

Cancers de l'ovaire : est-il temps d'intégrer KELIM dans nos algorithmes ?

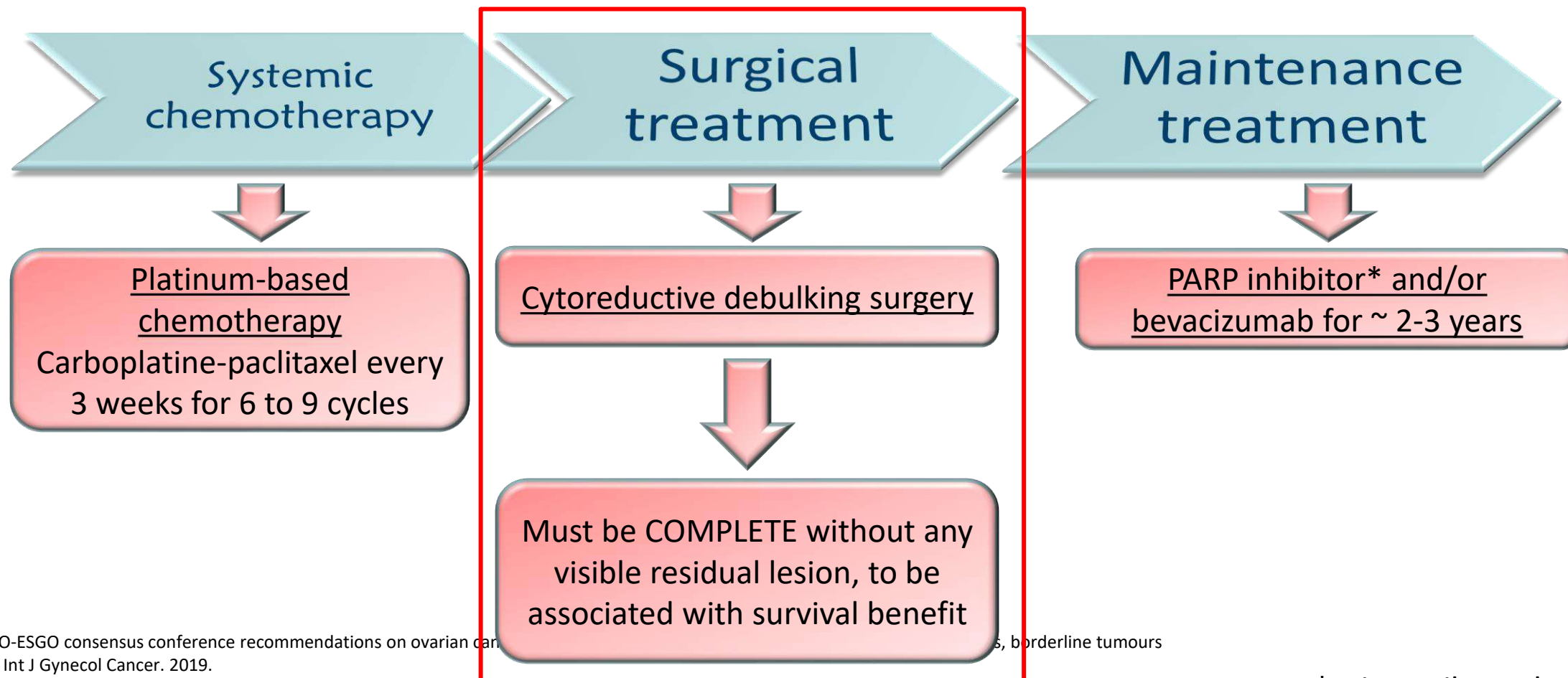
Lyon University Hospital, France
Université Claude Bernard Lyon 1, CICY
GINECO

Links of interest

- **Boards:** MSD, Astra-Zeneca, GSK-TESARO, BAYER, Roche-Genentech, ECS Progastrine, Novartis, LEK, Amgen, Clovis Oncology, Merck Serono, BMS, SEAGEN, Myriad, Eisai
- **Invitations congress:** Roche-Genentech, Astra Zeneca, BMS, MSD Oncology, Bayer, Boehringer Ingelheim
- **Symposium:** MSD, Astra-Zeneca, GSK-TESARO, BAYER, ECS Progastrine, Roche-Genentech, Novartis, LEK, Amgen, Clovis Oncology, Boehringer Ingelheim

Rationale and context: 1st line setting

The management relies on a medical & surgical treatment

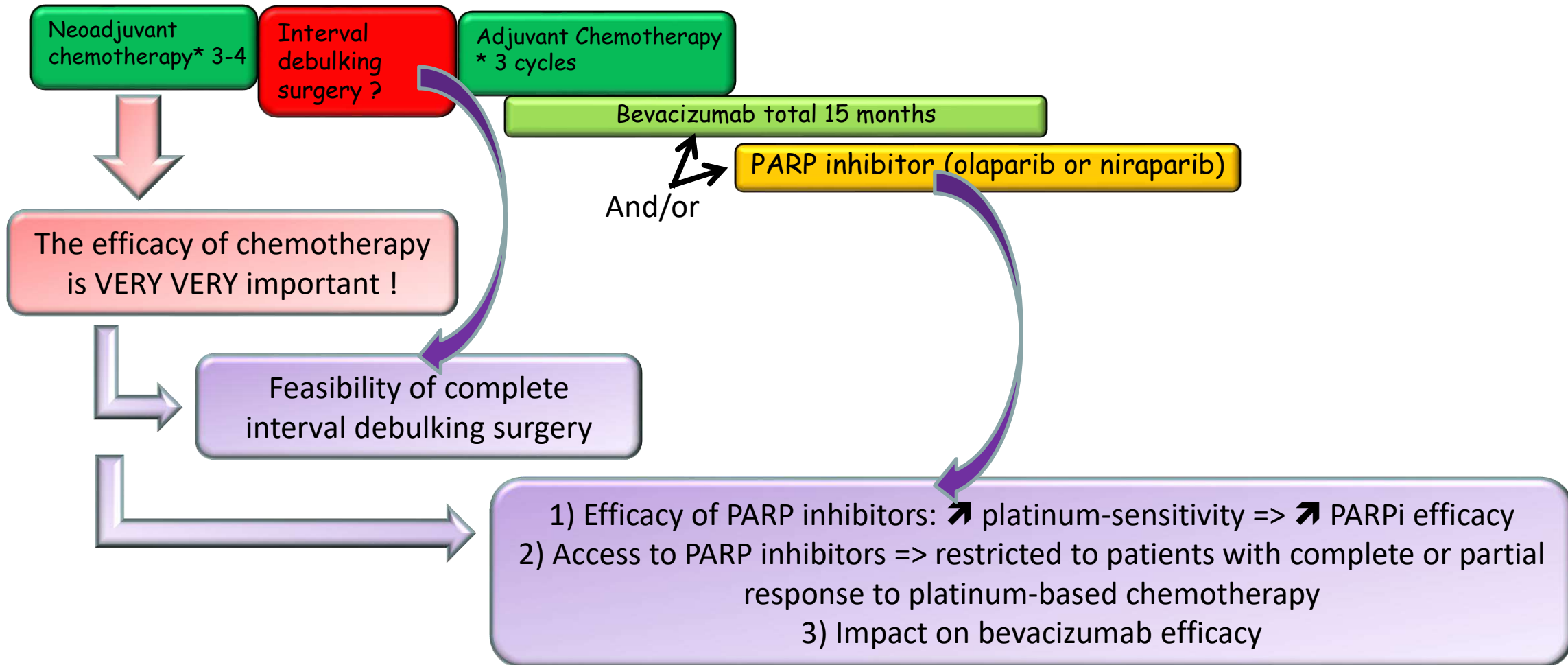


Colombo N, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: primary, relapsed, and borderline tumours and recurrent disease. Int J Gynecol Cancer. 2019.

Wright AA, et al. Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Guideline. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34:3460-73.

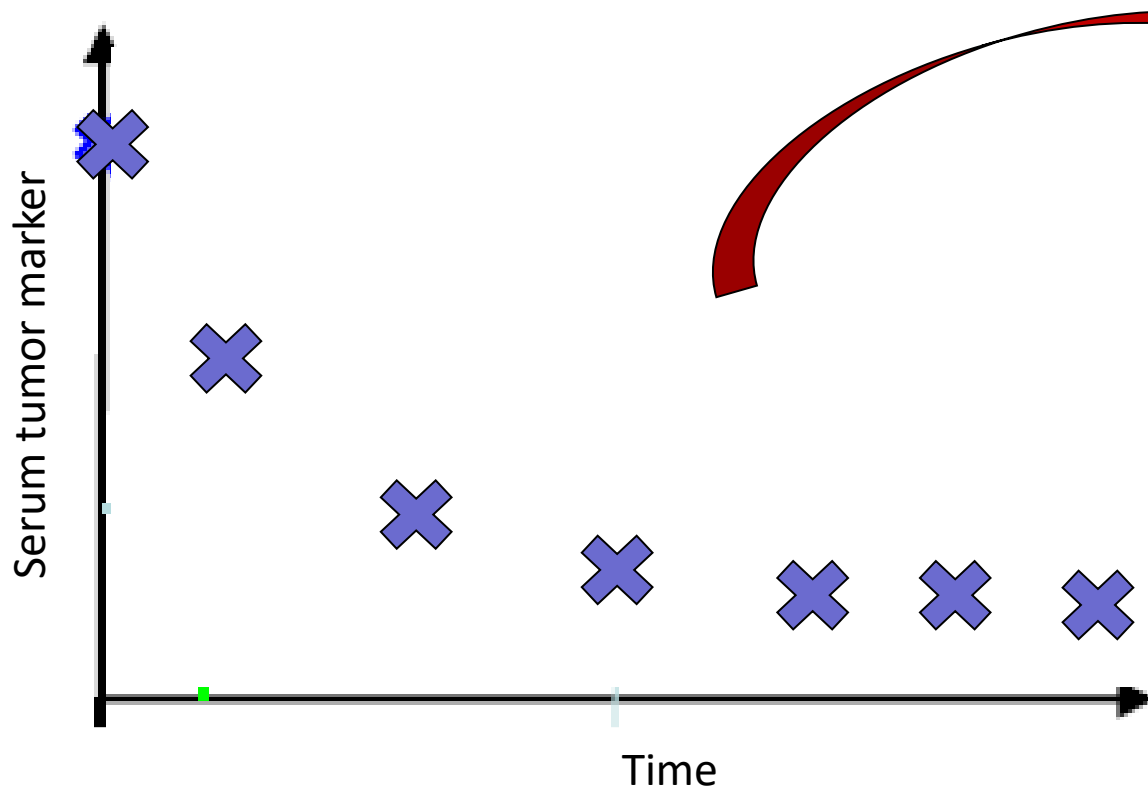
* Niraparib or olaparib

About the role of the tumor primary chemosensitivity



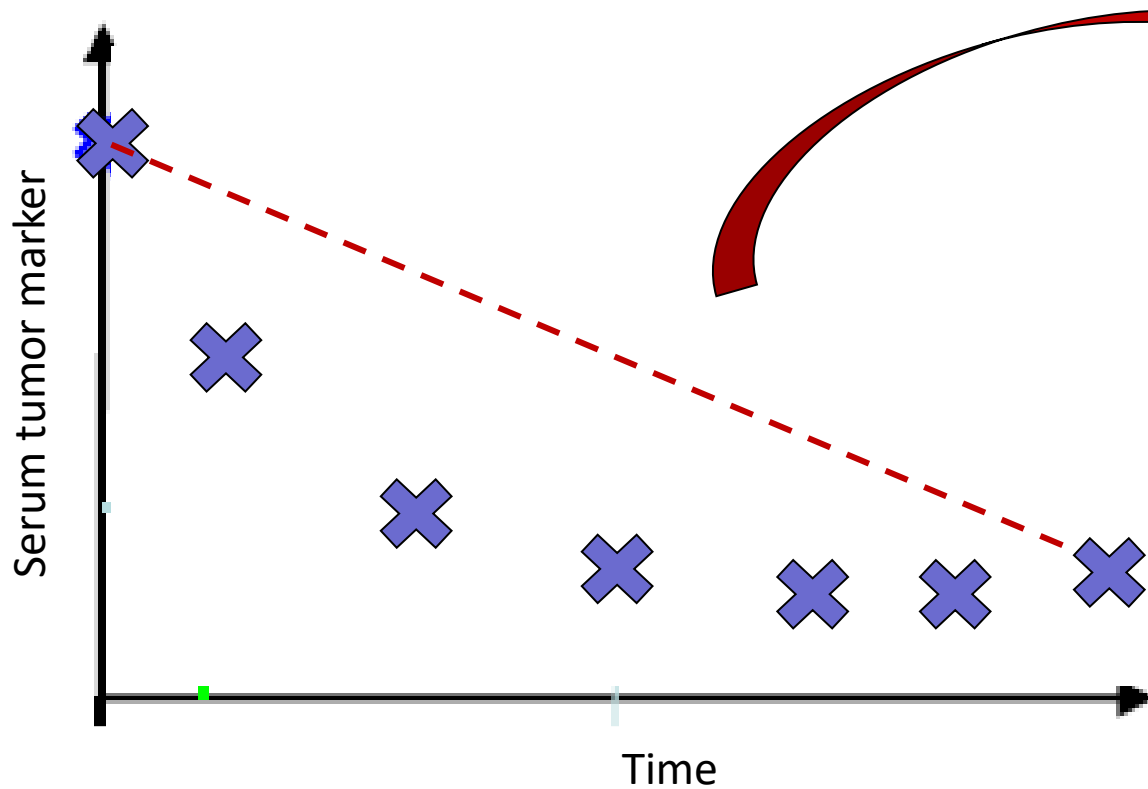
What is KELIMTM ?

The question to be addressed ...



