Essais précoces pédiatriques dans les tumeurs osseuses

GSF-GETO 2016

Nathalie Gaspar

rEECur
for recurrent and refractory Ewing Sarcoma

- **Trial Design:** a seamless Multi-Arm, Multi-Stage, randomised **phase II/phase III**, open-label multicentre trial

- Sponsor: University of Birmingham
- PI : Martin McCabe, Manchester
- Financement européen : FP7 – WP2
- Protocole enregistré ISCRTN 31/03/2014
- 25 pts inclus en Dec 2015
- Ouverture en France via EORTC, en cours depuis Janvier 201
- French national coordinateur : Nathalie Gaspar, Gustave Roussy

De 4 a 50 ans

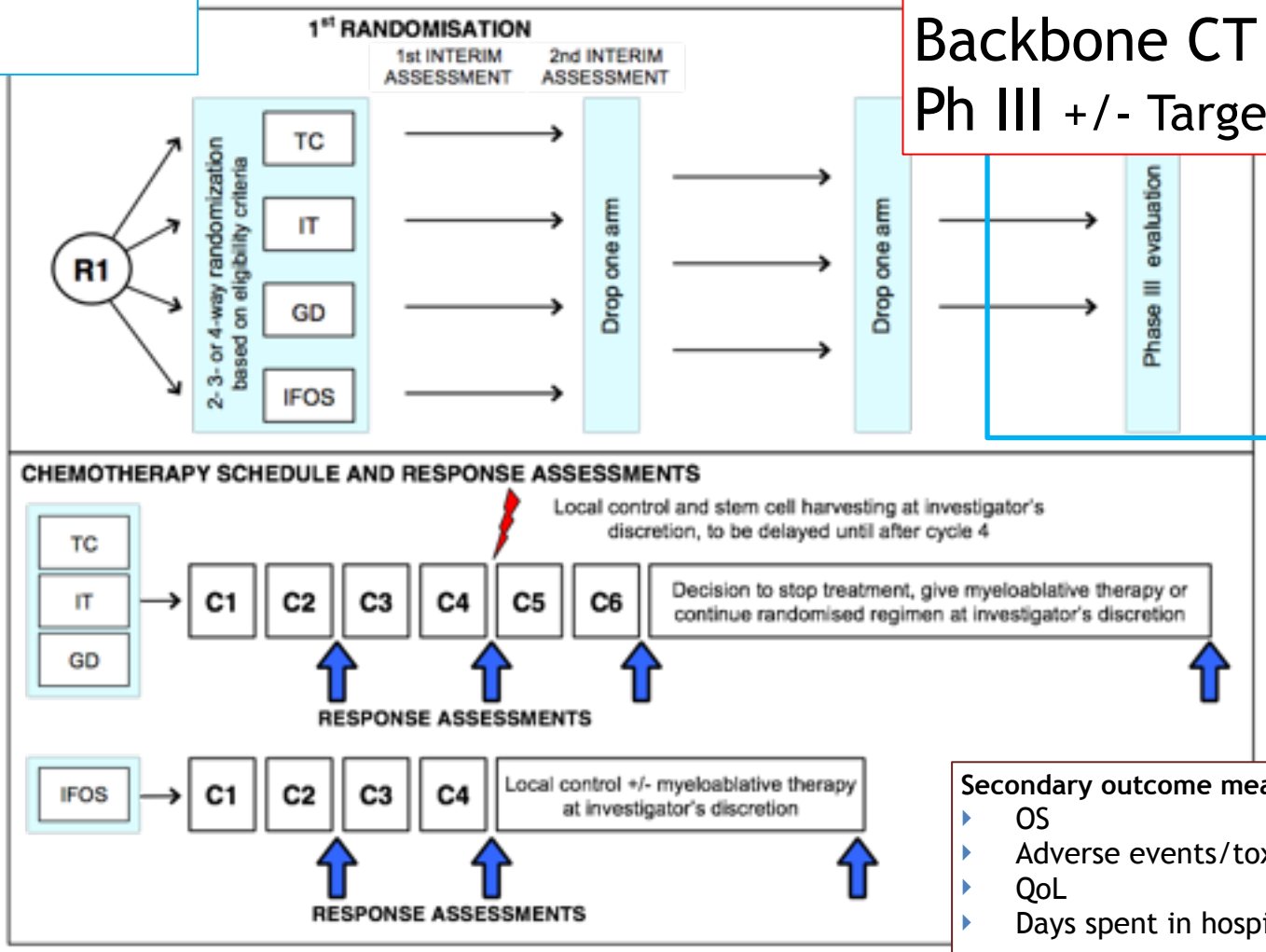
rEECur

Phase 2/3 randomisée
MAMS design
Age 4-50ans

275 patients
sur 3 ans
OR after cycle4 (RECIST)

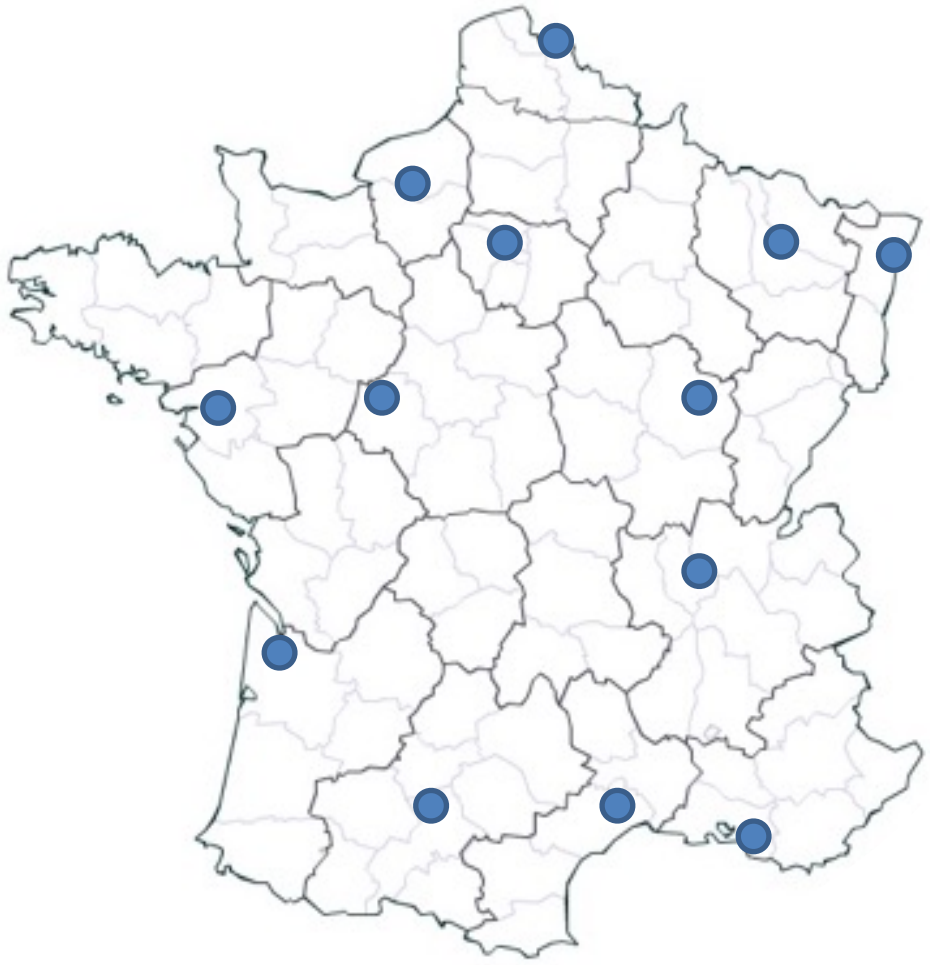
400 patients
sur 4 ans
EFS

Backbone CT
Ph III +/- Targeted thera



Secondary outcome measures
- OS
- Adverse events/toxicity
- QoL
- Days spent in hospital

10 centres ouverts / 21
6 recrutent
7 patients inclus



Institution	Initiation of recruitment
IGR Villejuif	Recruiting
Curie Paris	Recruiting
Claudius Regaud Toulouse	Recruiting
CHU de Nantes	Recruiting
Hop. Univ. de Strasbourg	Recruiting
Hopital Armand Trousseau Paris	Recruiting
C.H.U. De Toulouse	Not yet recruiting
Arnaud De Villeneuve Montpellier	Not yet recruiting
CLB Lyon	Not yet recruiting
ICL St Priest en Jarez	Not yet recruiting
Bergonie Bordeaux	Close to open
CHB Rouen	Close to open
Hôpital de La Timone Marseille	Close to open
CHU de Tours	Close to open
COL Lille	Close to open
CGFL Dijon	Close to open
IRC Montpellier	Close to open
Gauducheau - Nantes	Just contacted
CHU - Nancy-Brabois	Just contacted

nnovative Therapies for Children with Cancer

European Consortium

Innovative Therapies for Children with Cancer

ITCC

European consortium

A Phase 1/2, multicenter, open-label, dose-finding study to assess the safety, tolerability and preliminary efficacy of weekly **nab®-paclitaxel** in pediatric subjects with recurrent or refractory solid tumors.

ABRAXANE - ABI-007-PST-001 - ITCC-038

- Dose-escalation Part :
  - relapsed or refractory solid tumors, no CNS tumors
  - ≥6 months to < 18 years
- Phase 2 Part (2-stage Simon): *opening Dec 2015*
  - 3 strata: NB, RMS and other solid tumor (according to Phase 1)
  - ≥6 months to ≤ 21 years
- Abraxane iv D1, 8, and 15 of a 28 cycle
- PK Cycle 1: D1,2, 3 and 4
- Biomarker: SPARC

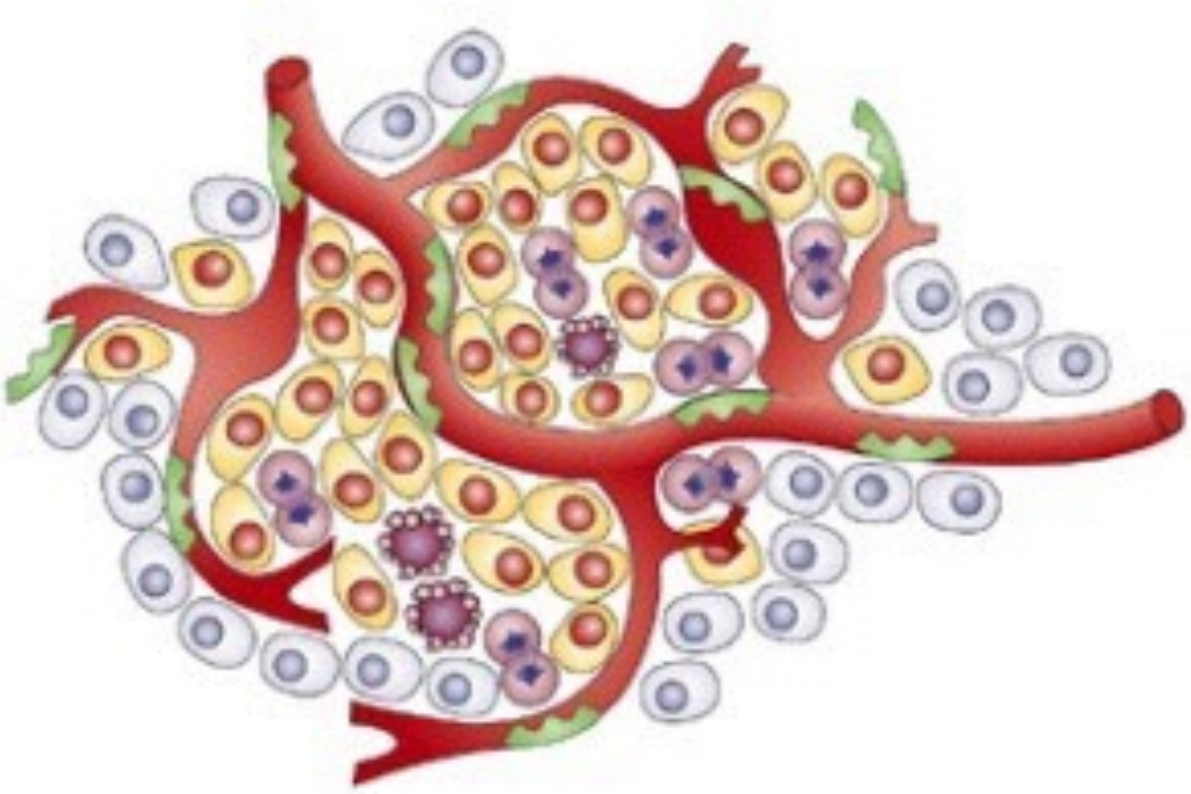
- Sponsor: Celgene; PI: G Vassal/B Geoerger
- Centers F/contact:
  - IGR: B Geoerger
  - Institut Curie: I Aerts
  - IHOP: D Frappaz
  - Nancy: P Chastagner

Phase I open label, dose escalation trial to determine the MTD, safety, PK and efficacy of AFATINIB monotherapy in with known ErbB pathway deregulation regardless of tumour histology

- Afatinib = irreversible Pan-ERB inhibitor (EGFR, HER2, ErbB3 and ErbB4)
- Solid tumors possibly ERBB-driven, Neuroectodermal tumors, RMS, others
- 2 years to<18 years
- Oral
- Dose finding (ongoing); then expansion phase
- Tox: skin, diarrhea, pulmonitis, nail abormalities

- Sponsor: Boehringer Ingelheim, PI: B. Geoerger
- Centers/contact (in France):
  - Gustave Roussy: B Geoerger
  - Institut Curie: I Aerts
  - COL: P Leblond
  - Toulouse: M Gambart
  - IHOP Lyon: D Frappaz

Angiogenesis



Phase I/IIa, Study of LENVATINIB in Children and Adolescents With Refractory or Relapsed Solid Malignancies

E7080-G00-207/ITCC-050

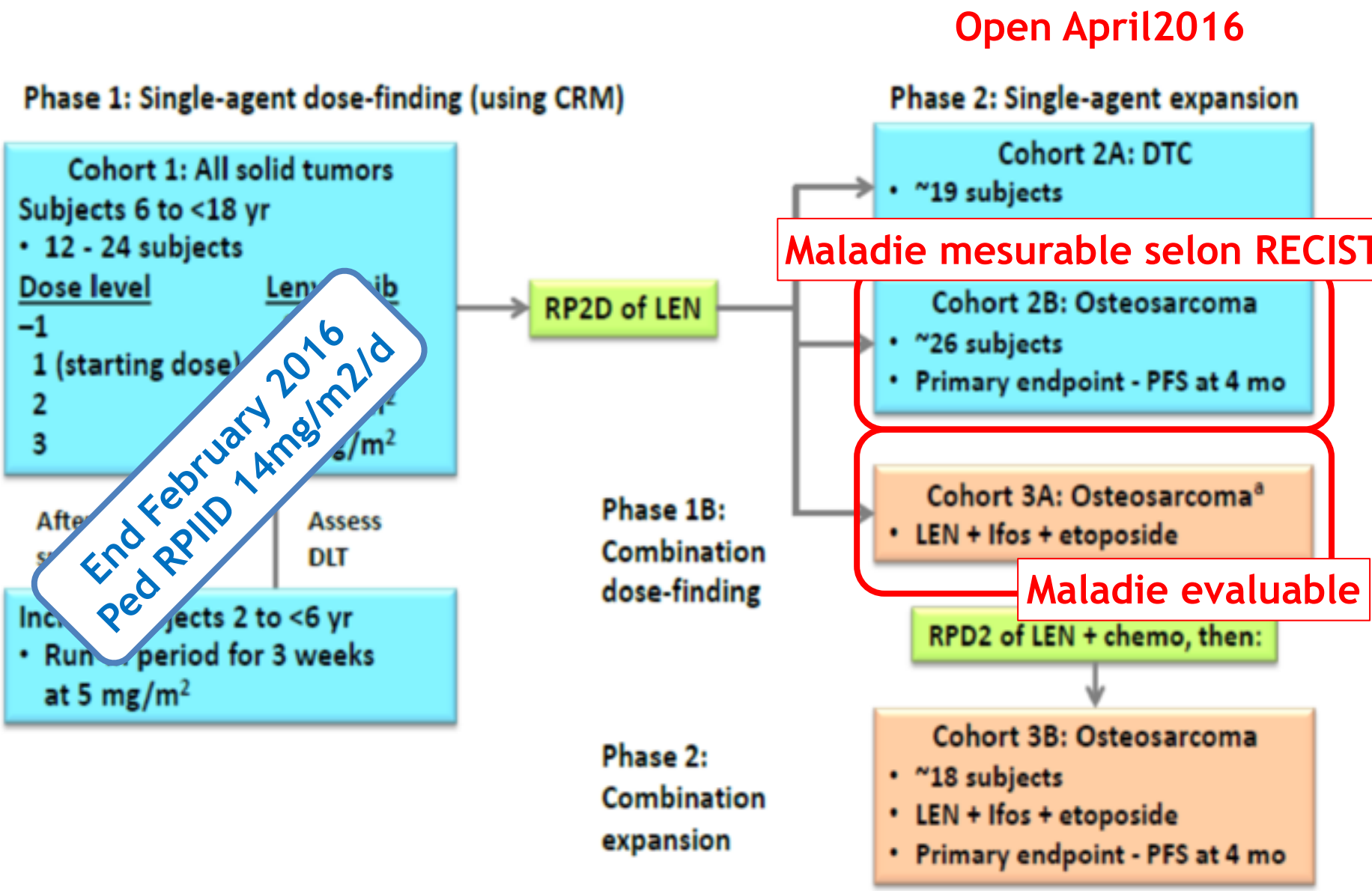
- Relapsed or refractory solid tumors
- > 2 years – < 18 years
- Lenvatinib = muti-targeting agent (RET, VEGFR1
  PDGFR-alpha, FGFR1, FGFR2, FGFR3, FG
- Cohort 1: Dose Escalation in solid tumors
- Cohort 2:
  - Cohort A: 131iodine-refrac
  - Cohort B: osteosarc
- Cohort 3:
  - Cohort A
  - C
- C
  - aspar
  - lerts

