CGFL
CENTRE GEORGES FRANÇOIS LECLERC
Ensemble, dépassons le cancer

ÉCOLE DOCTORALE
Environnements - Santé

L'université de Bourgogne est membre de
UBFC
UNIVERSITÉ BOURGOGNE FRANCHE-COMTÉ

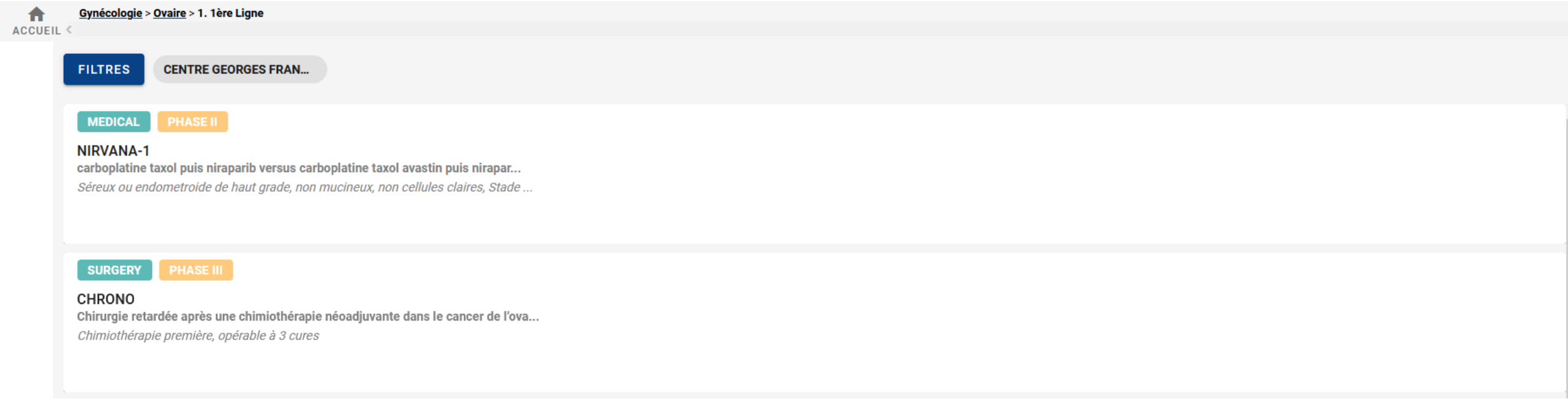
Réunion Onco-gynécologie Bourgogne Franche Comté

Les essais cliniques au CGFL

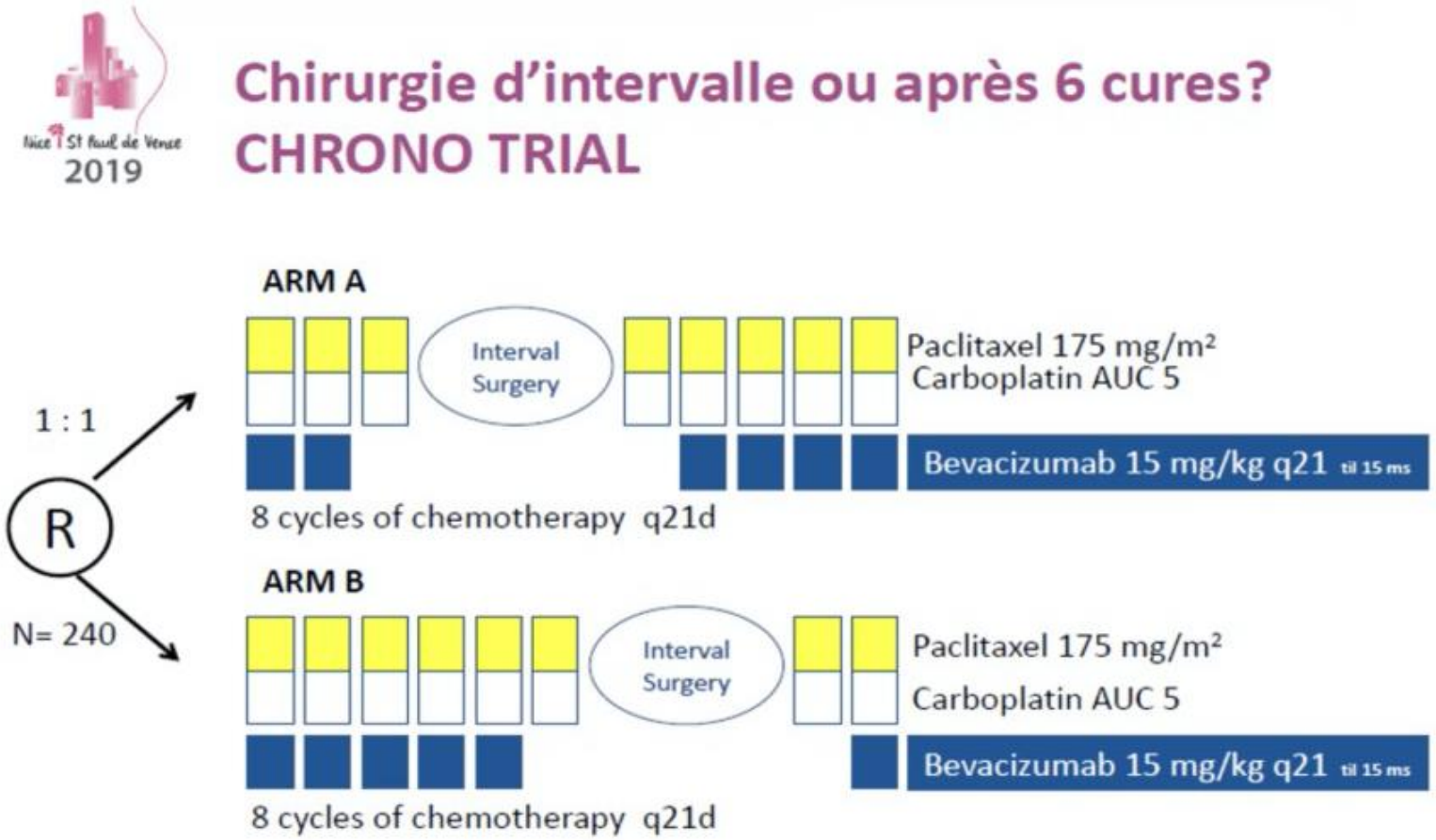
Le 28/03/2023

Dr Jean-David Fumet, M.D, PhD

Cancer de l’ovaire : 1ere ligne



CHRONO



J.M. Classe

Cancer de l’ovaire : Rechute platine sensible

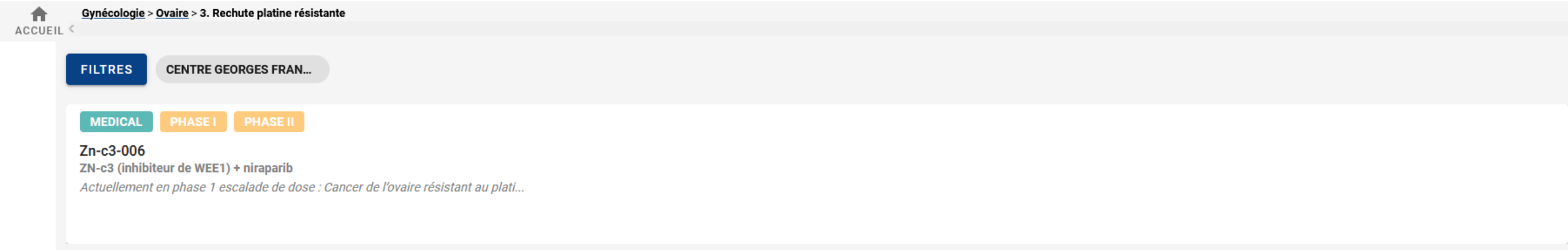
MEDICAL PHASE II

TEDOVA

Entretien par OSE2101 vs OSE2101 + Pembrolizumab vs rien

HLA-A2+, Rechute platine sensible, ayant déjà eu inhibiteurs de PARP et bevacizu...

Cancer de l’ovaire : rechute platine resistante



ZN-c3-006
SIV Training

A Phase 1/2 Dose-Escalation and Dose-Expansion Study of ZN-c3 in Combination with Niraparib in Subjects with Platinum-resistant Ovarian Cancer

Sponsor: K-Group Beta, Inc.