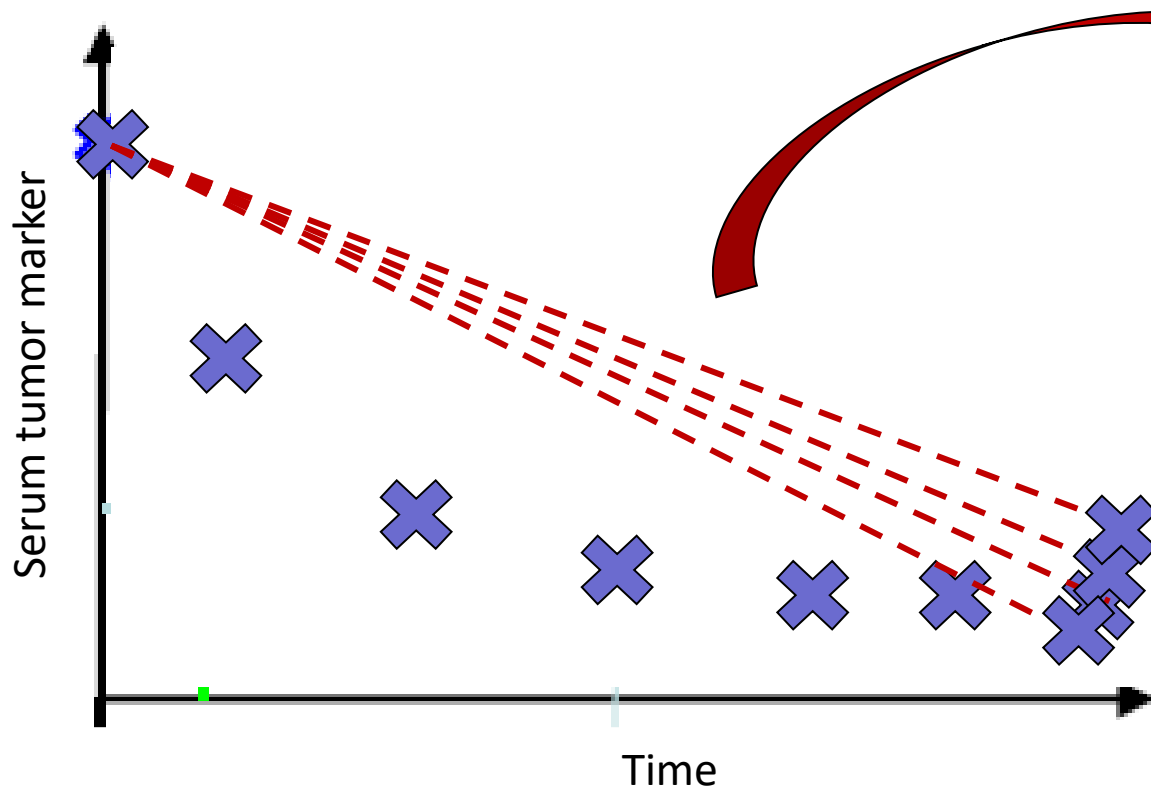
How to
interpret this
decline ?

The question to be addressed ...



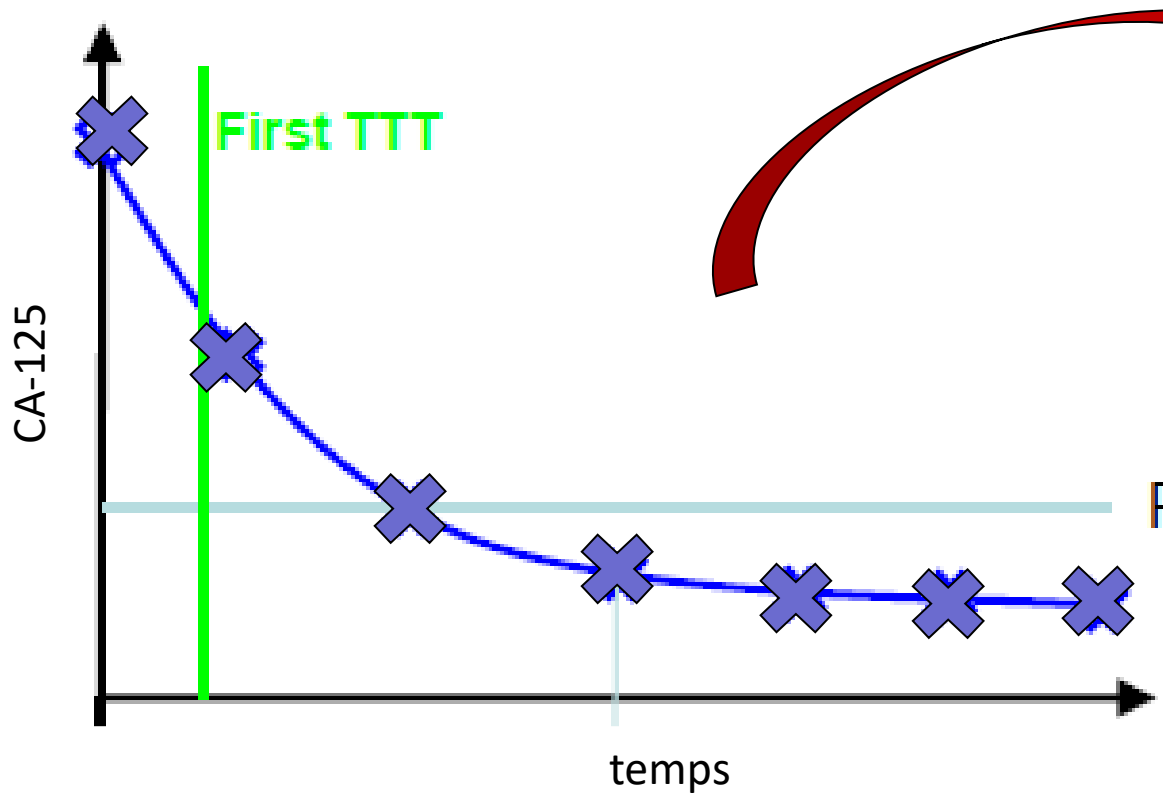
Two-time
points
strategies

The question to be addressed ...



Two-time
points
strategies

The question to be addressed ...



KELIM
calculation

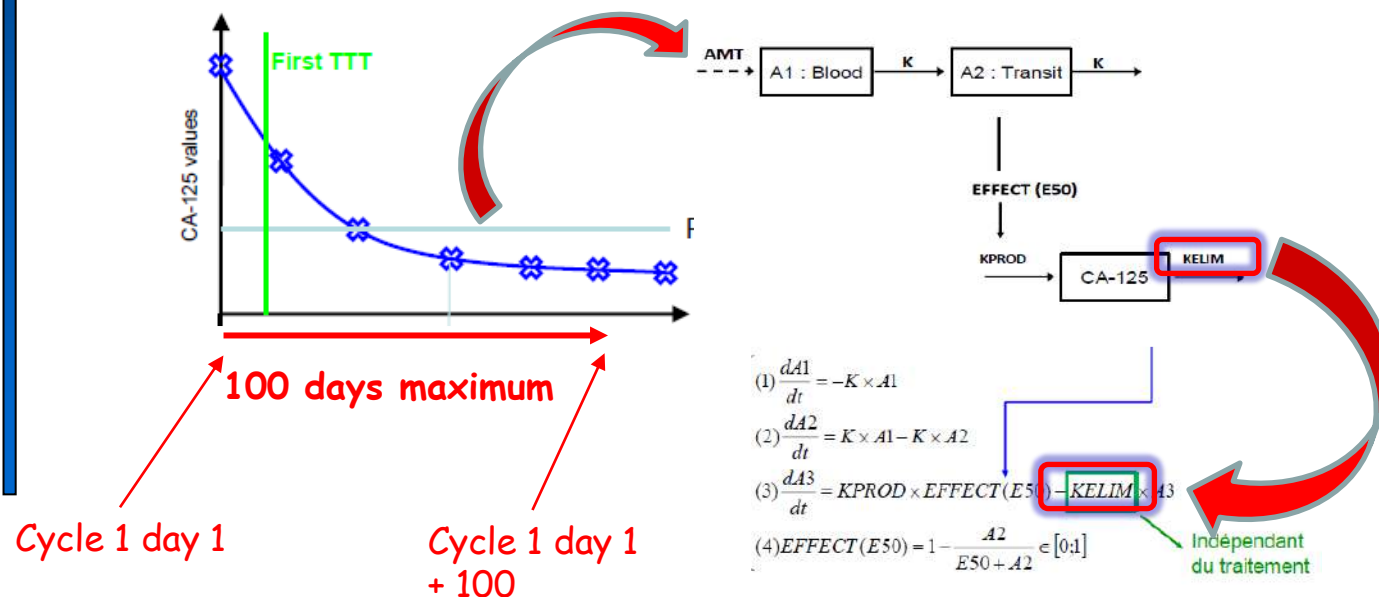
What is KELIM™ ?

KELIM™ = CA-125 elimination rate constant within the first 100 days (or less) of chemotherapy (neo-adjuvant or adjuvant chemotherapy)

Calculated with a mathematical model

A kind of « CA-125 clearance » ...

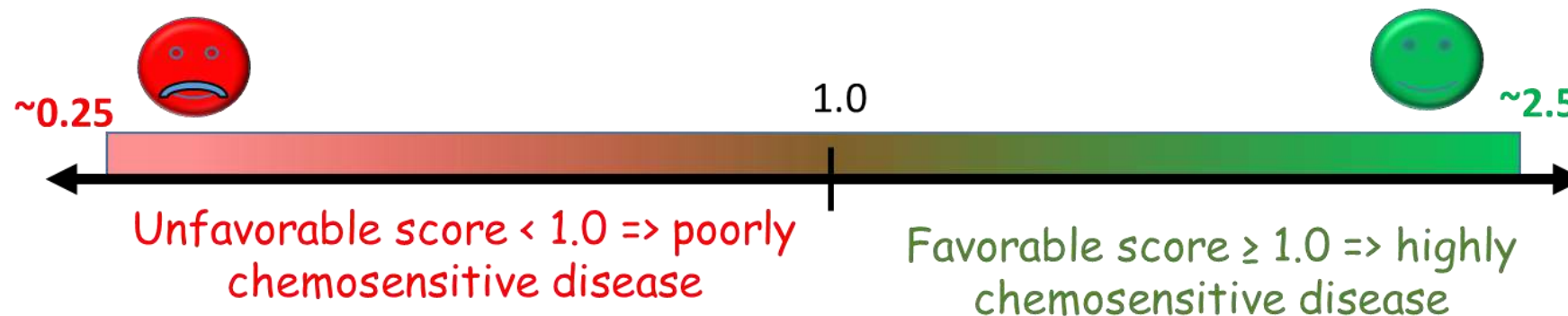
related to chemotherapy efficacy ...



What is KELIM™ ?

KELIM™ = CA-125 elimination rate constant during the first 100 days of chemotherapy (neo-adjuvant or adjuvant chemotherapy)

Standardized KELIM™ = Continuous data centered by « 1.0 »

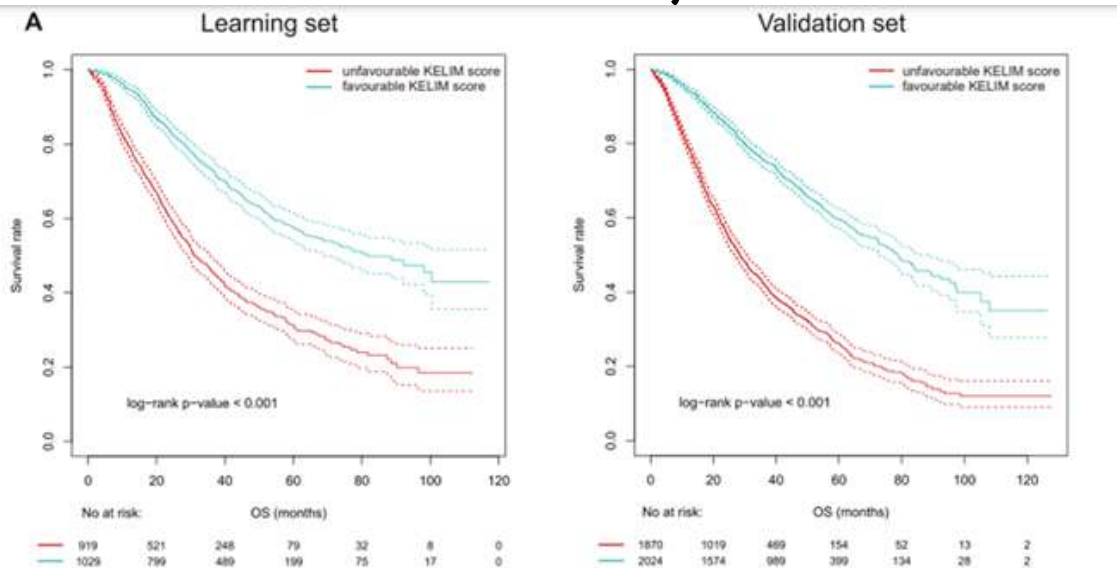


What information does KELIM provide ?

Data of > 15,000 patients enrolled in the major international trials
(AGO OVAR 7, AGO OVAR 9, ICON-7, ICON-8, GOG-0218....)
and national registries (ESME, IKNL, ...)

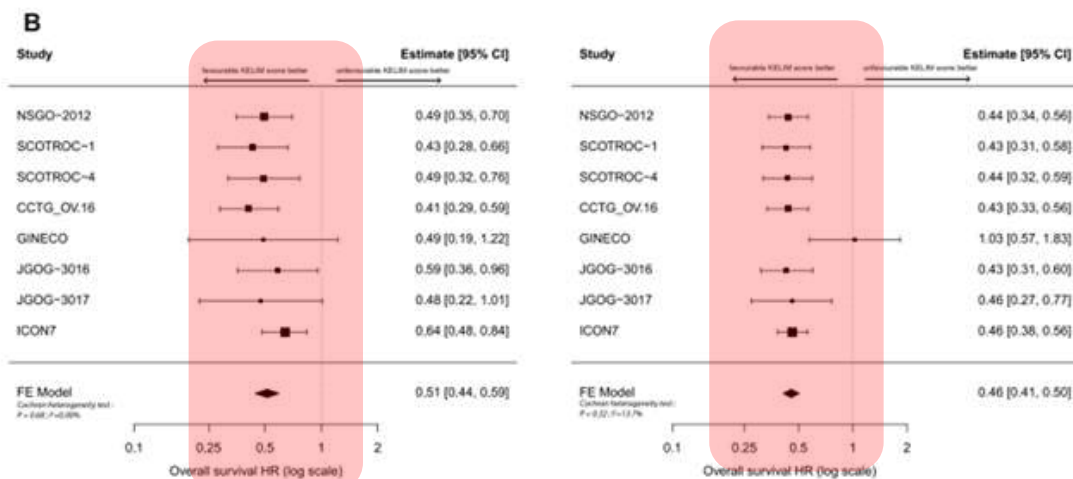
A strong prognostic information for PFS and OS