16 in osteosarcoma

- Nantes: S Dumoucel
- Toulouse: M Gambart

Fin de la phase I pédiatrique : 23 patients inclus, 2/3 en France
RPIID 14mg/m²/jours
Ouverture Phase Ib et extension « ostéosarcome » : avril 2016

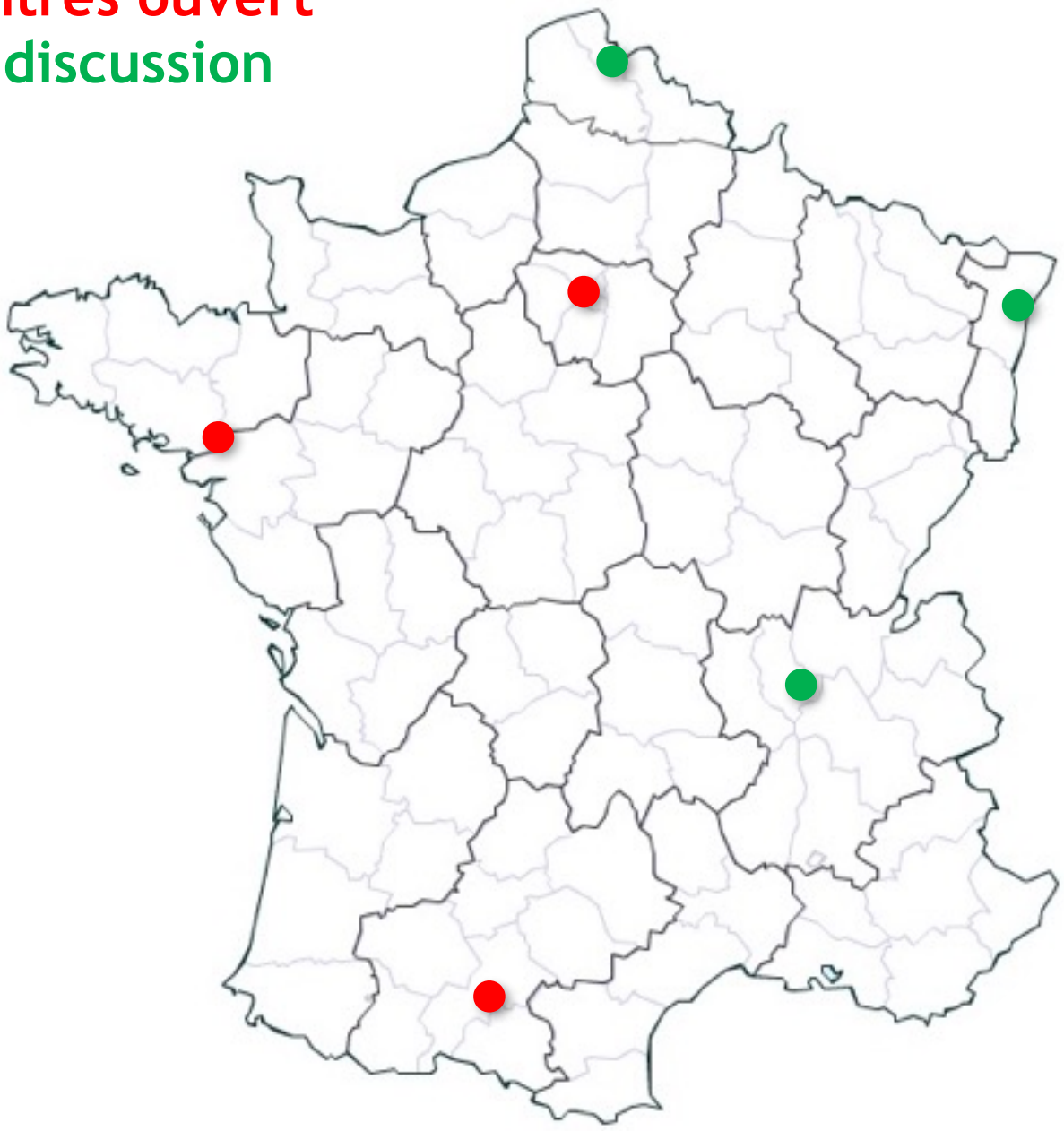
Ammendement to increase age up to 25 years in the osteosaroma cohorts



CRM= continuous reassessment method; LEN=lenvatinib; Ifos=ifosfamide.

[a] Lower levels of LEN will be explored.

4 centres ouvert
3 en discussion



UK
Spain
Italy
Allemagne ?

A Phase 1, multi-center, open-label, non-randomized, dose escalation design study of **REGORAFENIB** (BAY 73-4506) in paediatric patients from 6 months to less than 18 years with a solid malignant tumour refractory to standard therapy.

ITCC-047

- Recurrent or refractory solid tumors
- Regorafenib: muti-targeting agent (RET, VEGFR1, VEGFR2, VEGFR3 lpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BR , PTK5, and Abl)
- 1 yrs - ≤ 18 years
- Regorafenib oral D1-21 on/7 days off
- *Pending inclusion, Expansion phase opening in*

Fermée

- Sponsor: Bayer; PI: B. Geoerger
- Centers/contacts: 5 centers in F, UK
  - IGR: B Geoerger
  - I Curie: I Aerts
  - IHOP: D Frappaz

PROTOCOLE REGOBONE

SARCOME 12-UC-0150/1309

ETUDE DE PHASE II MULTICENTRIQUE, RANDO
CONTRE PLACEBO, ÉVALUANT L'EFFICACIT
TOLÉRANCE DU REGORAFENIB CHEZ DES PA NT
UN SARCOME DES OS MÉTASTAT

Discussion pour baisser l'âge d'inclusion à 10 ans avec une SC ≥ 1.3 m^2

Médecin coordonnateur :

- Pr Florence DUFFAUD La Timone, MARSEILLE

Statisticien :

- Dr Sylvie Chabaud, Centre Léon Bérard

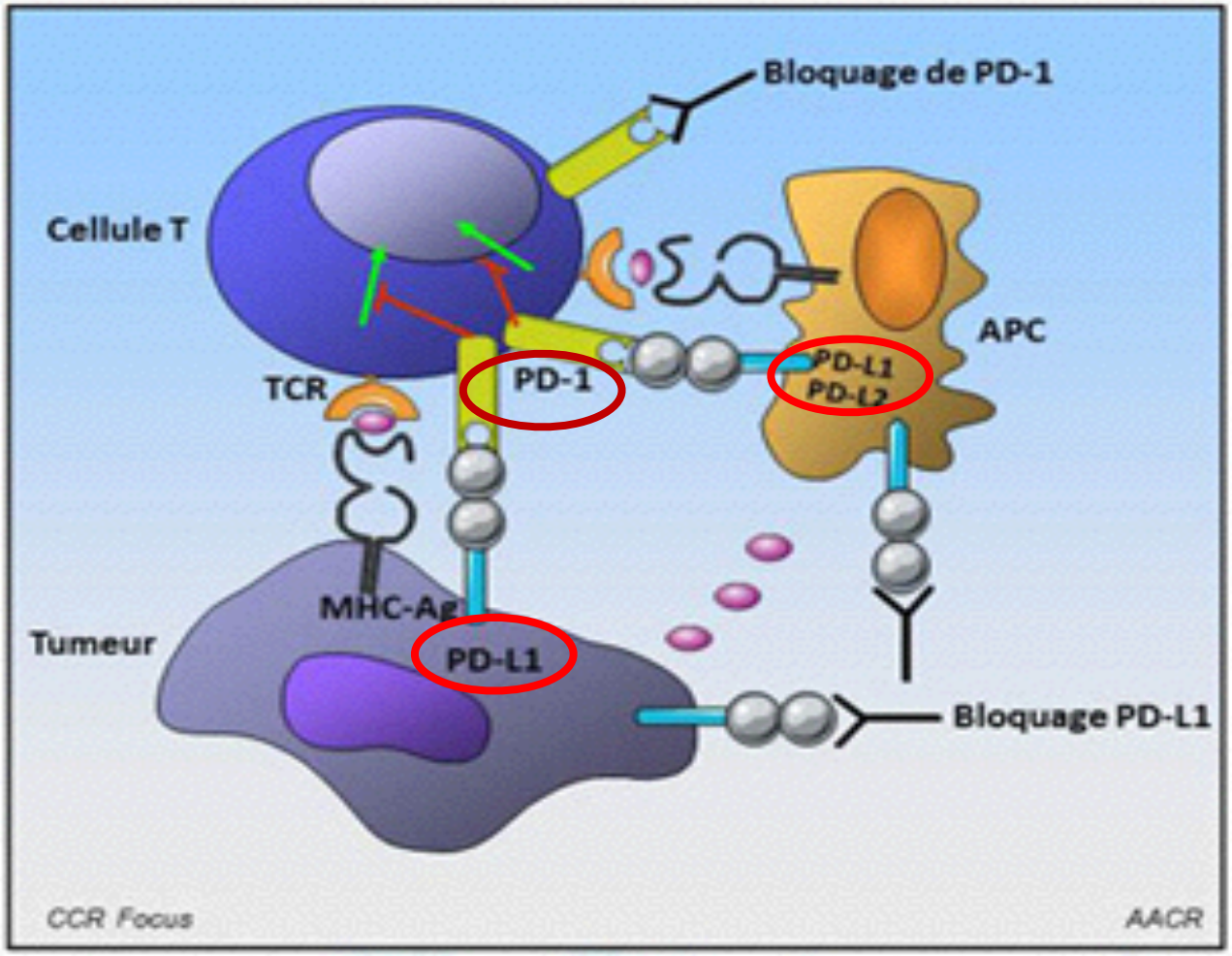
A Phase II Study of CABOZANTINIB in Treating Patients with Relapsed Osteosarcomas and Ewing Sarcomas

CABONE

- Cabozantinib = oral multi-tyrosine kinase inhibitor: VEGFR2, c-MET, RET, AXL, KIT, TIE-2
- **Metastatic bone sarcoma**
  - Osteosarcoma
  - Ewing sarcoma
- ≥ 12 years

- Sponsor: Institut Bergonie Bordeaux ; PI: A Italiano
- Centers/contact:
  - Marseille: F Duffaud
  - GR: S Dumont
  - I Curie: S Piperno-Neumann
  - Dijon: N Isambert
  - Toulouse: C Chevreau
  - Nantes: E. Bompas
  - Lille: P Nicolas
  - CLB Lyon: JY Blay

Anti-tumour immunity



Cross-Tumoral Phase II Clinical Trial Exploring Crizotinib (PF-02341066) in Patients with Advanced Tumors Induced by Causal Alterations of either ALK or MET

EORTC 90101 (CREATE)

- 6 Strata:
  - Anaplastic large cell lymphoma: ALCL; ALK alterations
  - Alveolar rhabdomyosarcoma: ARMS; MET and ALK alterations
  - Inflammatory myofibroblastic tumor: IMFT; ALK alterations
  - Alveolar soft part sarcoma: ASPS; MET alterations
- > 15 years (amendment upcoming for <15)
- Tumor material mandatory
- Biology-driven design and exploration

- Sponsor: EORTC; PI: P Schoeffski
- Centers F/Contacts:
  - IGR: B Geoerger
  - CLB: JY Blay
  - CGF Leclerc Dijon: I Nicolas
  - I Bergonie Bordeaux: N Houede-Tschen
  - La Timone Marseille: F Duffaut

A Study of PEMBROLIZUMAB (MK-3475) in Pediatric Participants With Advanced Melanoma or Advanced, Relapsed, or Refractory PD-L1-Positive Solid Tumors or Lymphoma - KEYNOTE-051

- Pembrolizumab = anti PD1 antibody
- PD-L1 positive solid tumors, CNS except DIPG
- Pre-screening mandatory at MSD: PD-L1 IHC (except Melanoma)
- Phase 1 dosevalidation; then phase 2
- 6 months to 17 years
- Measurable disease
- IV q 3 weeks

- Sponsor: MSD;
- Centers/contacts: 1 in F, + 1 UK
  - Gustave Roussy: B Ge

~~Phase 1 pédiatrique terminée~~
Ré-ouvert pour ostéo et Ewing mais ssi tumeur PDL1+

MERCK
Be well

An Early-Phase, Multicenter, Open-Label Study of the Safety and Pharmacokinetics of Anti−PD-L1 Antibody (MPDL3280A) in Pediatric and Young Adult Patients with Previously Treated Solid Tumors

ATEZOLIZUMAB - GO29664 / ITCC-058

- Atezolizumab = Anti-PD-1L antibody
- NB, RMS, STS, Osteosarcoma, Ewing, Wilms, HDL and NHL; other solid tumors (no CNS) with PD-L1+ or approval of Roche
- Up to 30 years
- Available tumor sample or biopsy
- Measurable disease
- IV q 3 weeks

- Sponsor: Roche Genentech, PI: B
- Centers/contact:
  - Gustave Roussy: B
  - Institut Curie: J
  - IHOP Lyon

Cohortes « Ostéosarcome » et « Sarcome d'Ewing » fermée

Roche

Innovative Therapies for Children with Cancer
ITCC
European Consortium

ITCC European Precision Medicine in Pediatric Oncology and Hematology – Early 2015

Children and adolescents with refractory or recurrent tumors or leukemia

MAPPYACTS in F, SP, I, Ir, Is
D: INFORM
NL: iTHER
UK: COMET

Signed informed consent

BIOPSY/ Surgery

Bioinformatics

Molecular analysis:
- WES
- RNAseq (RT-PCR confirmatory)
- IHC, FISH (confirmatory)

Exploratory:
- Methylation array
- miRNA
- Immunmarker/modulators

INCa-NGS Platforms: IGR, IC

Data interpretation & Therapy suggestion

Multidisciplinary Therapeutic Molecular Tumor Board (with signed report from biologists)

Clinical Relapse Tumor Board (RCPPI)

Clinical Trials

If actionable targets:

Ongoing targeted Phase I/II trials

Registered targeted agents in pediatric/adult cancer with pediatric dose recommendation:

ESMART prospective PoC trial:
IST multi-agent from pluri-company
European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors in children

Matrix Trial
Genentech Roche

If no actionable targets:

Ongoing non-targeted Phase I/II trials

institutCurie GUSTAVE ROUSSY ITCC

MAPPYACTS A multicentric, prospective proof-of-concept study MoleculAr Profiling for Pediatric and Young Adult Cancer Treatment Stratification NCT02613962

Recruitment period	December 2015 during 3 years
Patient population	~ 300 children and adolescents with solid tumors and leukemia
Main objective	To screen the maximum of relapsed or refractory pediatric patients to provide them with their individual molecular tumor profile and treat them with matched innovative targeted agents
Secondary objectives	OR, TTP, OS, detection of new targets, percentage of therapy suggestions, etc.
Primary Molecular Analysis	WES and RNA Seq
Secondary Molecular Analyses	Methylation array, miRNA expression "The Immune Contexture of Pediatric Cancers"
Ancillary Studies	Circulating DNA, Preclinical models and patient-derived xenografts

e★smart
European proof of concept therapeutic stratification trial of molecular anomalies in relapsed or refractory tumors in children

Basket trial to cover the targeting of several survival pathways in oncogenesis that are currently not adequately adressed in Children, adolescents and young adults with refractory or recurrent malignancies

ARM	Treatment	Pharma Partner	Investigator
Coordinating investigator			**Birgit Geoerger**
Trial statistician			**Xavier Paoletti**
Arm A – CDK4/6 inh	Ribociclib + TOTEM	Novartis	Francisco Bautista
Arm B – CDK4/6 inh	Ribociclib + Everolimus	Novartis	Francisco Bautista
Arm C – Wee1 inh	AZD1775 + Carboplatin	AZD	Francisco Bautista
Arm D – PARP inh	Olaparib + Irinotecan	AZD	Susanne Gatz
Arm E – TORC1/2 inh	AZD2014	AZD	Lynley Marshall
Arm F – TORC1/2 inh	AZD2014 + TOTEM	AZD	Lynley Marshall
Arm G – Ac anti-PD1	Nivolumab + Cyclophosphamide+/-RT	BMS	Claudia Pasqualini
…			

Writing Committee and Treatment arms

CDDF - ITCC - SIOPE 4th Paediatric Oncology Conference

ACCELERATING THE DEVELOPMENT OF NEW ONCOLOGY DRUGS FOR CHILDREN AND ADOLESCENTS

20-21 January 2016
Brussels, Belgium

TYA cancer New drug access

- EMA/PDCO
- Pharma compagnies
- Paed/Adult drug developers
- TYAC groups
- Paed/ad Pathology societies
- Patients /carrers

