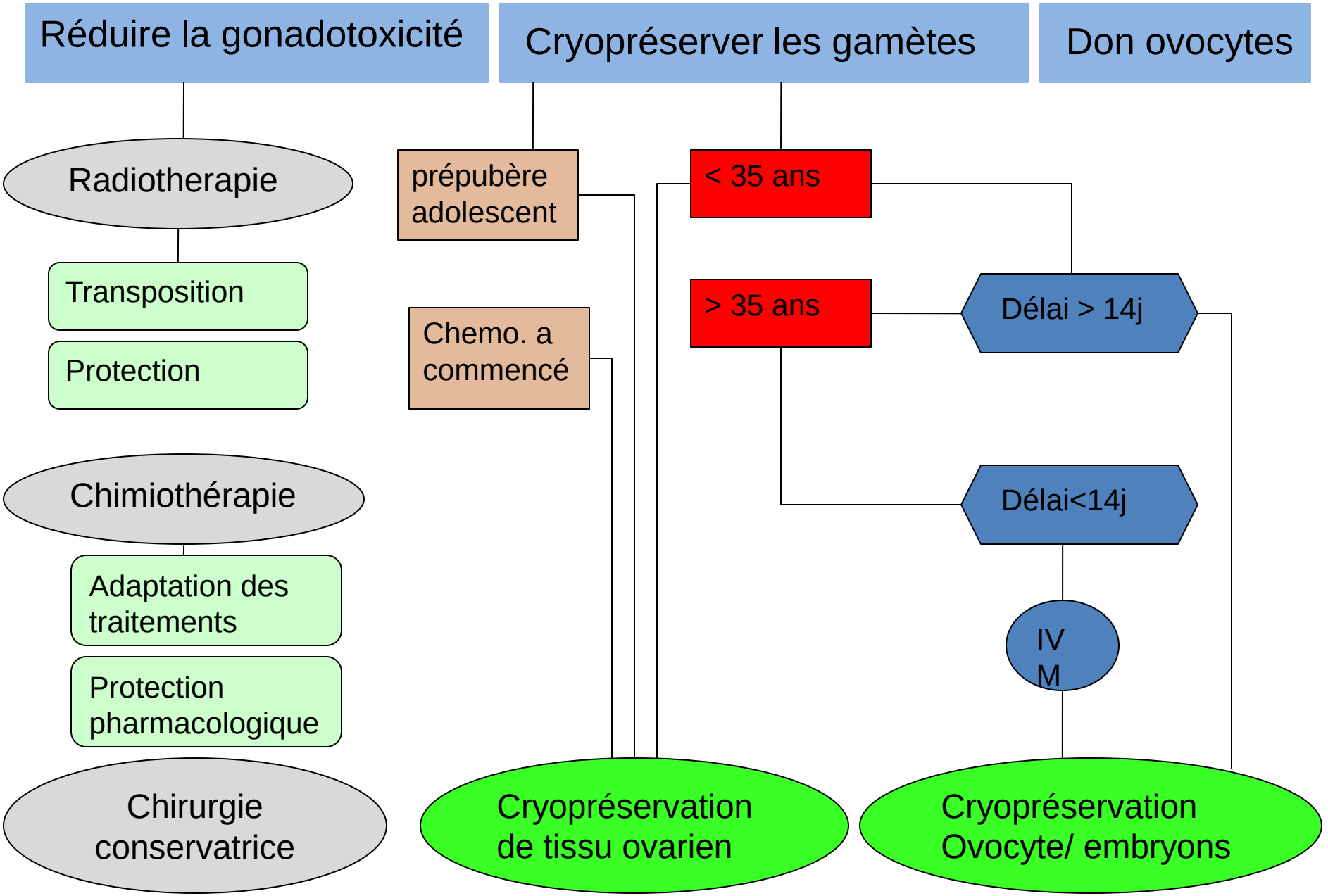
Age
Treatment

Ovarian reserve evaluation

Infertility risk

High
or moderate

Procédure de préservation de la fertilité



Cryopréservation du tissu ovarien:

Avantages

Pas de délai

Seule technique chez les patientes prépubères

Peut-être proposée même si la chimiothérapie a démarré

Procédure réalisée sur place

Large nombres de follicules congelés

Densité folliculaire (Poirot 2002)

20.36/mm² <7 ans

4.13/mm² 7-15 ans

1.63/mm² > 15 ans

“Coût”

Désavantages

Procédure invasive

Transplantation est la seule option pour restaurer la fertilité

Risque de retransmission de la maladie

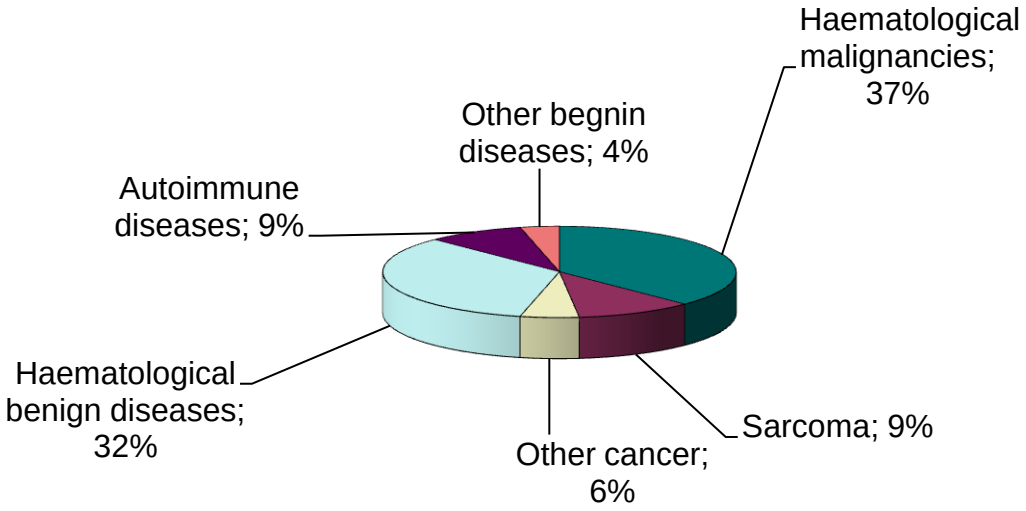
Perte de follicules (ischémie)

Critères d'inclusion du protocole de cryopréservation du tissu

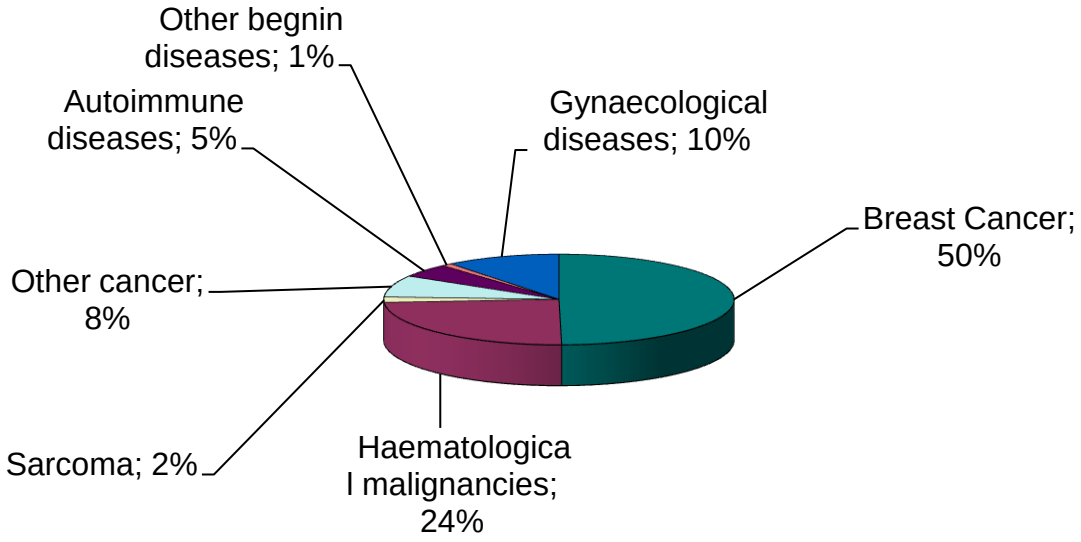
Critères d'inclusion	Critères d'exclusion
Moins de 36 ans (limite inf. à 3 ans si pas de chirurgie associée)	ATCD de traitement hautement gonadotoxique
Risque de DOP suite à un traitement gonadotoxique.	Défaillance ovarienne
Consentement éclairé	Sérologies positives
	Contre-indication chirurgicale