GCIG meta-analysis



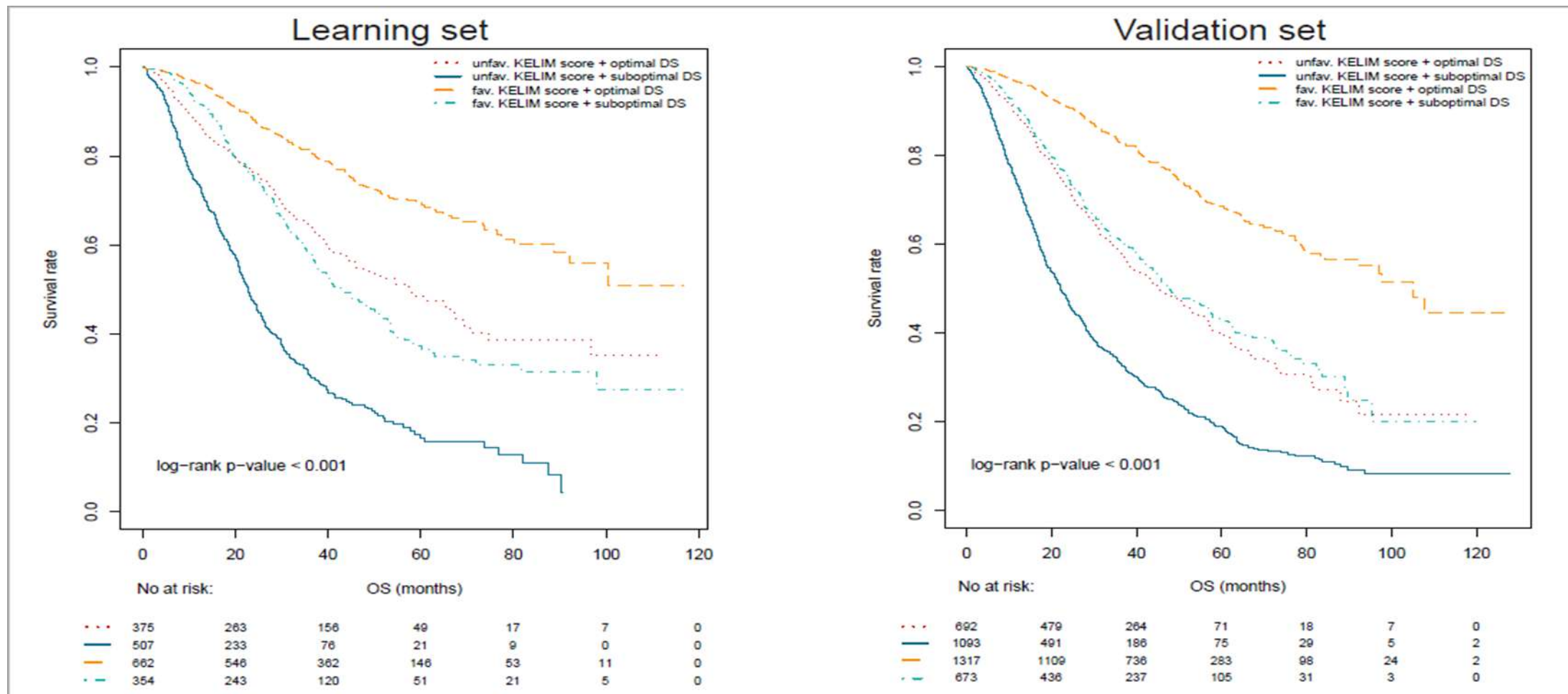
A favorable KELIM score > 1.0 is always associated with:

- **A better PFS: HR ~ 0.5 (median, 30 vs 10 months)**
- **A better OS: HR ~ 0.5 (median, 80 vs 30 months)**



A strong prognostic information for PFS and OS

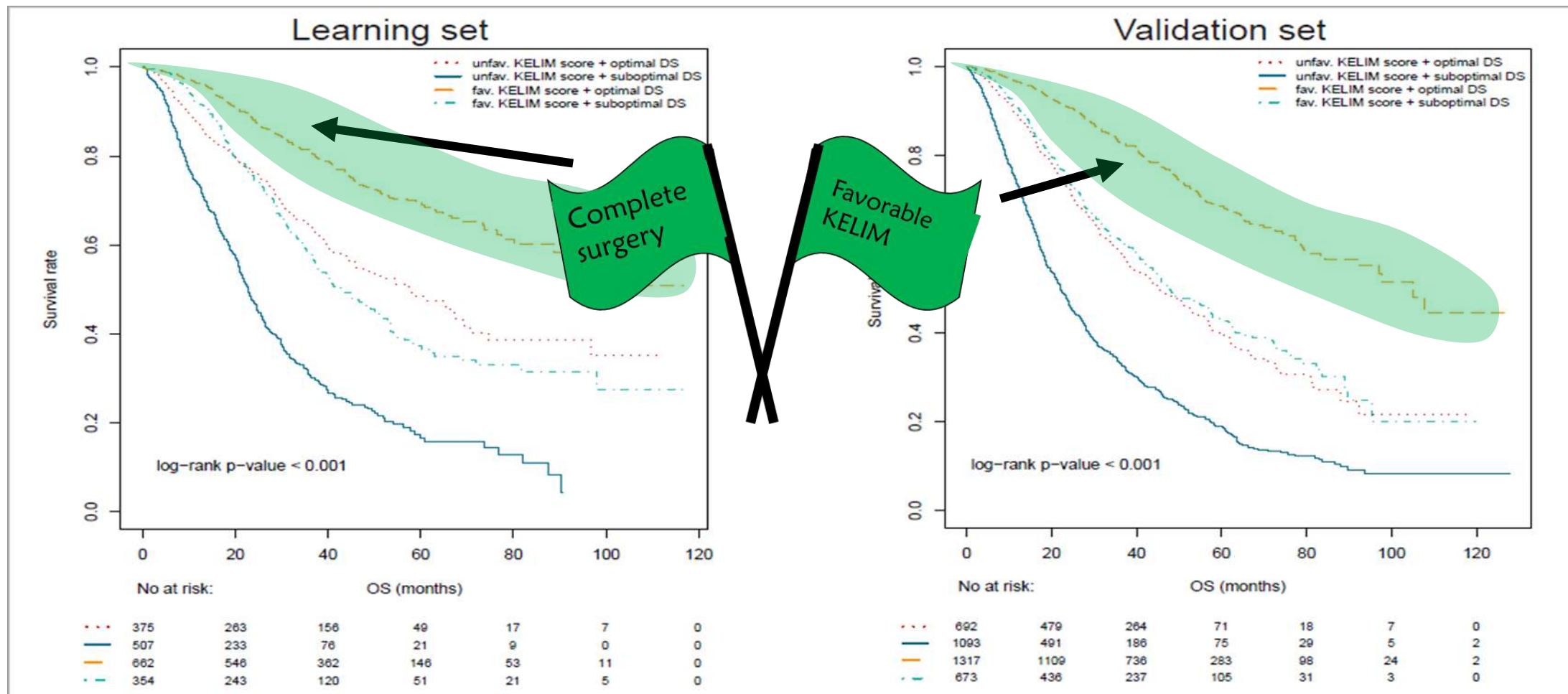
GCIG meta-analysis



56.

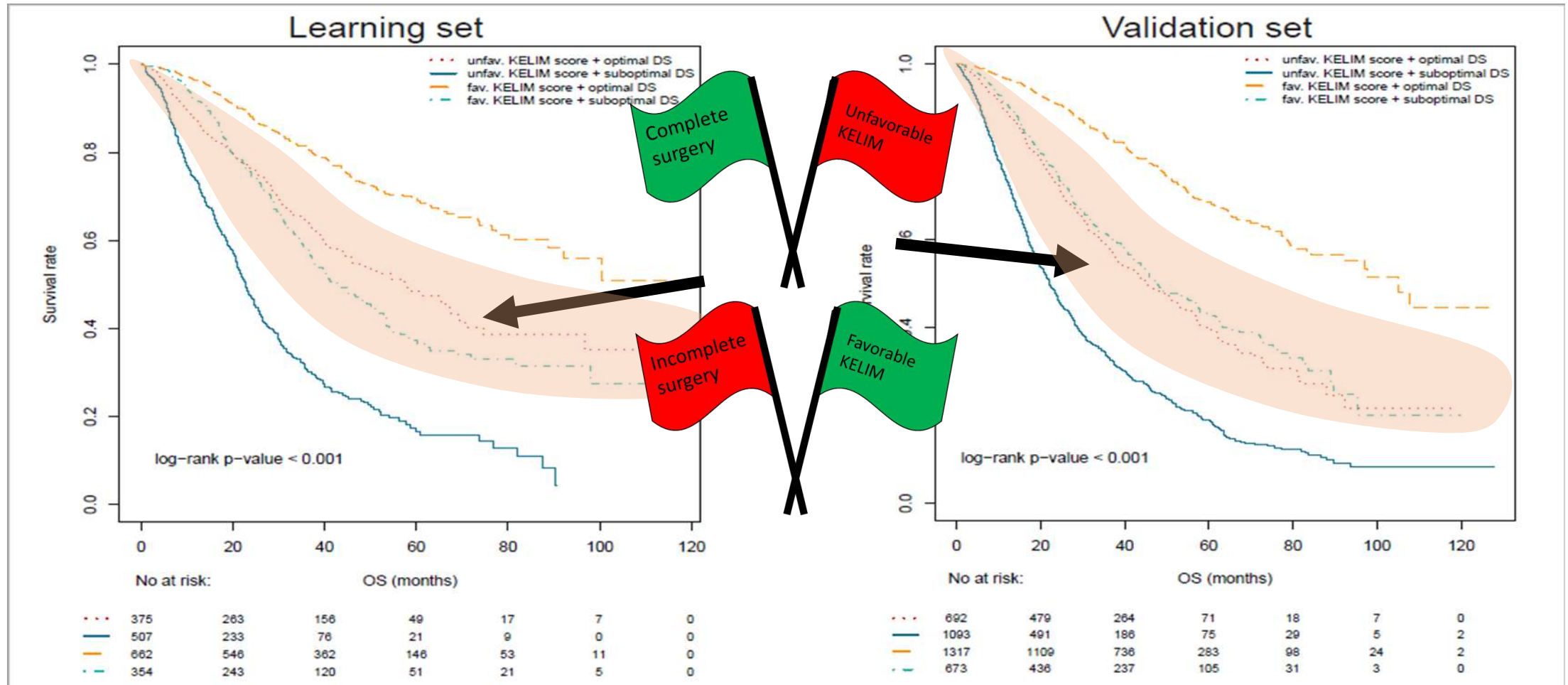
A strong prognostic information for PFS and OS

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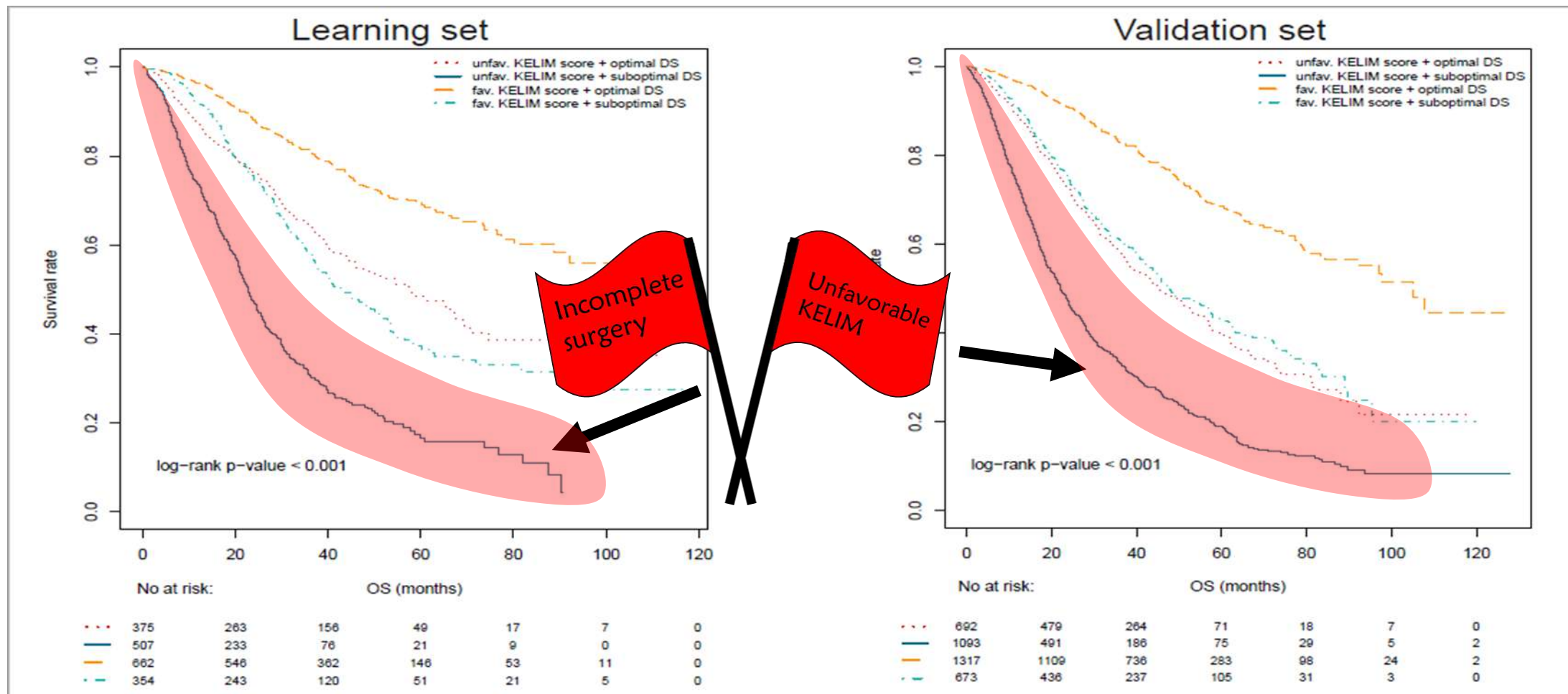
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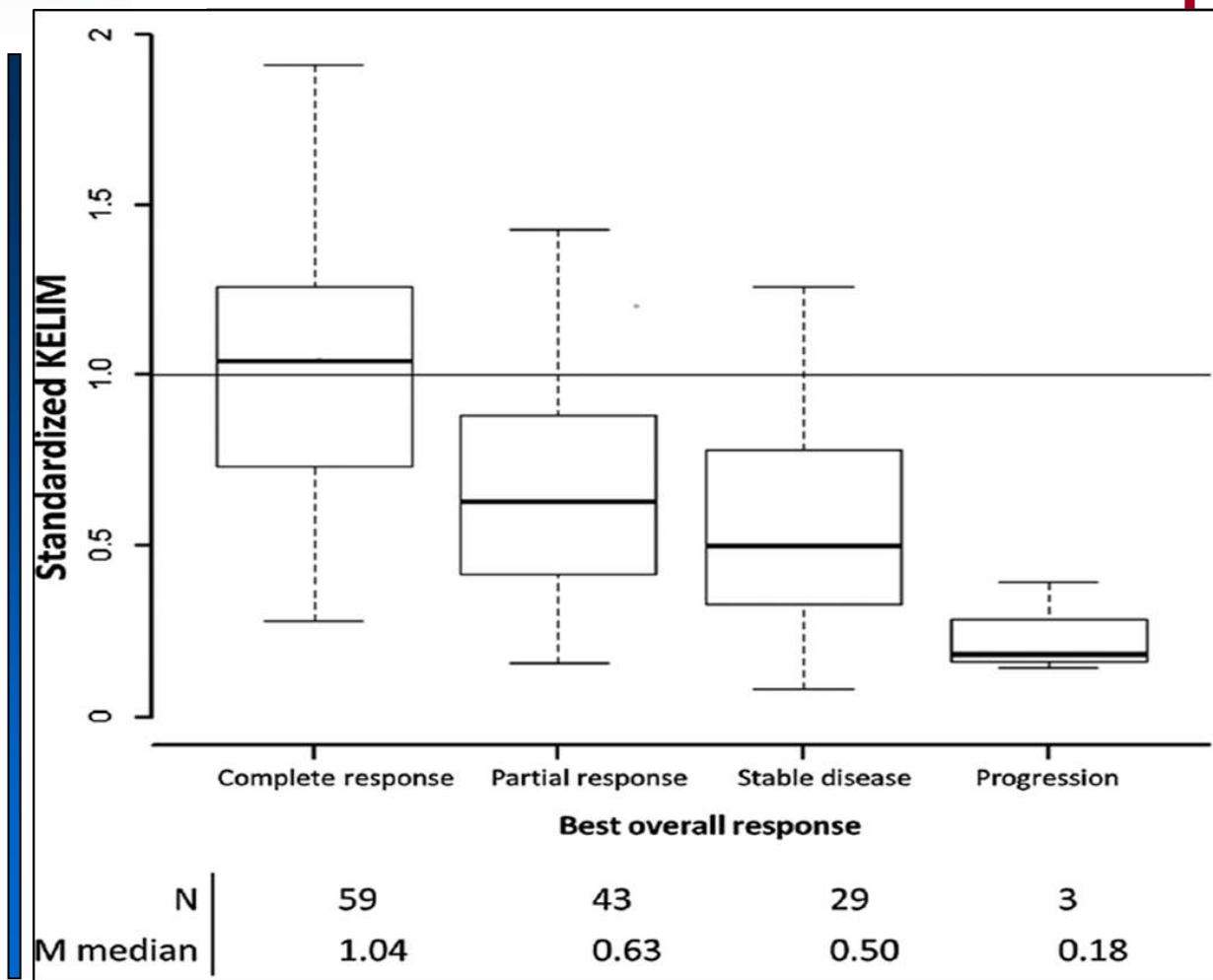