ACCELERATE platform

SIOPE/ESMO

ITCC

ENTYAC

COMBINAIR 3
Ewing très haut risque métastases extra-pulmonaires
2-50 ans

N. CORRADINI, pédiatre, IHOPE, Lyon; V. LAURENCE, oncologue médicale, Curie

Etude de phase II multicentrique non randomisée non comparative

Objectif primaire

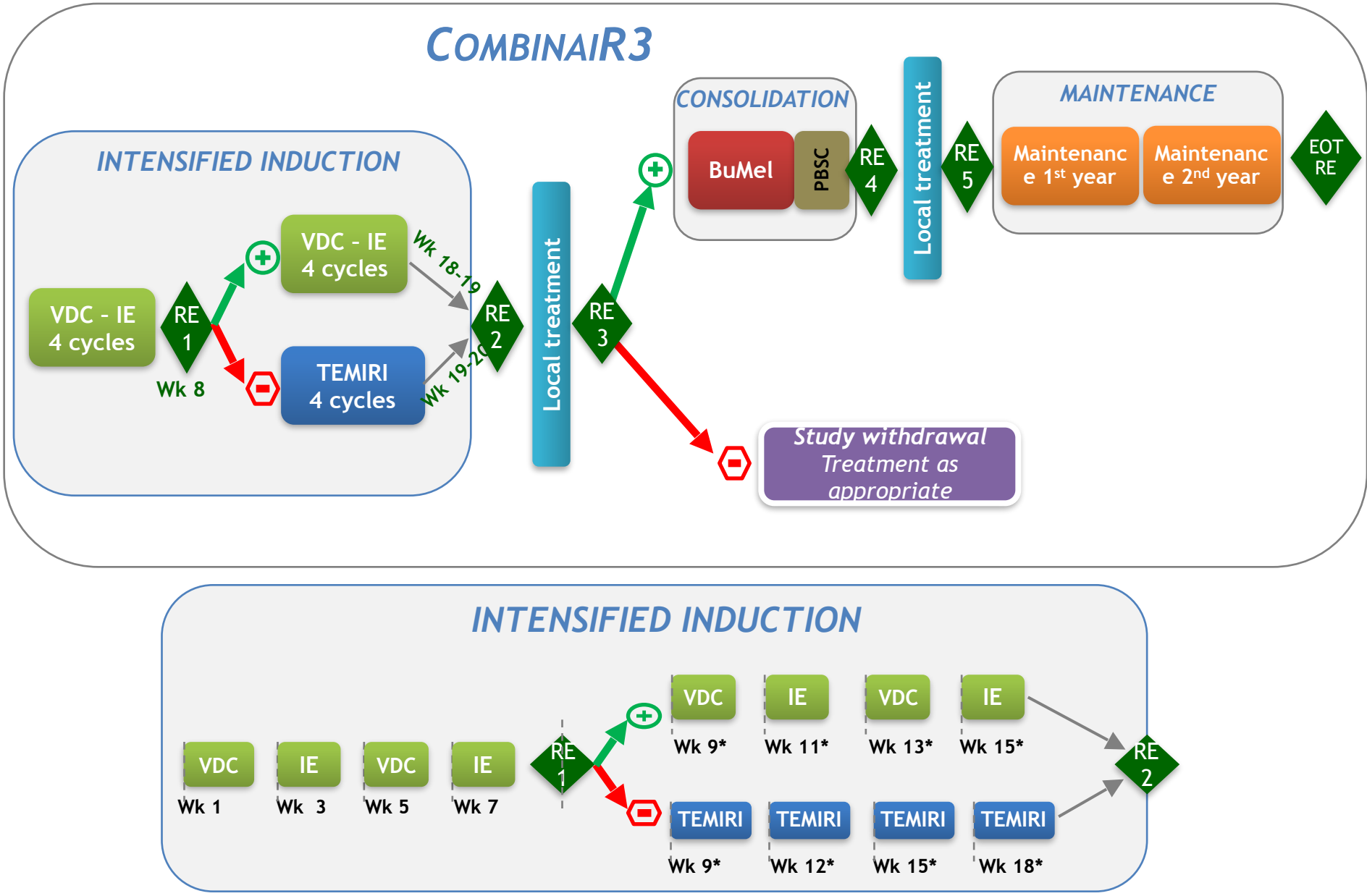
- effet antitumoral de cette stratégie évalué par EFS à 18 mois

Objectif secondaire

- taux de réponse
- nombre de patients éligibles pour Bu Mel
- 3 years outcome : 3 years EFS à 3 ans et SG à 3 ans
- profil de tolérance

Études ancillaires :

- évaluer les maladies résiduelles sanguines et médullaires.
- comparer les profils transcriptomiques entre maladie primitive et métastases ostéo-médullaires.


COMBINAIR3
INTENSIFIED INDUCTION
VDC - IE
4 cycles
RE
1
Wk 8
VDC - IE
4 cycles
Wk 18-19
TEMIRI
4 cycles
Wk 19-20
RE
2
Local treatment
RE
3
CONSOLIDATION
BuMel
PBSC
RE
4
Local treatment
RE
5
MAINTENANCE
Maintenanc
e 1st year
Maintenanc
e 2nd year
EOT
RE
Study withdrawal
Treatment as
appropriate

INTENSIFIED INDUCTION
VDC
Wk 1
IE
Wk 3
VDC
Wk 5
IE
Wk 7
RE
1
VDC
Wk 9*
IE
Wk 11*
VDC
Wk 13*
IE
Wk 15*
TEMIRI
Wk 9*
TEMIRI
Wk 12*
TEMIRI
Wk 15*
TEMIRI
Wk 18*
RE
2

Pouvoir ajouter nouvelle drogue dès que possible à ce schéma « standard »

Calendrier

Soumission ANSM mai 2016

Ouverture centres 4eme trimestre 2016

Financement

AO Enfants et Santé (SFCE)

Fonds privés

Sarcome 13

Phase 2 randomisée
d'association du MEPACT
à la chimiothérapie post-opératoire
dans les ostéosarcomes de haut risque (métastatiques ou localisés avec une mauvaise réponse histologique)

PI: Nathalie GASPAR, Sophie Piperno-Newman
Statisticien : Marie-Cécile Le Deley
Sponsor : UNICANCER

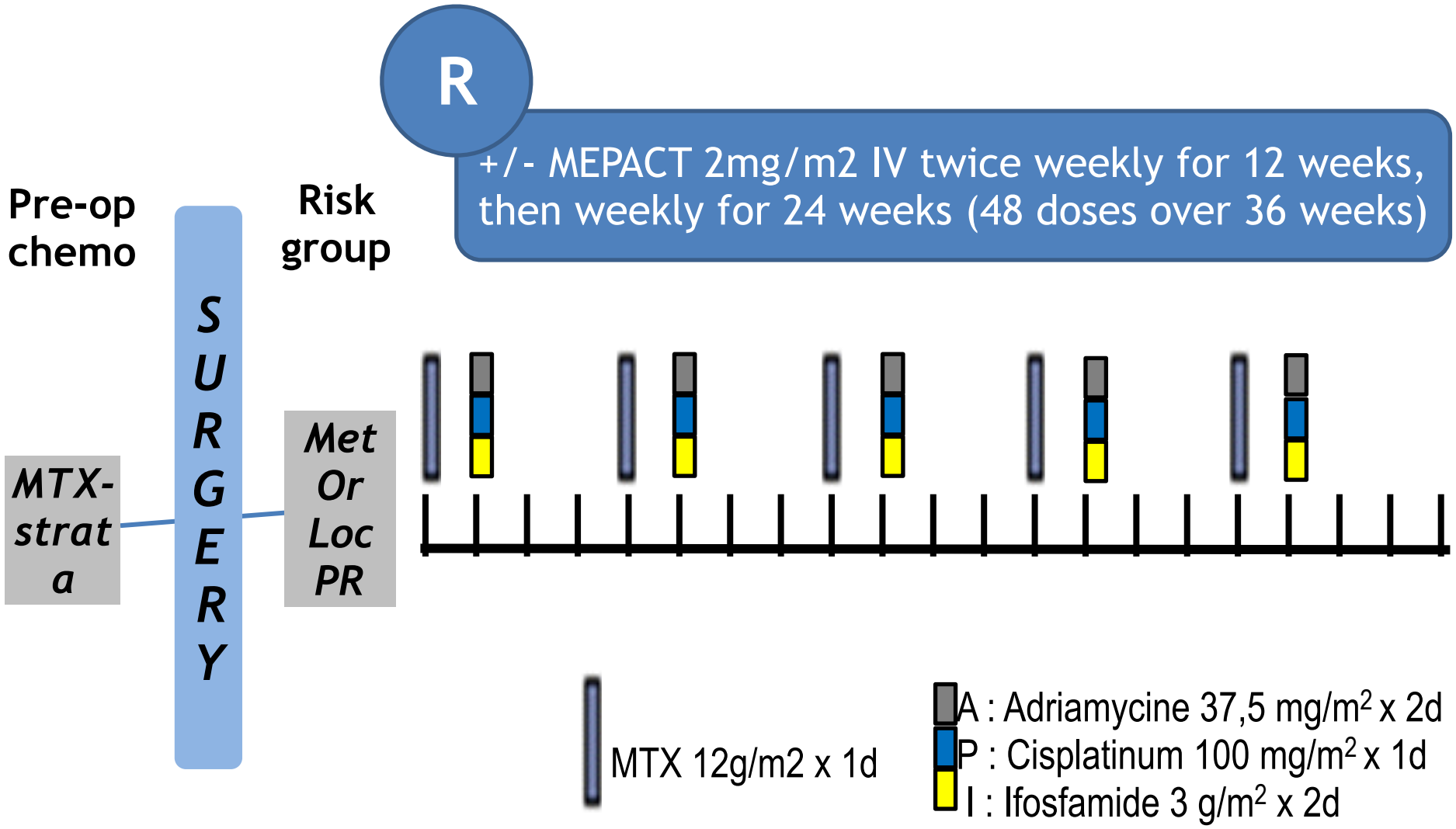
PHRC 2016 : Acceptation de la lettre d'intension

Sarcome 13

- A randomised phase 2 trial
  - Testing the efficacy of L-MTP-PE in high risk patients either poor histological response to chemotherapy and metastatic disease
  - All chemotherapy regimen containing ifosfamide, the potential ifosfamide/L-MTP-PE interaction, if it exists, would not be an issue
  - A realistic statistical approach with a small size trial in a reasonable timeframe and patient number calculation based on the number of patients that can be expected
- Main goal
  - This trial will produce new independent data
  - The analysis of these data combined with results from previous phase III trials and on the ongoing Italian trial may increase the level of evidence of L-MTP-PE efficacy

Accrual over a 3-year period

Sarcome 13



2 years Follow-up

Objectives

- Primary
  - To estimate the impact on the 3y-EFS of the addition of MEPACT during 36 weeks to first-line post-operative chemotherapy in patients < 40 years with high risk osteosarcoma (metastatic and/or with poor histological response)

- Secondary
  - To evaluate the impact on OS
  - To evaluate the feasibility of Mifamurtide administration
  - To evaluate the safety of Mifamurtide administration
  - To evaluate Mifamurtide effect on anti-tumor immunity in patients with sequential surgery of lung metastases.
  - To evaluate through an associated translational research program, Surrogate markers of Mifamurtide pharmacological efficacy, Predictive factors of efficacy and/or toxicity of Mifamurtide

End points

- Primary
  - Event-free survival estimated from the randomization date to the time of first event (loco-regional or distant relapse or progression, second malignancy, death) or to the last follow-up visit for the patients in first complete remission

- Secondary
  - Overall survival
  - Feasibility of the planned treatment with calculation of cumulative dose and dose intensity of MEPACT and chemotherapy
  - Short and long term toxicity
  - Quality of life
  - Mifamurtide Mechanism understanding benefits
    - Surrogate markers of pharmacological efficacy
    - Predictive efficacy factors and/or toxicity of Mifamurtide

Inclusion criteria

1. Patient with a histologically proven osteosarcoma
2. Primary tumor resected after pre-operative chemotherapy
3. Osteosarcoma classified as high risk because of at least one risk factor:
   - a poor histologic response (>10% viable tumor cells on the analysis of the primary tumor surgical specimen)
   - and/or presence of resectable metastases at diagnosis
4. Pre-operative chemotherapy combining Methotrexate-Etoposide-Ifosfamide (as in OS2006 protocol)
5. Age ≤ 40 years
6. No medical condition precluding treatment with protocol chemotherapy
7. Written informed consent
8. Patient fit to undergo protocol treatment and follow-up
9. Affiliation to a social insurance regimen

Exclusion criteria

1. Osteosarcoma with multiple metastases for whom complete removal is expected not to be feasible even after shrinkage with chemotherapy
2. Progressive osteosarcoma disease at any sites under initial chemotherapy, confirmed before randomisation time
3. Any medical condition precluding treatment with protocol chemotherapy
   - FR < 28% or EF< 50% before treatment
   - Glomerular filtration rate < 70ml/mn/1.73m^2
   - Serum bilirubin >2ULN
4. Patients for whom the follow-up will not be possible
5. Pregnancy or breast-feeding
6. Hypersensitivity to the active substance or to any of the excipients
7. Concurrent use of immunodrepressive treatment such as ciclosporine, tacrolimus or other calcineurin inhibitors
8. Concurrent use with high-dose non-steroidal anti-inflammatory drugs (NSAIDs, cyclooxygenase inhibitors)
9. Inflammatory or auto-immune disease, allergy or asthma requiring a chronic use of steroid treatment that cannot be stopped

Study design

Randomized phase II first-line trial, in high-risk newly diagnosed osteosarcomas (poor histologic response and/or metastatic status)

No interim analysis of efficacy planned.

Final analysis will be:

- performed as soon as 34 events have been observed, or 105 pts accrued
- based on all included patients (Intention-to-treat analysis)
- stratified on the following risk group:
  - Localized disease and poor histologic response
  - Metastatic disease and good histologic response
  - Metastatic disease and poor histologic response

  Heterogeneity of Mifarmutide effect by this stratification factor will be evaluated using heterogeneity tests and forest plots.

The usual hypothesis-driven approach based on trial data only will be completed with a Bayesian analysis combining information from previous trials in terms of Mifarmutide relative treatment effect (INT-033-trial publications: Meyers-2008, Chou-2009).

Sensitivity analyses will be performed considering several prior distributions for the treatment effect (Spiegelhalter-2004), including a more enthusiastic (that could be derived from the observed treatment effect in the Ifosfamide strata in Meyers2005), a sceptical and a non-informative priors.

Patient number calculation

Total=105 patients in 3 years (pragmatic considerations)

Based on observed HR pts in OS2006, 35 pts per year in France, with a baseline 40% 3y-EFS

105 patients would lead to approximately 51 events at the end of study (2 years of FUP of the last pt)

"Classical analysis"

- With a one-sided logrank test alpha=10%
- The comparison power is 80%
- If Mifarmutide is associated with a 20%-improvement of the 3y-EFS (40% versus 60%, equivalent to a HR=0.55 assuming a piecewise proportional hazards)

Bayesian analysis

- With the pre-specified decision rule, that is trial successful if Pr(HR<1)>90%,
- the 'power' is increased to 90 % if the true treatment effect is HR=0.55.
- If Mifarmutide effect is smaller than 0.55, the benefit associated with the Bayesian analysis is even greater.