Indication des cryopréservations de tissu ovarien

Children



Adult



Caractéristiques de la population

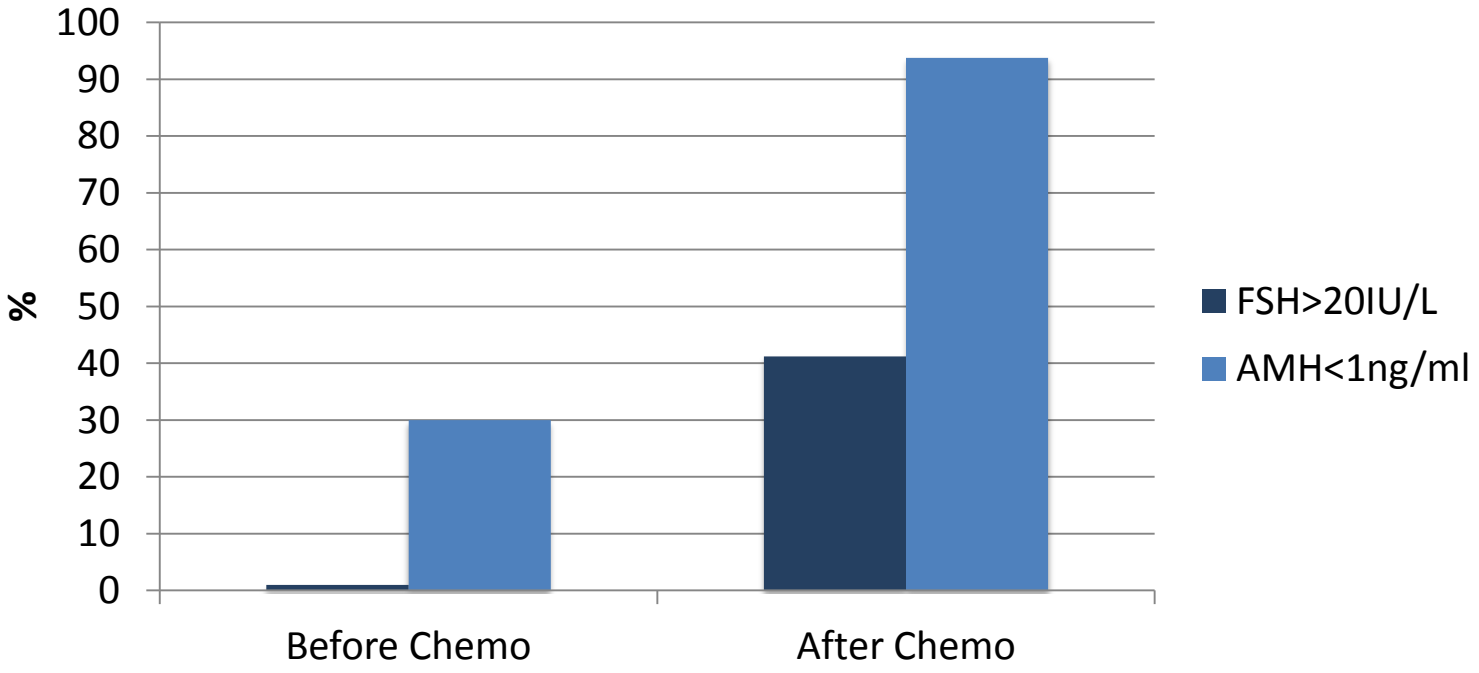
Pathologies	n	Age	Décès
Mal. Bénigne	20	8	-
Leucémie	20	16	44%
Lymphome	51	23	13%
	91	18	10,1%

Au moins 1 ovocyte a été congelé chez plus de la moitié des patientes

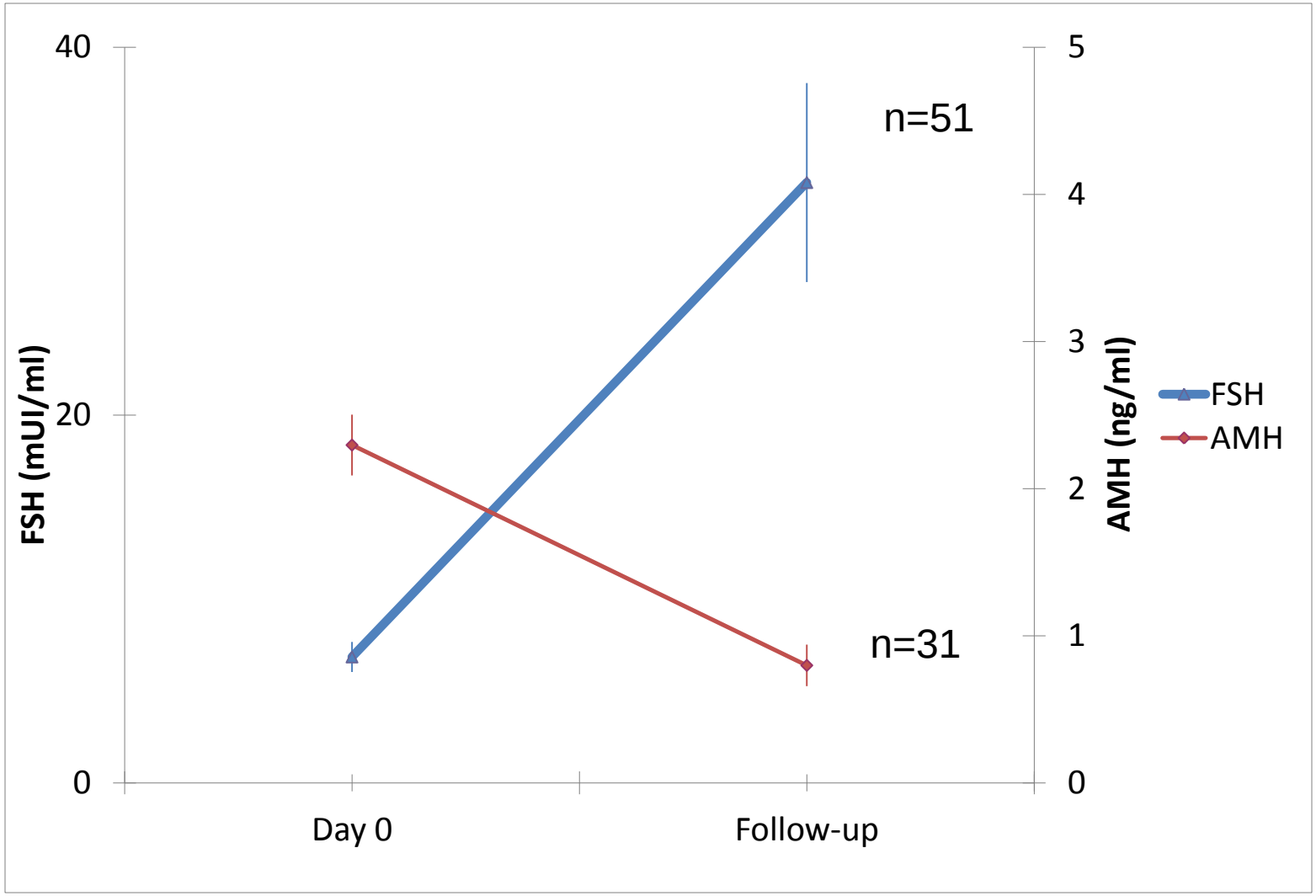
	Results	Comments
Age	24	Entre 1-35
GxP0	84%	
Chirurgie associée	52%	Césarienne, biopsie, PAC, transposition
Chimiothérapie démarrée	19.5%	
Complication	1	LED
Nber fragments/patient	20	Range 5-59
Biopsie	76%	
Follicles/mm2/fragment	6 (0-30)	11 patients: pas de follicles
Reserve ovarienne		
FSH	6.8±0.8	
AMH	2.3±0.2	