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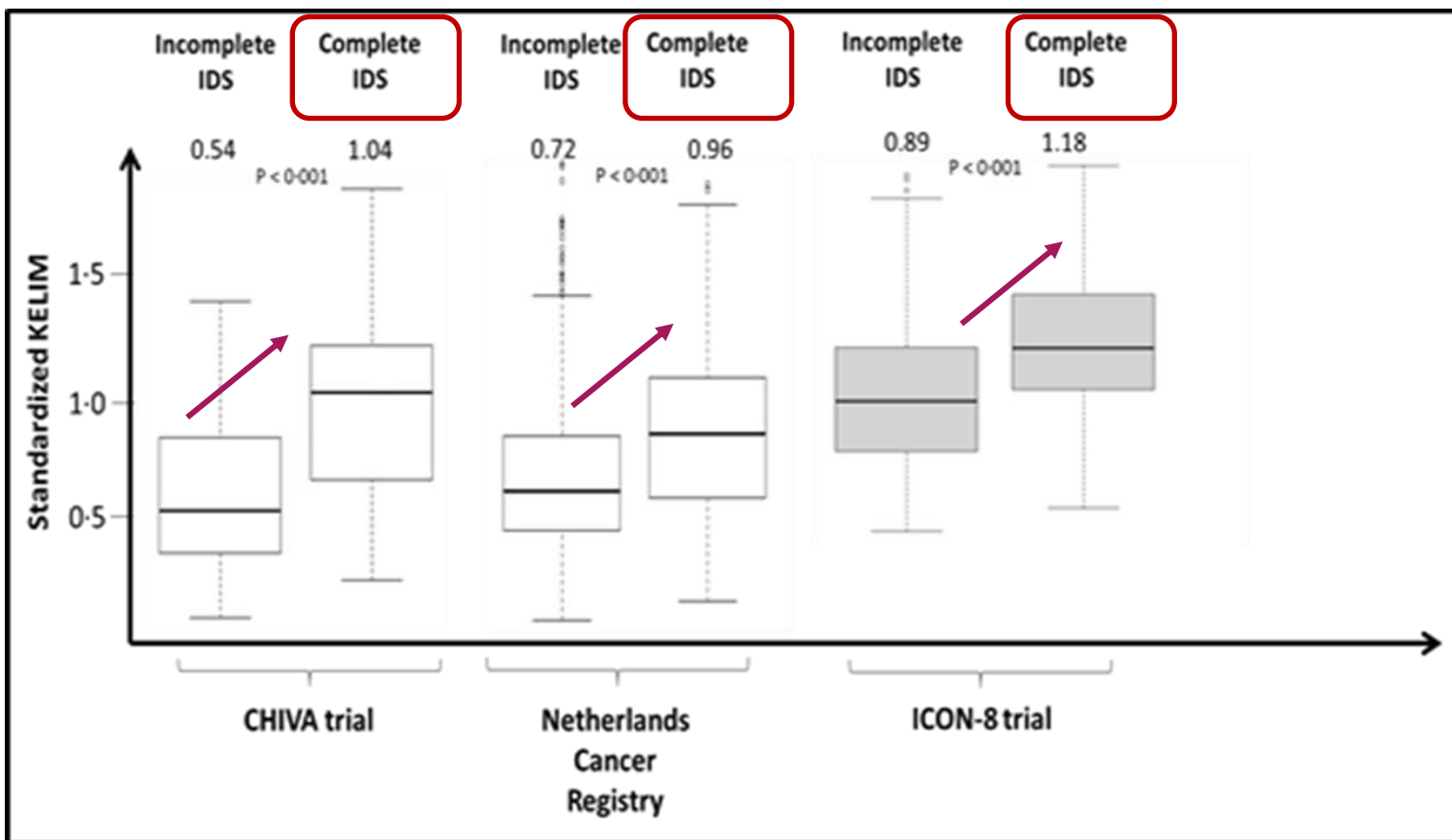


A strong indicator of the neo-adjuvant chemotherapy efficacy



KELIM is strongly related to the radiological response

A strong indicator of the neo-adjuvant chemotherapy efficacy



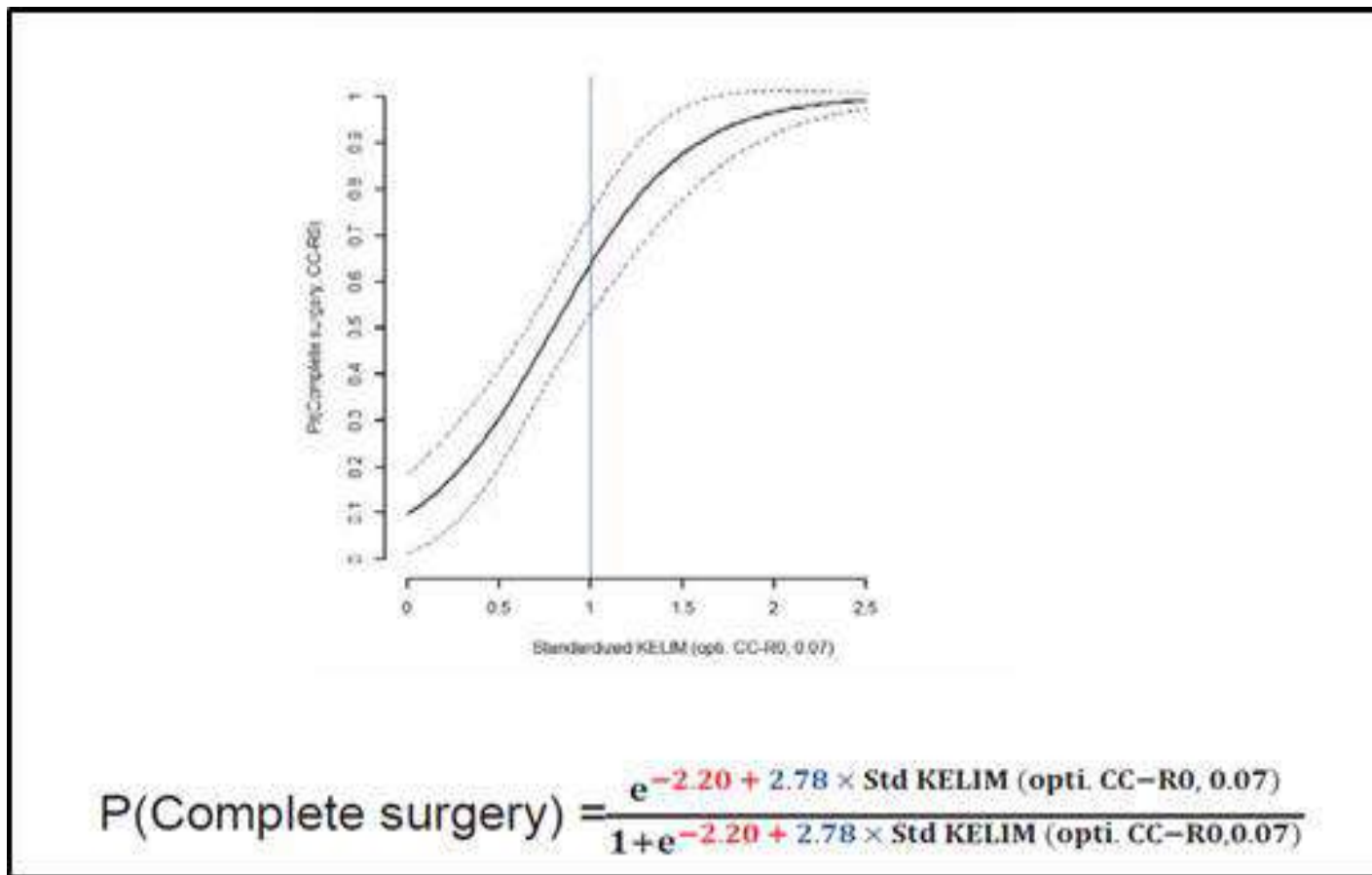
KELIM is strongly related to the probability of complete IDS

CHIVA. You et al. Clin Cancer Res 2019

Registre IKNL Van Wagenveld et al. Proc ESMO 2020

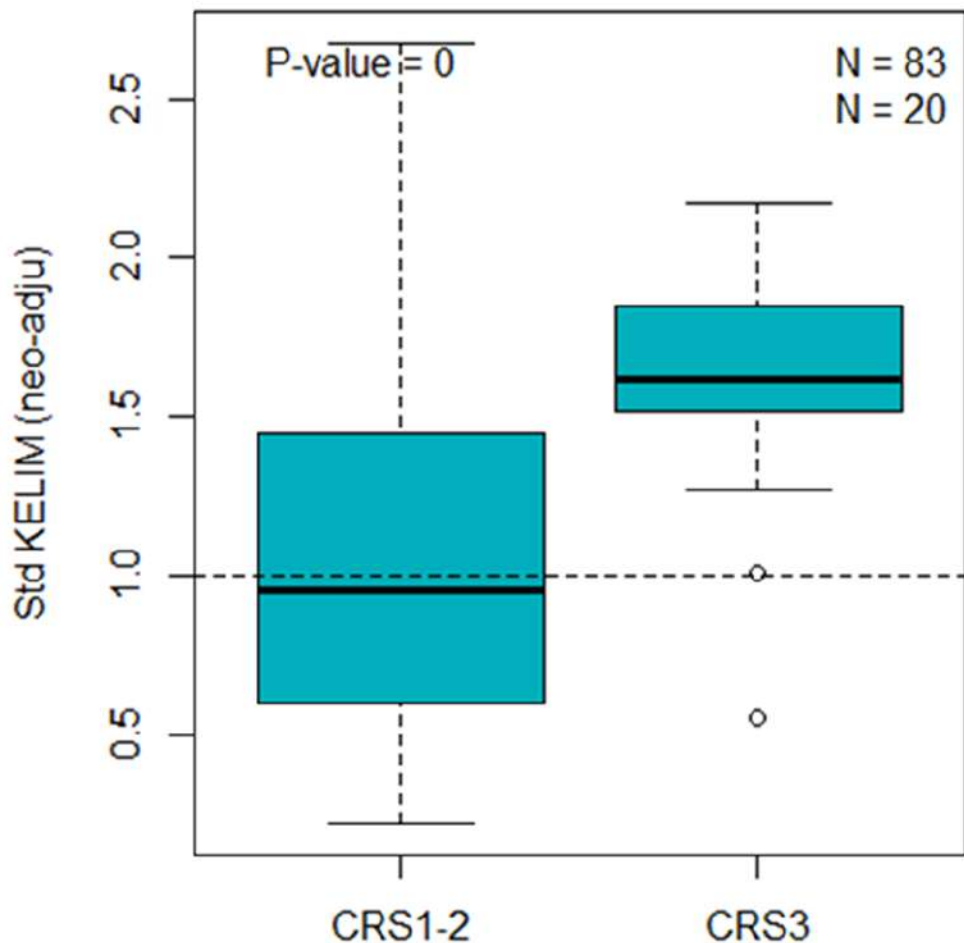
ICON-8. Colombari et al JCO CCI 2023

A strong indicator of the neo-adjuvant chemotherapy efficacy

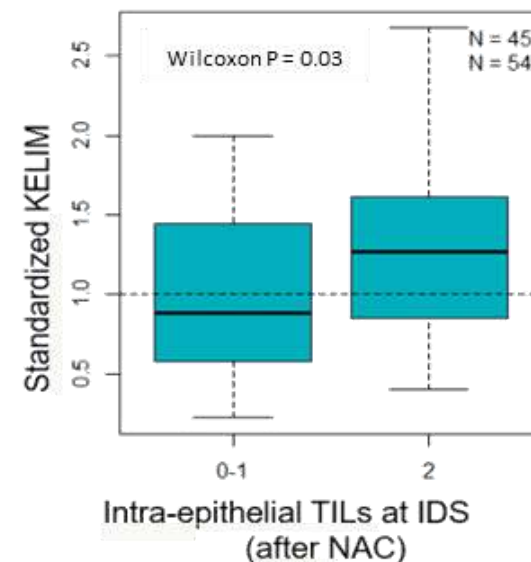


Probability of obtaining a complete interval debulking surgery according to KELIM during neo-adjuvant chemotherapy