Version 8.0

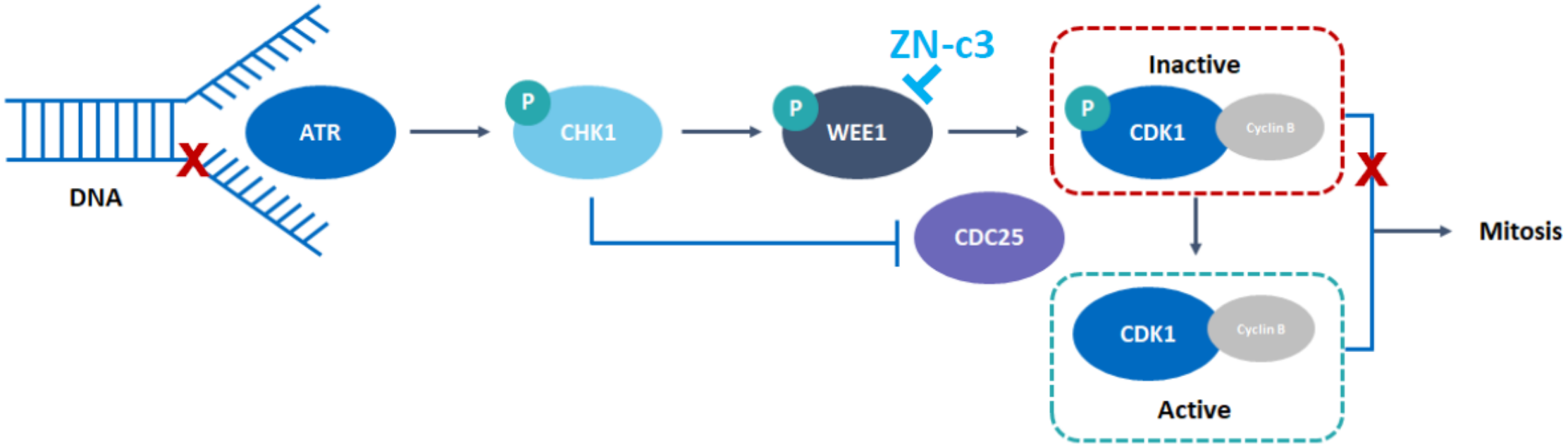
Site Name

SIV Date

zentalis

ZN-c3: A DNA Damage Response (DDR) Drug Candidate

MECHANISM OF ACTION

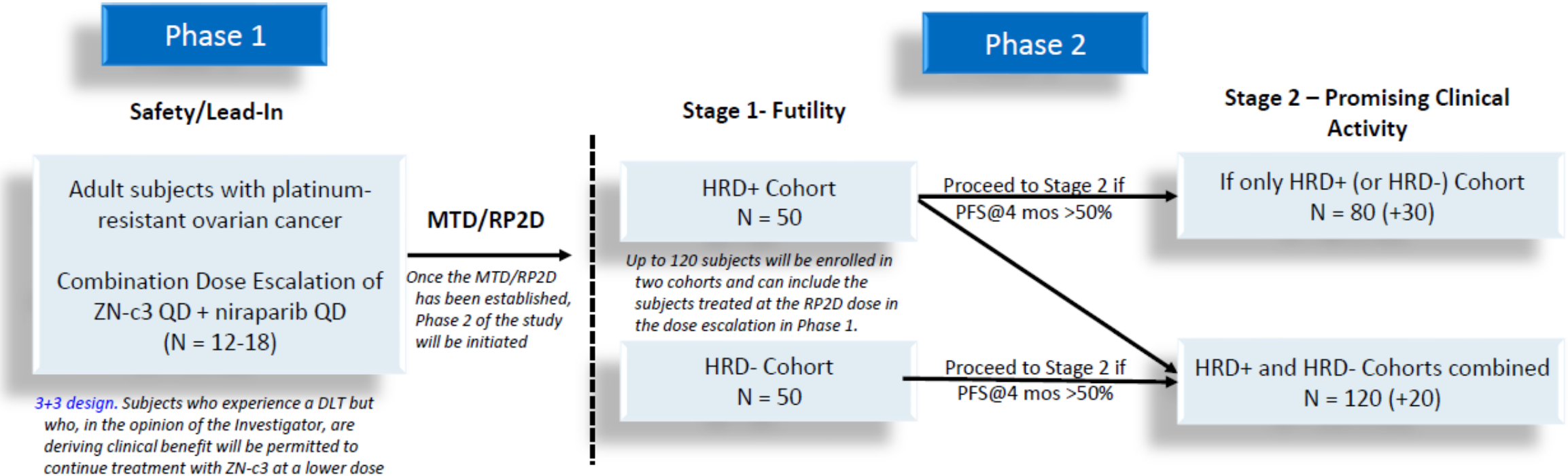


- WEE1 is a protein kinase expressed at high levels in many cancer types that prevents entry into mitosis in response to DNA damage by regulating the G2 checkpoint
- WEE1 inhibition causes cancer cells to proceed to mitosis without repairing DNA damage, resulting in premature mitotic entry and apoptosis
- ZN-c3 has demonstrated significant growth inhibition and induced apoptosis *in vitro* and anti-tumor activity *in vivo*

Source: Drawing based on Targeting WEE1 Kinase in Cancer. Matheson CJ, et al. Trends Pharmacol Sci. 2016

Overall Study Design

- **Phase 1/2 Study Design: ZN-c3 in combination with Niraparib**
  - Approximately 140 adult subjects with Platinum-resistant Ovarian Cancer will be enrolled
    - Adults with advanced platinum-resistant ovarian cancer who have failed PARP inhibitor (PARPi) maintenance therapy (PARPi treatment interval < 6 months due to progressive disease)



3+3 design. Subjects who experience a DLT but who, in the opinion of the Investigator, are deriving clinical benefit will be permitted to continue treatment with ZN-c3 at a lower dose that is deemed "safe" by the model, upon reasonable resolution of the DLTs.

Abbreviations: HRD= homologous recombination deficiency; N= number of subjects; PFS= progression-free survival

Cancer de l’ovaire en première ligne

Chirurgie première

(NIRVANA)

↓

Chirurgie intervallaire

CHRONO

↓

Cancer de l’ovaire en rechute platine sensible

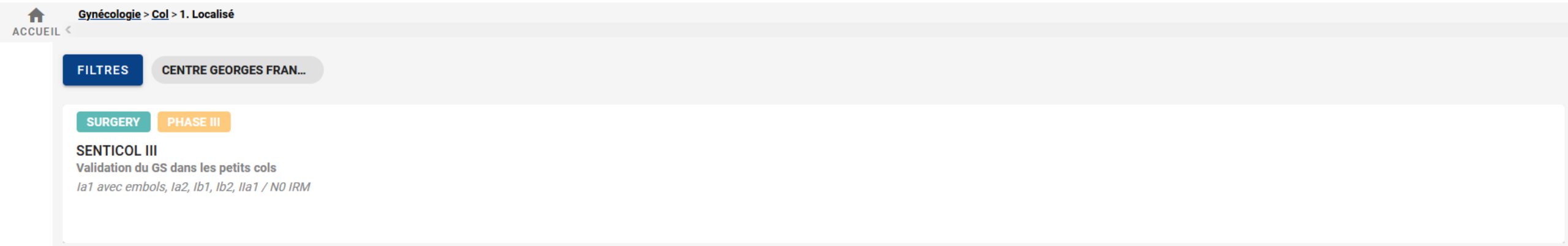
Reprise chimiothérapie par doublet de platine +/- maintenance

TEDOVA

Cancer de l’ovaire en rechute platine resistante

Chimiothérapie *Zn-C3-006*

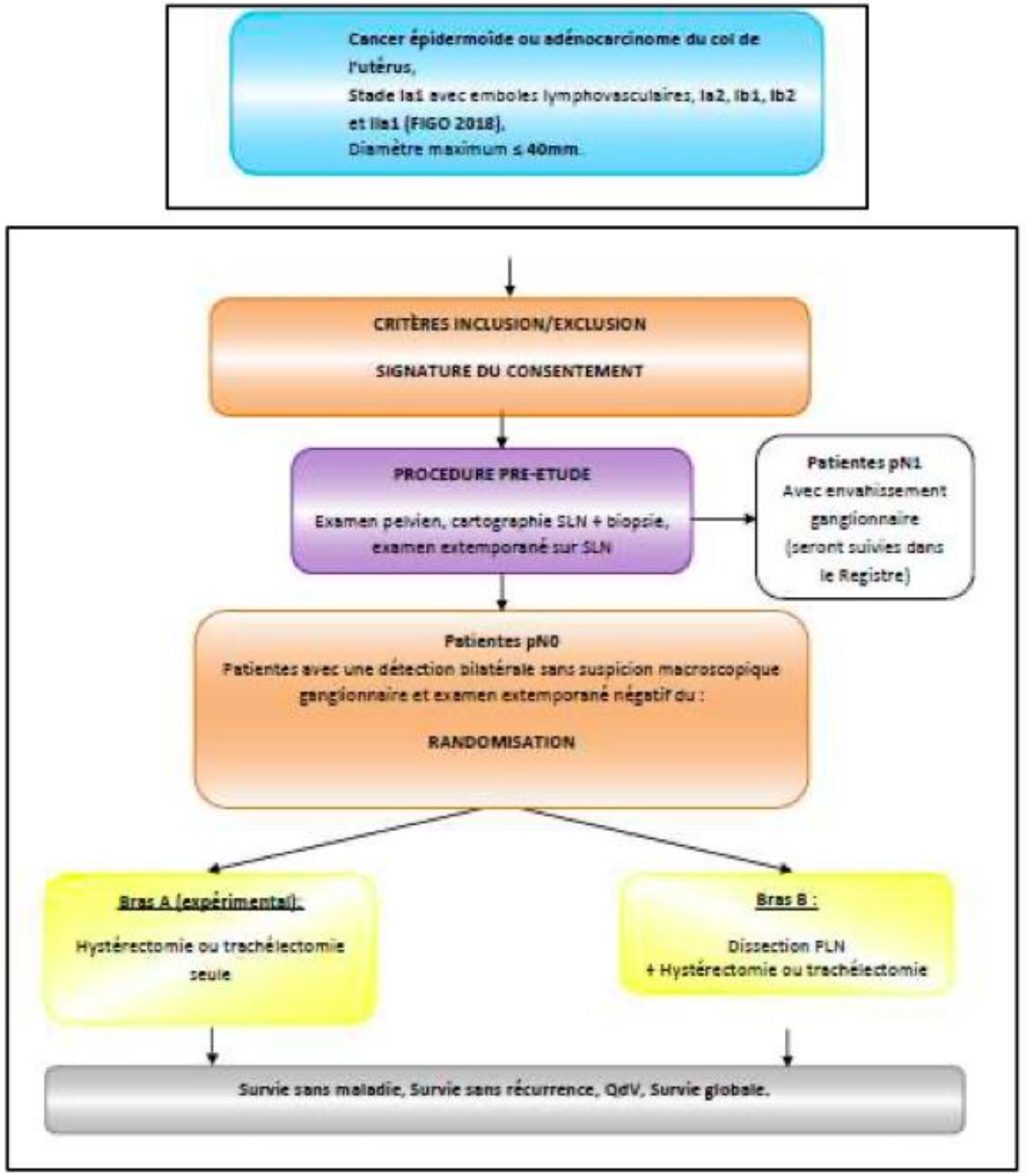
Cancer du col : localisé



SENTICOL III

CRITÈRES D'INCLUSION

1. Carcinome épidermoide ou un adénocarcinome du col de l'utérus (prouvé par une biopsie ou une biopsie conique),
2. Stade Ia1 avec emboles lymphovasculaires, Ia2, Ib1 et IIa1 (stade clinique) de la classification 2009 de la FIGO.
3. Diamètre maximal ≤ 40 mm à l'examen clinique et à l'imagerie par résonance magnétique (IRM),
4. INo ganglion suspect sur l'IRM pelvienne et abdominale avec une exploration jusqu'à la veine rénale fémorale gauche (selon RECIST 1.1),
5. Statut de performance 0-2 de l'Eastern Cooperative Oncology Group (ECOG),
6. Consentement éclairé signé et capacité à se conformer au suivi,
7. Sujets français : en France, un sujet sera éligible pour l'inclusion dans cette étude seulement s'il est soit affilié à, soit bénéficiaire d'une catégorie de sécurité sociale.