Follow-up (n=149)	**n**	
Death	16 (10.7%)	
Relapse	8 (5.4%)	
Fertility restoration (n=102)		
Bilateral ovariectomy	8 (7.8%)	
Pregnancies	13 (12.7%)	1 transposition 1 egg donation 1 transplantation 2 ART
Transplantation	4	1 miscarriage, 2 LB 2 failures 1 follow-up

FSH ET AMH


100
90
80
70
60
50
40
30
20
10
0
%
Before Chemo
After Chemo
FSH>20IU/L
AMH<1ng/ml

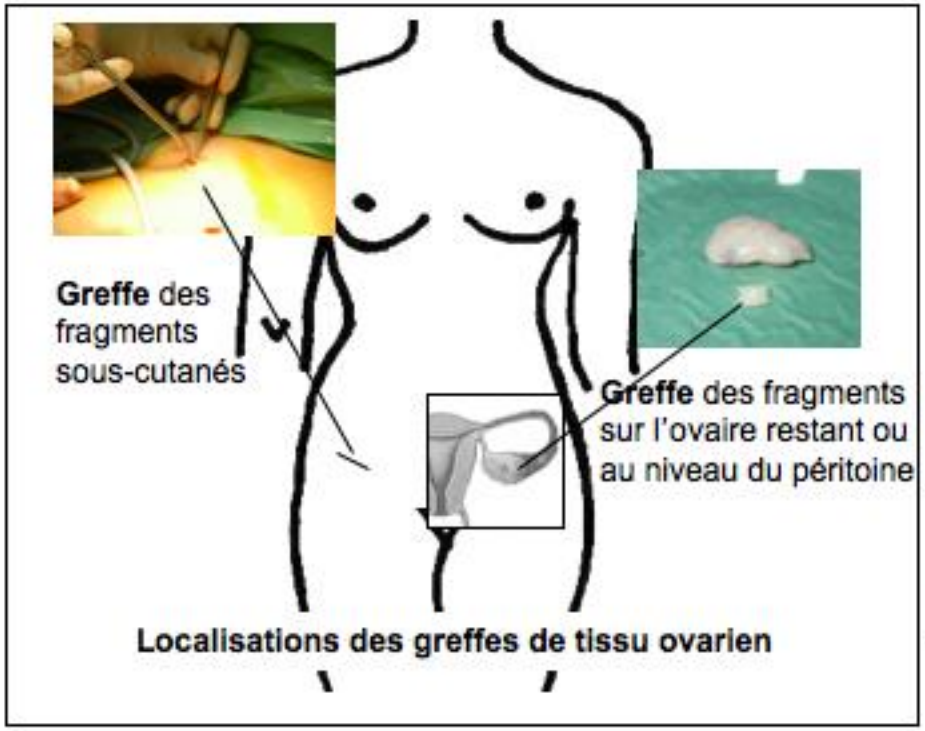
Evolution de la réserve ovarienne après traitement



Congélation et greffe des tissus ovarien

1. Diagnostic du cancer

2. Prélèvement de tissu ovarien en vue de préserver la fertilité



3. Congélation et conservation des fragments de tissu ovarien

4. Traitement du cancer

Rémission complète

Désir de grossesse

5. Décongélation des fragments

6. Greffe des fragments d'ovaire

Récupération des cycles menstruels

7. Grossesse

Procédure de transplantation du tissu ovarien

Thawed ovarian tissue → Histology → ▪ Follicular density ▪ Neoplastic cells detection

↓

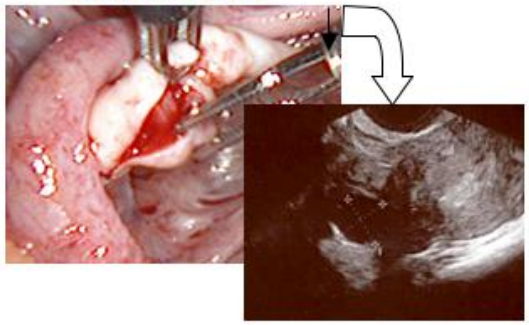
First step laparoscopy → ▪ Biopsy of the resting ovary (resting follicles detection) ▪ Control of tubal patency ▪ Preparation of the ovarian and peritoneal sites

↓ 1 week later

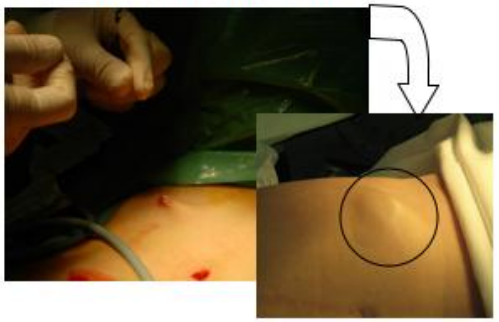
Second step laparoscopy → Transplantation of ovarian tissue

Peritoneal site

Ovarian site



Subcutaneous site



Ovarian tissue (cryopreserved)

Heterotopic

Subcutaneous (SC)
Kim 2001
Oktay 2001-2004
Rosendhal 2006

Abdominal muscle
Callejo 2001
Kim 2008

Orthotopic

Oktay 2000
Radford 2001
Schmidt 2004, 2005
Donnez 2004, 2005,2006
Meirow 2005
Demeestere 2006,2007
Anderson 2008,
Roux 2010
Sanchez-Serano 2010
Revel 2011
Schmidt 2011

Embryons transferred
Oktay 2004
Bioch Pregnancy
Rosendhal 2006
Spontaneous pregnancy
Oktay 2011

20 life birth (Spontaneous Pregnancies or IVF)

Donnez 2011 (review)

Whole ovary

Heterotopic

(fresh tissue)
Upper/Forearm
Leporrier 1987
Hilders 2004
Mathre 2005

Orthotopic

(fresh tissue)