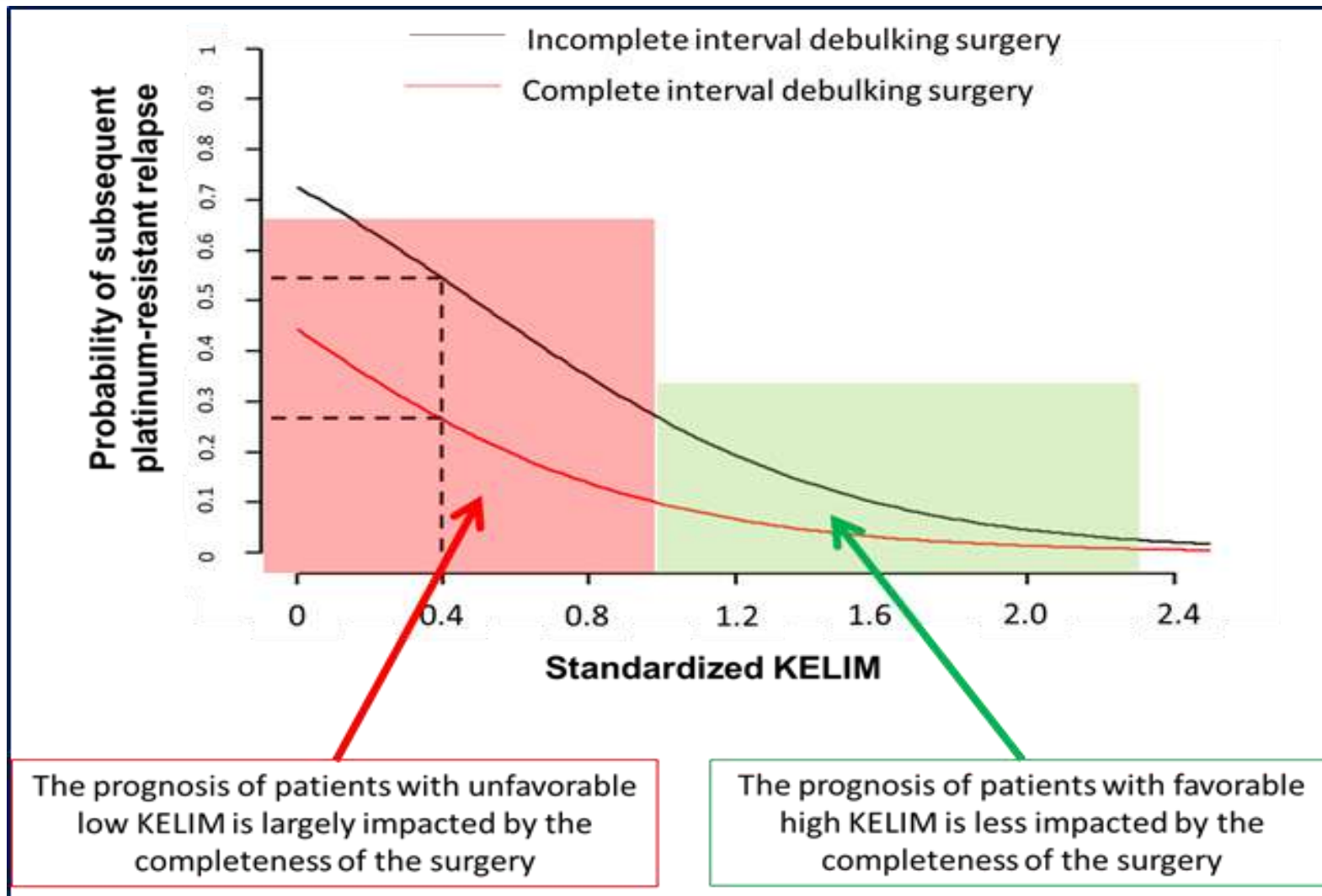
A strong indicator of the neo-adjuvant chemotherapy efficacy



KELIM is strongly related to the pathological chemotherapy response score (CRS) at IDS



Risk of early relapse according to KELIM and surgery outcome



Consistent data with a study about TILs:
Maximum benefit from optimal vs non-optimal debulking surgery in patients with low TILs (five-year OS rates, 41.2% and 25.1%, $P = 0.002$),

(Adams, et al Cancer 2009)

CHIVA. You et al. Clin Cancer Res 2019

KELIM induces a change of paradigm in the management of OC in first-line ...

Cancer Treatment Reviews 100 (2021) 102294

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

ELSEVIER

Check for updates

The role of the tumor primary chemosensitivity relative to the success of the medical-surgical management in patients with advanced ovarian carcinomas

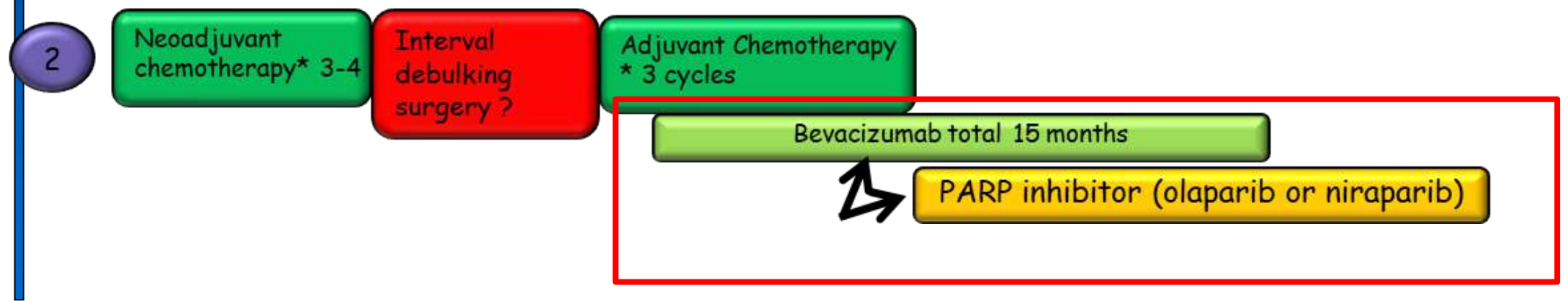
Benoit You^{a,b,c,*}, Gilles Freyer^{a,b,c}, Antonio Gonzalez-Martin^{d,e}, Stephanie Lheureux^f, Iain McNeish^g, Richard T. Penson^h, Sandro Pignata^{i,j}, Eric Pujade-Lauraine^k

^a GINECO, Paris, France
^b Université Lyon, Université Claude Bernard Lyon 1, Faculté de Médecine Lyon-Sud, EMR UCBL/HCL 3736, Lyon, France
^c Medical Oncology, Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL), CITOHL, Lyon, France
^d GEICO, Madrid, Spain
^e Clínica Universidad de Navarra, Madrid, Spain
^f Medical Oncology & Hematology, Princess Margaret Hospital Cancer Centre, Toronto, Ontario, Canada
^g Department of Surgery and Cancer, Imperial College London, London, United Kingdom
^h Harvard Medical School and Massachusetts General Hospital, Boston, MA, USA
ⁱ Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale Napoli, Italy
^j MITO, Italy
^k ARCAGY-GINECO, Paris, France

Experts representative of large international groups: France, Spain, Canada, UK, USA, Italy

Conclusion: Yes, the impact of the chemotherapy efficacy is major and the success of the 1st-line treatment cannot be explained by surgery outcome only

How KELIM could help for selecting the maintenance treatment ?



KELIM and Bevacizumab

ICON-7 and GOG-0218 trials

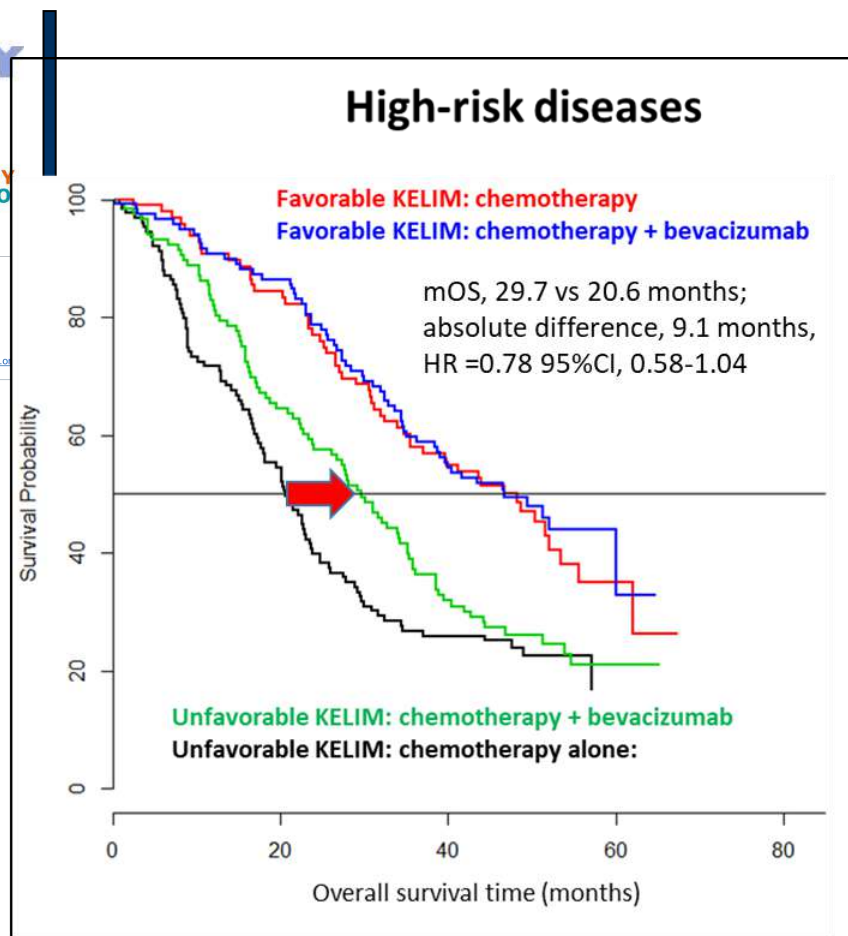
original reports

Identification of Patients With Ovarian Cancer Experiencing the Highest Benefit From Bevacizumab in the First-Line Setting on the Basis of Their Tumor-Intrinsic Chemosensitivity (KELIM): The GOG-0218 Validation Study

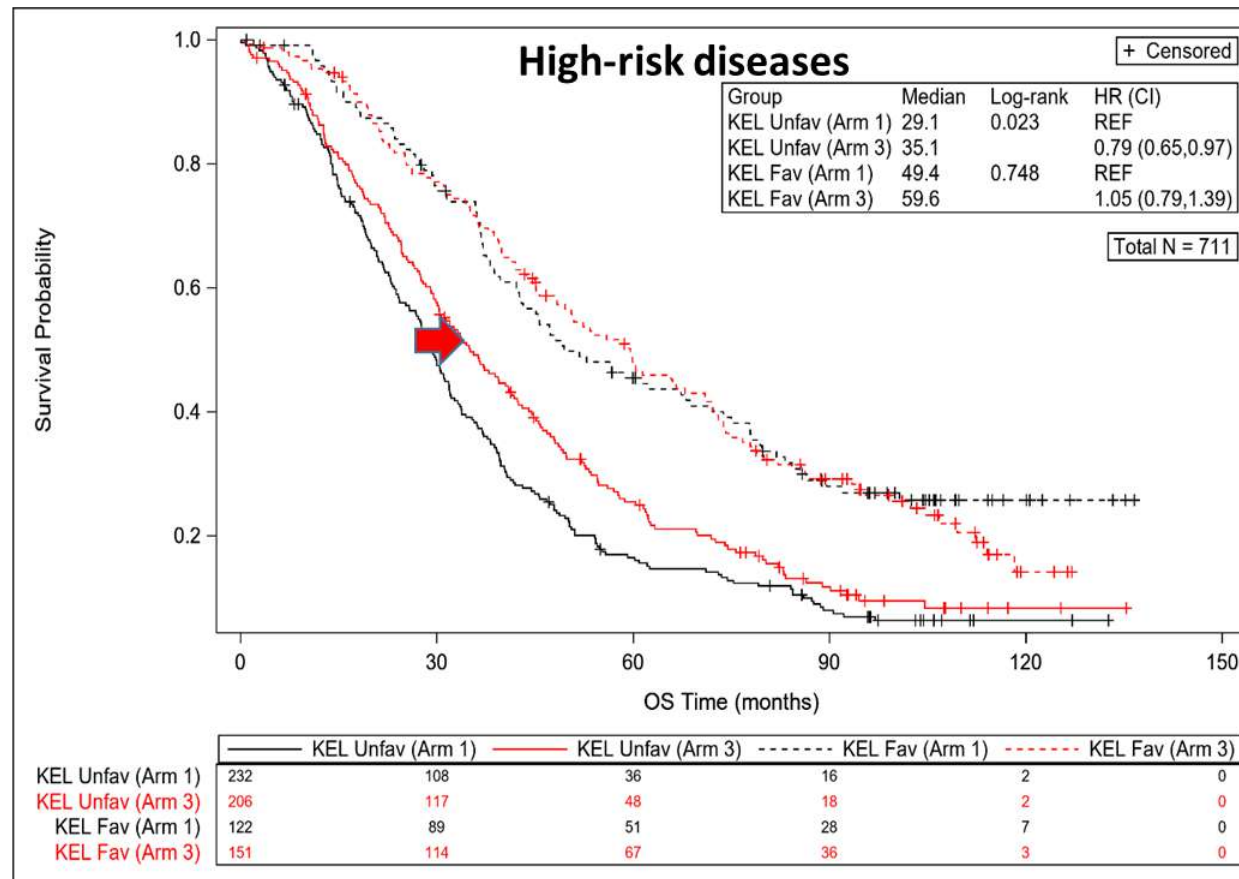
Benoit You, MD, PhD^{1,2}; Christopher Purdy, MA³; Larry J. Copeland, MD⁴; Elizabeth M. Swisher, MD⁵; Michael A. Bookman, MD⁶; Gini Fleming, MD⁷; Robert Coleman, MD⁸; Leslie M. Randall, MD⁹; Krishnansu S. Tewari, MD¹⁰; Bradley J. Monk, MD¹¹; Robert S. Mannel, MD¹²; Joan L. Walker, MD¹²; Fabio Cappuccini, MD¹³; David Cohn, MD⁴; Mahvish Muzaffar, MD¹³; David Mutch, MD¹⁴; Andrea Wahner-Hendrickson, MD¹⁵; Lainie Martin, MD^{16,17}; Olivier Colombari, MSc^{1,2}; and Robert A. Burger, MD^{16,17}

Journal of Clinical Oncology[®]
An American Society of Clinical Oncology Journal

KELIM and bevacizumab: maximum benefit from bevacizumab if KELIM score < 1.0 in high-risk disease