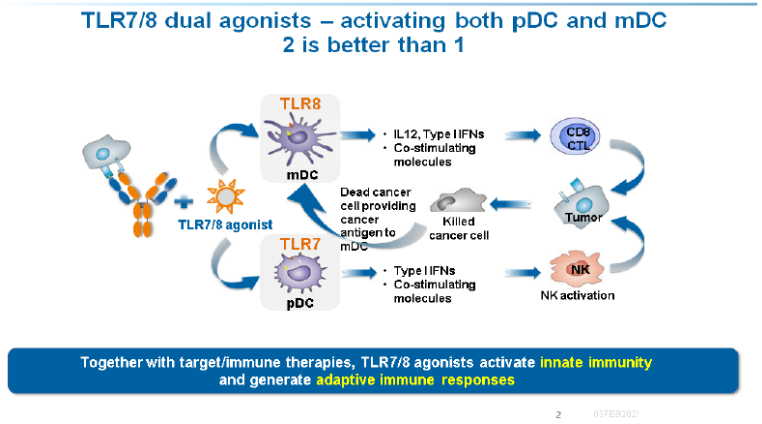
Cancer du col métastatique

- **2 enjeux :**
  - l’immunothérapie le plus précocement possible
  - Des solutions après immunothérapie

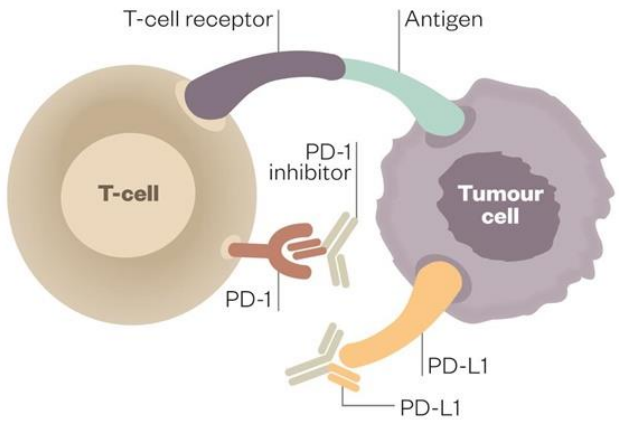
Rechute après platine : AGADIR

Etude AGADIR (Institut Bergonié)

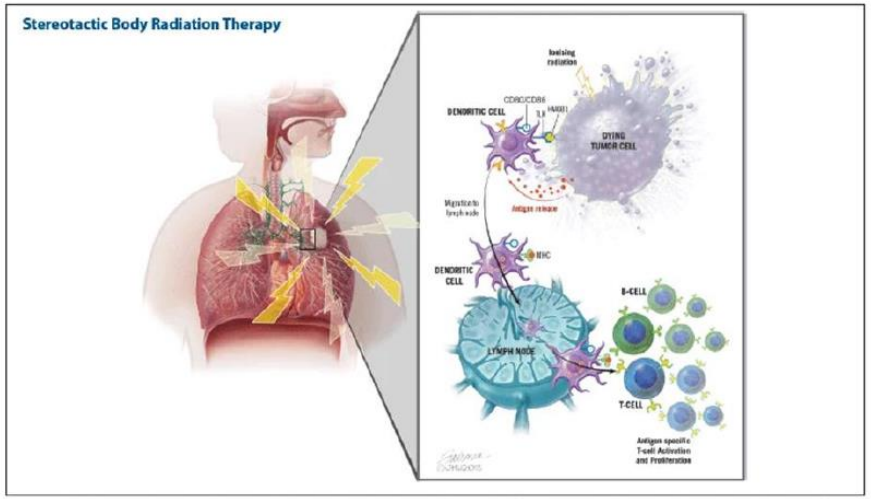
Résumé :
C'est une étude multicentrique, prospective, en ouvert, de type « basket » pour évaluer de manière indépendante et simultanée l'éfficacité de l'association atezolizumab + BDB001 + RT dans plusieurs types de tumeurs solides avancées.
-Population 1 : Cancer du pancréas
-Population 2 : Tumeurs viro-induites
-Population 3 : Cancer bronchiques non à petites cellules
-Population 4 : Sarcomes des tissus mous
-Population 5 : Cancer de la vessie
-Population 6 : Cancer du sein triple négatif
Le cycle du traitement dure 21 jours



+



+



Potential Immune-Stimulatory Effects of SBRT for Lung Tumors—SBRT induces inflammatory cell death and activation of dendritic cell and antigen presentation in the draining lymph node, resulting in antigen-specific adaptive immune responses. SBRT = stereotactic body radiation therapy.

CRITERES D'INCLUSION (1/4)

- 1. Histologie : diagnostic histologiquement confirmé de **cancer pancréatique** (population 1), de **tumeur virо-induite** [incluant les cancers liés au papillomavirus (col de l'utérus, tête et cou, anal), les cancers liés au virus Epstein-Barr (carcinome nasopharyngé), les sarcomes de Kaposi associés au virus de l'herpès] (population 2), de **cancer bronchique non à petites cellules** (population 3), **de sarcome des tissus mous** (population 4), de **cancer de la vessie** (population 5) ou de **cancer du sein triple négatif** (population 6). *Pour la population 4, le diagnostic devra être confirmé et revu dans le cadre du réseau RRePS selon les recommandations de l'Inca.*
- 2. Maladie **métastatique**,
- 3. Age ≥ 18 ans,
- 4. ECOG, Performance status ≤ 1,
- 5. Au moins 2 lésions : une **lésion qui peut être traitée par radiothérapie** et une **lésion mesurable selon les critères RECIST** [(plus grand diamètre) ≥ 10 mm et en dehors de champs d'irradiation, sauf si progressive à l'inclusion]. Cette dernière lésion ne devra pas être irradiée. A noter toutefois que les lésions qui seront traitées par radiothérapie pourront être considérées comme mesurables si elles répondent à la définition des critères RECIST. A noter que les lésions irradiées ne peuvent excéder une taille maximale de 3 cm,
- 6. Espérance de vie > 6 mois,
- 7. Présence d'**une lésion tumorale qui puisse être biopsiée pour la recherche**. Les lésions tumorales à proximité des structures vasculaires telles que les gros vaisseaux, anévrysme ou malformation artério-veineuse pulmonaire ne pourront être considérées comme des lésions pouvant être biopsiées,
- 8. Disponibilité de matériel tumoral archivé (FFPE) pour la recherche,

GYNET

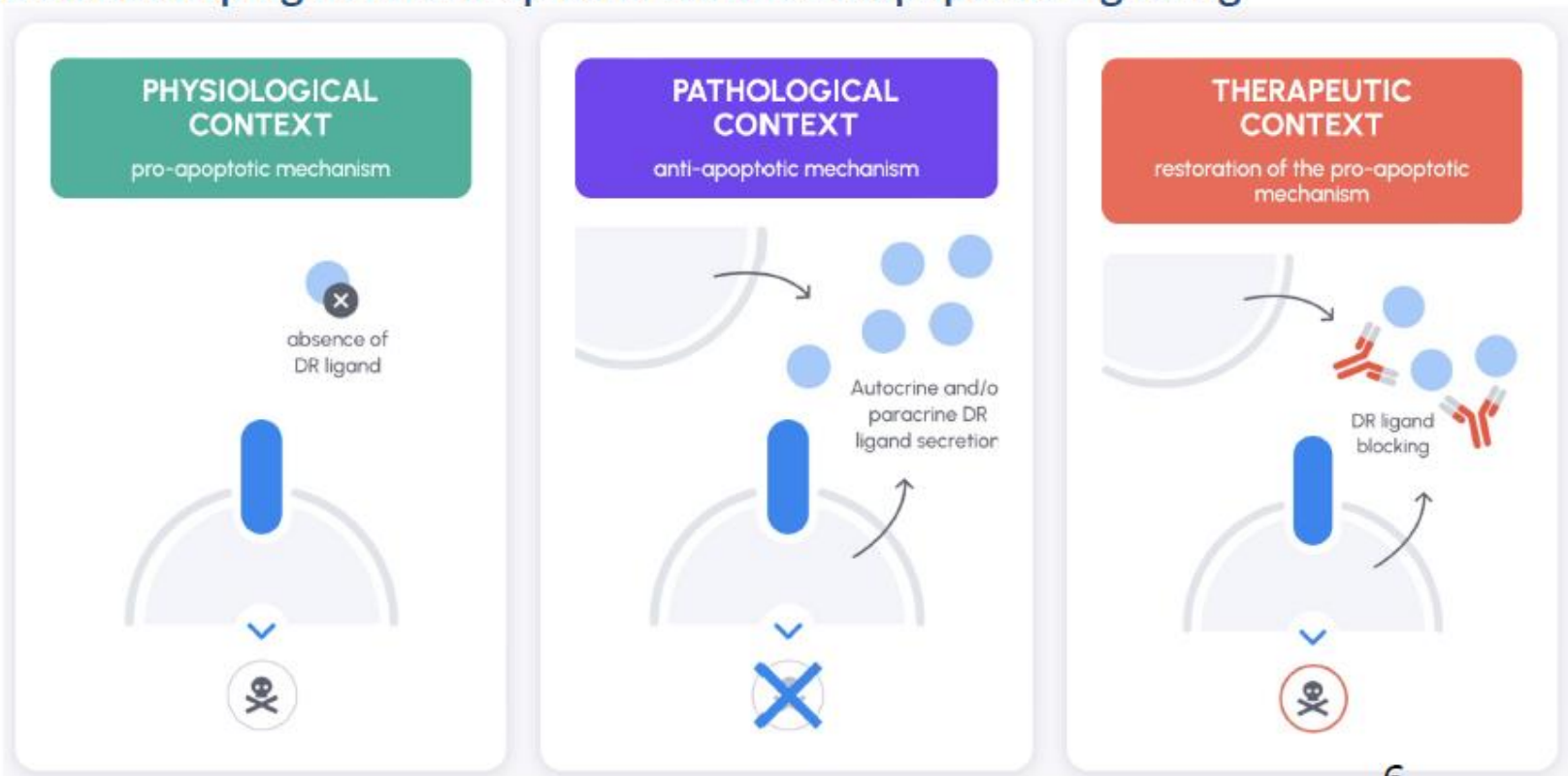
A randomised, multicentre, open label, Phase I/II study to evaluate the safety (Phase I - safety run in), clinical and biological activity (Phase II) of a humanized monoclonal antibody targeting Netrin-1 (NP137) in combination with carboplatin plus paclitaxel and/or pembrolizumab in patients with locally advanced/metastatic endometrial carcinoma or cervix carcinoma progressing/relapsing after at least one prior systemic chemotherapy.