Silber 2008

No pregnancy using cryopreserved ovary

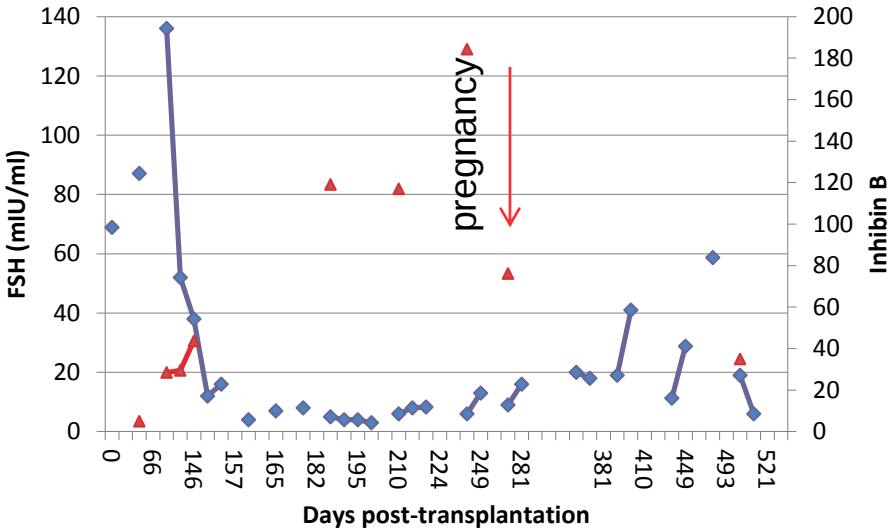
Isolated follicles

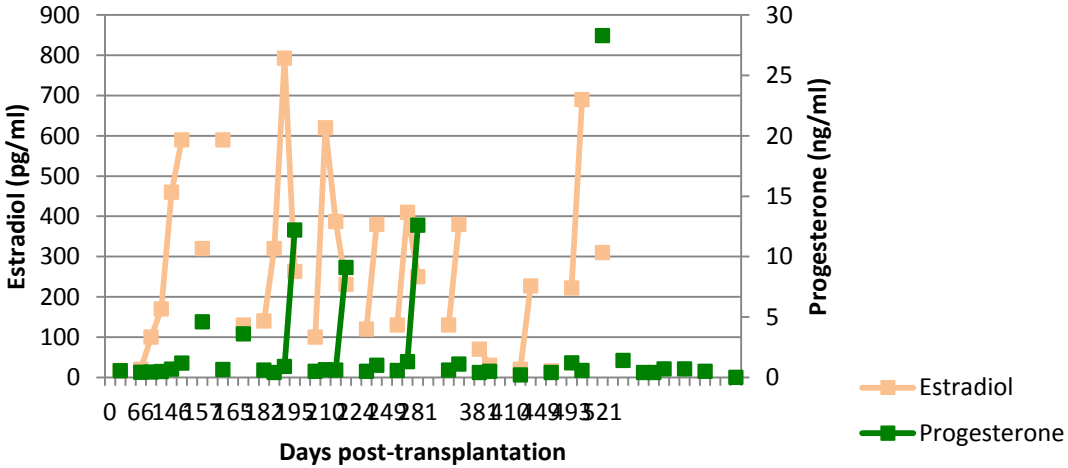
Orthotopic

Xenograft

Experimental

Ovarian function after transplantation





Enfants nés suite à une transplantation de tissu ovarien cryopréservé

References	Age	Diseases	Delay	Pregnancies	LB
Donnez, 2004	25	Lymphoma (H)	11 months	Spontaneous	1
Meirow, 2005	28	Lymphoma (NHL)	9 months	IVF	1
Demeestere 2007 Demeestere, 2011	24	Lymphoma (H)	6 months (2 Transp.)	Spontaneous	2
Andersen, 2008	26	Lymphoma (H)	7 months (2 Transpl.)	IVF	1
Andersen, 2008 Ernst, 2010	27	Ewing sarcoma	16 months	Stimulation Spontaneous	3
Silber, 2008	20	Lymphoma (H)	8 months	Spontaneous	1
Silber, 2010, 2012	37	Lymphoma	-	Spontaneous	2
Sanchez-serrano, 2010	36	Breast cancer	12 months	IVF	2 (twin)
Roux, 2010	20	Sickle cell anemia	7 months	Spontaneous	1
Piver, 2011	27	Microscopis polyangitis	14 months	IVF	1
Revel, 2011	19	Thalassemia	10 months (3 Transpl.)	IVF	2
Donnez, 2011	17	Neurestodermic tumor (Orbit)	6 months	Spontaneous	1
Dittrich, 2012	25	Lymphoma (H)	6 months	IVF	1
Müller, 2012	25	Lymphoma (H)	6 months	Stimulation	1
Donnez, 2012	18	Benign disease		IVF	1
Revelli, 2012	21	Sickle cell anemia	16 months	Spontaneous	1

Evaluation du risque de transmission de la maladie

Low risk (<0.2%)	Moderate risk (0.2-11%)	High risk (>11%)
Wilm's tumor NHL HL Osteogenic sarcoma Squamous cell carcinoma of uterine cervix Ewing's sarcoma	Breast cancer Adenocarcinoma of uterine cervix (pelvis) NHL (Burkitt)	Leukemia Neuroblastoma

Risque de transmission

- **HL**: Detection by immunohistology (anti CD30-anti Ki67)
- Immunohistolgy neg (56 patients)
- Autopsy: 1-5% ovarian metastasis
- positive biopsies (Bittinger 2010)
- xenotransplantation of ovarian tissue in mice: no recurrences? (Kim 2006, Shaw 2006)

- **NHL**: Detection Immunohistology/ PCR (B-T cell rearrangement)
- Macroscopic: 2 ovarian mass (tissue not collected): Burkitt and LNH cell B high grade
- Histology: negative 16/16 fragments PCR: Negative 2/2 fragments (Meirow 2008)
- xenotransplantation of ovarian tissue in mice: no recurrences (Kim 2006)

- **Leukemia**: Positive PCR in more than 50%
- Controversies regarding the risk of transmission when tissue is frozen after the first chemotherapy regimen….

Cryopréservation d'ovocytes matures

Avantages

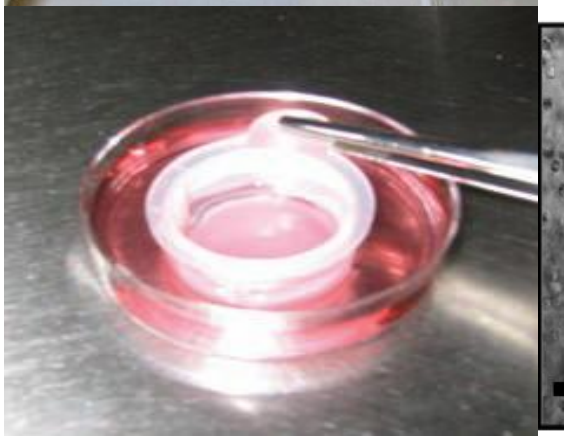
- Vitrification ovocytaire développée depuis quelques années (option si pas de partenaire ni recours au don de sperme)
  - Taux de survie post décongélation 96,8%
  - Taux de fécondés par ICSI 76%
  - Taux de grossesses cliniques de 30-40%, comparable aux cycles ICSI frais chez les moins de 35 ans
- Taux de d'anomalies congénitales comparables à la FIV classique

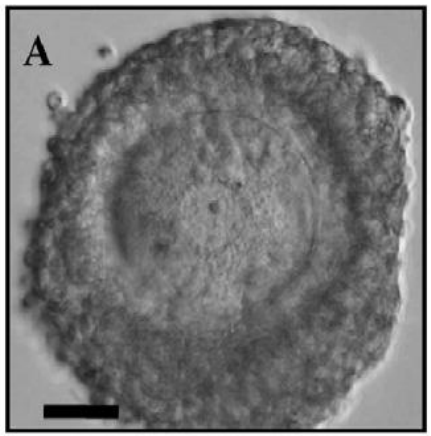
(Noyes et al. Reprod Biomed Online 2009)

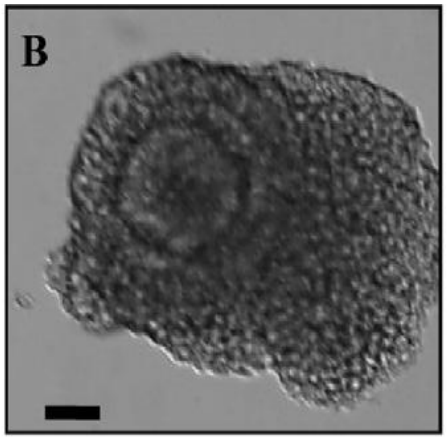
Désavantages

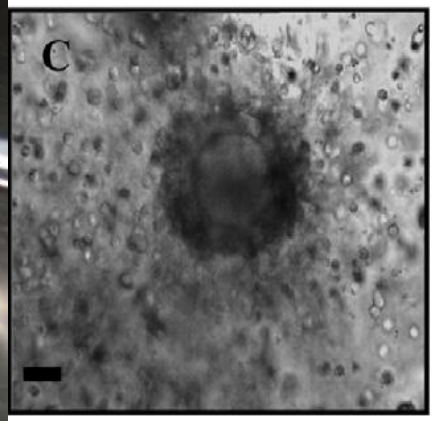
- Nécessite une stimulation ovarienne
- Tumeur hormono-sensible
- Délai (13 jours min)
- Coût

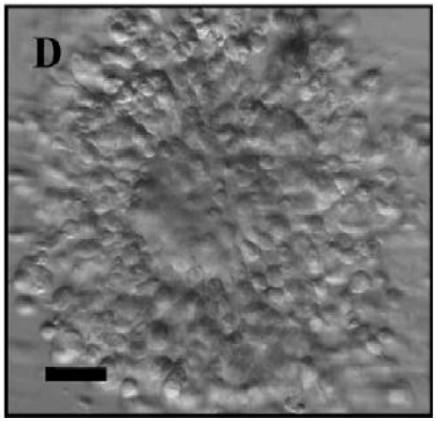
Vitrification of in vitro matured oocytes collected from antral follicles at the time of ovarian tissue cryopreservation.