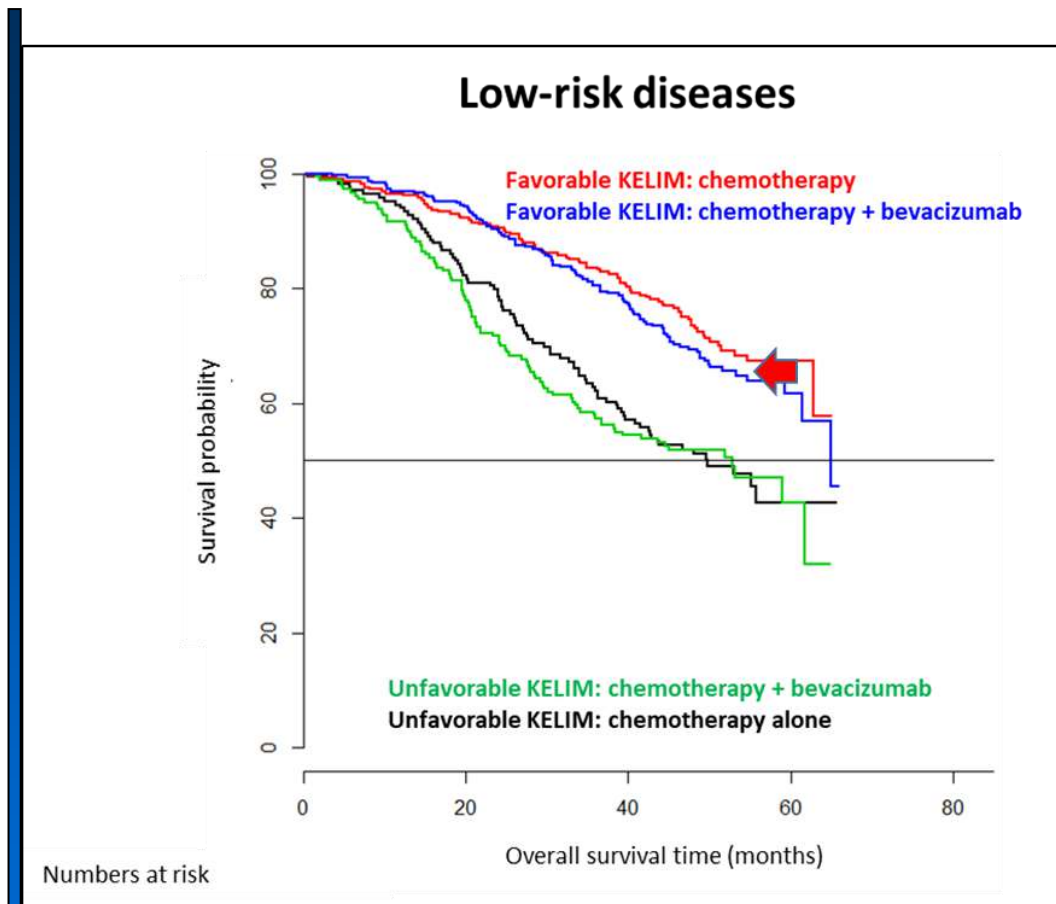


A Initial study in ICON-7 phase III trials.
Colomban et al JNCI CS 2020

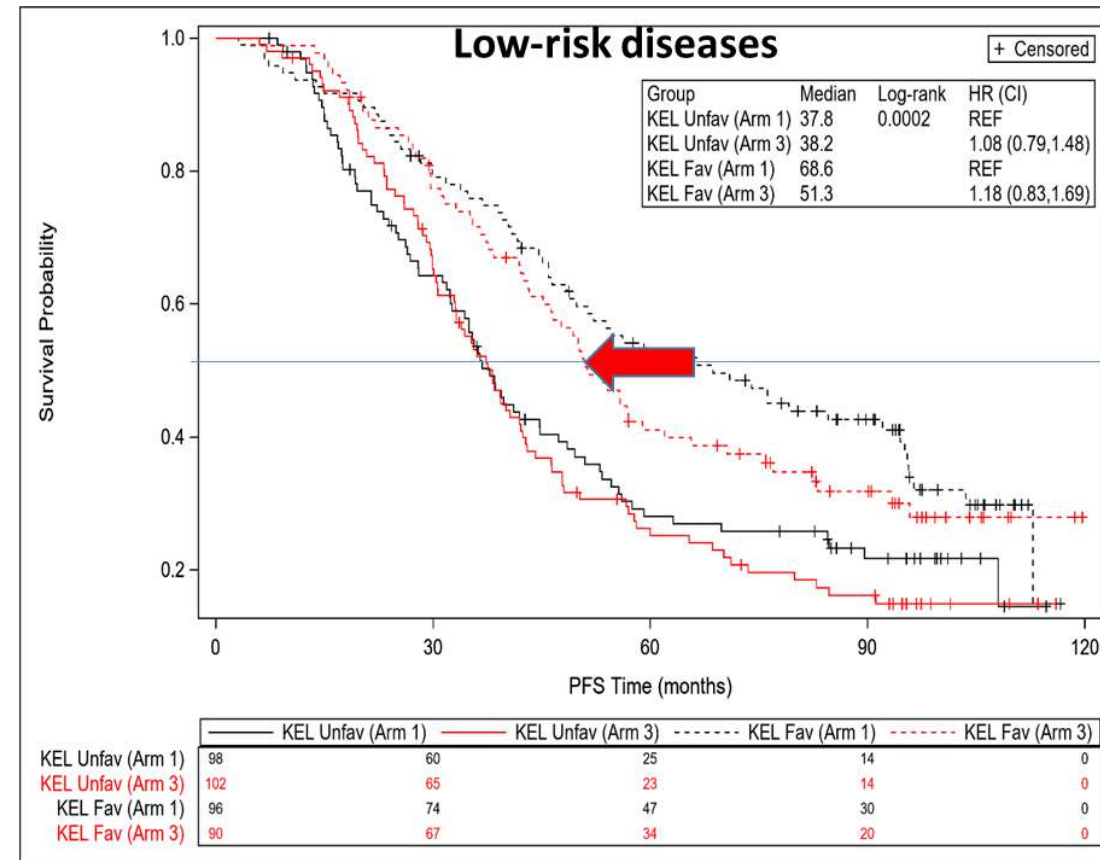


B External validation study in GOG-0218 phase III trials.
You et al J Clin Oncol 2022

KELIM and bevacizumab: maximum benefit from bevacizumab if KELIM score < 1.0 in high-risk disease



A Initial study in ICON-7 phase III trials.
(Colomban et al JNCI CS 2020)



B External validation study in GOG-0218 phase III trials.
Present study submitted to J Clin Oncol

You et al JCO 2022

KELIM and PARP inhibitor

Check for updates

original reports

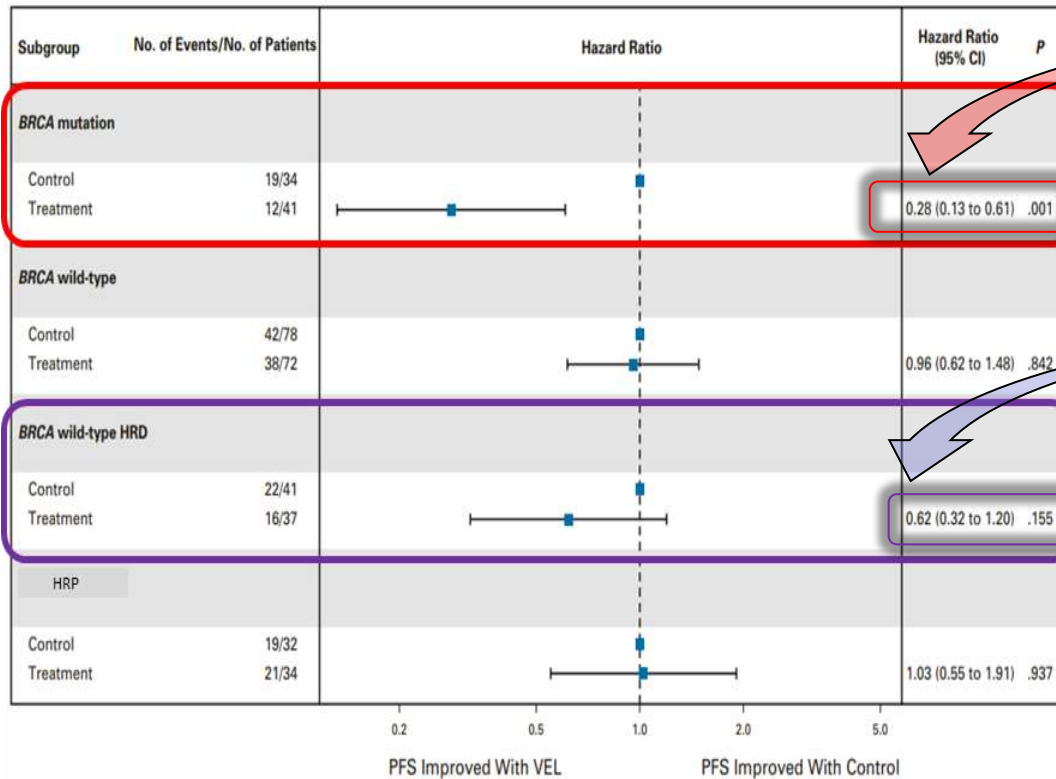
CA-125 KELIM as a Potential Complementary Tool for Predicting Veliparib Benefit: An Exploratory Analysis From the VELIA/GOG-3005 Study

Benoit You, MD, PhD^{1,2}; Vasudha Sehgal, PhD³; Balakrishna Hosmane, PhD³; Xin Huang, PhD³; Peter J. Ansell, PhD³; Minh H. Dinh, MD³; Katherine Bell-McGuinn, MD, PhD³; Xizhi Luo, PhD³; Gini F. Fleming, MD⁴; Michael Friedlander, PhD⁵; Michael A. Bookman, MD⁶; Kathleen N. Moore, MD⁷; Karina D. Steffensen, MD, PhD⁸; Robert L. Coleman, MD⁹; and Elizabeth M. Swisher, MD¹⁰

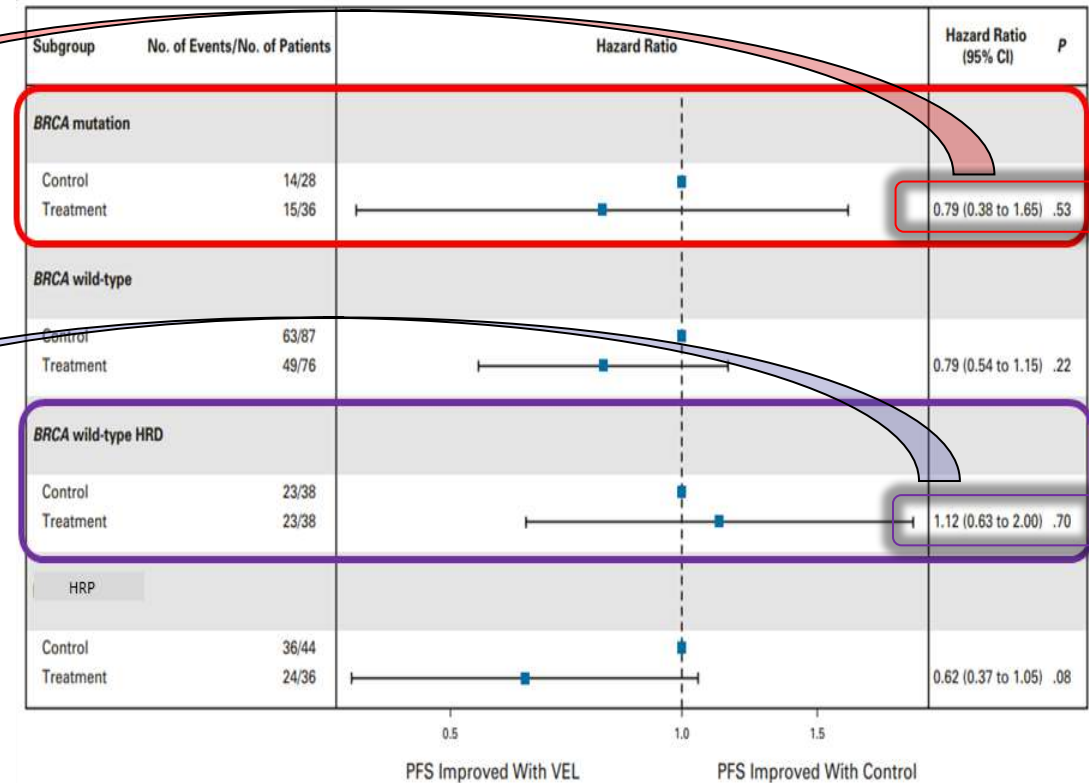
Journal of Clinical Oncology[®]
An American Society of Clinical Oncology Journal

KELIM in VELIA trial

KELIM favorable

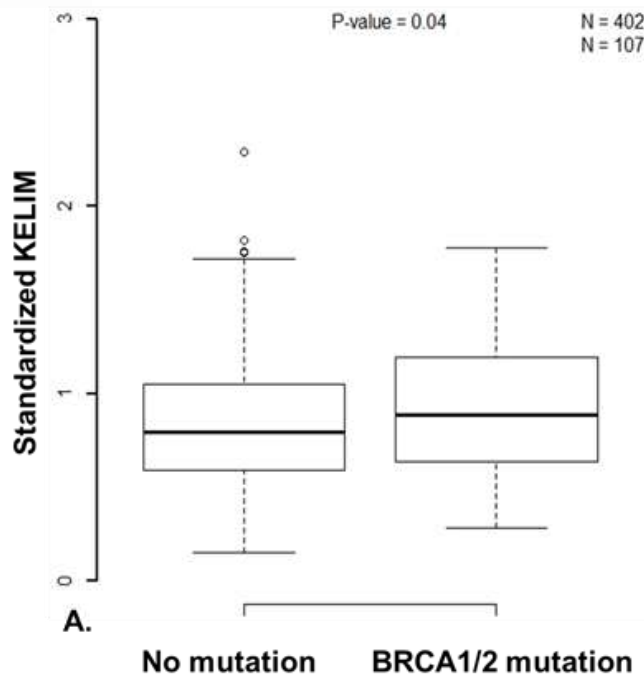


KELIM défavorable

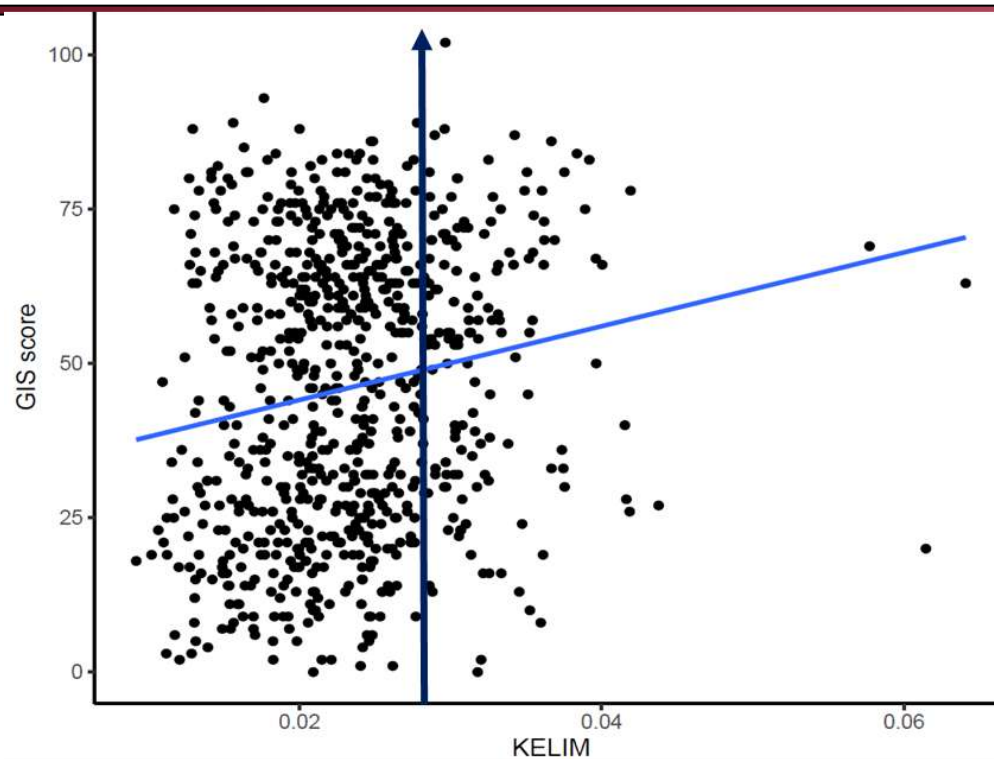


74% of patients with BRCA mutation and unfavorable KELIM treated with veliparib had short PFS < 18 months.

