Cancéropôle
Grand Sud-Ouest

15th ANNUAL MEETING OF THE SMAC CLUB

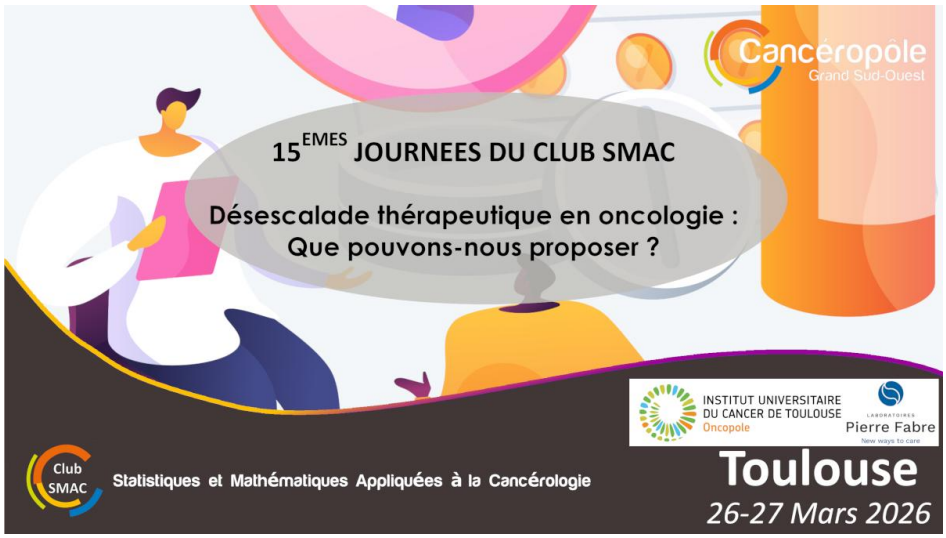
STATISTICS & MATHEMATICS APPLIED TO CANCER

THERAPEUTIC DE-ESCALATION IN ONCOLOGY: WHAT CAN WE OFFER?

Club SMAC

TOULOUSE, FRANCE
26 – 27 MARCH 2026

Table des matières



Acknowledgements

We warmly thank all those who contributed to the success of the **15th edition of the SMAC Club Conference (2026)**.
Our thanks go to the organizing committee and the scientific committee of the SMAC Club for their commitment throughout the preparation of the event, as well as to the invited speakers for the quality of their presentations.
We also sincerely thank our partners and sponsors : **Institut Universitaire du Cancer de Toulouse - Oncopole**, **Laboratoires Pierre Fabre**, **La Ligue contre le Cancer**, **Société Française du Cancer**, **La Région Occitanie / IA pour la Santé**, **AMIES**, **France 2030**, and the **Fondation ARC pour la Recherche sur le Cancer,** for their valuable support of this edition.
We are particularly grateful to **IUCT-Oncopole** for kindly hosting the event.
We would also like to extend our special thanks to **Laboratoires Pierre Fabre** for organizing the after-work event at their site on Thursday evening, as well as for offering participants the opportunity to visit their laboratories on Friday afternoon. These moments of conviviality and discovery greatly contributed to the warm atmosphere of this edition.

Finally, we extend our sincere gratitude to all participants who attended over the two days, whose interest and active engagement greatly enriched the discussions.

Partenaires et sponsors :

Introduction

These Days were a major national event that annually brings together the community of researchers and professionals in mathematics and biostatistics applied to cancer research, around a theme related to the evolution of oncology. In total, more than 50 professionals with diverse backgrounds in mathematics and biostatistics attended. The free admission helped ensure the participation of young researchers.

With a strong focus on developments in clinical research in oncology, this year's theme revolved around therapeutic de-escalation, under the title:

"Therapeutic De-escalation in Oncology: What Can We Propose?"

In light of evolving knowledge and new therapeutic strategies, therapeutic de-escalation has become a priority theme of the French National Cancer Strategy 2021–2030. It consists notably in proposing modulated therapeutic strategies to limit sequelae and improve quality of life while maintaining equivalent efficacy.
The gold standard for evaluating modulated therapeutic strategies is the multicenter randomized phase 3 non-inferiority trial. Beyond efficacy, it is essential to also consider patient-centered endpoints to quantify improvements in quality of life, and to conduct relevant analyses of adverse effects or costs, in order to confirm that the residual risk of a "small loss" in survival is outweighed by the benefits.

The design of non-inferiority trials is associated with numerous challenges, particularly the definition of the non-inferiority margin. Such trials require many years, large sample sizes, and significant financial investment. A recent publication has questioned the framework of non-inferiority trials: *"The tyranny of non-inferiority trials"* (Tannock, Lancet Oncol 2023). For its part, the European Society of Medical Oncology has proposed a three-level evidence classification for therapeutic de-escalation (IA – Randomized controlled trial, IB – Single-arm study with external control, IC – Prospective-retrospective validation), emphasizing the importance of designing high-quality studies with fewer patients and shorter durations, particularly in very low-risk populations (Trapani, Annals of Oncol 2022). On this last point, a parallel can be drawn with the 2023 SMAC Days, which had highlighted the importance of implementing new methodological approaches in the evaluation of novel therapies to achieve a high level of evidence.