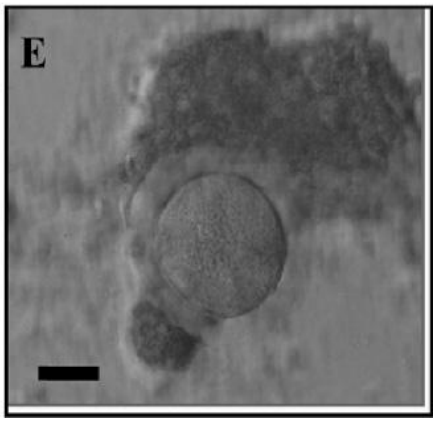




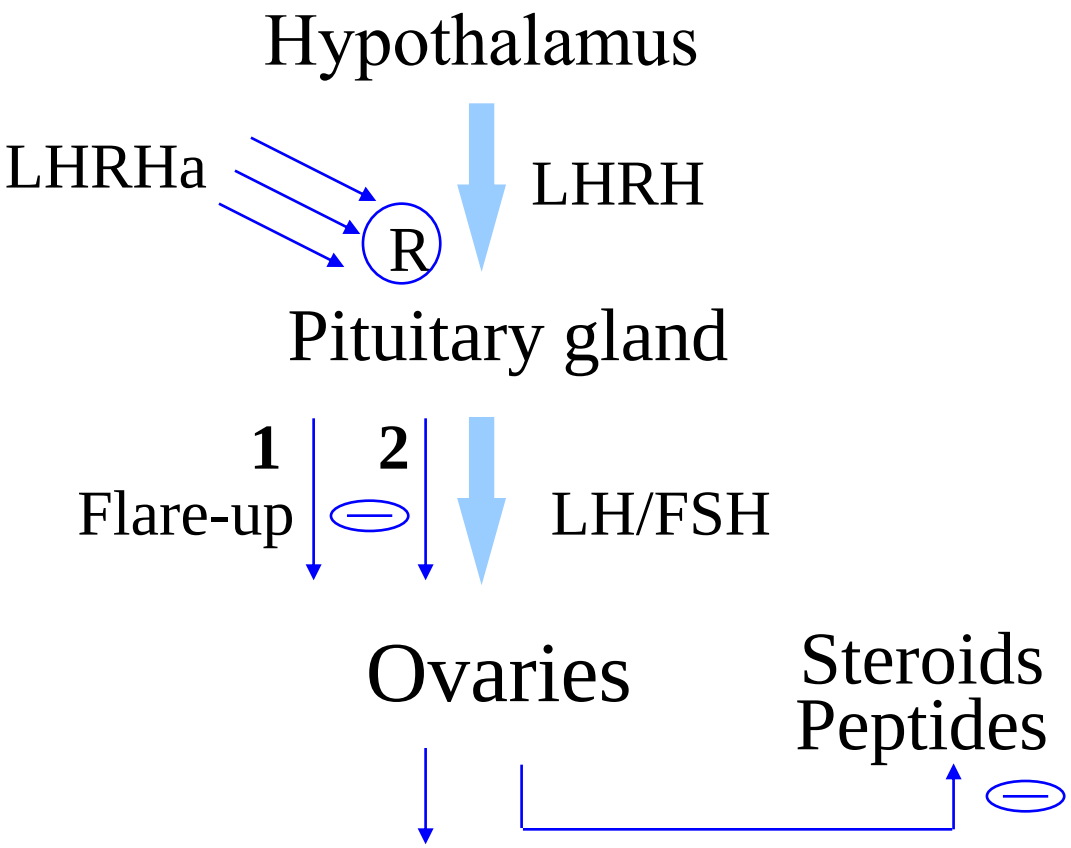








Protection pharmacologique: Analogues de la GnRH ?



A/ Inhibition of the follicular growth

B/ Reduction of the vascularisation

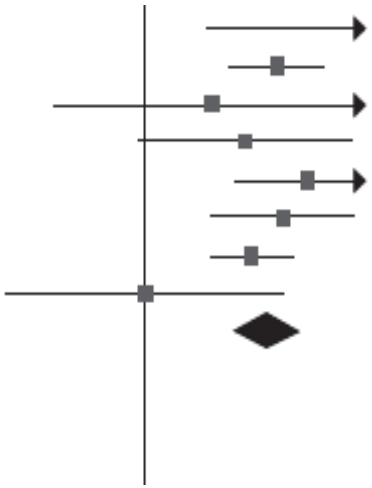
Etude animale

References	Species	Analogues	Effects
Ataya 1988	Rat	Agonist	Ovarian protection
Bokser 1990	Rat	Agonist	Ovarian protection
Montz 1991	Rat	Agonist	Ovarian protection as efficient as progesterone. No fecondity protection
Ataya 1995	Monkey	Agonist	Ovarian protection
Meirow, 2004	Mice	Antagonist	Ovarian protection
Letterie, 2004	Rat	Agonist	No effect on secondary follicles
Yuce, 2004	Mice	Agonist	Partial protection only when associated with high doses CY
Danforth, 2005	Mice	Ago/antago	Ovarian protection with agonist but not antagonist
Lemos, 2010	Rat	Antagonist	Partial fertility protection. No difference in the follicular count
Zhao, 2010	Rat	Antagonist	Protection through decrease of mitochondria dependant apoptosis

Efficiency of GnRH agonist to protect ovary during chemotherapy in human: non randomized studies

Study or sub-category	GnRHa (+) n/N	GnRHa (-) n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Pereyra Pacheco, 2001	12/12	0/4		2.67	225.00 [3.86, 13113.77]
Blumenfeld, 2005	70/75	38/82		15.80	16.21 [5.93, 44.32]
Dann, 2005	7/7	5/6		3.66	4.09 [0.14, 120.69]
Somers, 2005	19/20	14/20		7.01	8.14 [0.88, 75.48]
Castelo-Branco, 2007	27/30	6/26		11.33	30.00 [6.68, 134.68]
Brumenfeld, 2008	63/65	29/46		11.11	18.47 [4.00, 85.26]
Huser, 2008	57/72	13/45		17.30	9.35 [3.96, 22.10]
Nitzschke, 2009	9/10	9/10		4.66	1.00 [0.05, 18.57]
Subtotal (95% CI)	291	239		73.55	13.00 [7.37, 22.92]

Total events: 264 (GnRHa (+)), 114 (GnRHa (-))
Test for heterogeneity: Chi?= 7.61, df = 7 (P = 0.37), I?= 8.0%
Test for overall effect: Z = 8.86 (P < 0.00001)



Kim, 2010

"**Large randomized clinical studies of ovarian suppression should be performed** with fertility preservation, not just menstruation, as the outcome measure."

ASCO recommendations, JCO, 2006

"We conclude that there is **not enough evidence** at this time to resolve this issue. That is not to say that the opposite has been proven either, i.e. that GnRH agonists do not help preserve fertility but rather that the time has come for a large, well-designed, prospective randomized study with a long follow-up period."

Beck-Fruchter et al, HRU, 2008

"Finally, we are not sure if GnRH analogue treatment is "10" times more effective in reducing the risk for ovarian failure, compared with controls, and if this hazard ratio is an unbiased estimate of the true effect, and **if this estimate will be reproduced in future studies, especially well-designed and managed RCTs** that will estimate average causal effects."