Sponsor : Netris Pharma
Chief Investigator : Pr Isabelle Ray Coquard,
Coordinating center : DRCI – Centre Léon Bérard

ANR-18-RHUS-0009 EudraCT Number: 2020-000172-38 Sponsor ID: NP137-CT-02 / ET 20-049

Netris Pharma, in a glimpse

- NETRIS Pharma is a privately held biotech based in Lyon, France
- First Spin-off from Centre Léon Bérard
- Focused on developing novel therapies to restore DR apoptosis signaling



STUDY DESIGN

Overview

Cohort 1: locally advanced / metastatic endometrial carcinoma

Cohort 2: locally advanced / metastatic adenocarcinoma or epidermoid cervix carcinoma

R

- **Arm A : Carboplatin + Pactitaxel**
- **Arm B : Carboplatin + Pactitaxel + NP137**
- **Arm C : NP137 + Pembrolizumab**
- **Arm D : Carboplatin + Pactitaxel + Pembrolizumab + NP137**

Validation by an iDMC

BAYESIAN APPROACH

Phase I	Phase II	
SAFETY RUN IN N = 6 à 12	**PRELIMINARY PHASE** N = 14	**EXPANSION PHASE** N = 22 ; 30

NP137 Dose Level : 14mg/Kg

- Independently of tumour type

N = 6 to 12 patients

- Per tumour type
- Sequential analysis

Up to 30 patients per arm and per cohort (including patients from Safety run in period)

- **Stratification criteria :**
  - The number of prior chemotherapy lines before inclusion (1L versus > 2L or 3L)
  - The mutational status (MSI/MSS) for endometrium carcinoma only
- **No cross over allowed**

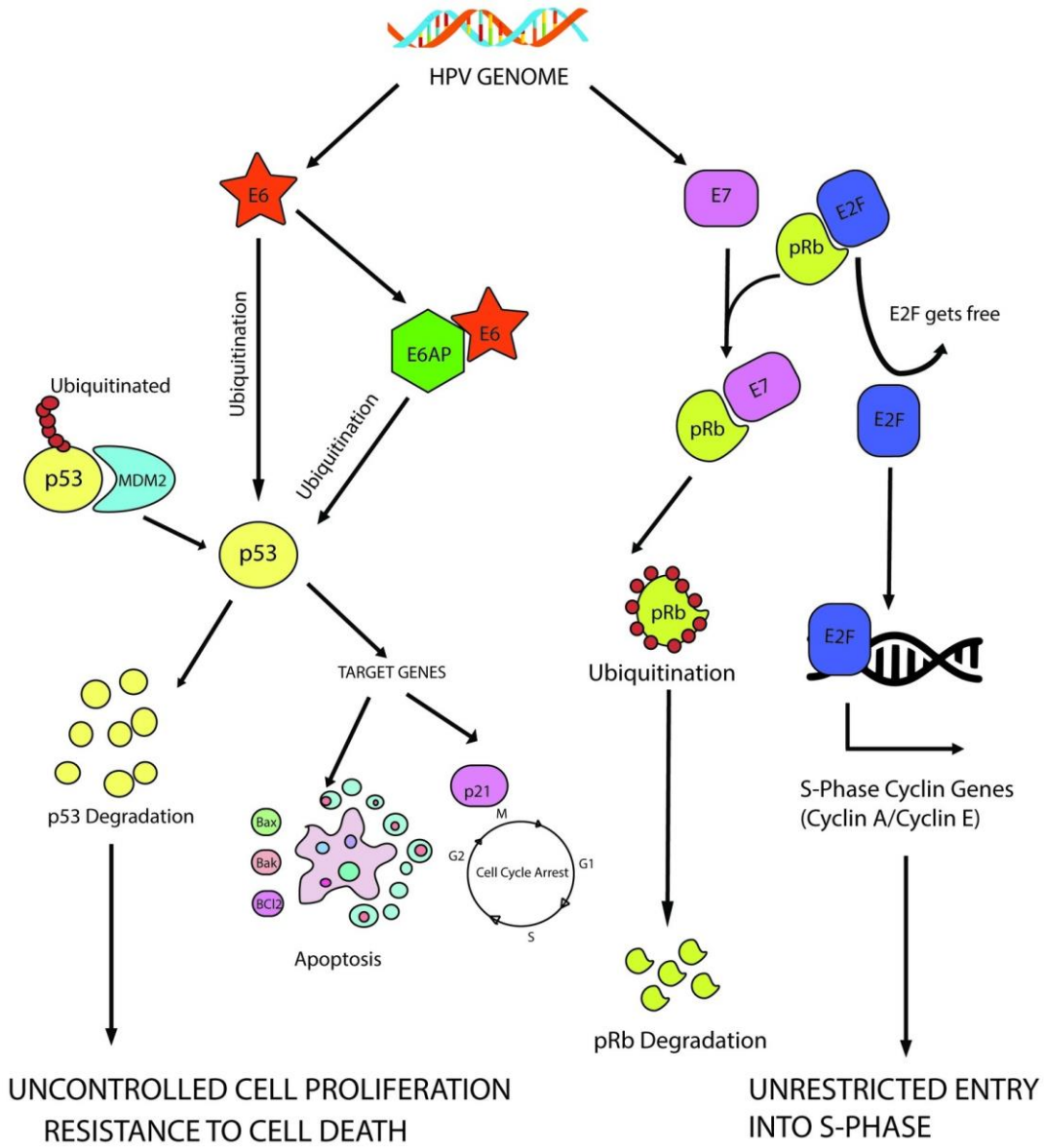
Stop for futility if Prb (ORR < 20%) > 95%

Stop for efficacy if Prb (ORR ≥ 30%) > 90%

TG4001 therapeutic vaccination combined with PD-L1 blocker avelumab in Human Papilloma Virus HPV-16+ malignancies

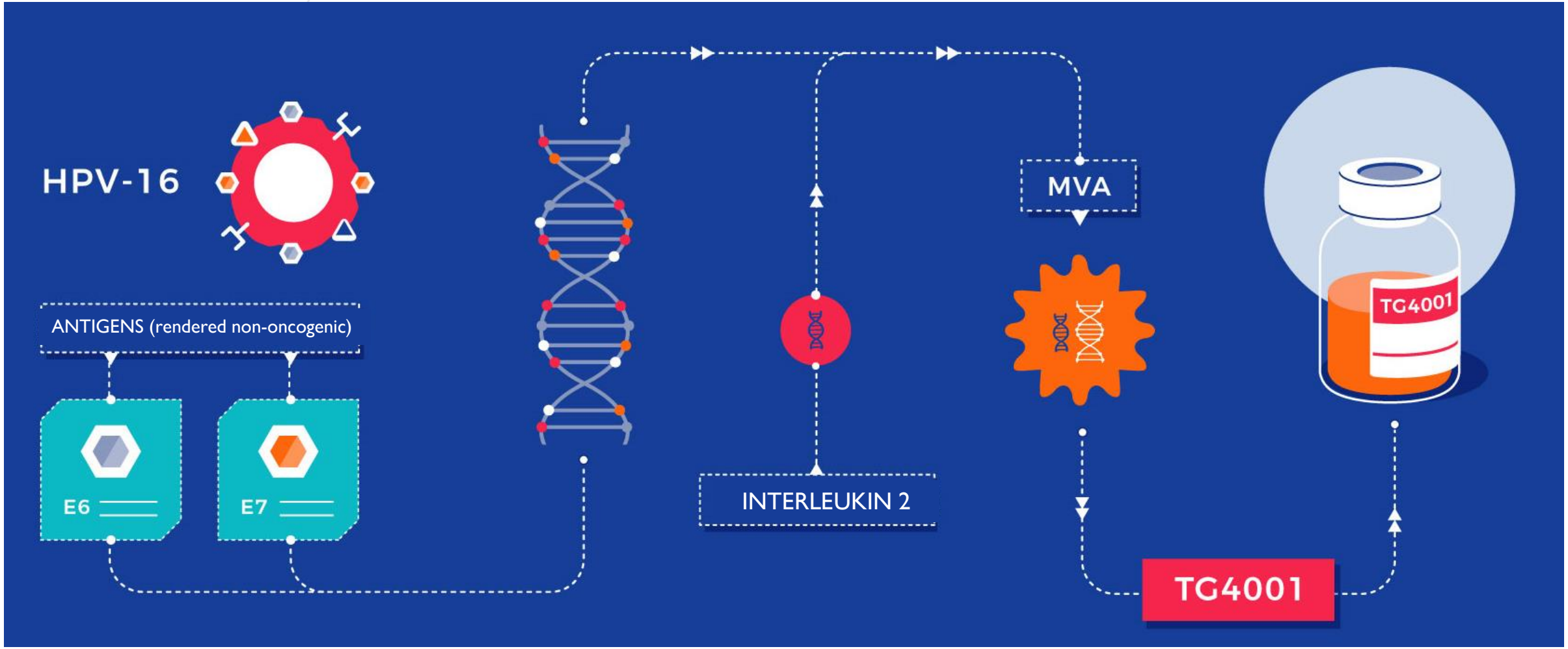
Clinical Trial TG4001.12

18 January 2023


HPV GENOME
E6
E7
E2F
pRb
E2F gets free
Ubiquitination
E6AP
E6
Ubiquitinated
p53
MDM2
Ubiquitination
E7
pRb
E2F
p53
pRb
Ubiquitination
E2F
TARGET GENES
p21
M
G2
Cell Cycle Arrest
G1
S
Bax
Bak
BCl2
p53 Degradation
Apoptosis
S-Phase Cyclin Genes
(Cyclin A/Cyclin E)
pRb Degradation
UNCONTROLLED CELL PROLIFERATION
RESISTANCE TO CELL DEATH
UNRESTRICTED ENTRY
INTO S-PHASE