Scenario regarding the true treatment effect	Power of the trial with standard frequentist approach with one-sided-alpha=0.10	'Power' of the trial with the proposed Bayesian approach
HR=0.55 (optimistic scenario)	80%	90%
HR=0.79 (historical data)	35%	83%
HR=0.89 (pessimistic scenario)	20%	71%

European paediatric Soft tissue sarcoma Study Group

Etudes STM pédiatriques en cours

European paediatric Soft tissue sarcoma Study Group

14th Report for the EpSSG RMS 2005

Co-ordinating Group meeting

Amsterdam, 9th - 11th December 2015

Coordinateur national : C Bergeron

Table 6: Enrolled patients by country

COUNTRY	PATIENTS ENROLLED	
	#	%
France	405§	26.5
UK & EIRE	364	23.8
Italy	306	20.0
Spain	119	7.8
The Netherlands	82	5.4
Belgium	72	4.7
Israel	62	4.1
Czech Rep.	39§	2.5
Brazil	35	2.3
Norway	18	1.2
Argentina	8	0.5
Slovakia	7	0.5
Slovenia	7	0.5
Switzerland	4	0.3
Total	**1528**	**100.0**

§= 1 patient with pleomorphic RMS

ELIGIBLE FOR REGISTRATION

A pathologically proven diagnosis of RMS
Age < 21 years
Previously untreated except initial surgery
No pre-existing illness preventing treatment
No previous malignant tumours

Diagnosed ≤ 8 weeks
Pathology available for central review
Available for follow up
Written consent for treatment available

YES → NO → Registration only

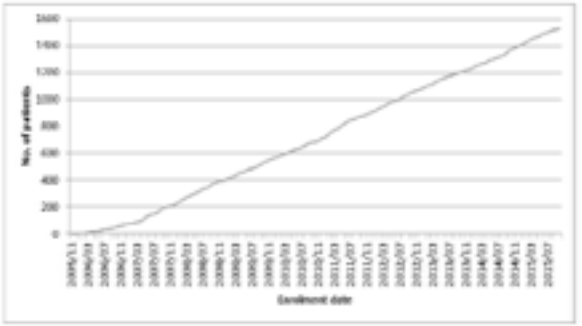
Evidence of Distant Metastases

NO → YES → *Treat in EpSSG Stage IV Study*

ELIGIBLE FOR RMS 2005 PROTOCOL

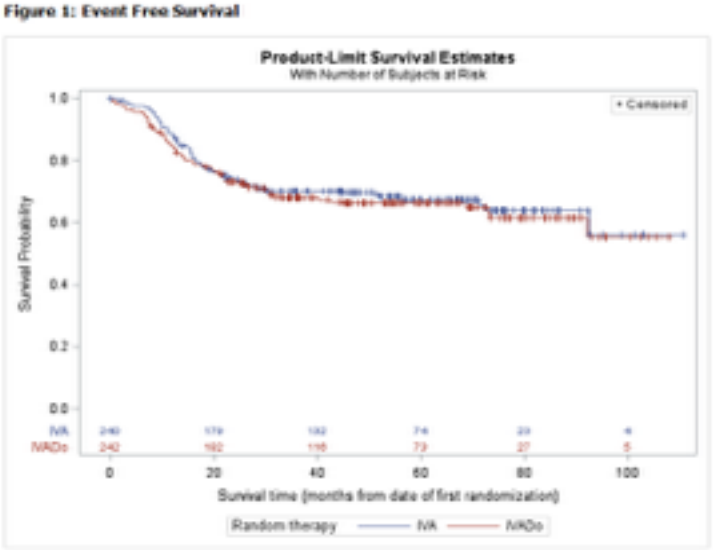
Low Risk Group	Standard Risk Group	High Risk Group	Very High Risk Group
Subgroup A: ♦ VA xB	*Subgroup B:* ♦ IVA + VA *Subgroup C:* ♦ IVA ±VA *Subgroup D:* ♦ IVA	*Subgroup E* *Subgroup F* *Subgroup G* if -Age > 6 months -Informed consent given **Randomised trial No.1** *(IVA vs. IVADo)* if -In CR or with minimal anomalies at the end of treatment **Randomised trial No.2** (stop treatment vs. maintenance)	**Subgroup H** ♦ **IVADo + maintenance**

Figure 5: Cumulative frequencies by month of enrollment[1]



[1] = the month the eligibility form was sent

European paediatric Soft tissue sarcoma Study Group



RMS 2005 -

Groupe HR :

IP national :
V Minard-Colin

- 1ère RDZ **fermée** :
  - 5 Y-EFS **67,5% IVA** vs. **66,2% IVaDo**
  - 3 Y-OS **81%** vs **78%**
- **2nde RDZ** en cours jusqu'en décembre 2016 : 355 pts (/370).

  R2 si RC après 9 IVA : STOP **vs** Navelbine-Endoxan 6 mois.

RMS 2005 -

Groupe THR : 4 IVADo + 5 IVA + Nvb-Edx 6 mois.

MTS 08 : 4 IVADo + 5 IVA + Nvb-Edx 12 mois.

RMS 2005 - Mémo :

- **Inclusion** dans l'étude **<21ans**
- **Enregistrement** des **adultes** avec RMS **<25ans**
- Penser à la **double lecture anapath** (81.6% de concordance entre le diagnostic pathologique local et la revue nationale)
- Déclarer les **rechutes** en tant réel **<48h** via la base Cineca, surtout si dans le groupe randomisé

European paediatric Soft tissue sarcoma Study Group

RMS2005 - Décisions EpSSG :

- Faire pour tous les **aRMS** une **recherche de transcrit**
- Faire les **examens protocolaires** ++

  RMS membres et Para-Testis >10 ans et >5 cm :

  examen morphologique + PET

  +/- si examens douteux ou négatifs : **exploration ganglionnaire chirurgicale** (RPLND…)

- Ne **pas changer** de chimiothérapie pendant l'induction

  (uniquement si MP ou difficulté pour ttt local conservateur)

- Si **RMS orbitaire** : ne plus omettre la radiothérapie

  en cas de RC à l'IRM

European paediatric Soft tissue sarcoma Study Group

RMS
réfractaire/rechute

- **Phase II VIT** (AS Defachelles):
  - étude conjointe EpSSG-ITCC : **VI +/- Temozo**
  - amendement pour élargir le nombre de patients présentant un **RMS en rechute** : 30 patients suppl. à inclure
  - **accord** VHP et ANSM début janvier 2016
  - **réouverture** des centres anglais depuis mai 2016
    (1 nouveau patient inclus le 16/06)
  - **attente accord CPP** pour réouverture en France :
    accord attendu pour **mi-juillet 2016**
  - important pour **RMS FaR ++**

NRSTS 2005
PROTOCOL

"first objective of the study is to make uniform the treatment of NRSTS patients in Europe"

Coordinateur national : D Orbach

- Synovial sarcoma
- "Adult-type" STS

prospective non-randomized historically-controlled trials

- Other histotypes

guidelines

Other histotypes

1. Infantile fibrosarcoma
2. Desmoplastic small round cell tumour
3. Undifferentiated sarcoma of the liver
4. Malignant ectomesencymoma
5. Mesenchymal chondrosarocma
6. Epithelioid hemangioendothelioma
7. Myofibroblastic lesions and aggressive fibromatosis
8. Extracranial rhabdoid tumour

Second-line therapies

STM non-RMS

European paediatric Soft tissue sarcoma Study Group

14th Report for the EpSSG NRSTS 2005

Co-ordinating Group meeting

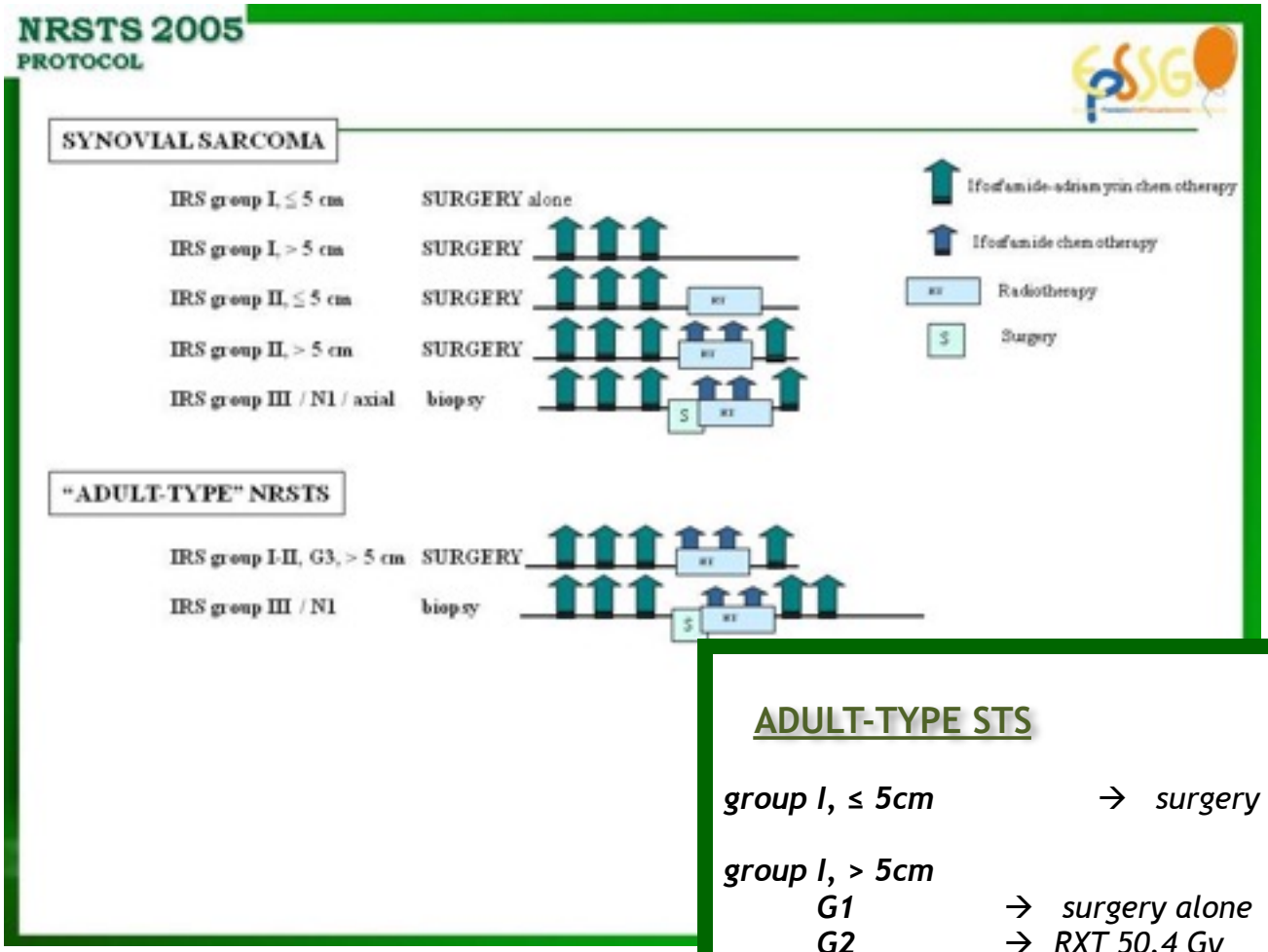
Amsterdam, 9th - 11th December 2015

Table 7: Enrolled patients by country

COUNTRY	PATIENTS ENROLLED	
	#	%
Italy	332	35.0
France	288	30.3
UK & EIRE	152	16.0
The Netherlands	57	6.0
Spain	34	3.6
Belgium	31	3.3
Israel	21	2.2
Czech Rep.	15	1.6
Argentina	7	0.7
Norway	7	0.7
Denmark	2	0.2
Slovakia	2	0.2
Slovenia	1	0.1
Total	**949**	**100.0**

Table 9: Clinical characteristics of all enrolled NRSTS

	# Patients n=949	%
Age (yrs) at diagnosis		
≤ 1	140	14.8
1-9	334	35.2
10-17	439	46.3
≥ 18	36	3.8
Gender		
Female	418	44.0
Male	531	56.0
Histology		
Alveolar soft part sarcoma	19	2.0
Angiosarcoma of soft tissue	9	0.9
Clear Cell Sarcoma of soft tissue	14	1.5
Dermatofibrosarcoma protuberans	47	5.0
Desmoid-type fibromatoses	8	0.8
Desmoplastic small round cell tumour	8	0.8
Ectomesenchymoma	4	0.4
Epithelioid haemangioendothelioma	12	1.3
Epithelioid sarcoma	32	3.4
Ewing tumour pPNET (extraskeletal)	69	7.3
Fibrosarcoma – adult type	14	1.5
Fibrosarcoma – infantile type	76	8.0
Hemangioperycytoma	3	0.3
Inflammatory myofibroblastic tumour	57	6.0
Leiomyosarcoma	19	2.0
Liposarcoma	30	3.2
Malignant Fibrous Histiocytoma	6	0.6
Malignant Peripheral Nerve Sheath Tumour (Malignant Schwannoma)	55	5.8
Malignant mesenchymoma	1	0.1
Mesenchymal Chondrosarcoma	7	0.7
Myxoid Chondrosarcoma ("chordoid" type) (extraskeletal)	3	0.3
Neoplasms with perivascular epithelioid cell differentiation	3	0.3
Other	87	9.2
Rhabdoid tumour	86	9.1
Sarcoma N.O.S.	38	4.0
Synovial Sarcoma	184	19.4
Undifferentiated Soft Tissue Sarcoma	58	6.1



ADULT-TYPE STS

group I, ≤ 5cm → *surgery alone*

group I, > 5cm

- ***G1*** → *surgery alone*
- ***G2*** → *RXT 50.4 Gy*
- ***G3*** → *IFO-DOXO x 3 - IFO x 2 + RXT 50.4 Gy - IFO-DOXO x 1*

IRS Group II / N0

- ***G1*** → *surgery alone*
- ***G2-G3, ≤ 5 cm*** → *RXT 54 Gy*
- ***G2, > 5 cm*** → *RXT 54 Gy*
- ***G3, > 5 cm*** → *IFO-DOXO x 3 - IFO x 2 + RXT 54 Gy - IFO-DOXO x 1*

IRS III & N1 → *IFO-DOXO x 3 - S/RXT+IFO x 2 + IFO-DOXO x2*

SYNOVIALOSARCOMES

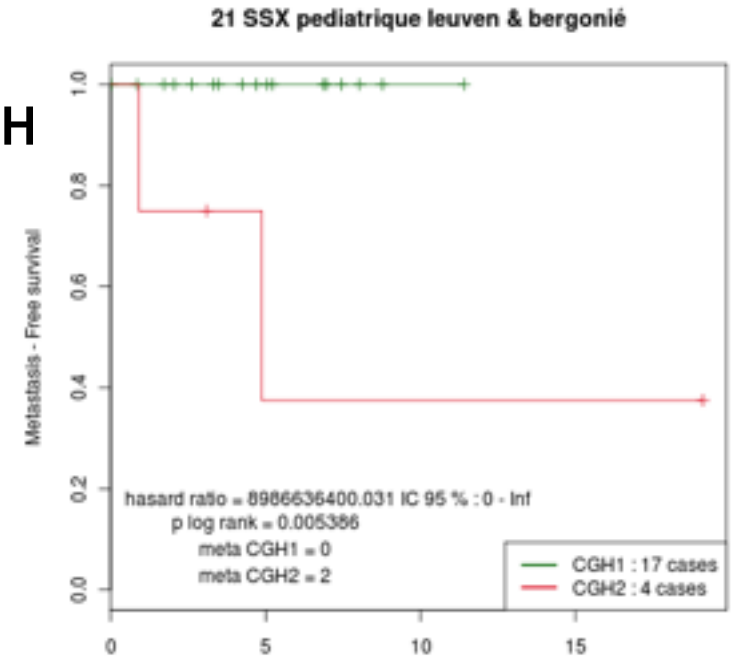
SYNO BIO study

D Orbach.

- Could we have a tool to predict metastatic outcome in children and adolescents with synovial sarcoma?

Pediatric SS
don't metastazise
unless there genomic profile
is rearranged

CGH



Pediatric cases

SYNO BIO study

Select all pediatric patients included in NRSTS 05 study (138 pts)

Analyze all tumor samples in Lyon (D Ranchère, Lyon)

Compare MFS to GI (Dr V Mosseri, I Curie, Paris)

- **Collaborateurs principaux** :

- France : Dr D Orbach (coordinateur principal, Institut Curie, Paris), Dr D Ranchère (IHOP, Léon Bérard, Lyon), Dr V Mosseri (service de biostatistiques, Institut Curie, Paris).

Kelsey (Manchester, UK), Dr R Alagio (Padova, talie), Pr G Bisogno (Padova, Italie).

:

Bordeaux), D Pissaloux (biologiemoléculaire, CL

Info Sarcomes
Ensemble contre les Sarcomes

SYNO BIO study

Update in May 2016

- Expected samples needed: at least 50 samples
- May 2016: **42 samples analyzed**

➢ Dead lines: final samples collection (1 July), biostatistical analysis during summer, first results 1 September.

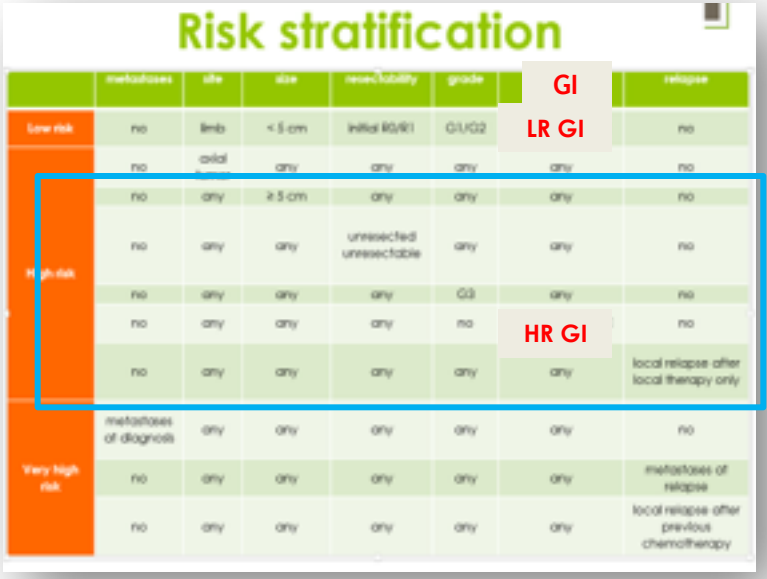
➢ À suivre….