Sonmezer & Oktay, the oncologist, 2008

"Given the observational evidence available to date, both proponents and opponents of GnRHa suppression agree **that a large randomized controlled trial is needed**."

Clowse et al, JWH, 2009

A PROSPECTIVE OPEN RANDOMIZED TRIAL ON THE EFFICACY OF GONADOTROPIN-RELEASING HORMONE AGONIST DEPOT –TRIPTORELIN- TO PREVENT CHEMOTHERAPY-INDUCED PREMATURE OVARIAN FAILURE FOR LYMPHOMA.

POF

Promoter: Pr .Y Englert, Hospital Erasme, Brussels

Project Responsible: Dr Demeestere

Principal investigators (coordinator):

France: Dr. P Brice (Saint Louis, Paris)

Belgium: Pr. D Bron (Bordet, Belgique)

Italy: Pr. A Fedro Peccatori (IEO, Milano)

STUDY DESIGN:

Open, prospective, randomized, multicentric study

OBJECTIVES:

Primary endpoint:

Evaluation of the efficacy of triptorelin depot plus progestin versus progestin alone to prevent POF induced by chemotherapy treatment. POF is defined as FSH level ≥40 mIU/ml.

Secondary endpoints:

- the effect on the ovarian reserve
- the impact of the interval between the triptorelin injection and the start of the chemotherapy on the efficiency to protect ovarian function.
- the compliance of the treatment.
- the adverse effects

MAIN INCLUSION CRITERIA

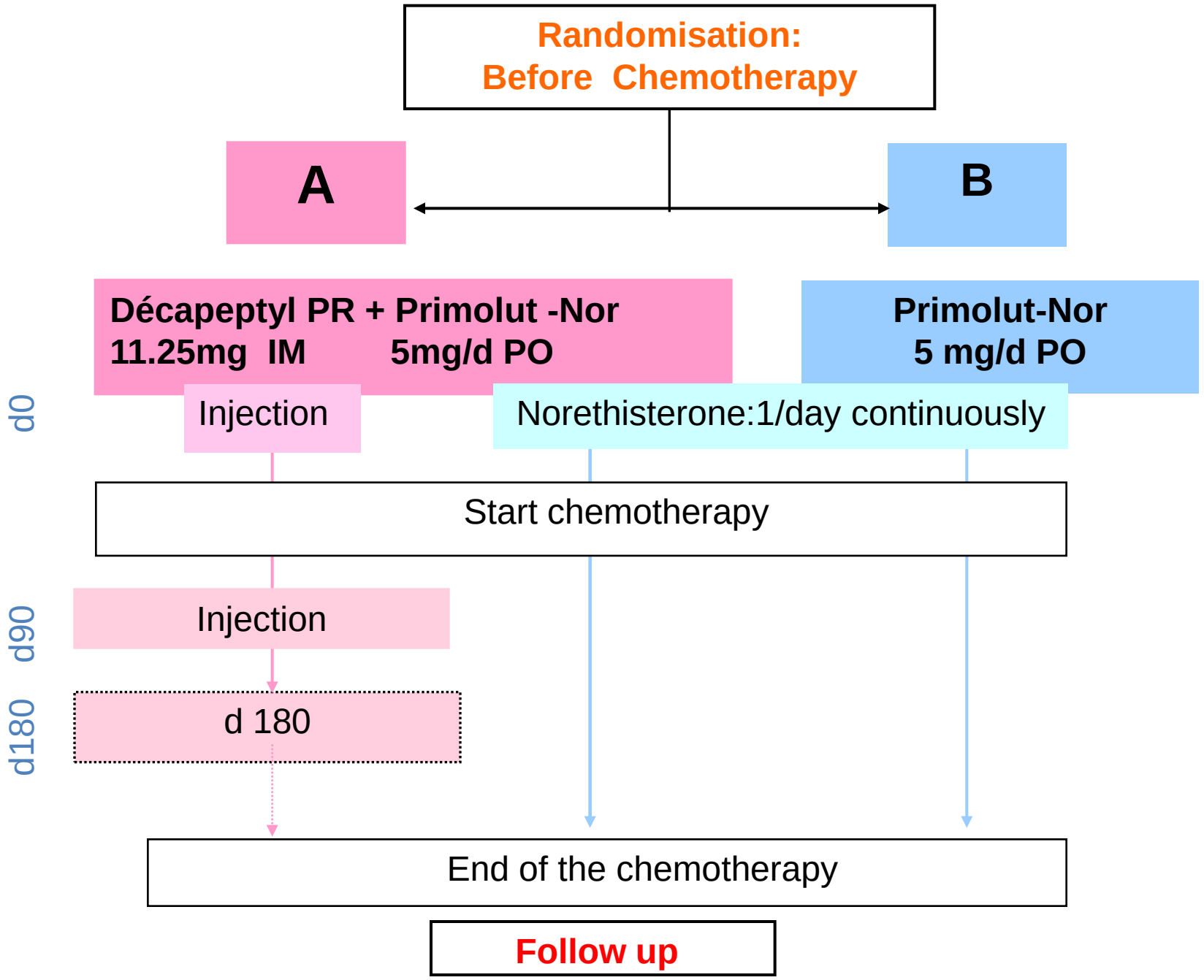
Women between 18 and 45 years old, treated by chemotherapy-induced ovarian failure including alkylant agents for lymphoma.