TG4001 | Therapeutic Vaccine Targeting HPV-Positive Cancers

Click to edit Master title style



TG4001 – Therapeutic vaccine

Click to edit Master title style

Vector

Attenuated MVA

(Modified Vaccinia virus, strain Ankara)
highly attenuated
used for small pox eradiacation campaign

E6 and E7 antigens

(rendered non-oncogenic)

IL-2

DESIGNED TO **BOOST** THE **PATIENT'S IMMUNE SYSTEM** AGAINST THE TUMOR

1. **Targeted response against tumor cells carrying the HPV-16 E6 & E7 antigens**
2. **Stimulate the infection-clearing activity** of the immune system through **interleukin 2 (IL-2)**
3. Well established **safety profile**

transgene

TG4001 | Randomized Controlled Phase II Trial Supported by Clinicians

Main Cohort: Patients with HPV16+ recurrent / metastatic anogenital cancer

Without liver metastases at Baseline

Randomized (1:1)

Arm **A** — TG4001 + avelumab

Arm **B** — Avelumab single agent

PRIMARY ENDPOINTS

- **Progression-Free Survival** (RECIST 1.1)

SECONDARY ENDPOINTS

- **Overall Response Rate**
- **Disease Control Rate**
- **Overall Survival**
- **Other Immunological Parameters**

Ancillary Cohort: Patients with HPV16+ recurrent / metastatic anogenital cancer

With liver metastases at Baseline

Randomized (1:1)

Arm **A** — TG4001 + avelumab

Arm **B** — Avelumab single agent

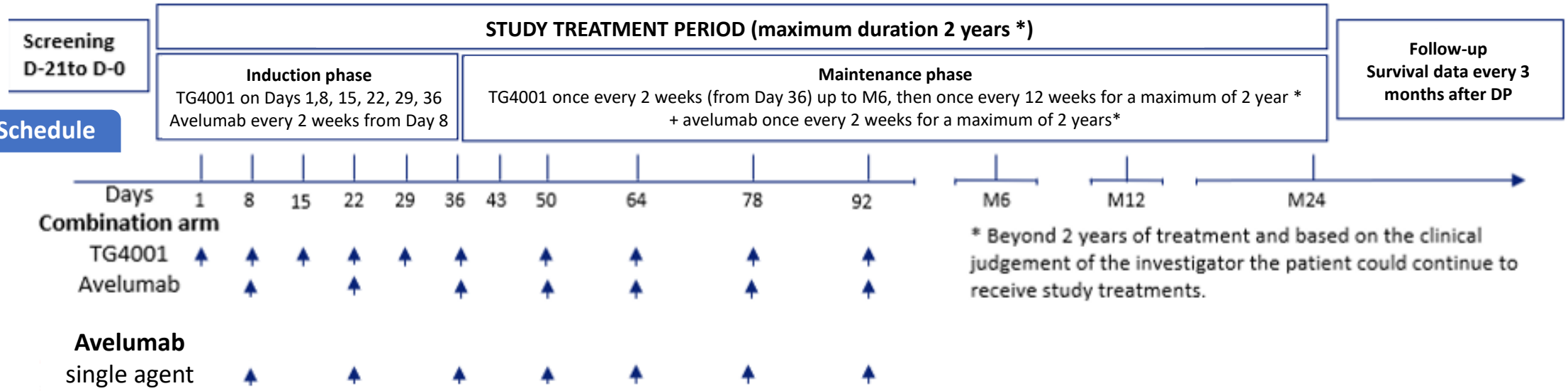
ENDPOINT : **Percentage of progressors at Day 43, max. 10 patients per arm**

transgene

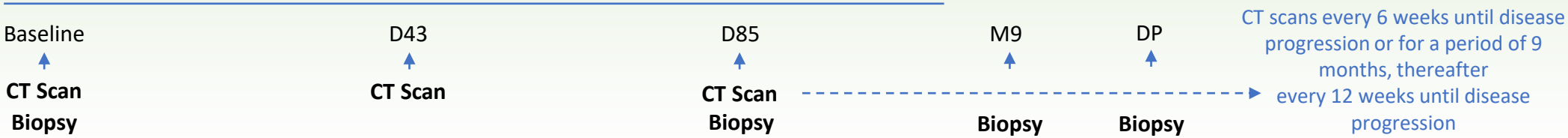
TG4001 + Avelumab (Randomized Ph II part 2) | Administration Schedule

Click to edit Master title style

Schedule



Monitoring & samples



Blood samples *(immuno): Please refer to study flowchart*

- **TG4001:** $5x10^7$ pfu – administered SC
- **Avelumab:** 800mg – administered IV

TG4001.12 Phase II part 2 Eligibility

Inclusion Criteria

1. Signed written informed consent to accordance with ICH-GCP and national/local regulation before any protocol-related procedures that are not part of normal patient care *(e.g. CT or MRI, biopsy, determination of HPV-16 positivity by specified central laboratory)*
2. Female or male patients, aged 18 to 80 years
3. Eastern Cooperative Oncology Group (ECOG) **Performance Status 0 or 1** (Appendix I)
4. Life expectancy of at least 3 months
5. Patients with histologically or cytologically documented metastatic or refractory/recurrent **HPV-16+ cancer (determined in an accredited central laboratory using a validated assay)**
6. **Patients with HPV-16+ cancers including cervical, vulvar, vaginal, penile, and anal cancer**
7. Disease MUST not be amenable to curative surgery resection or curative radiotherapy with documented disease progression after concertation with multidisciplinary board

transgene

*amendement on going: not approved yet

TG4001.12 Phase II part 2 Eligibility

Inclusion Criteria

8. **Prior therapy: For recurrent /metastatic disease no more than one prior line of chemotherapy which can contain a platinum**

Prior treatment for recurrent or metastatic disease is not required for:

- Patients - Patients whowith recurrence/progression within 6 months after completion of prior multimodal therapy for localized or locally advanced disease not amenable to curative treatment

are unsuitable for platinum-based therapy

- Patients who refuse chemotherapy or other standard therapies for the treatment of metastatic or recurrent disease. The benefit of an immunotherapy over standard therapies must be validated by the medical board and duly documented.

A minimum of 4 weeks interval should have elapsed between the completion of the last chemotherapy and study treatment start

A minimum of 4 weeks interval between palliative bone directed radiotherapy and the start of the study treatment provided that radiation therapy does not affect the unique measurable lesion, if applicable

9. **For patients with hepatic metastases**

- no more than 3 hepatic lesions in total (target and non-target lesions)