KELIM and BRCA/HRD status



The Netherlands Cancer Registry



VELIA trial

KELIM and HRD status are slightly linked but not superimposable ...

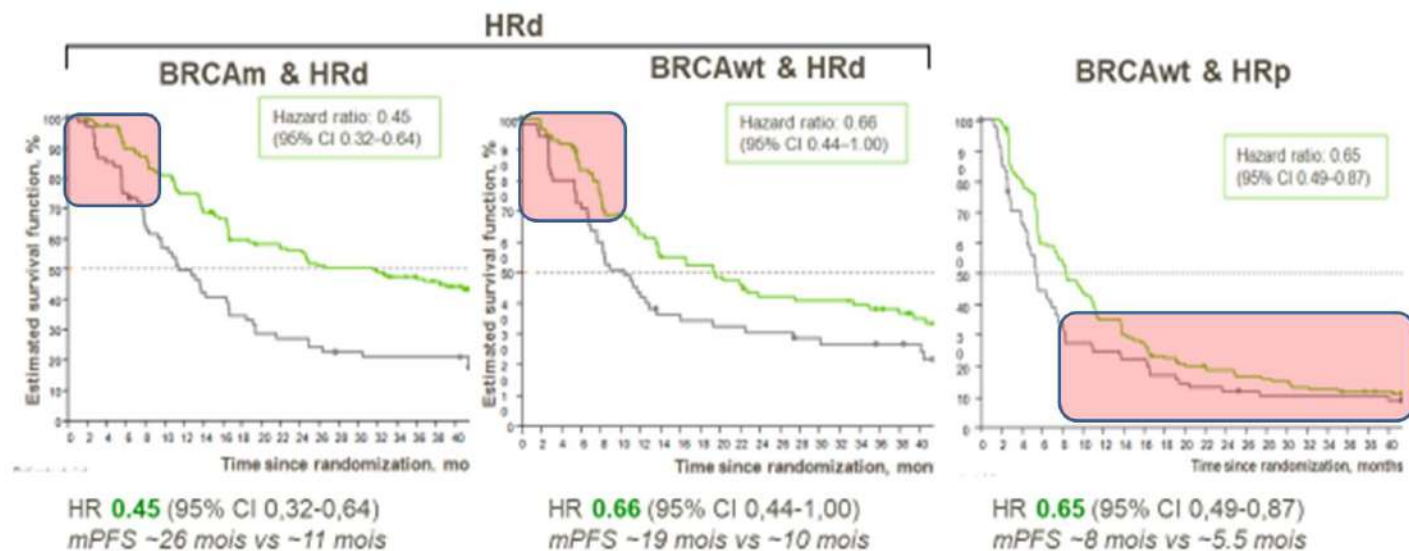
and probably complementary ...

In summary ...

Could KELIM help identify the best maintenance treatment ?

- Bevacizumab is encouraged in patients with high-risk disease & unfavorable KELIM score < 1.0 (benefit in OS)
- PARP inhibitor likely to be more active for patients with favorable KELIM score ≥ 1.0

↳ Would an unfavorable KELIM score < 1.0 be an indicator of poor efficacy of PARP inhibitor ?



What about use of KELIM in the real-life routine ?

**Cited in ESMO-ESGO guidelines 2022
and French RPC St Paul 2023 guidelines**

Italian guidelines

Table 7
Proposed scoring system for evaluating the response to adjuvant chemotherapy.

(A) Individual scores assigned to the parameters considered for response evaluation

RECIST	KELIM
1 = Partial response	0 = KELIM <1
2 = Complete response	1 = KELIM ≥1

Interpretation of total scores

Total score	Response definition
<2	Moderate
≥2	Good

(B) Individual scores assigned to the parameters considered for response evaluation

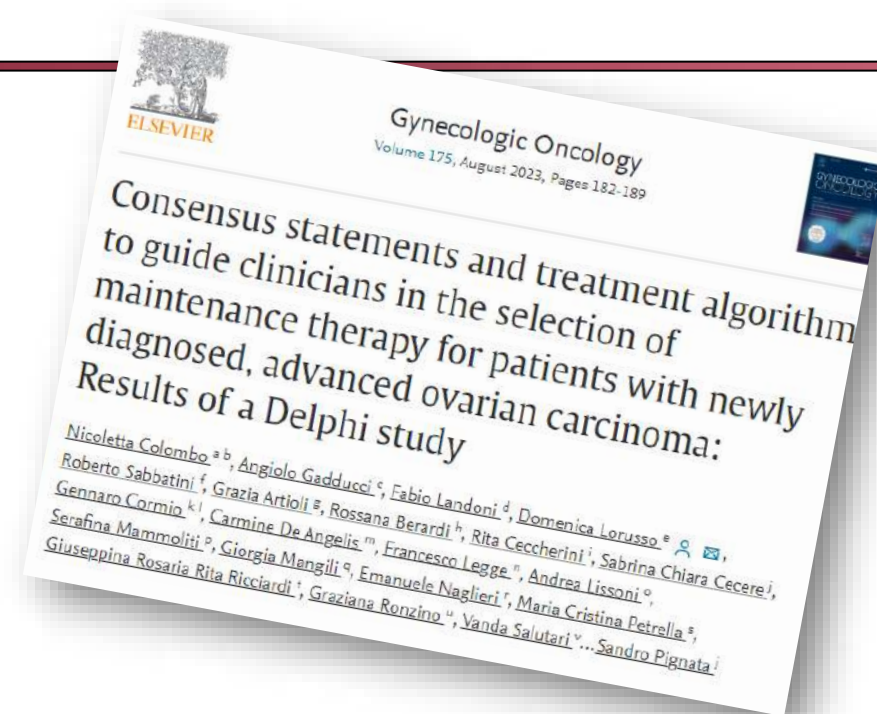
Pathology	KELIM	Surgical outcome
1 = Partial ^a	0 = KELIM <1	0 = Residual tumor
3 = Near-complete/Complete ^b	1 = KELIM ≥1	1 = No residual tumor

Interpretation of total scores

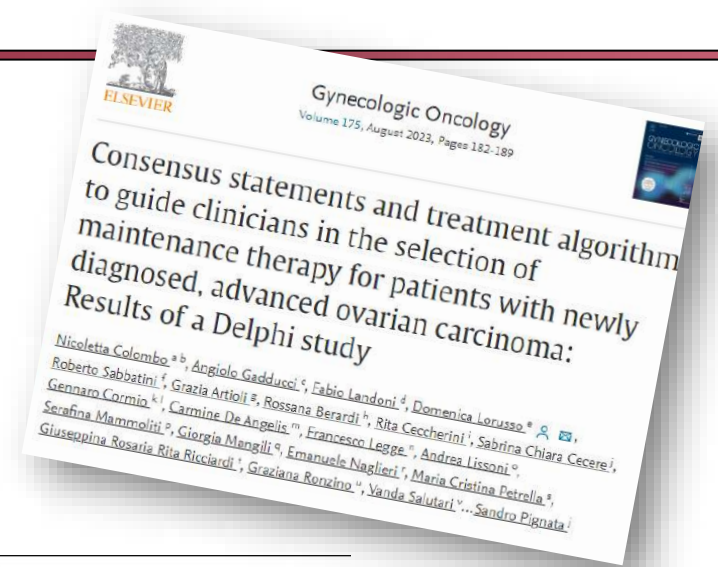
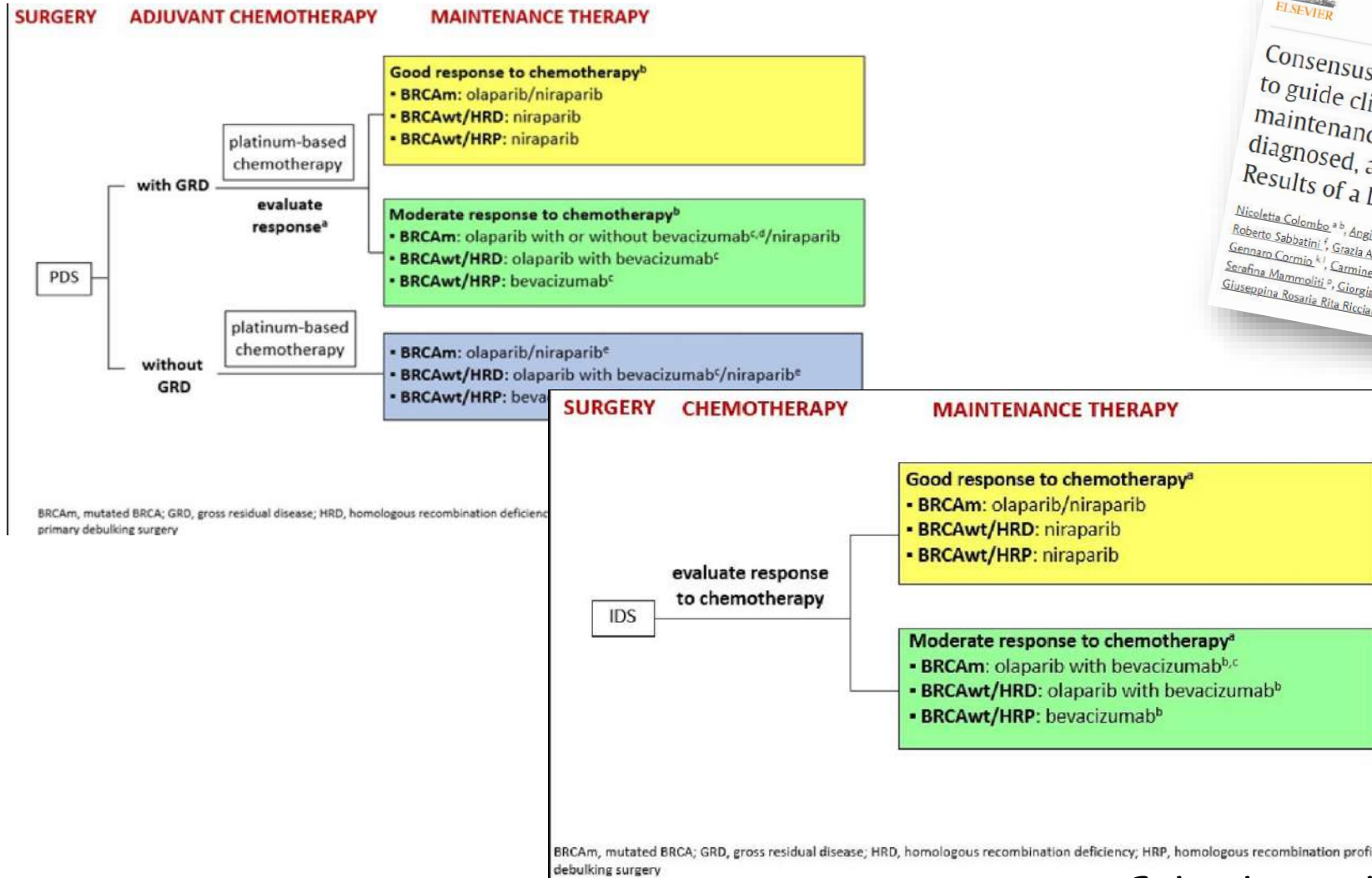
Total score	Response definition
<3	Moderate
≥3	Good

^a Chemotherapy Response Score 2.

^b Chemotherapy Response Score 3.



Italian guidelines



https://www.biomarker-kinetics.org/

Biomarker-Kinetics™ : CA-125 KELIM™ Calculator in Ovarian Cancer & Other Biomarkers

Changes in serum tumor biomarkers may indicate treatment efficacy. Mathematical modeling allows calculation of the equations describing the longitudinal tumor biomarker time-changes. The model-based population kinetic approach is particularly relevant as it enables determination of individual kinetic profiles parameters based on a few timepoints, with limited impact of inter- and intra-individual variability of timepoints and assays.

Our tools

- CA-125 neo-adjuvant**
CA-125 KELIM™ in patients with stage III-IV high grade serous ovarian carcinomas treated in first-line setting with neo-adjuvant chemotherapy (disease in place) with the intent of a potential interval debulking cytoreductive surgery.
- CA-125 adjuvant**
CA-125 KELIM™ in patients with stage III-IV high grade serous ovarian carcinomas treated in first-line setting with adjuvant chemotherapy after primary debulking surgery.
- PSA**
clearance after radical prostatectomy in patients with low-risk prostate cancer.
- hCGres**
in patients with low-risk gestational trophoblastic neoplasias treated with the 8-day Methotrexate regimen.

The team

The models were developed by Team 3 of EA3738 iCLY of Lyon University (Université Claude Bernard Lyon 1, France) and Lyon University Hospital (Hospices Civils de Lyon, France), in collaboration with the collaborative French GINECO Group, under the supervision of Prof Benoit You MD PhD. The internet site and the smartphone application were developed with the support of HCL Foundation.

BK™ Smartphone App

Biomarker-Kinetics.org™ also works on your smartphone!

To add it to your home screen:

- 1 Open Safari or Chrome
- 2 tap the icon in Safari, or tap the icon in Chrome
- 3 Select "Add to Home Screen"

News

KELIM™ prognostic value in the GCG meta-analysis dataset accepted in EJC

We are pleased to announce that the article about KELIM™ prognostic value in the GCG meta-analysis dataset written by Pauline Corbau was accepted for publication in the European Journal of Cancer!

CA-125 KELIM™ was presented at the June 2021 MITO group (Napoli, Italy)

The Italian MITO group, celebrating the 25 years old anniversary of the foundation by Dr Sandro Pignata, invited Dr Benoit You to present the latest results of KELIM™ in patients with ovarian cancer. The session was entitled "Time to incorporate KELIM™ in our algorithms?".

Interested in collaboration for your datasets or your innovative drugs ? So are we!