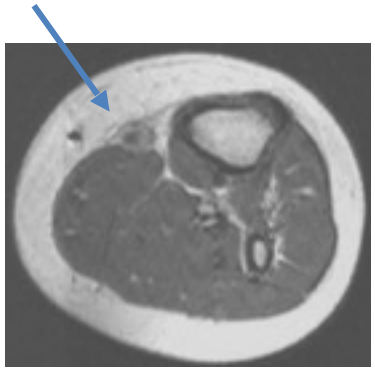
SYNO BIO study

If study conclusive

- Included in the Eurojosss stratification

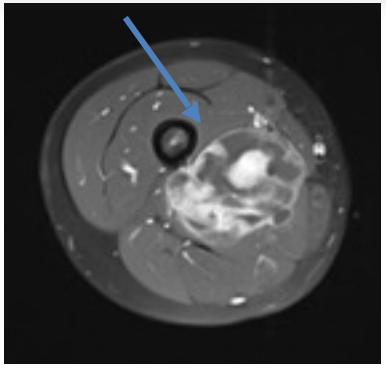
- Correlate to clinic-radiologic presentation





Small tumor, indolent

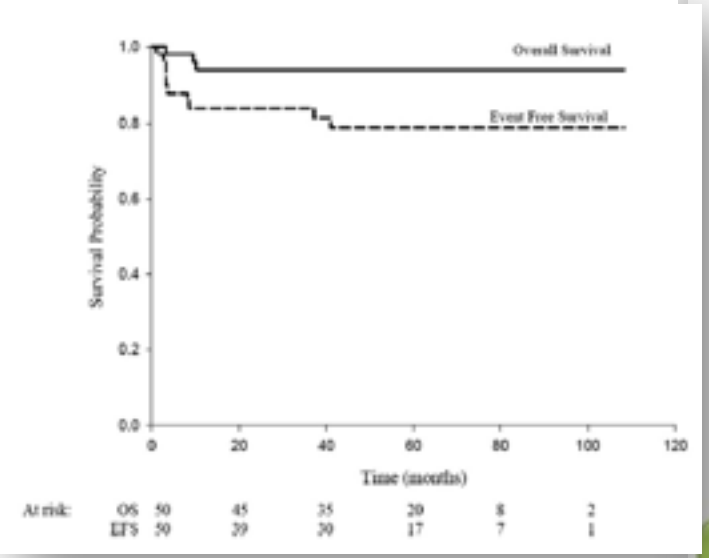
GI ?

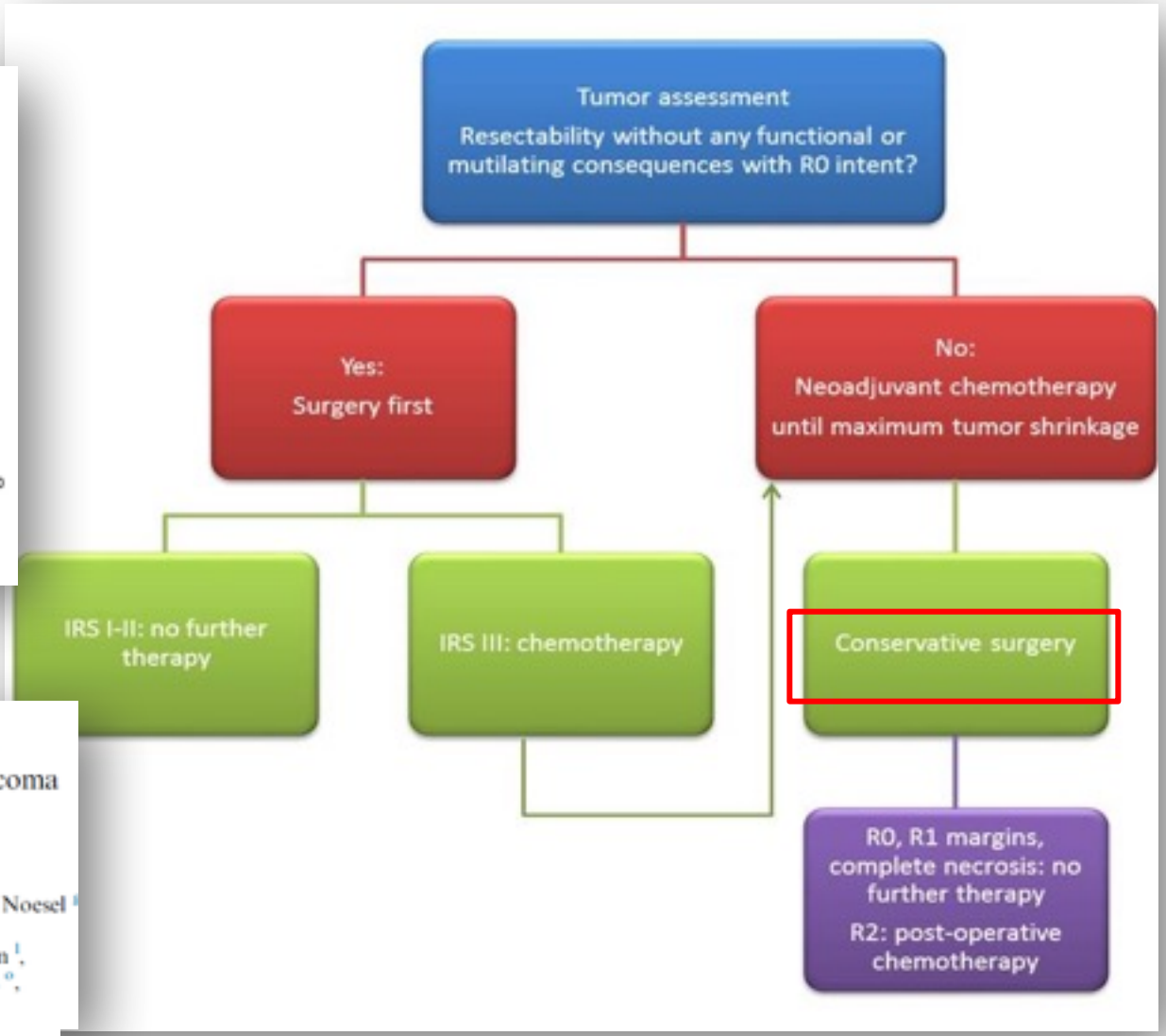


Large tumor, rapidly progressive

Fibrosarcomes infantiles

European paediatric Soft tissue sarcoma Study Group





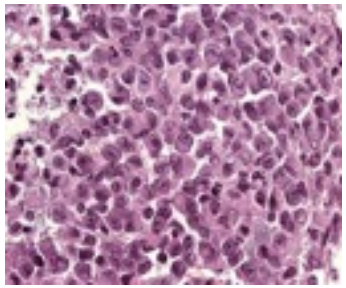
Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience

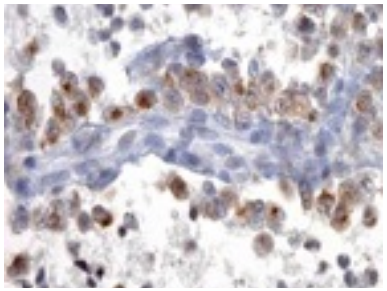
Daniel Orbach [a,*], Bernadette Brennan [b], Angela De Paoli [c], Soledad Gallego [d], Peter Mudry [e], Nadine Francotte [f], Max van Noesel [g], Anna Kelsey [h], Rita Alaggio [i], Dominique Ranchère [j], Gian Luca De Salvo [c], Michela Casanova [k], Christophe Bergeron [l], Johannes H.M. Merks [m], Meriel Jenney [n], Michael C.G. Stevens [o], Gianni Bisogno [p], Andrea Ferrari [k]

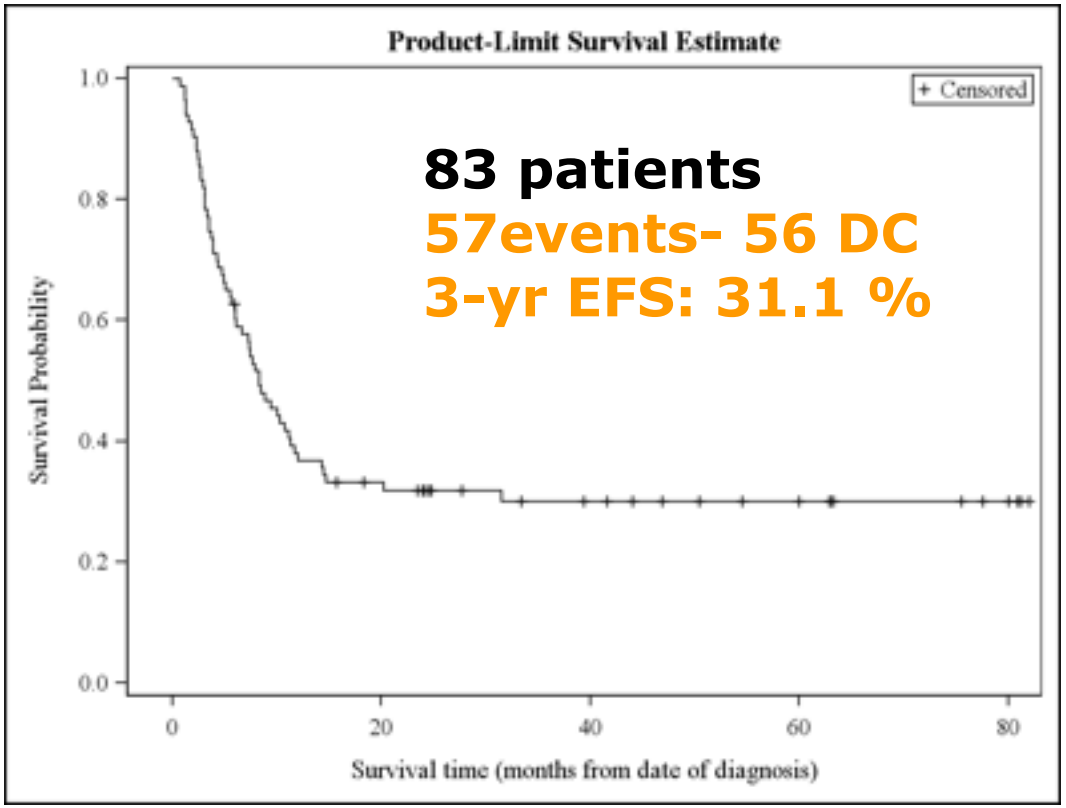
European Journal of Cancer 57 (2016) 1–9

European paediatric Soft tissue sarcoma Study Group

Tumeurs rhabdoïdes







➢ **NRSTS 05, V 1.1**: publié

Echec…

European paediatric Soft tissue sarcoma Study Group

Tumeurs rhabdoïdes

➢Guidelines **NRSTS 05, V 1.2**

Overview of Treatment plan

Week

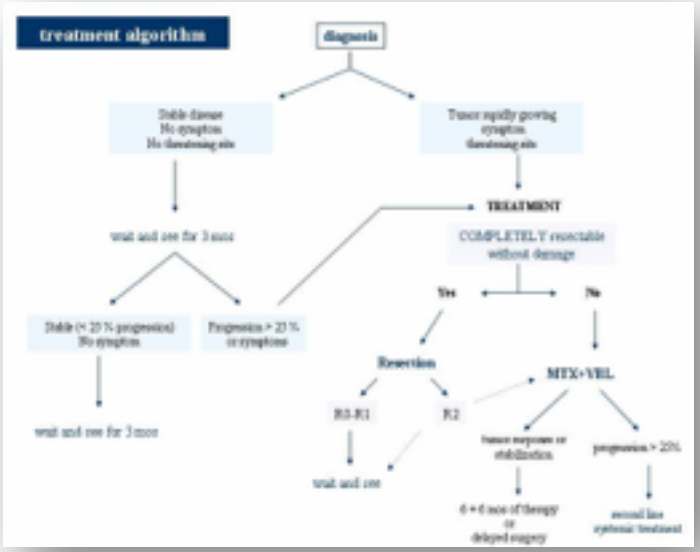
1	2	3	4	5	6	7	8	9	10	11	12
V		I		V		I		V		I	
D		E		D		E		D		E	
Cy				Cy				Cy			

13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
V		I		V		I		V		I		V		I	
D		E		D		E		C		E		C		E	
Cy				Cy											

Rôle de la maintenance?
Rôle de la CT HD ?

V	**Vincristine**	0.025mg/kg/day IV x 1 as bolus for infants < 12 month 0.05mg/kg/day IV x 1 as bolus for children 12 mo.-3 yr 1.5 mg/m²/day xl as bolus for children ≥ 3 years old
D	**Doxorubicin**	1.25mg/kg/day IV x 2 days over 15 minutes for infants <12 month 37.5mg/m²/day IV x 2 days over 15 minutes for children ≥ 12 months
Cy	**Cyclophosphamide**	40 mg/kg/day IV x 1 day over 1 hour for infants < 12 months 1200 mg/m²/day IV x 1 day over 1 hour for children ≥ 12 months
I	**Ifosfamide**	900 mg/m²/day IV over 1 hour x 5 days for infants < 12 months 1800 mg/m² dayIV over 1 hour x 5 days for children ≥12 months
E	**Etoposide**	3.3mg/kg/day IV over 1 hour x 5 days for infants < 12 months 100mg/m²/day IV over 1 hour x 5 days for children ≥ 12 months

TUMEURS DESMOÏDES



- **Base EpSSG : CRF spécifiques**

- **Projet ALTITUDES** (N Penel) **:**

Base clinico-biologique nationale des cas incidents :
- constitution d'une **banque de tumeurs virtuelle**

\+ ADN lymphocytaire (+/- recherche d'une mutation constitutionnelle d'APC)

- constitution d'une sérothèque (au dg et lors d'évènements tumoraux)
- recueil des données clinico-biologiques et des traitements

http://www.sos-desmoide.asso.fr

SOS DESMOÏDE

European paediatric Soft tissue sarcoma Study Group

Etudes EpSSG : au total

- (Très) **bon recrutement**, mais pas (encore) systématique dans certains centres … **y penser lors des RCP** !

  Bonne participation de la France et de plus en plus au sein des **unités d'AJA** : réseau **NetSarc** et **RCP** interR sarcomes**.**

- **Poursuivre inclusion dans RMS 2005** si RMS HR et <21 ans :

  randomisation R2 : STOP **vs** Navelbine-EDX**.**

- **Et enregistrements** si <25ans et **RMS** de risque standard, **THR**, **MTS 08**, ou si **NRSTS**

Frontline and Relapse study for patients with RMS

The **FaR-RMS** Study

Gianni Bisogno
Gian Luca de Salvo
Anna Kelsey
Henry Mandeville
Kieran McHugh
Veronique Minard-Colin
Joshua Savage
Keith Wheatley
Julia Chisholm
Nicola Fenwick
Meriel Jenney
Helene Martelli
Hans Merks
Veronica Moroz
Janet Shipley

Principles

- "**Overarching**" study for all newly diagnosed **and** relapsed patients

- Children **and** Adults

(exclusion pleiomorphic RMS)

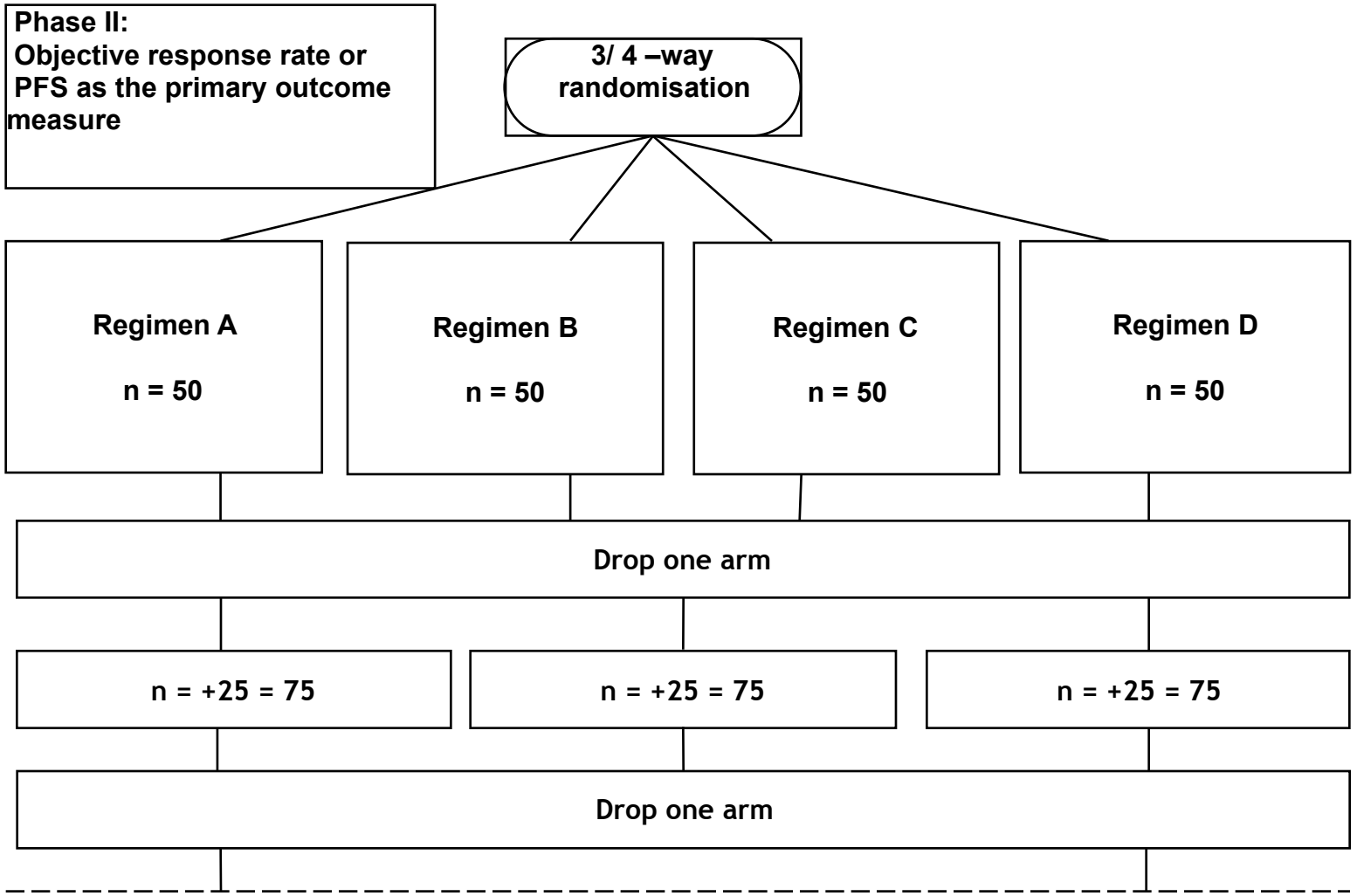
- Build Structure to be able to bring in new agents and **adapt** protocol