- maximum size of hepatic target disease ≤ 30 mm according to RECIST 1.1

transgene

Cancer du col localisé

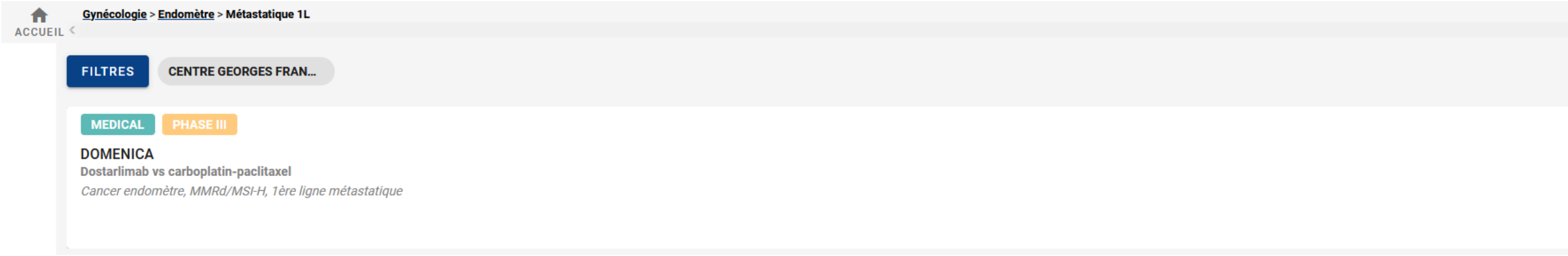
Petit col : *SENTICOL III*

Cancer du col métastatique

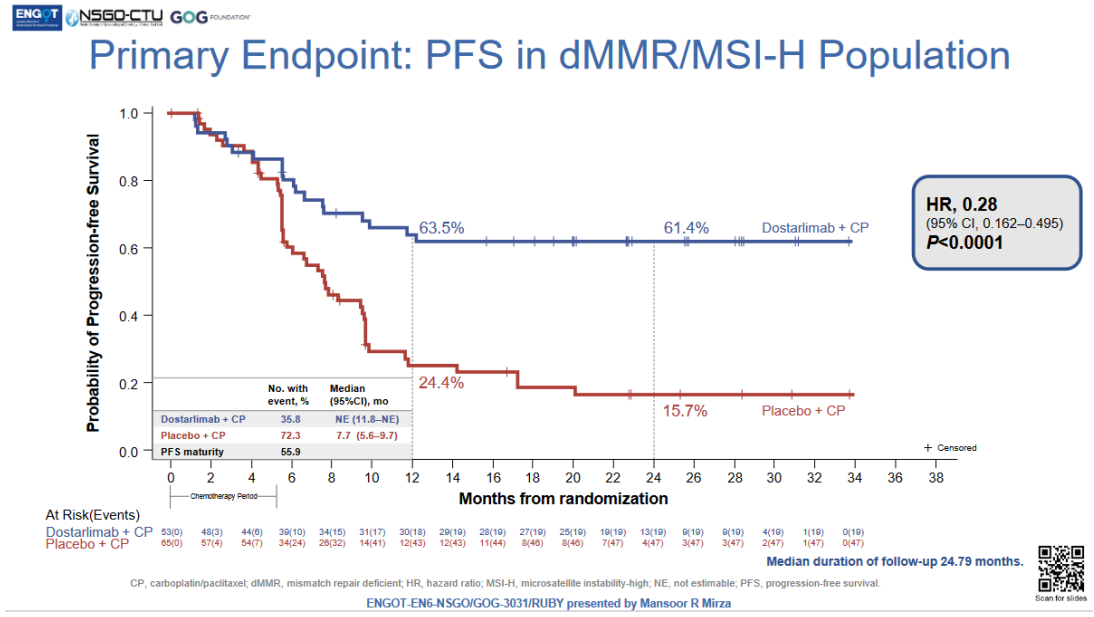
1ere ligne : *TRANSGENE à venir*

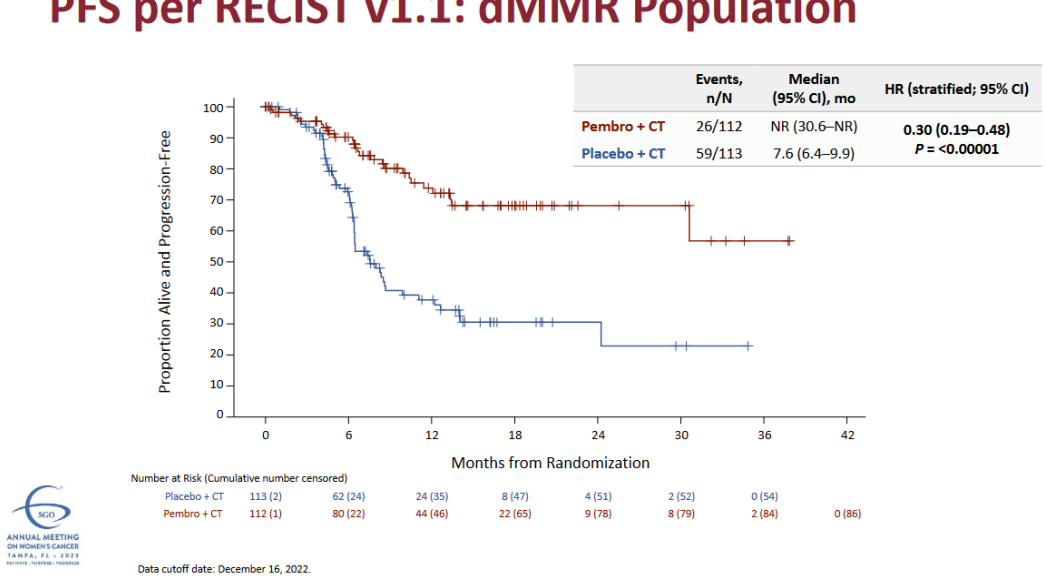
2e ligne et plus :
HPV16+ *: TRANSGENE à venir*
HPV +/- : *GYNET*

Cancer de l’endomètre métastatique



RUBY et NRG GY018

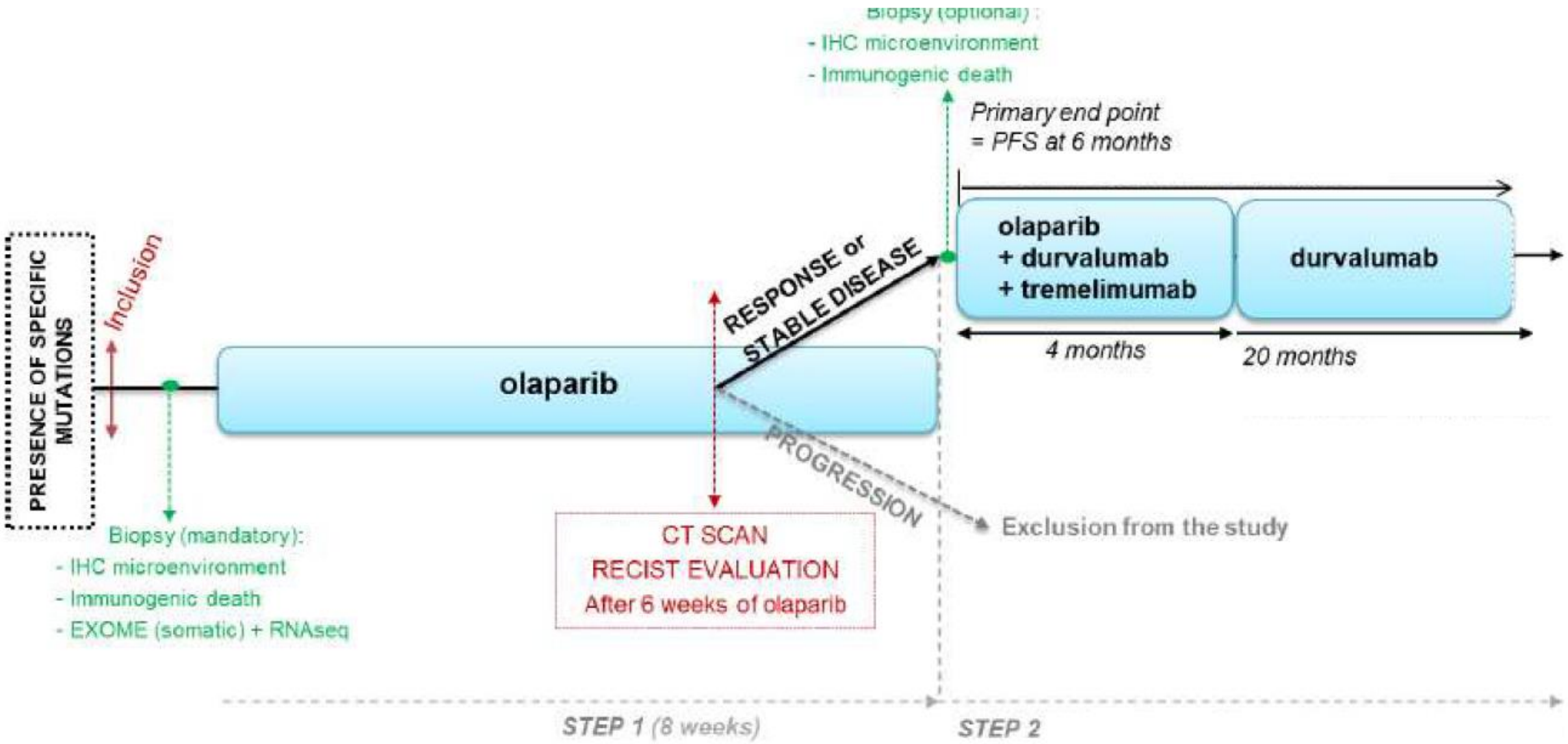




Cancer de l’endomètre

- <u>Métastatique</u>
  - L2 et plus :
    - *GYNET*
    - selon les biologie moléculaire : *GUIDE2REPAIR, RLY 4008-101, NAV-1003*

Etude GUIDTOREPAIR

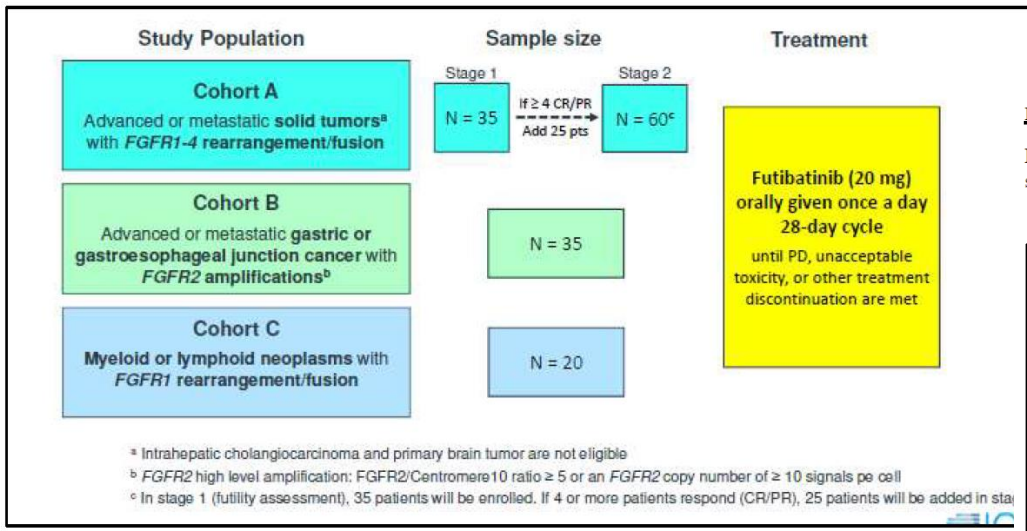


En cas d'anomalie FGFR (10-12% des cancers de l'endomètre)

Etude RELAY RLY-4008-101
Phase I

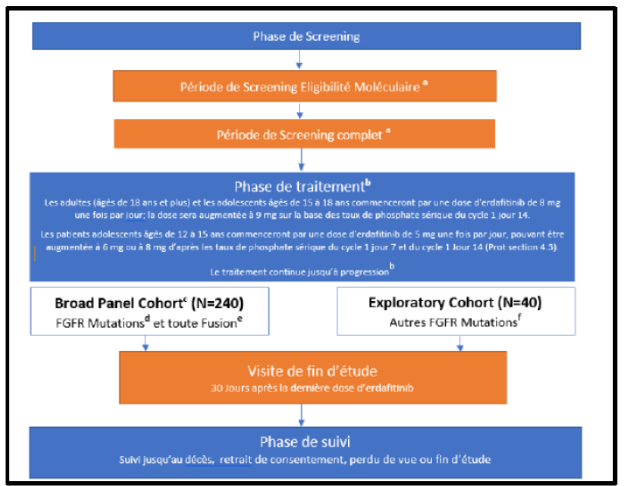
Résumé :
C'est une première étude chez l'homme évaluant un inhibiteur hautement séléctif du FGFR2, le RLY-4008, chez des patients atteints de cholangiocarcinome intrahépatique (CCI) et d'autres tumeurs solides à un stade avancé.
Le cycle du traitement dure 4 semaines (28 jours)

« TAS 120 »
Etude du futibatinib chez des patients atteints d'altération de FGFR.



