Prognosis and grading of tumours in the molecular era:

**CINSARC** signature as a prognostic marker for clinical outcome in soft tissue sarcomas

.....and behind

S. Le Guellec
Department of Pathology, Institut Claudius Regaud
ONCOSARC- Team 19, INSERM UMR 1037, CRCT
Toulouse, France
Plan

1- Prognosis and grading of soft tissue sarcomas

2- What is CINSARC?

3- Application of CINSARC for pathologists?

4- CINSARC: universally predict outcome?
Prognosis and grading of soft tissue sarcomas

FNCLCC Grade

n=1240
FNCLCC Grade

Prognosis and grading of soft tissue sarcomas

« FNCLCC grade » = major limitations:

- 40% = grade 2
- bad reproducibility
- difficult to apply to microbiopsies,
- not applicable to all sarcomas

1980

FFPE

Microscope

n=1240
Discovery of **CINSARC** signature

- **Microscope**
- **Microarrays**
- **FFPE**
- **Frozen**

1980  //  2010

**FNCLCC Grade**  //  **CINSARC**

*Chibon et al. (2010), Nat Med*
*Lagarde et al. (2012), Clin Cancer Res*
*Lagarde et al. (2013), J Clin Oncol*

\[n=1240\]
What is **CINSARC**?

- **Complexity INdex in SARComas**
- A transcriptomic signature (67 genes)
- Involved in chromosome biogenesis, mitosis control and chromosome segregation

**Chibon et al. (2010), Nat Med**
**Lagarde et al. (2012), Clin Cancer Res**
**Lagarde et al. (2013), J Clin Oncol**

- **highly versus lowly rearranged sarcomas**
- **FNCLCC G3 versus G2 sarcomas**
What is CINSARC?

Particularly interesting in soft-tissue sarcomas because:

1. Reflects their chromosomal instability

Chibon et al. (2010), Nat Med
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What is CINSARC?

Particularly interesting in soft-tissue sarcomas because:

1. Reflects their chromosomal instability

2. A predictive marker of metastatic outcome (independant, several histotype)

UPS

Synovial sarcoma

Chibon et al. (2010), Nat Med
Lagarde et al. (2012), Clin Cancer Res
Lagarde et al. (2013), J Clin Oncol
What is CINSARC?

Particularly interesting in soft-tissue sarcomas because:

1. Reflects their chromosomal instability
2. A predictive marker of metastatic outcome (independant, several histotype)
3. A better biomarker compared to the reference FNCLCC grading system

Chibon et al. (2010), Nat Med
Lagarde et al. (2012), Clin Cancer Res
Lagarde et al. (2013), J Clin Oncol
Discovery of **CINSARC** signature

1980 // 2010

**FNCLCC Grade**

**CINSARC**

- Chibon *et al.* (2010), Nat Med
- Lagarde *et al.* (2012), Clin Cancer Res
- Lagarde *et al.* (2013), J Clin Oncol
Application of **CINSARC** for pathologists

- **Microscope**
- **Microarrays**
- **RNA-seq**?

**FNCLCC Grade**

**CINSARC**

- 1980
- 2010
- 2016

- FFPE
- Frozen
- Frozen

**n=127**

- CINSARC

- CINSARC

**n=1240**

- **n=127**
Application of CINSARC for pathologists

Lesluyes et al. (2016), EurJ Cancer

RNA-seq versus microarrays

1980 n=95

2010 n=127

2016 n=1240

FNCLCC Grade

CINSARC

CINSARC

n=127
n=1240
Application of CINSARC for pathologists

Microscope

Microarrays

RNA-seq

FNCLCC Grade

CINSARC

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n=127

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Application of CINSARC for pathologists

Lesluyes et al. (2016), *Eur J Cancer*

RNAseq: ~60% of FFPE blocs could be processed ➔ Degraded RNA

FFPE

Frozen

Microscope

Microarrays

RNA-seq

1980

2010

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FNCLCC Grade

CINSARC

CINSARC

n=1240

n=127

Lesluyes et al. (2016), *Eur J Cancer*
Application of **CINSARC** for pathologists