- Ask randomised questions where evidence is not clear

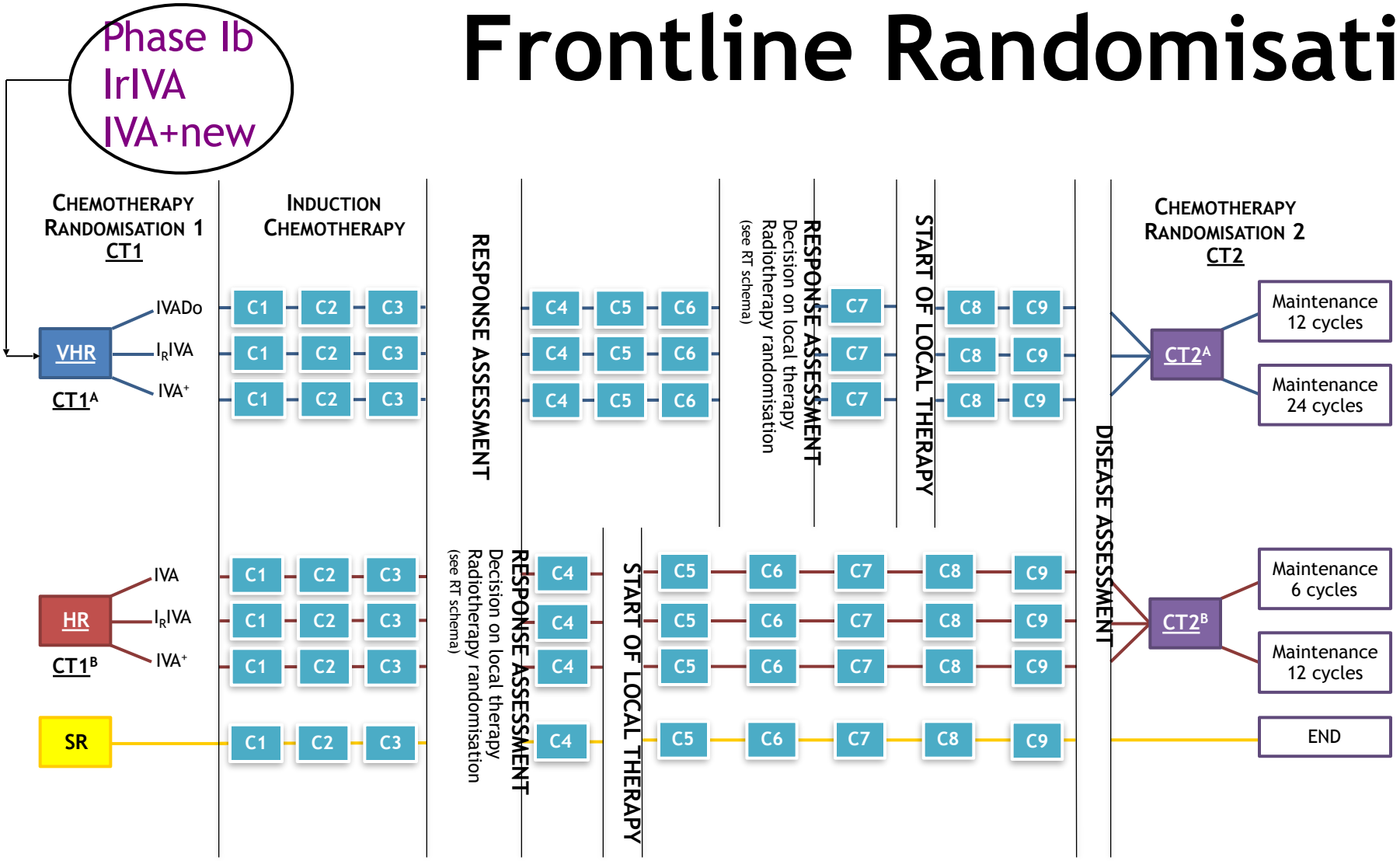
Principles

- **PAX-FOXO 1 fusion gene status for risk stratification**
- Systemic therapy: frontline and relapse questions
- Radiotherapy & imaging questions
- **Sample collection/biology** – underpins overarching study

Chemotherapy questions MAMS design



Frontline Randomisation



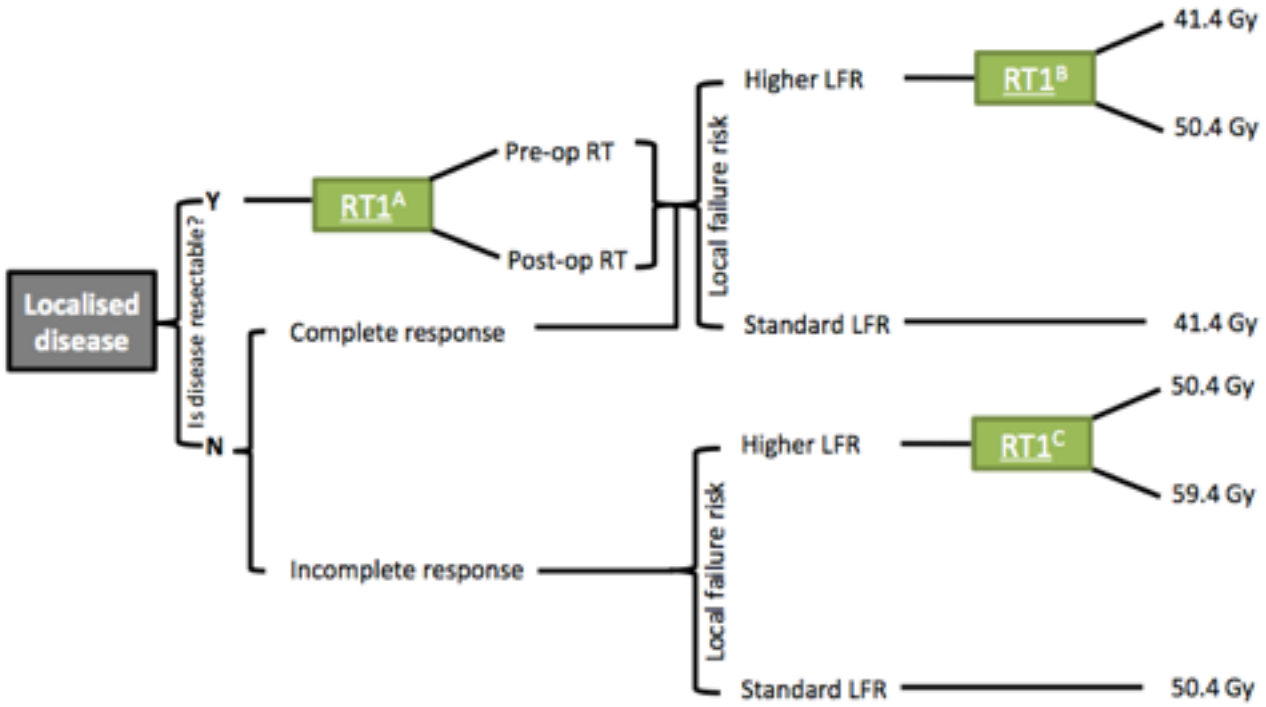
FaR-RMS
Trial Schema

v1.0, 27-Nov-2015

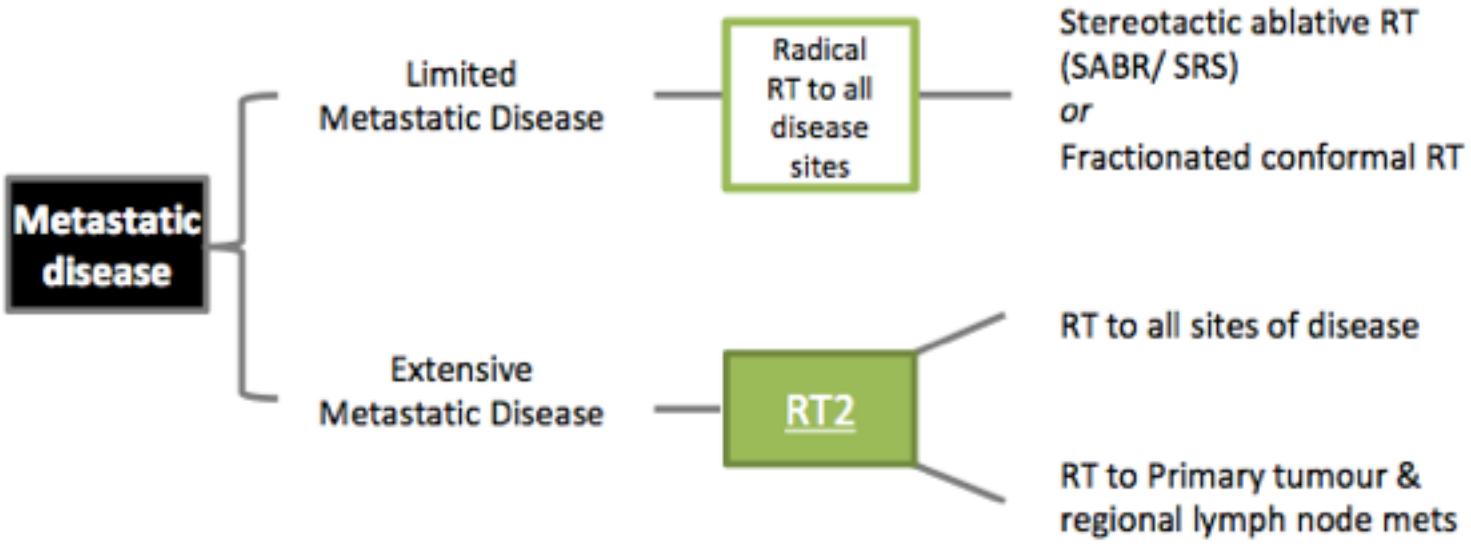
Radiotherapy randomisation

FaR-RMS

Trial Schema



Radiotherapy randomisation



Relapses Randomisations

FaR-RMS
Trial Schema

European paediatric Soft tissue sarcoma Study Group

Etudes STM pédiatriques à venir

Annals of Oncology 26: 567–572, 2015
doi:10.1093/annonc/mdu562
Published online 8 December 2014

Synovial sarcoma in children and adolescents: the European Pediatric Soft Tissue Sarcoma Study Group prospective trial (EpSSG NRSTS 2005)

A. Ferrari[1*], G. L. De Salvo[2], B. Brennan[3], M. M. van Noesel[4], A. De Paoli[2], M. Casanova[1], N. Francotte[5], A. Kelsey[6], R. Alaggio[7], O. Oberlin[8], M. Carli[9], M. Ben-Arush[10], C. Bergeron[11], J. H. M. Merks[12], M. Jenney[13], M. C. Stevens[14], G. Bisogno[9] & D. Orbach[15]

European Journal of Cancer 57 (2016) 1–9

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com
ELSEVIER
EJC

Original research

Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience

Daniel Orbach [a,*], Bernadette Brennan [b], Angela De Paoli [c], Soledad Gallego [d], Peter Mudry [e], Nadine Francotte [f], Max van Noesel [g], Anna Kelsey [h], Rita Alaggio [i], Dominique Ranchère [j], Gian Luca De Salvo [c], Michela Casanova [k], Christophe Bergeron [l], Johannes H.M. Merks [m], Meriel Jenney [n], Michael C.G. Stevens [o], Gianni Bisogno [p], Andrea Ferrari [k]

European Journal of Cancer 60 (2016) 69–82

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com
ELSEVIER
EJC

Clinical Trial

Outcome of extracranial malignant rhabdoid tumours in children registered in the European Paediatric Soft Tissue Sarcoma Study Group Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study—EpSSG NRSTS 2005

Bernadette Brennan [a,*], Gian Luca De Salvo [b], Daniel Orbach [c], Angela De Paoli [b], Anna Kelsey [d], Peter Mudry [e], Nadine Francotte [f], Max Van Noesel [g], Gianni Bisogno [h], Michela Casanova [i], Andrea Ferrari [i]

NRSTS 2005

✓Epithelioid sarcoma
✓Low-risk synovial sarcoma

Joint analyses with COG

✓ MPNST
✓ DSRCT (+ données de NetSarc)
✓ Desmoid-type fibromatosis

➢ Alveolar soft part sarcomas
➢ “Surgery only” cases
➢ IMT
➢ DFSPT
➢ …

Teenage and Young Adult Meta-analysis Oncology Co-operation (TYAMOC)

Soft tissue Sarcoma sub-protocol

Evaluating the relationship between dose, toxicity and clinical outcomes

in teenagers and young adults with Synovial Sarcoma

A pooled analysis using individual patient data

- ✓ **EORTC**
- ✓ **COG**
- ✓ **EpSSG**
- ✓ **…**

EpSSG NRSTS Committee meeting
to discuss strategy for the future

Euro EWING S.S.S
European Ewing Sarcoma Study

Desmoid-type fibromatosis project

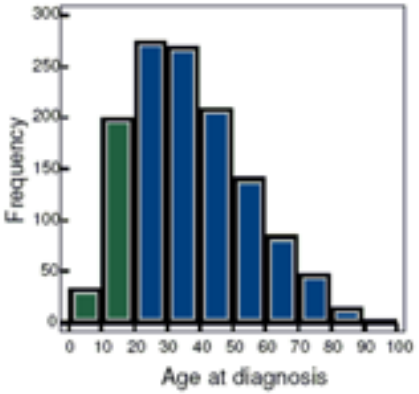
EURO RHABDOID 2017

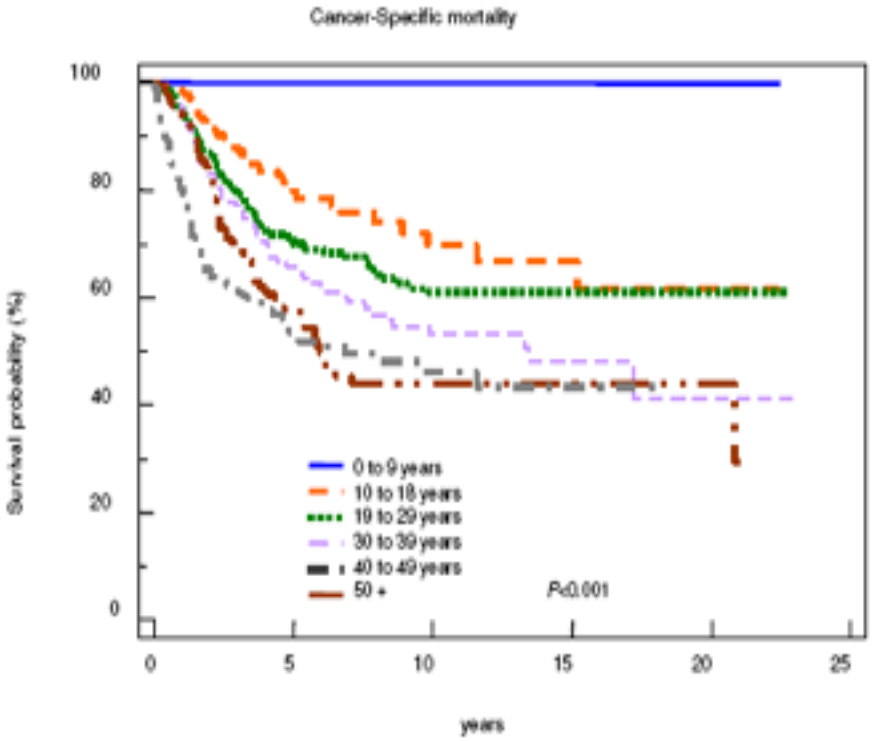
A Italiano, D Orbach, A Ferrari

Comparing Children and Adults With Synovial Sarcoma in the Surveillance, Epidemiology, and End Results Program, 1983 to 2005

An Analysis of 1268 Patients

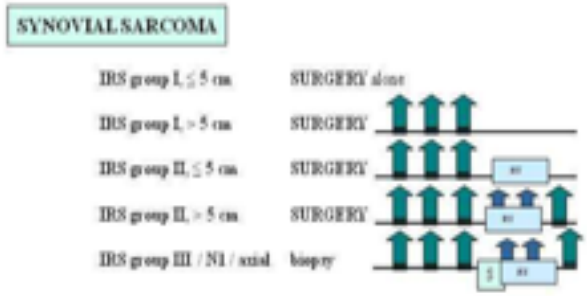
Iyad Sultan, MD[1]; Carlos Rodriguez-Galindo, MD[2]; Raya Saab, MD[3]; Sameer Yasir, MD[4]; Michela Casanova, MD[5]; and Andrea Ferrari, MD[5]