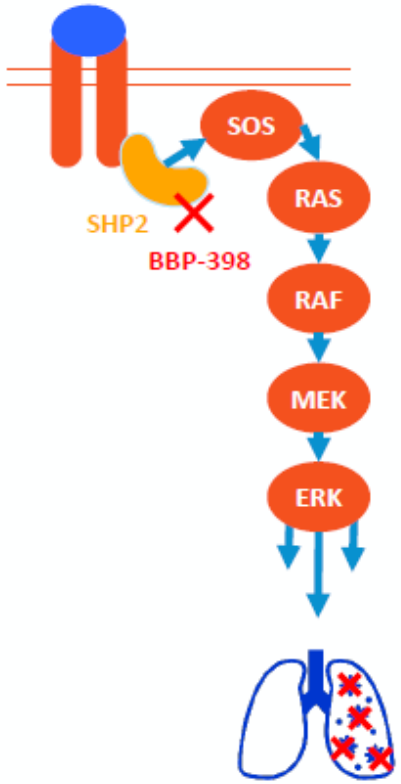
RAGNAR

Étude de Phase 2 évaluant l'erdafitinib chez les patients atteints de tumeurs solides avancées avec des altérations des gènes FGFR.

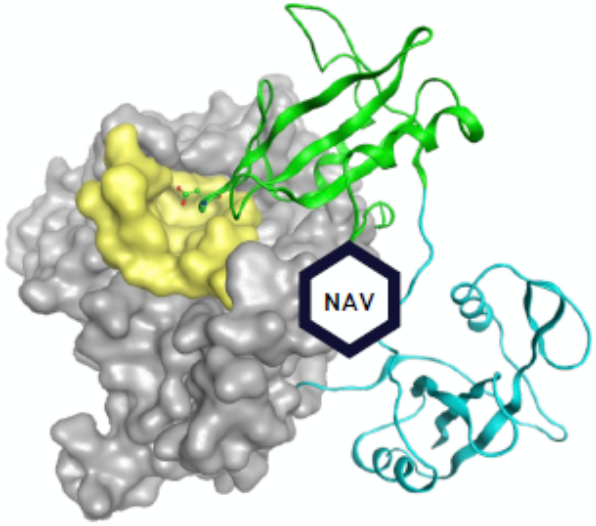


Navire has developed “molecular glue” that holds SHP2 in its inactive confirmation

Illustration of Navire’s mechanism of selective SHP2 inhibition

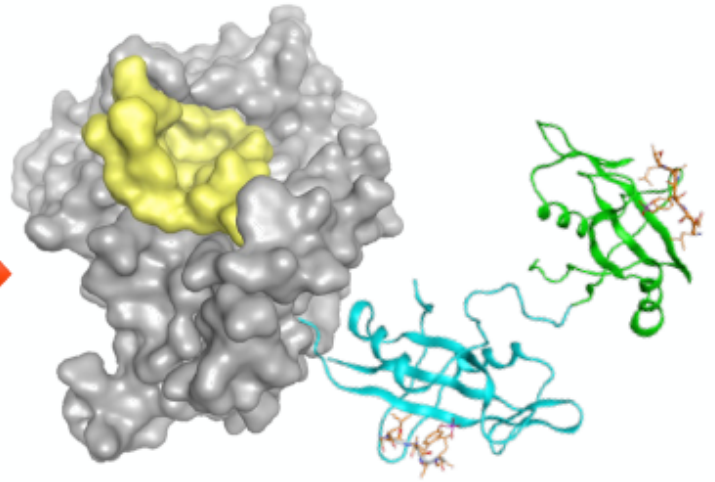


Inactive SHP2



BBP-398 interacts with all three key domains (PTP, N-SH2, C-SH2) to favor SHP2’s inactive conformation

Active SHP2



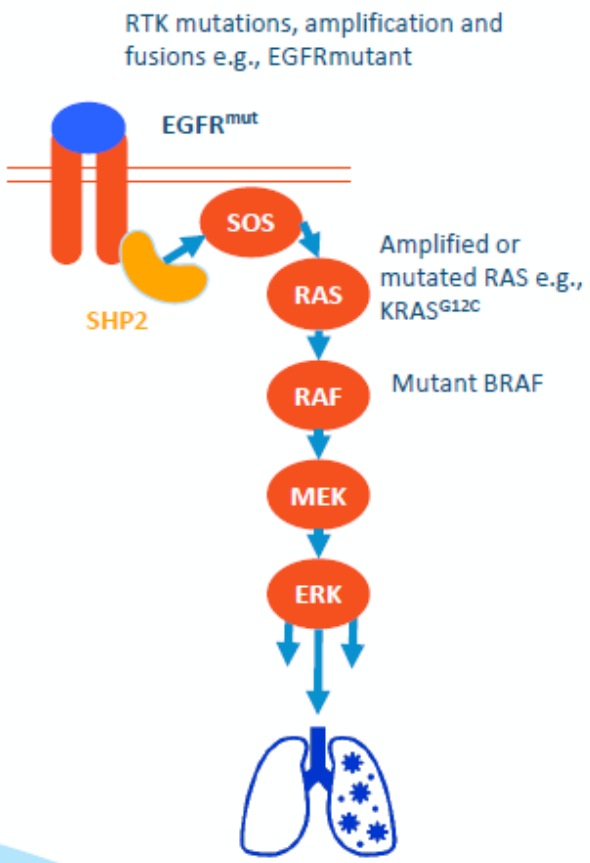
Stabilization of SHP2’s inactive confirmation reduces the concentration of active SHP2 in this equilibrium

» BBP-398 is a selective, orally bioavailable, allosteric inhibitor of SHP2, offering potential to treat the variety of tumors that rely on SHP2 activity for proliferation/survival

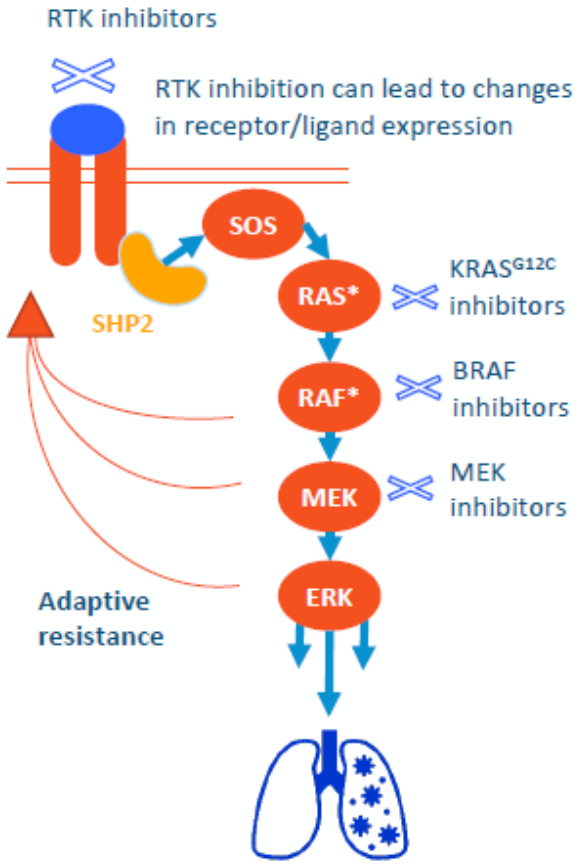
SHP2 is a regulator of the MAPK pathway; its inhibition mitigates cancer signaling and resistance

MAPK signaling drives proliferation, survival, adhesion, and migration

Overactive MAPK activity leads to oncogenesis, tumor growth and invasion



SHP2 regulates adaptive resistance, including RTK/GF expression changes and relief from feedback inhibition



Key inhibitor properties for a wildtype target in the MAPK pathway (e.g., SHP2i and MEKi)

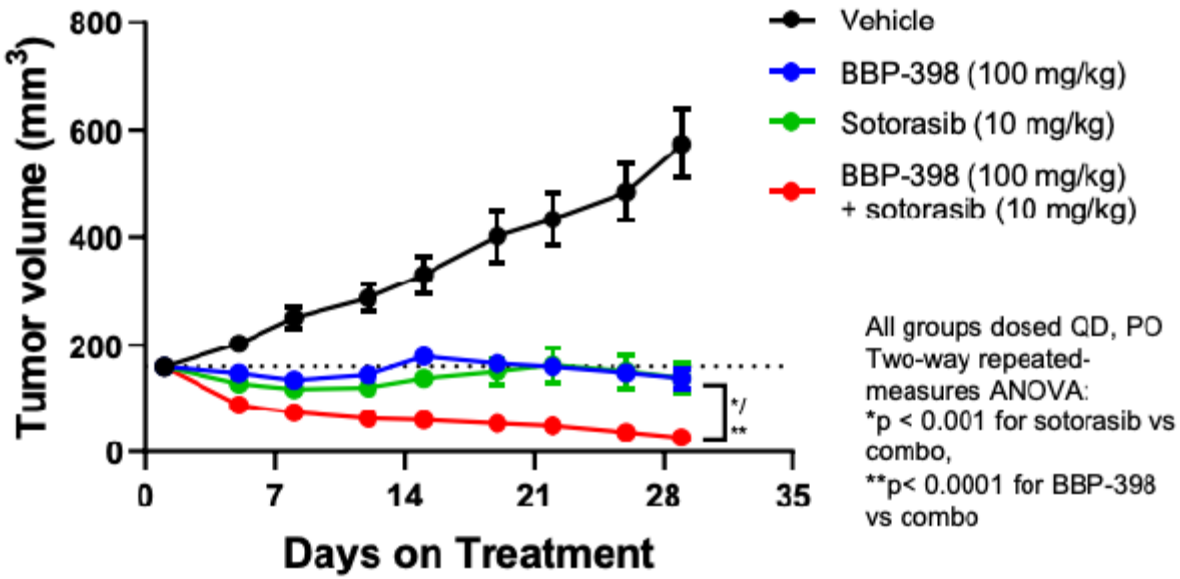
Potency: demonstrates robust target engagement at tolerated doses

Relatively short half-life: providing target coverage over threshold for most of the PK interval (70-80%), while allowing for recovery underneath threshold for normal cells

- Most importantly, this PK profile permits dose reduction in combination that still achieves meaningful target inhibition

Tolerable continuous daily dosing: convenient for dose optimization in combination