Lesluyes et al. (2016), *EurJ Cancer*

**Frozen**

**RNA-seq:**

~60% of FFPE blocks could be processed

➔ Degraded RNA

**CINSARC applicability in daily routine practice?**

➔ feasible RNA FFPE blocks

Lesluyes *et al.* (2016), *EurJ Cancer*
direct digital measurement of transcript abundance (no reverse transcription, no cDNA amplification)
- Applicability FFPE blocks
- Applicability core-needle biopsies (minimal RNA input)
- Cost Nanostring < microarrays /RNAseq

NanoCind®: A codeset of 75 genes (67 CINSARC + 8 HK)

Application of **CINSARC** for pathologists

Le Guellec et al. (2018), *Ann Oncol*
Application of CINSARC for pathologists

1- Does it work with FFPE blocks (Nanostring technology)?
2- CINSARC (NanoCind®) on FFPE blocks is it still better than the FNCLCC grading?
3- Does it stratify grade 2 (intermediate) tumours?

Le Guellec et al. (2018), Ann Oncol

47 FFPE cases + 20 core-needle biopsies
Application of CINSARC for pathologists

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Le Guellec et al. (2018), Ann Oncol
Application of **CINSARC** for pathologists

Lesluyes *et al.* (2016), *EurJ Cancer*
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Application of **CINSARC** for pathologists

Lesluyes et al. (2016), *Eur J Cancer*
Le Guellec et al. (2018), *Ann Oncol*
CINSARC = A predictive marker of metastatic outcome in all FNCLCC grade !!!!
Application of CINSARC for pathologists

Lesluyes et al. (2016), EurJ Cancer
Le Guellec et al. (2018), Ann Oncol
• Clinical trials to evaluate CINSARC prognosis

  - retrospectively :
    • « ISG-STS 1001 » trial : effect of histotype-tailored neoadjuvant ChT in localized STS
    • « STRASS » trial : role of preoperative Rx in retroperitoneal STS

  - prospectively :
    • « NEOSARCOMICS » trial : value in predicting response to neoadjuvant ChT
    • « CHIC-STS » trial : treatment of patients with localized STS determined by the CINSARC risk
CINSARC to universally predict outcome?

◆ Pan-cancer study
  CINSARC significantly enriched with top-ranked poor prognosis genes in 21 out of 39 cancer types

◆ Prognostic value CINSARC was tested with OS and DSS analyzes in 27 cancer types
  CINSARC = significant predictor in 63% cancer types

◆ Main cancer types:
  - carcinoma (Colon, liver, ovarian, lung, prostate, bladder, breast...)
  - Hematological
  - Brain-related.....

Global marker for tumor aggressiveness

Lesluyes et al. (2017), SciRep
Is CINSARC better compared to reference grading systems in other tumour types?

**Uterine carcinoma**

Does CINSARC detect the rare patients with a poor prognosis in endometrial carcinoma?
Is CINSARC better compared to reference grading systems in other tumour types?

**Uterine carcinoma**

Does CINSARC detect the rare patients with a poor prognosis in endometrial carcinoma?

**Ovarian carcinoma**

Does CINSARC detect patients with advanced ovarian carcinoma who will benefit from surgery and adjuvant chemotherapy?

Financial support: obtained!
Begin in 2020
Application of CINSARC for pathologists

Lesluyes et al. (2016), EurJ Cancer
Le Guellec et al. (2018), Ann Oncol
Cancer Research Center of Toulouse (CRCT)
UMR1037-INSERM (ONCOSARC, Team 19)
Frédéric Chibon (PI)
Tom Lesluyes
Gaëlle Perot
Philippe Rochaix
Valentin Thibaut
Gwenael Ferron

Institut Claudius Regaud, IUCT-OncoPôle
(Multidisciplinary Team Sarcoma)
Christine Chevreau (Oncology)
Anne Ducassou (Radiotherapy)
Berenice Boulet (Radiology)
Thomas Meresse (Chirurgy)
Dimitri Gangloff (Chirurgy)

Genomic and Transcriptomic Unit (CRCT)
Emeline Sarot
Carine Valle

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