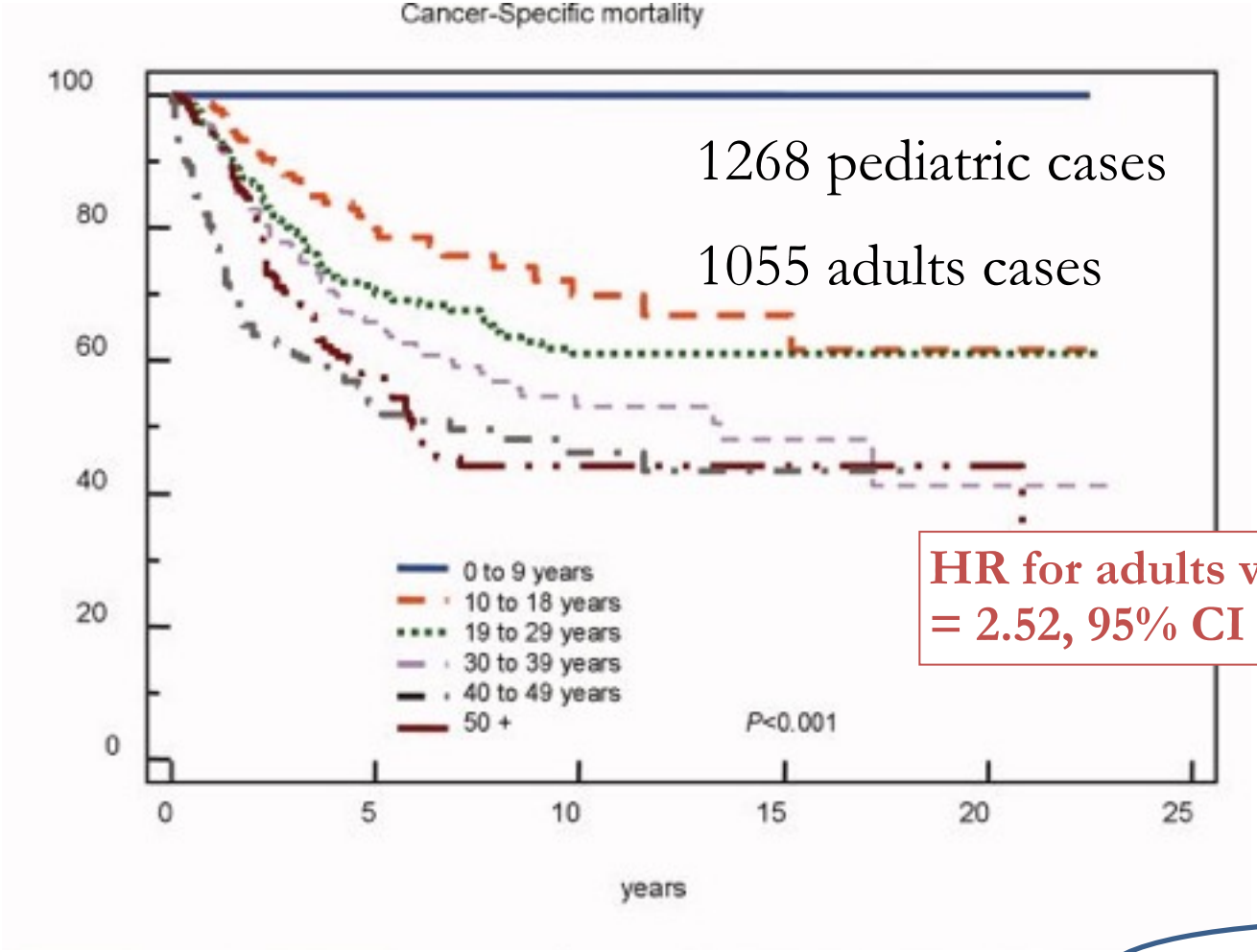


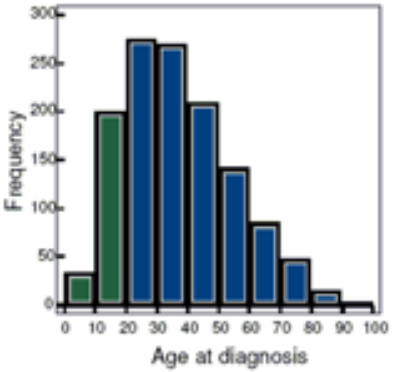
Since relatively high response rates to chemotherapy have been well documented in pediatric series, pediatric oncologists approached SS as a **chemosensitive tumor** (“*rhabdomyosarcoma-like” tumor*), and designed treatments around this concept, particularly in Europe (all patients receiving systemic treatment, regardless of stage)

By contrast, adult SS has usually been treated as the other adult STS, generally regarded as **poorly chemosensitive tumor** and for which the standard therapeutic approach was focused on local control



Pediatric and adult synovial sarcoma: the same disease?





HR for adults vs children/adolescents = 2.52, 95% CI = 1.56 to 2.56; $P < .001$

The outcome is clearly worse in adult than in paediatric cases

WHY ?

- **Biological differences ?**
- **Treatment differences ?**

Sultan *et al.* 2009

VOLUME 31 · NUMBER 5 · FEBRUARY 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

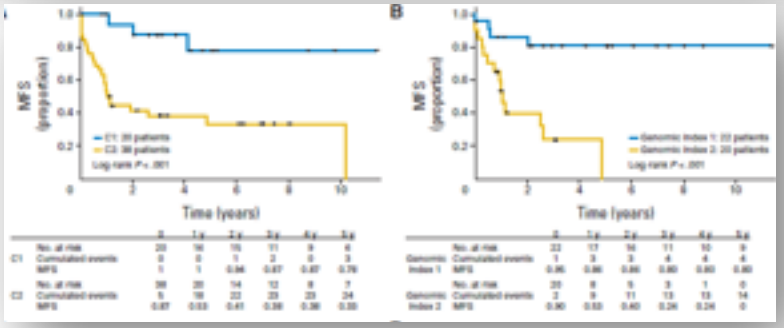
Chromosome Instability Accounts for Reverse Metastatic Outcomes of Pediatric and Adult Synovial Sarcomas

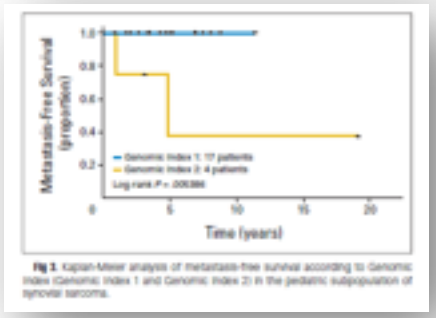
Pauline Lagarde, Joanna Przybyl, Céline Brulard, Gaëlle Pérot, Gaelle Pierron, Olivier Delattre, Raf Sciot, Agnieszka Wozniak, Patrick Schöffski, Philippe Terrier, Agnès Neuville, Jean-Michel Coindre, Antoine Italiano, Daniel Orbach, Maria Debiec-Rychter, and Frédéric Chibon

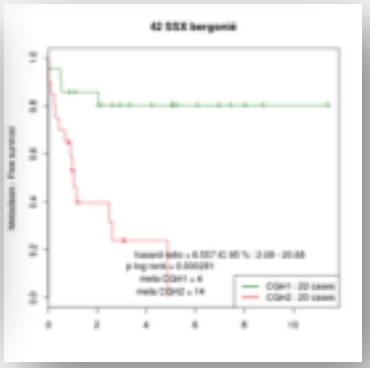
Annals of Oncology 25: 2267–2271, 2014
doi:10.1093/annonc/mdu362
Published online 28 July 2014

Response to chemotherapy is not related to chromosome instability in synovial sarcoma

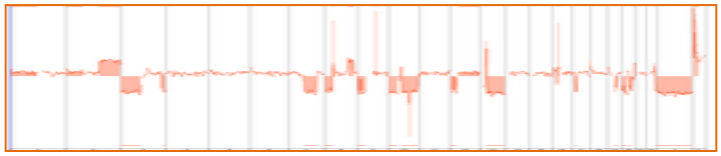
C. Chaklba[1,2,3], P. Lagarde[2,3,4], D. Pissaloux[5], A. Neuville[2,3,4], C. Brulard[3], G. Pérot[3,4], J. M. Coindre[2,3,4], P. Terrier[6], D. Ranchere-Vince[5], A. Ferrari[7], P. Collini[8], A. J. H. Suurmeijer[9], J. Y. Blay[10], S. A. Terrisse[11], S. Pipemo-Neumann[12], G. Averous[13], B. Bui[1,3], D. Orbach[14], A. Italiano[1,3] & F. Chibon[3,4]*



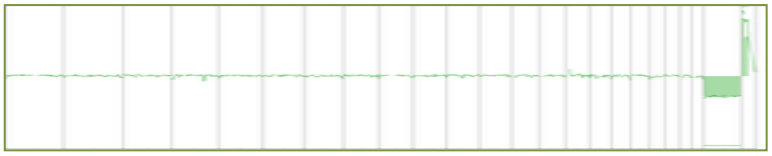


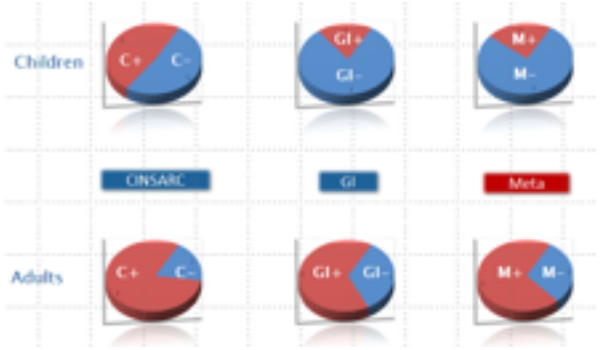


All patients



Children





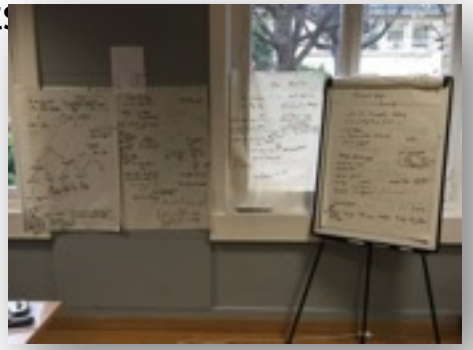
EuroEWS.S.S

European Joint Synovial Sarcoma Study

➢ First prospective joint (adult and children) international (European) study on synovial sarcoma (in particular, pediatric and adult synovial sarcoma together, for the first time)

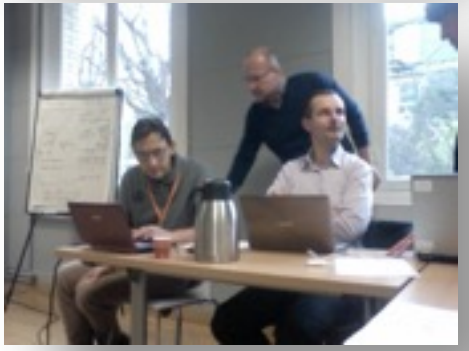
➢ Overarching protocol for all patients, according to a biological driven risk factors stratification, based on the new molecular insights emerging in synovial sarcoma

➢ Comparative prospective randomized study for high risk patients



➢ Role of targeted agent in addition to conventional chemotherapy in a perioperative setting

➢ Ancillary biological studies to analyze prospectively the value of biological features: e.g. expression profile, DNA circulating, minimal disease. The study will have the possibility to investigate differences of biology crosswise the ages



➢ The local therapy will be adapted to the concept of the "best local treatment"

➢ This study may be a model for further collaboration between pediatric and adults groups on other cross border tumor types.

	metastases	site	size	resectability	grade	GI	relapse
Low risk	no	limb	< 5 cm	initial R0/R1	G1/G2	Low Risk	no
High risk	no	axial tumor	any	any	any	any	no
	no	any	≥ 5 cm	any	any	any	no
	no	any	any	unresected unresectable	any	any	no
	no	any	any	any	G3	any	no
	no	any	any	any	no	High Risk	no
	no	any	any	any	any	any	local relapse after local therapy only
Very high risk	metastases at diagnosis	any	any	any	any	any	no
	no	any	any	any	any	any	metastases at relapse
	no	any	any	any	any	any	local relapse after previous chemotherapy

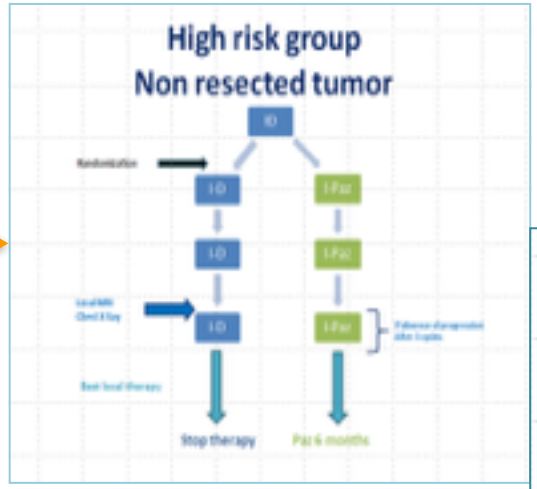
GI: Genomic Index = chromosme instability in Synovial Sarcoma

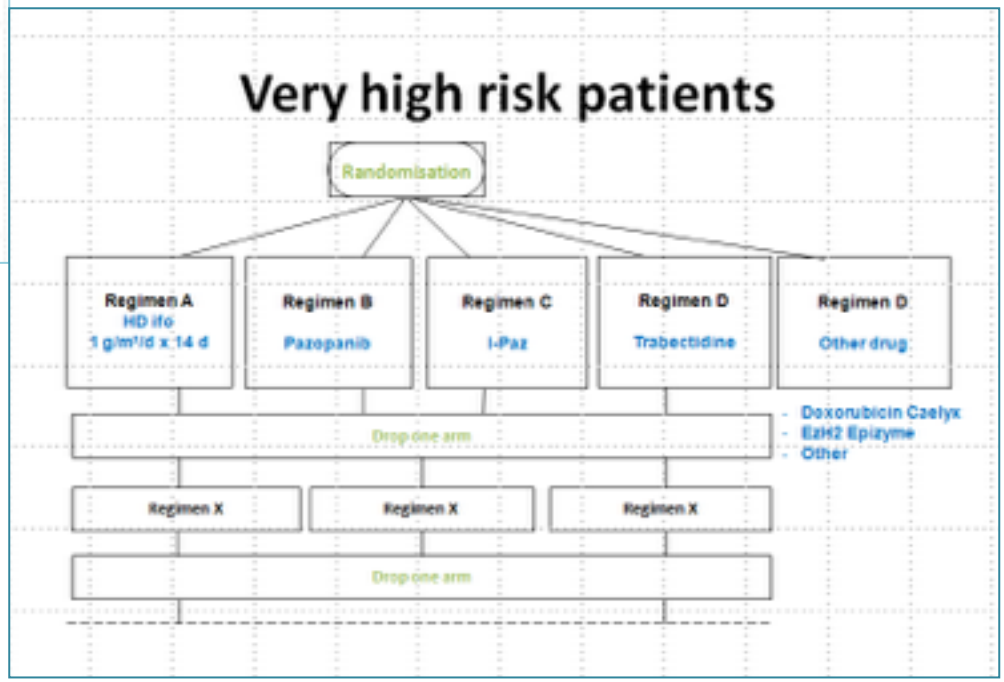
Euro EWING S.S.S

European Joint Special Sarcoma Study

TREATMENT guidelines

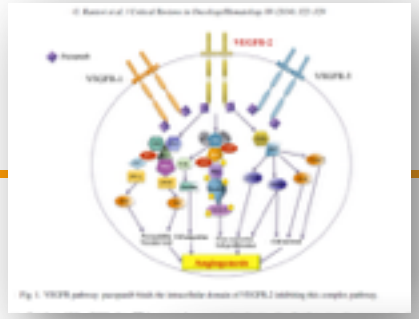
Low risk
High risk
Very high risk





PHRC 2016 : refused…

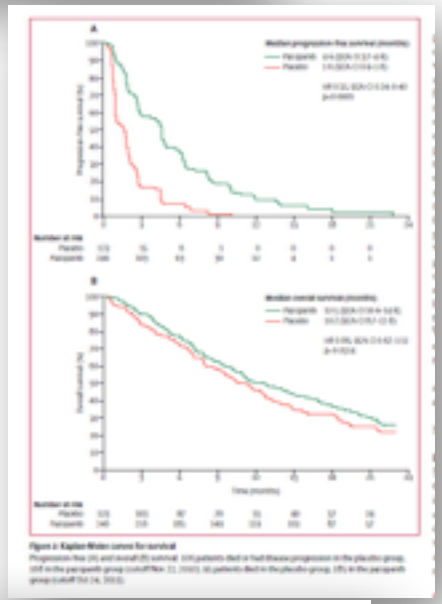
Pazopanib



Multitargeted tyrosine kinase inhibitor (against VEGFR1, VEGFR2, VEGFR3, PDGF)

Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial

Winette T A van der Graaf, Jean-Yves Blay, Sant P Chawla, Dong-Wan Kim, Binh Bui-Nguyen, Paolo G Casali, Patrick Schöffski, Massimo Aglietta, Arthur P Staddon, Yasuo Beppu, Axel Le Cesne, Hans Gelderblom, Ian R Judson, Nobuhito Araki, Monia Ouali, Sandrine Marreaud, Rachel Hodge, Mohammed R Dewji, Cornel Coens, George D Demetri, Christopher D Fletcher, Angelo Paolo Dei Tos, Peter Hohenberger, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group and the PALETTE study group