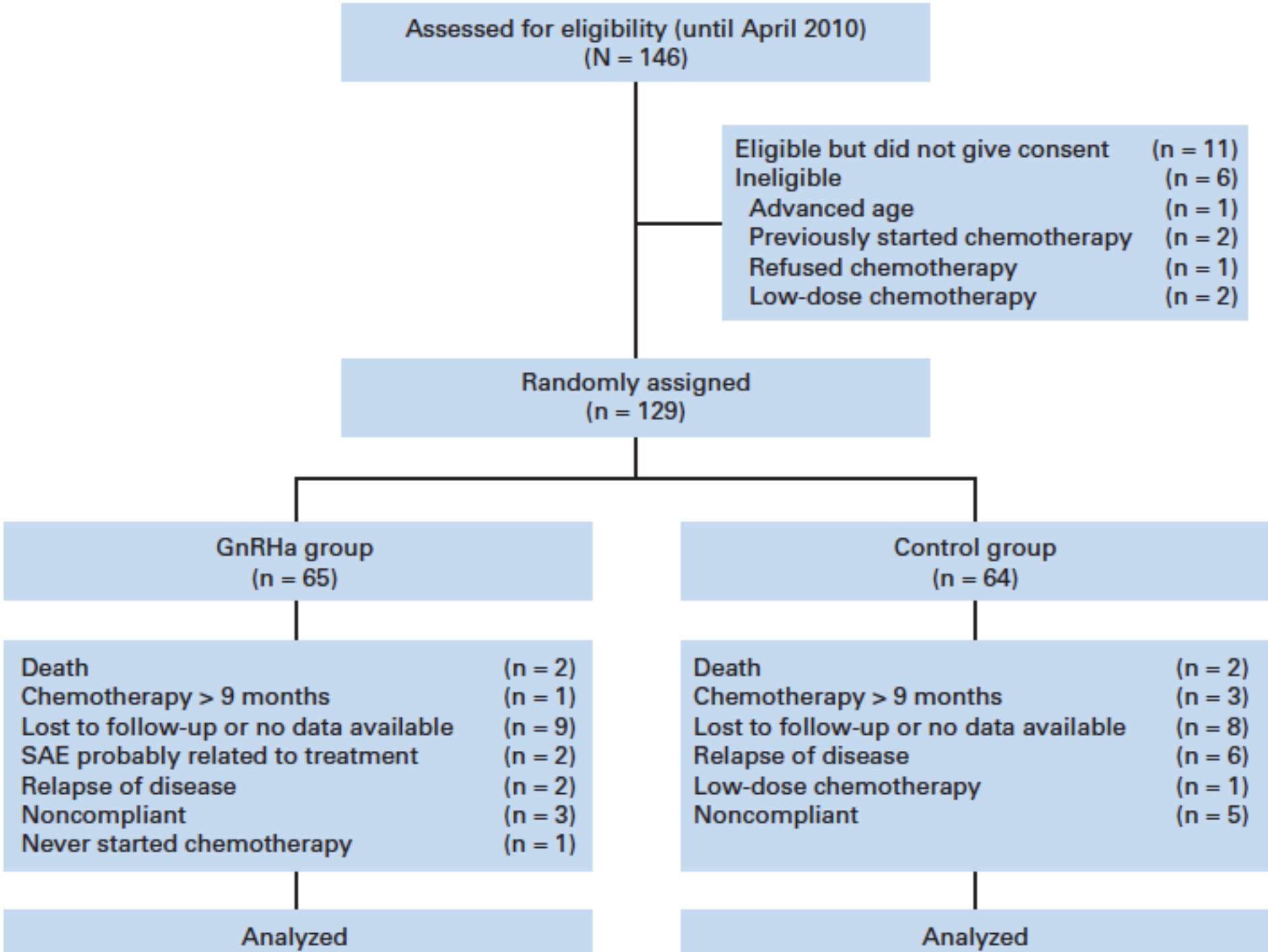
STATISTICS

Sample size: 157 patients

Calculated based on a difference of 20-25% of POF rate between groups and drop-out of 20% (power 80% and error probability of 5%).

Enrollment was discountinued after randomization of 129 patients as an interim analysis showed that the study was unliked to meet the primay endpoint.


Randomisation:
Before Chemotherapy
A
B
Décapeptyl PR + Primolut -Nor
11.25mg IM 5mg/d PO
Primolut-Nor
5 mg/d PO
d0
Injection
Norethisterone:1/day continuously
Start chemotherapy
d90
Injection
d180
d 180
End of the chemotherapy
Follow up


Assessed for eligibility (until April 2010)
(N = 146)
Eligible but did not give consent (n = 11)
Ineligible (n = 6)
Advanced age (n = 1)
Previously started chemotherapy (n = 2)
Refused chemotherapy (n = 1)
Low-dose chemotherapy (n = 2)
Randomly assigned
(n = 129)
GnRHa group
(n = 65)
Control group
(n = 64)
Death (n = 2)
Chemotherapy > 9 months (n = 1)
Lost to follow-up or no data available (n = 9)
SAE probably related to treatment (n = 2)
Relapse of disease (n = 2)
Noncompliant (n = 3)
Never started chemotherapy (n = 1)
Death (n = 2)
Chemotherapy > 9 months (n = 3)
Lost to follow-up or no data available (n = 8)
Relapse of disease (n = 6)
Low-dose chemotherapy (n = 1)
Noncompliant (n = 5)
Analyzed
Analyzed

Characteristic of the population

	GnRHa group (n=45)	Control group (n=39)
Age – yr. mean± SEM (range)	25.57± 0.81 (18-38)	27.27± 0.80 (18-38)
BMI mean± SEM	20.97 ± 0.41	21.73 ± 0.56
Race or ethnic group – no. (%)		
Caucasian	43 (95.5%)	35 (89.7%)
North African	2 (4.5%)	1 (2.6%)
Asian	0	1 (2.6%)
Others	0	1 (2.6%)
Unknown	0	1 (2.6%)
Smoking Habits – no. (%)		
No	35 (77.8%)	29 (74.3%)
Yes	8 (17.8%)	6 (15.4%)
Unknown	2 (4.5%)	4 (10.3%)
Fertility history – no. (%)		
Previous infertility	0	0
Conception	12 (26.7%)	10 (25.6%)
Live Birth	11 (24.4%)	10 (25.6%)
Abortion	3 (6.7%)	6 (15.4%)
Unknown	3 (6.7%)	0
Contraception at randomization– no. (%)		
None	18(40%)	20 (51.3%)
Oral contraceptive	24 (55.3%)	16 (41%)
IUD	1 (2.2%)	1 (2.6%)
Others	2 (4.5%)	2 (5.1%)
Diagnosis– no. (%)		
Hodgkin Lymphoma	24 (53.3%)	26 (66.7%)
Non Hodgkin Lymphoma	21 (46.7%)	13 (33.3%)
Chemotherapy regimen– no. (%)		
Conditioning regimen (BEAM)	3 (6.7%)	6 (15.4%)
ACVBP ± consolidation	9 (20%)	8 (20.5%)
(Escaladed) BEACOPP	8 (17.8%)	9 (23.1%)
(R-) CHOP or R-CHOEP	8 (17.8%)	1 (2.6%)
ABVD (≥ 8 cures)	7 (15.5%)	4 (10,2%)
CHLVVP/ABVVP	6 (13.3%)	9 (23%)
Other	4 (8.9%)	2 (5,1%)

Cumulative doses of Cy

Mean cumulative doses of alkylating agents Š no. (mg/m^2 ± SEM)		
Melphalan	3 (140±0.0)	7 (140±0.0)
Dacarbazine	10 (4590.6±920.4)	5 (3820±850.8)
Cyclophosphamide	30 (5224.8±322.7)	24 (5300±431.3)
Ifosfamide	4 (4875±718.1)	7 (5285.7±510.1)
Chlorambucil	6 (207.3±14.1)	9 (214.7±11.7)
Carmustine	3 (300±0.0)	7 (300±0.0)
Chlormethine	2 (27±9)	1 (18±0.0)
Procarbazine	12 (3398.3±493.4)	17 (3207±331)