Learn more >

SalvQvar
Learn more about the future European clinical phase III trial SALVQVAR, where the patients with unfavorable KELIM scores < 1.0 and a disease not amenable to complete interval debulking surgery after 3 to 4 cycles standard neo-adjuvant chemotherapy will be randomized to the continuation of the standard 1-weekly regimen, or a salvage regimen with weekly dose-dense carboplatin-paclitaxel.
Visit website >

<https://www.biomarker-kinetics.org/>

The screenshot shows the website interface with two main calculator sections. The top section is for 'CA-125 neo-adjuvant' and the bottom section is for 'CA-125 adjuvant'. Both sections include a calendar and a list of dates with corresponding values.

Page for neo-adjuvant chemotherapy calculator

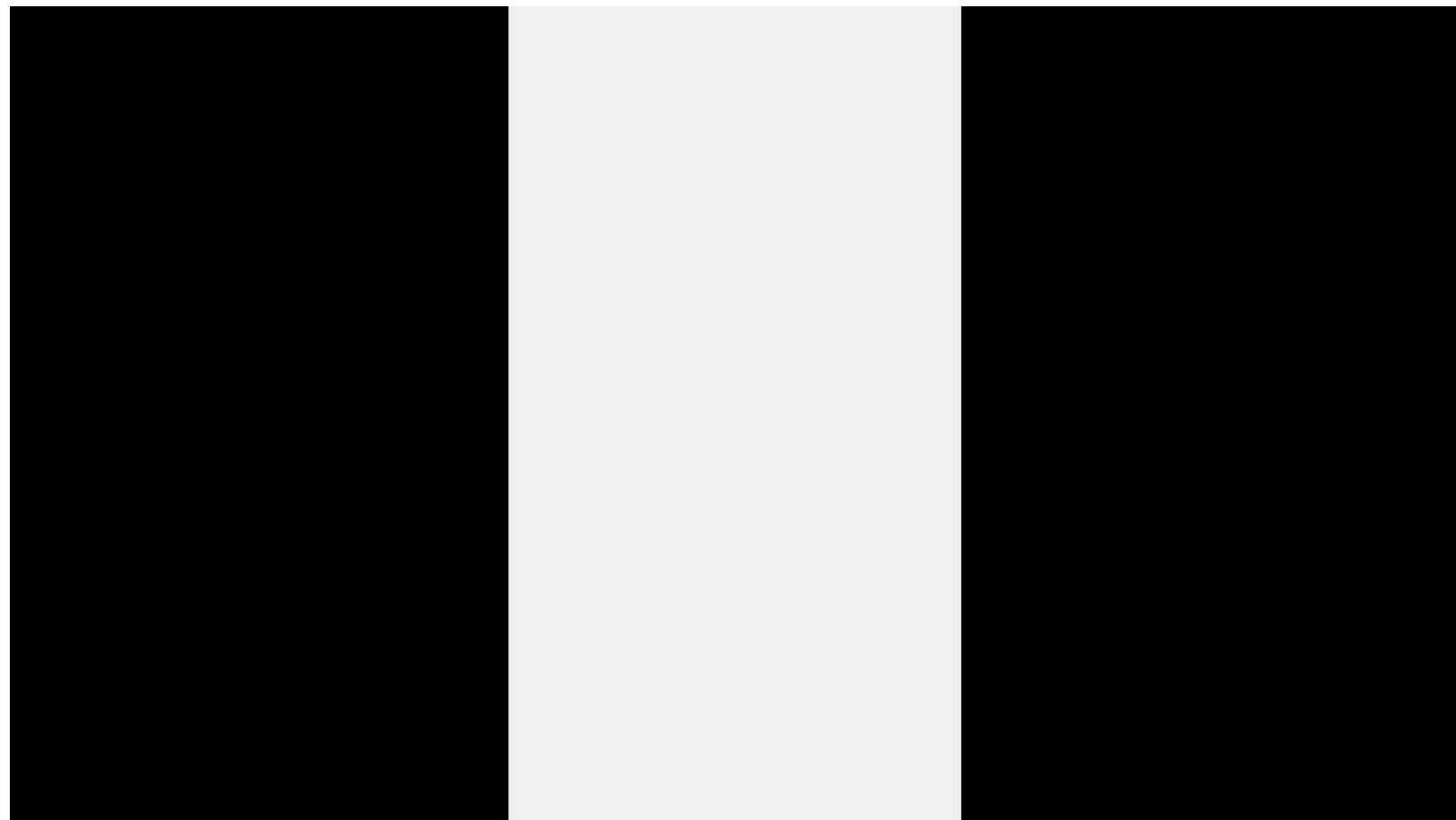
Chemotherapy dates*
2023-05-02
2023-05-23
2023-06-13

Dates of neo-adjuvant chemotherapy

Date*	Value*
2023-05-04	2598
2023-05-19	1691
2023-05-31	1478

Dates and values of CA-125

<https://www.biomarker-kinetics.org/>



<https://www.biomarker-kinetics.org/>

14.2k

Views +14.2k

5.07k

Visitors +5.07k

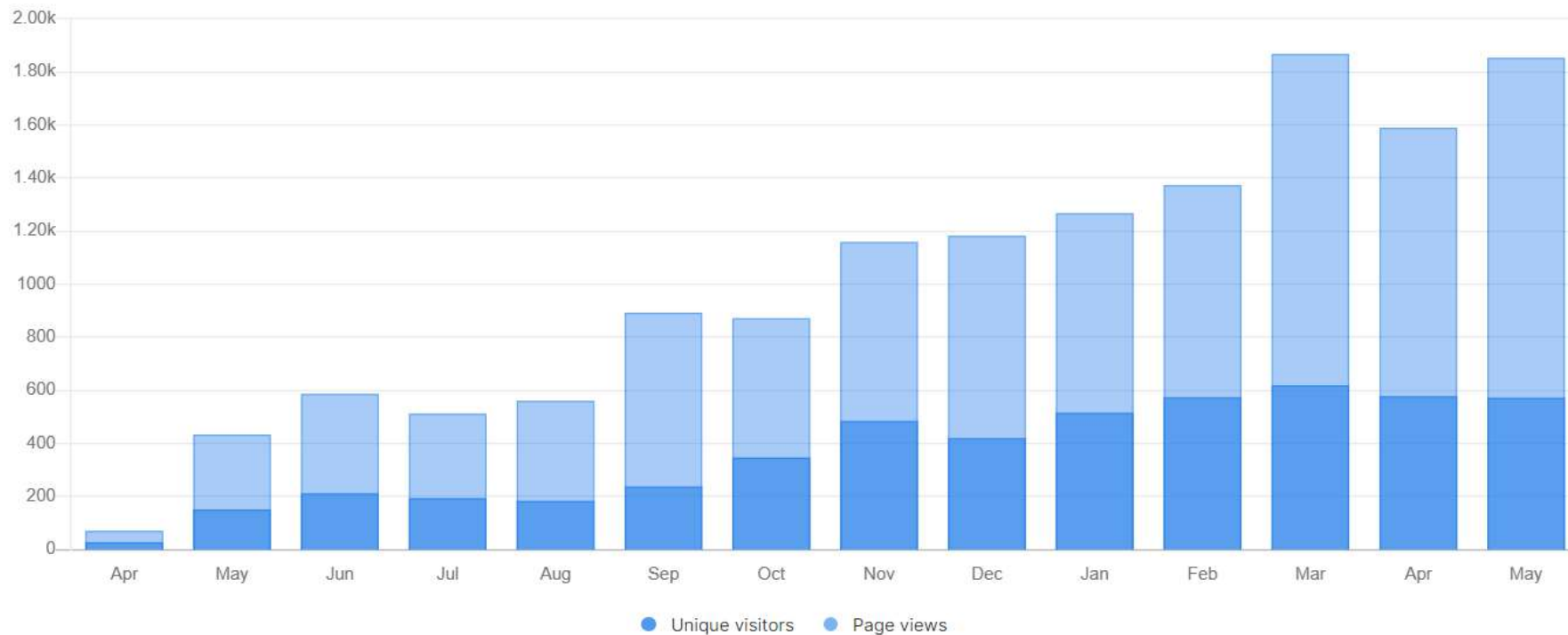
100%

Bounce rate

1m 59s

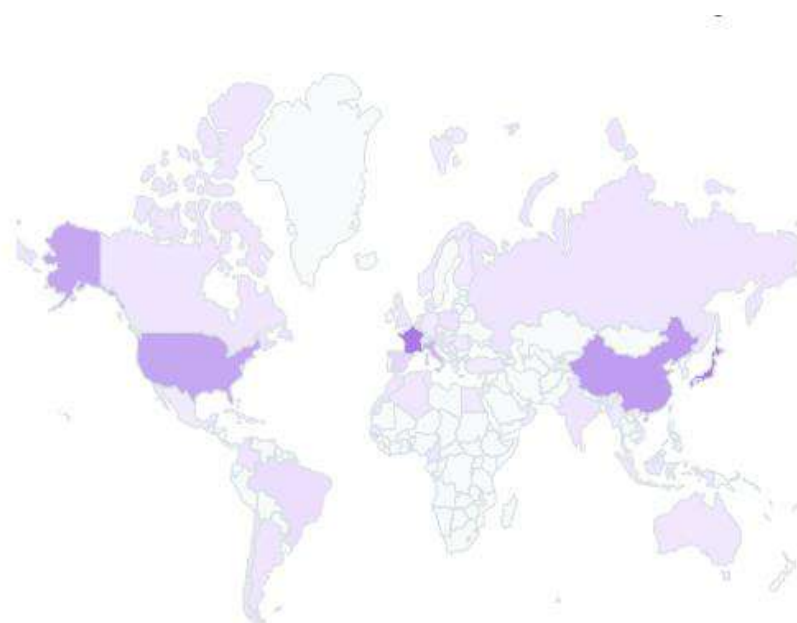
Average visit time

All time



~ 1,800 connections / month in the world

<https://www.biomarker-kinetics.org/>



Countries

Map [Countries](#) [Regions](#) [Cities](#)

Country	Visitors
JP Japan	241
FR France	235
CN China	165
us United States	143
IT Italy	115
es Spain	39
BR Brazil	26
AT Austria	17
TW Taiwan	16

Many ongoing studies about KELIM in the world:

- Japan
- India
- South America
- USA
- Europe ...

The GCIG KELIM international working group



GCIG
GYNECOLOGIC
CANCER INTERGROUP

Objective: To accompany the development of KELIM™

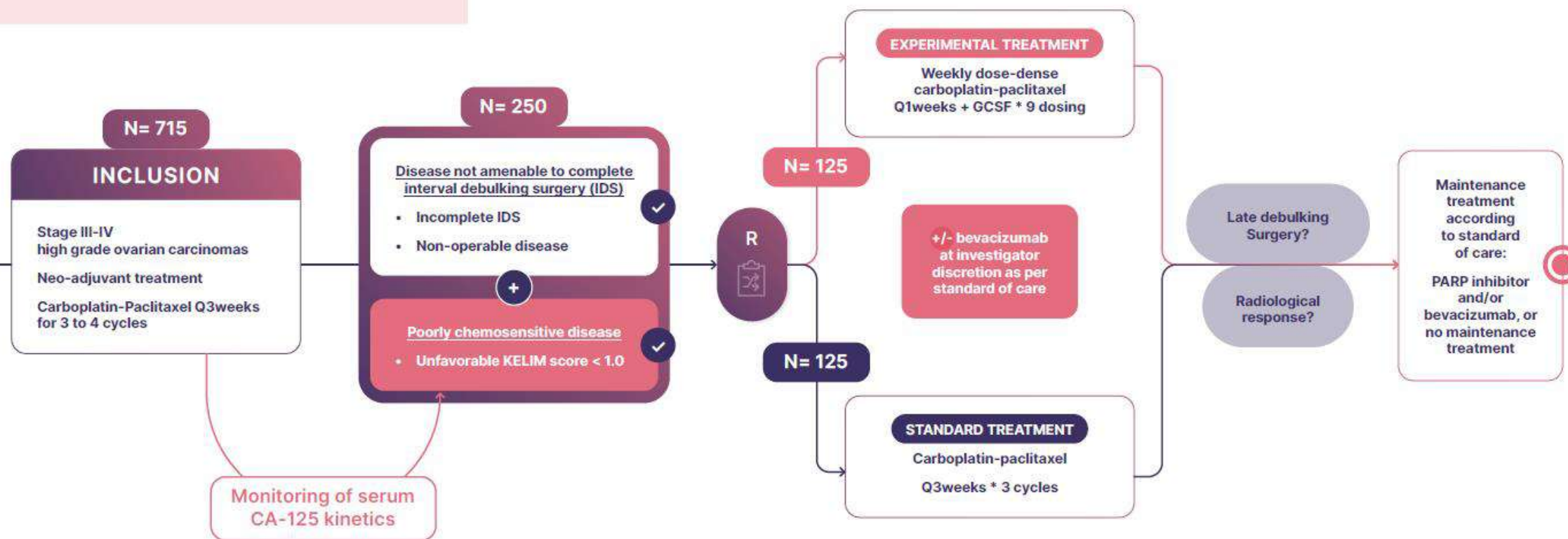
Members of the group

- Canada : Stephanie Lheureux and Stephen Welch
- France : Laurence Gladiëff, Gwenael Ferron, and Fabrice Lecuru
- Greece : John Syrios
- Italy : Sabrina Cecere
- Korea : Adrian Kim
- Norway : Kristina Lindemann
- Spain : J. Alejandro Pérez-Fidalgo
- UK : Andrew Clamp and Ros Glasspool
- USA : Bradley Monk and Elizabeth Swisher



A population with unmet medical need

Design



Co-primary endpoints

- Benefit in overall survival with HR = 0.61 (mOS from 20.0 to 32.8 months)
- Increase in the feasibility of late complete debulking surgery (from 5% to 20%)

Secondary endpoints

- Safety
- Radiological response rate
- Rate of patients benefiting from PARPi and/or bevacizumab as maintenance treatment

Stratification

- Recruiting country
- KELIM strata (very unfavorable < 0.7 vs moderately unfavorable 0.7-1.0)
- Likelihood for a future delayed surgery: definitively not amenable, vs potentially amenable

<https://www.salvoovar.eu/>

Conclusion: Time to incorporate KELIM in our algorithm?

KELIMTM = numeric tool able to reveal “one” characteristics of the patient tumor

- Pragmatic indicator of the tumor primary chemosensitivity
- Prognostic value for PFS, OS and long disease-free, complementary to surgery outcome

⇒ 2 independent flags ...

↳ Weekly dose-dense chemotherapy in patients with 2 red flags ?

-Predictive value regarding the neo-adjuvant chemotherapy effect on the disease extend, and the **complexity of surgical effort**... but also about the **relative prognostic benefit** of interval debulking surgery

-Better **selection of patients for bevacizumab** among those with **high-risk** disease ?

-**Complementary to BRCA-HRD status** regarding the **benefit from PARPi**

-BRCA mutation (or event HRD) with unfavorable KELIM < 1.0

⇒ **Caution !**

- **HRP status**: selection between **bevacizumab** or **niraparib** ?



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