NCI-H358 ($KRAS^{G12C}$) - NSCLC CDX

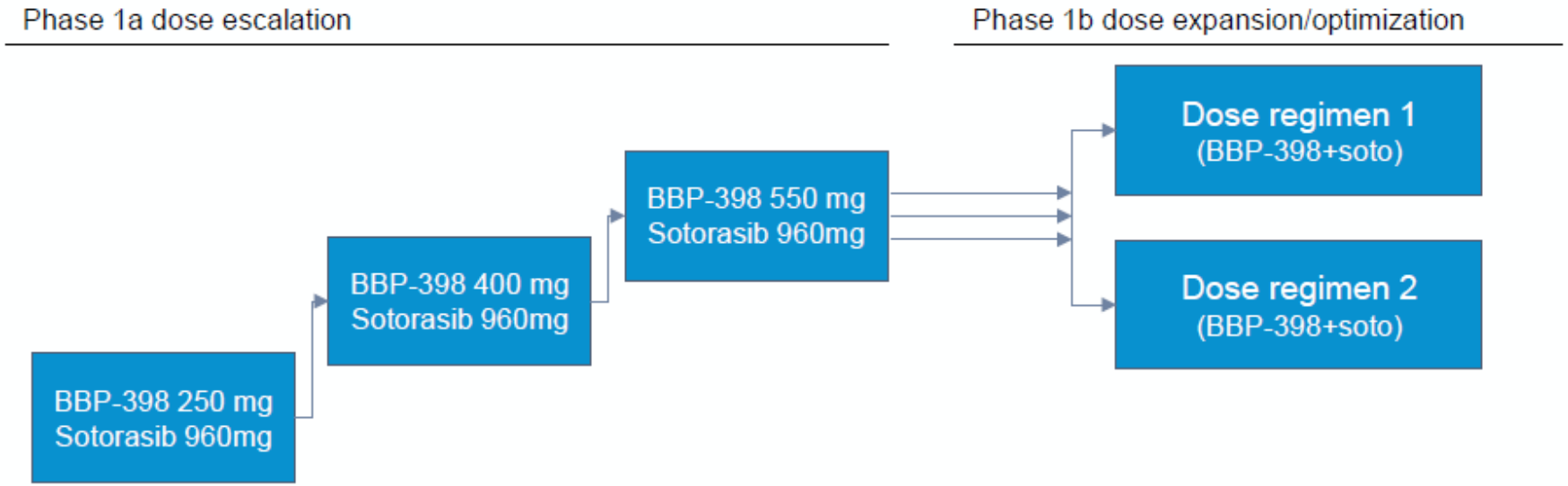


All groups dosed QD, PO
Two-way repeated-measures ANOVA:
*p < 0.001 for sotorasib vs combo,
**p< 0.0001 for BBP-398 vs combo

Group (n=10)	Day 29		
	Mean tumor regression	Number of regressions	Mean body weight change
Vehicle	-	0/10	+5.1%
BBP-398 (100 mg/kg)	14%	8/10	-6.5%
Sotorasib (10 mg/kg)	13%	9/10	-0.3%
BBP-398 (100 mg/kg) + sotorasib (10 mg/kg)	83%	10/10	-2.4%

NAV-1003: a Phase 1 study investigating BBP-398 and sotorasib for KRAS-G12C mutant solid tumor/NSCLC

Study Schematic



- BOIN dose escalation
- N=~5 per dose level
- Number of sites: ~12

- N= ~30 per cohort
- Number of sites: ~30
- Subjects randomized

Projected trial timelines

Q3 2022 → Q4 2022 → Q2 2023 → Q3 2023

Patient population highlights:

- Diagnosis of local advanced (primary or recurrent) and unresectable or metastatic solid tumor
- Documentation of a KRAS G12C mutation from a local or central laboratory in tumor or liquid biopsy samples collected within 2 years prior to screening
- In dose expansion only:
  - NSCLC naïve to treatment with KRASG12Ci
  - Documentation of progression or recurrent disease on or after one prior line of systemic therapy, which must include platinum-based doublet chemo and/or anti-PD-(L)1 therapy

Inclusion Criteria (1/3)

1. **Individuals ≥18 years old and be willing and able to provide signed informed consent** at the Screening Visit as well as comply with all study visits and requirements through the end of the study.

2. **Documentation of a KRAS-G12C mutation** from local or central laboratory testing in tumor or liquid biopsy samples, collected within 2 years prior to screening, and have no other previously identified targetable driver mutations.

3. **Measurable disease** by **RECIST v1.1.**

4. **Minimum life expectancy of >12 weeks** after the start of study treatment according to the investigator's judgement.

5. Women of **childbearing potential** MUST have:

- **Negative serum human chorionic gonadotropin test** during screening and within 48 hours of initiating dosing or
- Had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy, or
- Had menopause (defined as 12 consecutive months of amenorrhea; if not known, FSH should be performed to confirm).

Cancer de l’endomètre localisé

Pas d’études disponibles

Cancer de l’endomètre métastatique

1ere ligne : *DOMENICA si MSI + inclusion EXOMA 2*

2e ligne
- Anomalie RH : *GUIDTOREPAIR*
- MSS/MSI : AAP Levantinib Pembrolizumab ou *GYNET*
- Anomalie FGFR : *RELAY*
- KRAS G12C : *NAV-1003*

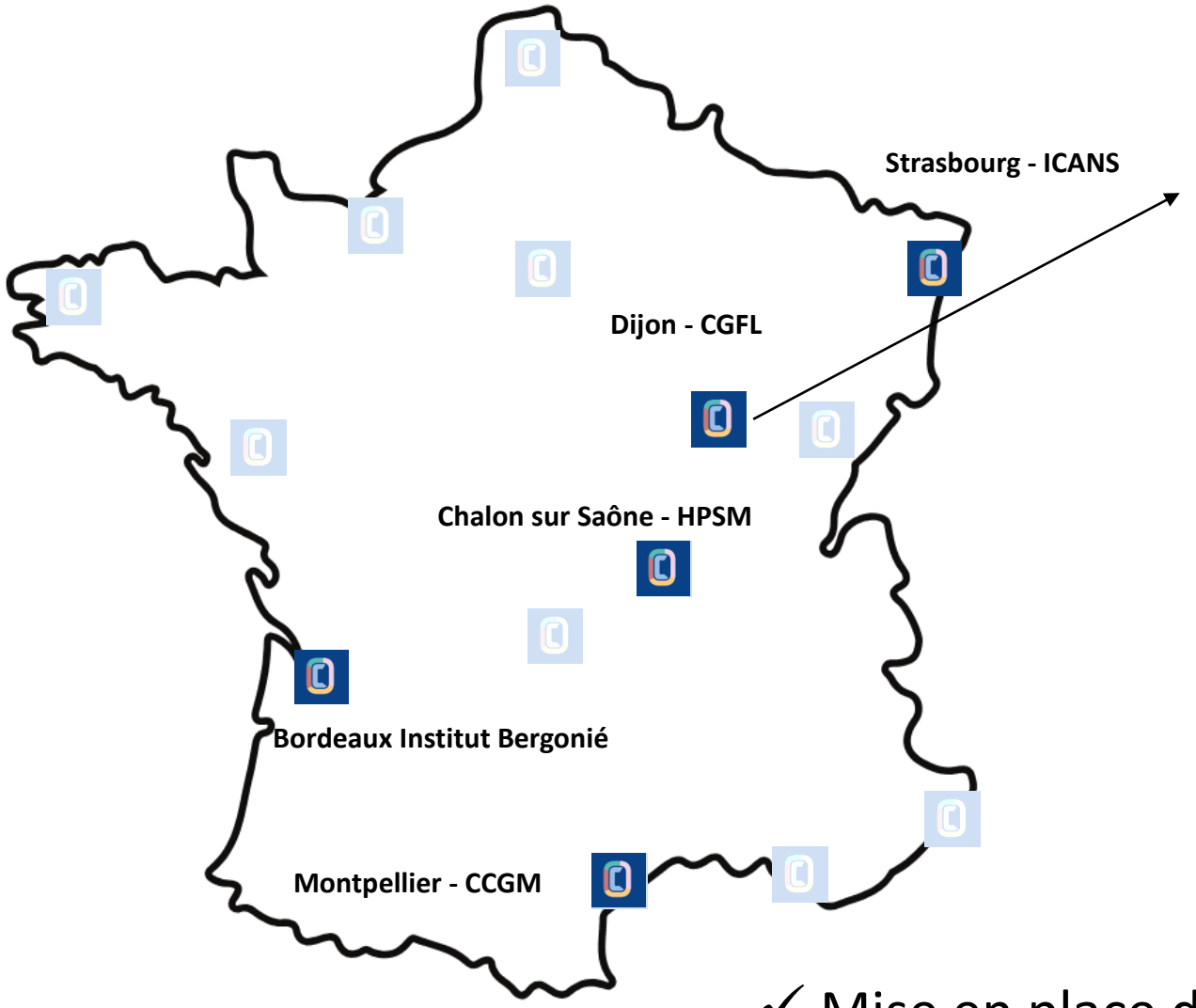
Notre objectif : informer, assister et accompagner !

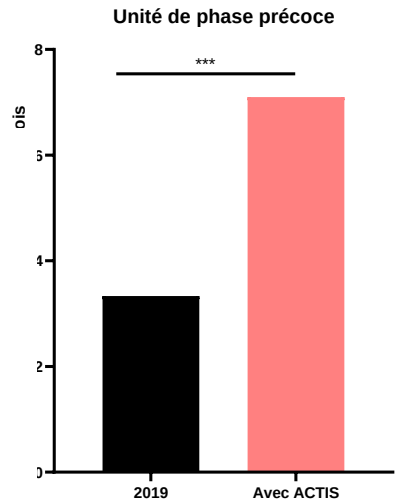
OncoClic

est la première application à destination des professionnels de santé en Oncologie.

ACTIS oncology

est le 1er moteur de recherche innovant à vision stratégique des essais cliniques.





✓ Mise en place d'une étude *Proof of concept* pour ACTIS oncology

CGFL
CENTRE GEORGES FRANÇOIS LECLERC
Ensemble, dépassons le cancer

ÉCOLE DOCTORALE
Environnements - Santé

L'université de Bourgogne est membre de
UBFC
UNIVERSITÉ BOURGOGNE FRANCHE-COMTÉ

Réunion Onco-gynécologie Bourgogne Franche Comté

Les essais cliniques au CGFL

Le 28/03/2023

Dr Jean-David Fumet, M.D, PhD