Results: Mean FSH levels

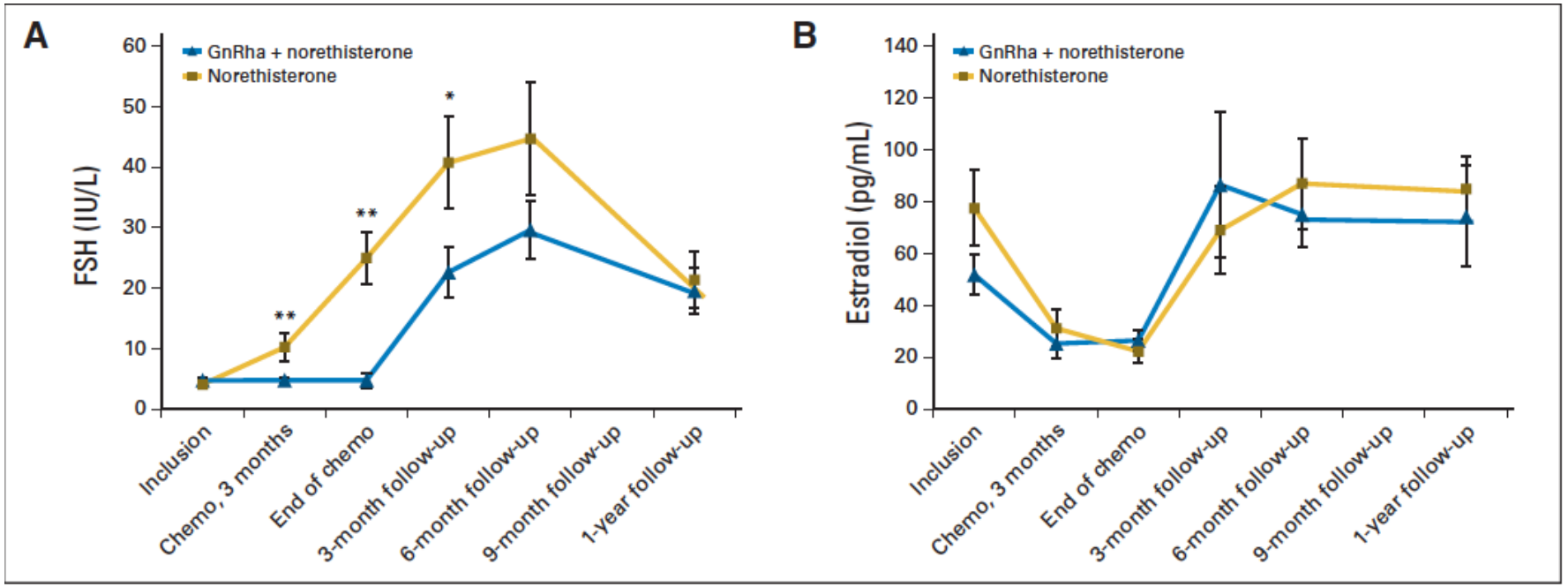
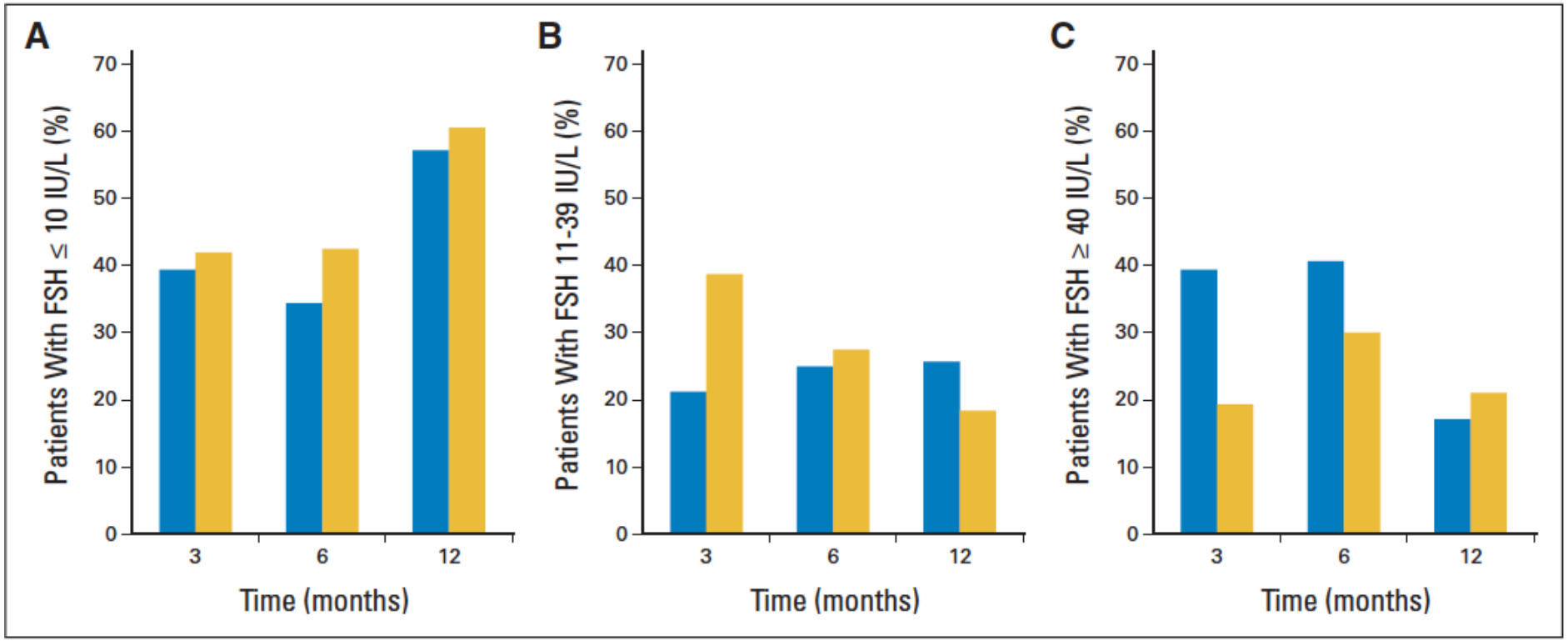


Fig 2. Ovarian function follow-up. Mean (A) follicle-stimulating hormone (FSH) and (B) estradiol values (± SEM) at the following time points: at inclusion; after 3 months of chemotherapy (chemo); at completion of chemotherapy; and at 3, 6, and 12 months of follow-up. (*) $P < .05$. (**) $P < .01$. GnRHa, gonadotropin-releasing hormone agonist.

Demeestere et al, 2012 JCO

Premature ovarian failure rate



Demeestere et al, 2012 JCO

Adverse events

Table 2. Adverse Events During Treatment

Adverse Event	GnRHa Group (n = 45) No.	GnRHa Group (n = 45) %	Control Group (n = 39) No.	Control Group (n = 39) %	*P*
Estradiol deficiency symptoms					
Sweating	21	46.6	14	35.9	.377
Hot flushes	11	24.4	12	30.7	.629
Vaginal dryness	7	15.5	5	12.8	.764
Headaches	14	31.1	16	41	.370
Vaginal bleeding	7	15.5	15	38.4	.024

Abbreviation: GnRHa, gonadotropin-releasing hormone agonist.

Efficiency of GnRH agonist to protect ovary during chemotherapy in human: randomized studies Lymphoma

	Mean age		N		FU		**Outcomes and results**
	Study	Control	Study	Control	Study	Control	
Waxman, 1987	28,5	25,9	8	10	2,3y	2y	No effect
Guisepe,2007	24,3	24,3	15	14	2,4y	5,9y	Protection (Menstruation)? No effect on ov. reserve
Behringer , 2010 (BEACOPP)	25,9	25,2	10	9 (OC)	≥1	≥1	No effect Amenorrhea Control 3/9 Treated 1/10 (1 unknown) Similar hormonal profile
Demeestere, 2012	25,6	27,2	45	39 (prog)	1	1	No effect POF rate 20% vs 19% AMH values in favor of GnRha (n=31)

Efficiency of GnRH agonist to protect ovary during chemotherapy in human: randomized studies
Breast cancer

References	Mean age		N		FU		Outcomes and results
	Study	Control	Study	Control	Study	Control	
Badawy, 2008	30	29,2	39	39	0,7	0,7	Protective effect Resumption of menses 33 vs 89% POF 11 vs 66% (mean FSH≤15mIU/ml?)
Sverrisdottir, 2009	45	45	22*	20*	3	3	Protective effect Resumption of menses 10 vs 36%
Del Mastro, 2011	39	39	148	133	1	1	Protective effect Amenorrhea 9 vs 26%
Gerber , 2011	38,5	35	30	31	≥2	≥2	No effect Resumption of menses 100% vs 100%
Munster , 2012	39	38	26	21	≥1,5	≥1,5	No effect Resumption of menses 88 vs 90% No difference in FSH level

* Patients allocated to CMF group

Is GnRHa prevent chemotherapy induced POF?

No evidence of the efficiency of GnRHa to prevent premature ovarian failure in patients treated with high doses chemotherapy for lymphoma.

The acute effect of the chemotherapy during the first 6 months is observed whatever the treatment.

AMH results may suggest a benefit of the GnRHa treatment on the ovarian reserve in young lymphoma patients but this results must be confirm by long-term follow-up.

GnRHa treatment may promote better control of amenorrhea during chemotherapy.

The protective effect of GnRHa is **questionable and controversial**.

ISFP recommendation, 2012

Conclusion

- La préservation de la fertilité est généralement justifiée chez les patientes atteintes d'affections cancérologiques mais pas dans tous les cas.
- Au vue de l'âge moyen des patientes, la cryopréservation de tissu ovarien reste le premier choix.
- Des alternatives doivent être cependant envisagées chez les patientes de plus de 30 ans.
- Pas de possibilités actuellement d'envisager une transplantation chez les patientes atteintes de leucémies.
- Pas de preuves d'un effet bénéfique des analogues GnRH au niveau du risque de défaillance ovarienne.
- Autres agents protecteurs pourraient être développés dans l'avenir (S1P, imatinib, AS101).

PINK RIBBON PROJECT 2012

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