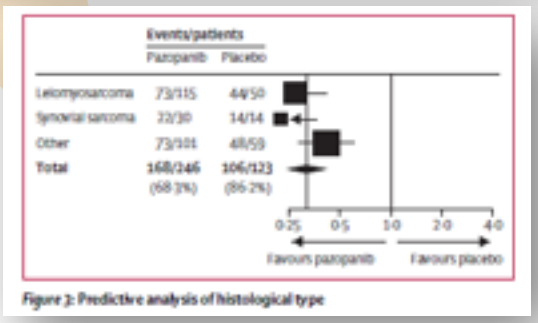


Figure 3: Predictive analysis of histological type

Phase III, adult population,

Pazopanib vs. placebo in Metastatic STS

VOLUME 31 · NUMBER 24 · AUGUST 20 2013
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Phase I Pharmacokinetic and Pharmacodynamic Study of Pazopanib in Children With Soft Tissue Sarcoma and Other Refractory Solid Tumors: A Children's Oncology Group Phase I Consortium Report

Julia L. Glade Bender, Alice Lee, Joel M. Reid, Sylvain Baruchel, Timothy Roberts, Stephan D. Voss, Bing Wu, Charlotte H. Ahern, Ashish M. Ingle, Pamela Harris, Brenda J. Weigel, and Susan M. Blaney

- Phase I, pediatric population, solid tumors
- DMT 450 mg/m² for tablets and 160 mg/m² for suspension

If Pazopanib non available:

think to REGORAFENIB (cf ASCO 2016)

- **Bayer contacted and OK**
- **Phase Ib in association with Ifo. to be done…**

EURO RHABDOID 2017

European Extra-CNS/CNS Rhabdoid project

EpSSG

1	2	3	4	5	6	7	8	9	10	11	12	Week			
V		I		V		I		V		I					
D		E		D		E		D		E					
Cy				Cy				Cy							
13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
V		I		V		I		V		I		V		I	
D		E		D		E		C		E		C		E	
Cy				Cy											

Dose-compressed chemotherapy

EU-RHAB

Germany

Registry study initiated in 2005 to establish basis for phase I/II study

To define standard of care in Germany, to develop biology study

One therapy for all location

- 297 cases registered from 17 countries (60% German)
- 65% AT/RT, 26% STS/others, 9% renal
- Standard - 9 courses VDC/ICE: **6-year EFS 45%**
- CNS AT/RT – high dose CARBO/TT

Next – Histone De Acetilase Inhibitors – reminostat, 4sc-202

French AT/RT

France

New study with standard chemo + valproic acid – high-dose chemo – maintenance therapy with celecoxib/fluvastativ

NOPHO

Nordic goup

AT/RT in EU-Rhab

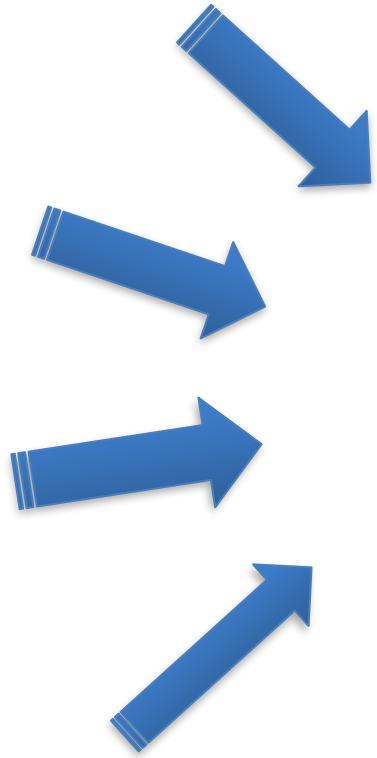
STS in EpSSG or CWS

Kidney in SIOP Renal Group

EU-RHAB

French AT/RT

NOPHO



EURO RHABDOID 2017

Randomized phase II study is possible (a lot of events)

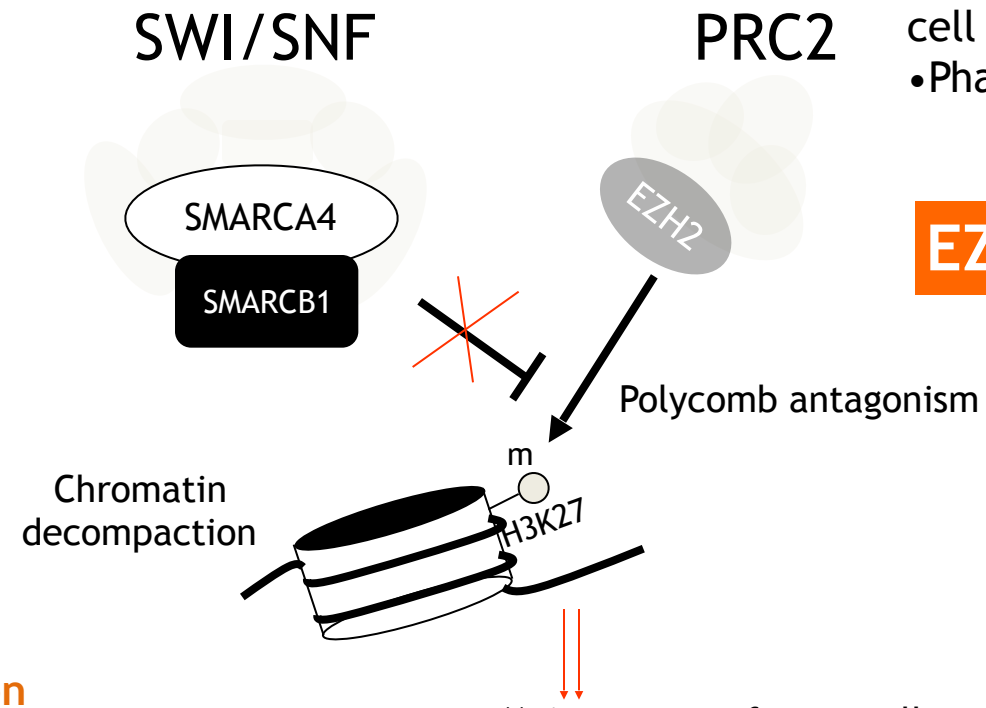
Parallel biological study

New agents (ITCC)

Attract funding

Aurora kinase Inhibitors

- Kinase aurora A – down stream target of SMARCB1
- Radiosensitizer- in vitro AT/RT cell lines
- Phase I study AT9283- CRUK



EZH2 INHIBITOR

HDAC Inhibition

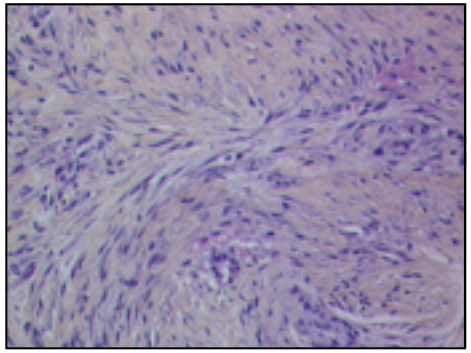
- Restores regulation process and tumour suppression
- Sodium valporate- dose too high
- Vorinostat- Phase I child

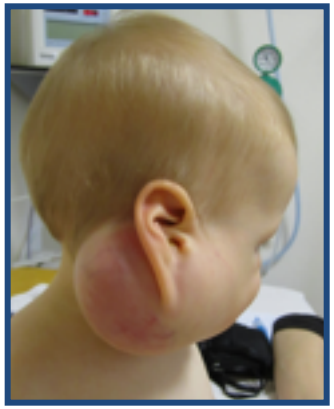
CDK inhibitors

- Cyclin D1
- LEEO11 – CDK 4/6 –phase I

Desmoid tumor project update
Preliminary data on epidemiology

D Orbach





Work in progress…

- Number of patients registered in the EDC system: **172**
  [131 early diagnosed patients + 41 currently diagnosed (new)]
- Case Report Forms being reviewed for accuracy and completeness
- Information on **163 patients**

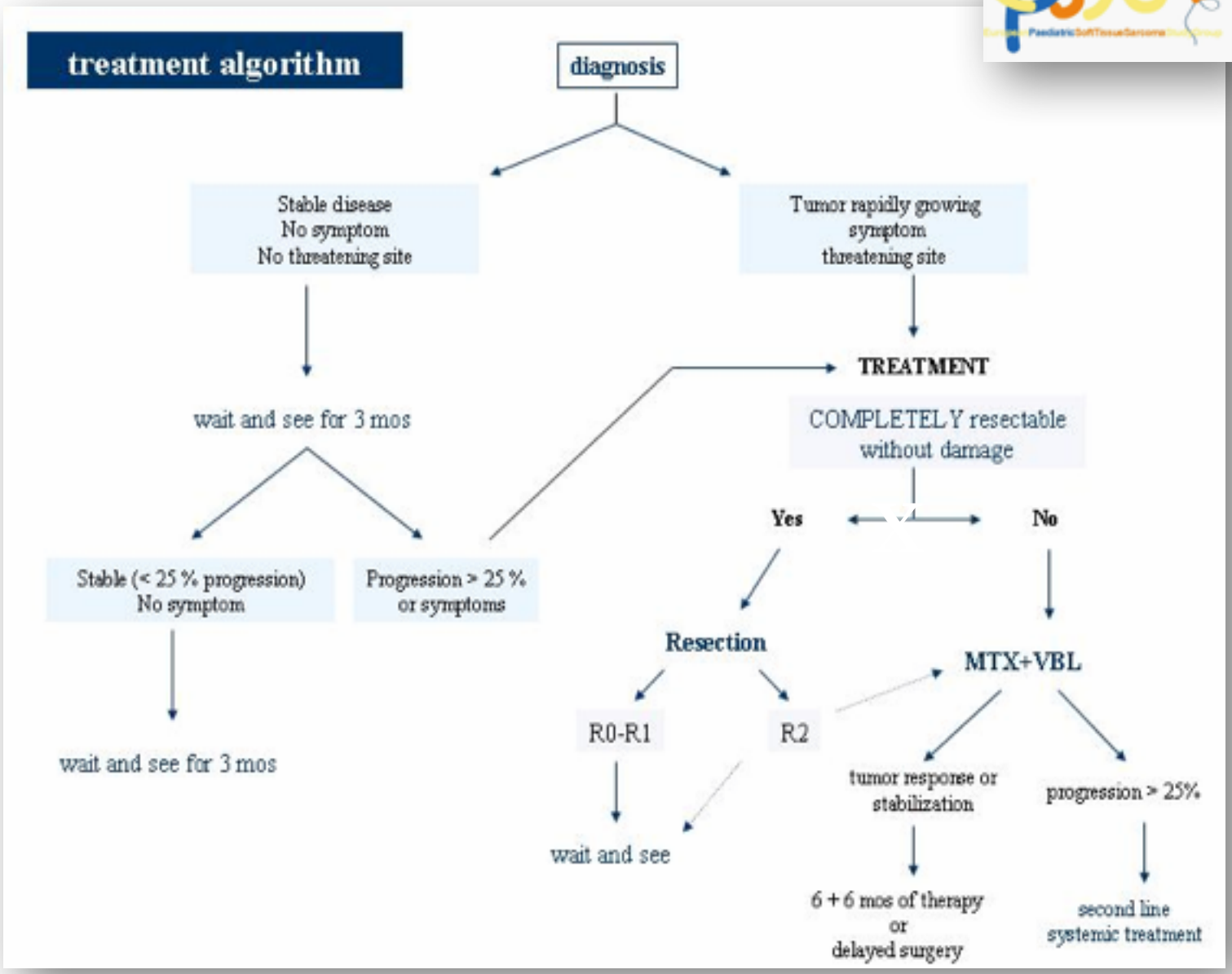
➢ Epidemiologic and clinical data

Population

- 2005-2016 : **163 pediatric** patients
- **Median age: 11.4 Y [0.06-24.19]**
  - **< 1 Y: 9%**
  - **≥ 18 Y: 3%**
- **Male/Female: 0.5**
- **<u>Family history</u>:**
  - **2 APC / 136 pts**
  - **10 colonic tumors / 128 pts**
- **<u>Previous trauma</u>: 10 / 143 pts (7**

All patients registered by country

COUNTRY	PATIENTS REGISTERED	
	#	%
Belgium	4	2.5
Czech Rep.	2	1.2
France	71	44.2
Israel	8	4.9
Italy	45	27.0
The Netherlands	9	5.5
UK & EIRE	24	14.7
Total	**163**	**100.00**



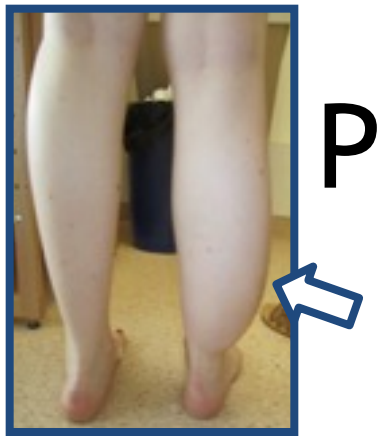
NRSTS 05 protocol

First therapy

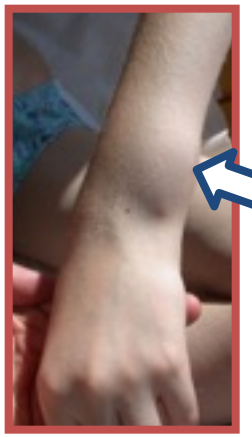
- **IRS staging:**
  - **IRS I** **11.0%**
  - **IRS II** **11.7%**
  - **IRS III a** **68.1%**
  - **IRS III b** **9.2%**

First therapeutic decision

	# Patients n=142	%
Observation	68	47.9
Treatment	74	52.1
Surgery	15	20.3
CT + Surgery	2	2.7
Only CT	57	77.0
Total	**142**	**100.0**



Preliminary conclusions



- **Not a so rare disease:**
  - 163 pts (184 SS in NRSTS 05 – 12/2015)
  - Lack of recruitment nevertheless
    - Only observational study
    - < 18 y
    - Missing patients in some countries or centers
- **Large prospective series:**
  - **[Meazza 2010 - 94 pts; Oudot 2012 - 57 pts; Soto-Miranda 2013 - 39 pts]**
- **Difficult disease with many different events:** regression, progression, relapse …
- **Different from adults:**
  - **few Trauma**
  - **few genetic APC association … (but all analyzed ?)**
  - **less mesenteric primaries**

➢ **Work in progress to analyze the EpSSG strategy**

➢ **Step for the next prospective study**

Fibrosarcome infantile
Inh. transcrit NTRK3-ETV6

- **Phase I ped. du COG quasi finalisée** avec **LOXO-101= inh TRK (actif sur la fusion NTRK3-ETV6)** = 1er inh de transcrit

Pediatr Blood Cancer 0000;00:000–000

BRIEF REPORT

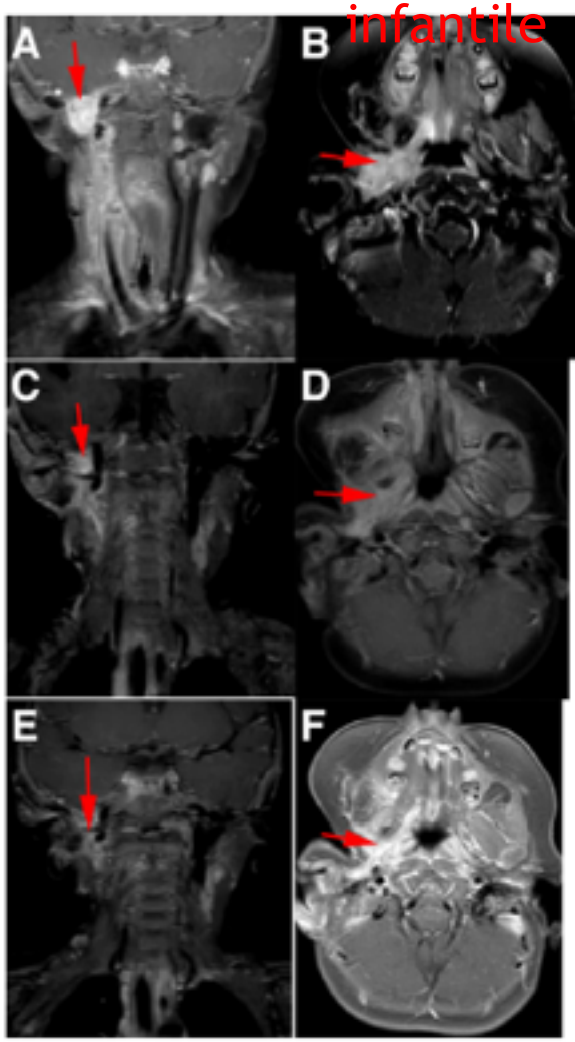
Infantile Fibrosarcoma With *NTRK3–ETV6* Fusion Successfully Treated With the Tropomyosin-Related Kinase Inhibitor LOXO-101

Ramamoorthy Nagasubramanian, MD,[1]* Julie Wei, MD,[1] Paul Gordon, MD,[1] Jeff C. Rastatter, MD,[2] Michael C. Cox, Pharm.D., MSHs,[3] and Alberto Pappo, MD[4]

Abstract ASCO 2016 : carcinomes thyroïdiens, leucémies, tumeurs rares, et 3 FS infantiles = très rapidement efficace, sans toxicité immédiate importante.

Fibrosarcome infantile

Baseline



Après 1 mois

Après 2 mois

- Labo « LOXO oncologie » : **phase II** internationale (US, canada, Europe) à ouvrir rapidement **en France** (1-2 centres), avec patients sélectionnés à la rechute via MAPPYACT sur anomalie de **TRK.**