For this reason, the Cancéropôle Grand Sud-Ouest initiated this event to discuss and share insights on the topic, inviting renowned speakers from various specialties and backgrounds (biostatisticians, oncologists, clinicians, from academia or the private sector). These speakers led four sessions focused on different themes:

- Non-inferiority trials: From clinical problem to implementation
- Patient-centered endpoints and analysis strategies
- Non-inferiority trials in specific populations and evaluation of innovative therapies: the same challenge?

An opening session introducing the concept of reinforcement learning and its medical application known under the acronym DTR (Dynamic Treatment Regimes)
The event concluded with a roundtable bringing together clinicians and statisticians to debate the key methodological and clinical challenges raised throughout the two days.

Presentation of the SMAC Club

The **SMAC club** (**S**tatistics & **M**athematics **A**pplied to **C**ancer**)** brings together statisticians and mathematicians from the *Cancéropôle GSO* wishing to participate in a community of researchers interested in cancer research.

The *Cancéropôle GSO* brings together about 500 scientific and medical research teams from the South West of France (GSO = Grand Sud Ouest = South West French Region) around collaborative projects. The *Cancéropôle GSO* runs a dynamic cancer research network and offers coordinated synergy between Institutions, Territories and Disciplines for the benefit of the patient.

The objective of the SMAC Club is to strengthen links between biostatistics, statistics and mathematics teams, as well as with teams who, in human and social sciences and epidemiology, use statistics. It aims both to help develop the skills of statistical teams, and to make these skills better known to “statistics users”. To do this, it notably organizes an annual conference on a theme chosen by the club. The themes that have been worked on by the SMAC Club in previous years are very varied (cohorts, dynamic prediction models, quality of life, test simulation, imaging). The 2026 edition focused on therapeutic de-escalation in oncology.
>> smac.canceropole-gso.org

SMAC Scientific committee

Carine Bellera – Bordeaux Population Health Equipe EPICENE (Inserm U1219) et Inserm CIC1401 (Institut Bergonié, CLCC), Bordeaux
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Program

15th Annual Meeting of the SMAC Club
Statistics & **M**athematics **A**pplied to **C**ancer
26–27 March 2026, Toulouse, France
Therapeutic De-escalation in Oncology:
What Can We Offer?

Thursday, 26 March 2026

Time	Details
8:30	Welcome coffee & registration
9:00	Opening remarks *(Jean-Pierre Delord, Thomas Filleron, Nicolas Savy)*
9:15	The INCa Ten-Year Cancer Strategy: Focus on Therapeutic De-escalation *Claude Linassier, Institut National du Cancer, Paris*
[SESSION 1]	**Non-Inferiority Trials in Oncology: From Clinical Challenge to Implementation**
9:30	The clinician's point of view *Gwenaelle Gravis, Institut Paoli-Calmettes, Marseille*
10:00	Designing a non-inferiority trial according to best practice *Xavier Paoletti, Institut, Paris*
10:30	Coffee break
11:00	Non-Inferiority Trials: Handling Non-Adherence and Defining Estimands *Clémence Leyrat, Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom*
11:30	The sponsor's point of view *Muriel Dahan, Unicancer, Paris*
11:50	Discussant followed by open exchange with speakers and audience
12:10	Lunch break
[SESSION 2]	**Therapeutic Escalation and De-escalation in Breast Cancer & Complementary Approaches**
13:30	Therapeutic Escalation and De-escalation in Breast Cancer: The Clinician's Perspective *Luc Cabel, Institut Curie, Paris*
14:00	Complementary Approaches in Non-Inferiority Trials: Pragmatic Trials and Single-Arm Trials

	Stefan Michiels, Gustave Roussy, Université Paris-Saclay, INSERM U1018, Villejuif
14:30	External Control Arms and Non-Inferiority Trials *Jérôme Lambert, Université Paris Cité, Service de Biostatistique et Information Médicale, Hôpital Saint-Louis, AP-HP, Paris*
15:00	Target Trial Emulation for Non-Inferiority Studies *Raphaël Porcher, Université Paris Cité, Paris*
15:30	Discussant
15:40	Coffee break
[SESSION 3]	**Reinforcement Learning and Dynamic Treatment Regimes**
16:00	Reinforcement Learning and Dynamic Treatment Regimes *Nicolas Savy, Institut de Mathématiques de Toulouse, Université Paul Sabatier, Toulouse*
16:30	**Dynamic Treatment Regimes** *Michael Kosorok, Department of Biostatistics, University of North Carolina Remote*
17:00	End of Day 1
17:30	**After-Work Social Event** *(Pierre Fabre)*
20:00	Speakers' Dinner

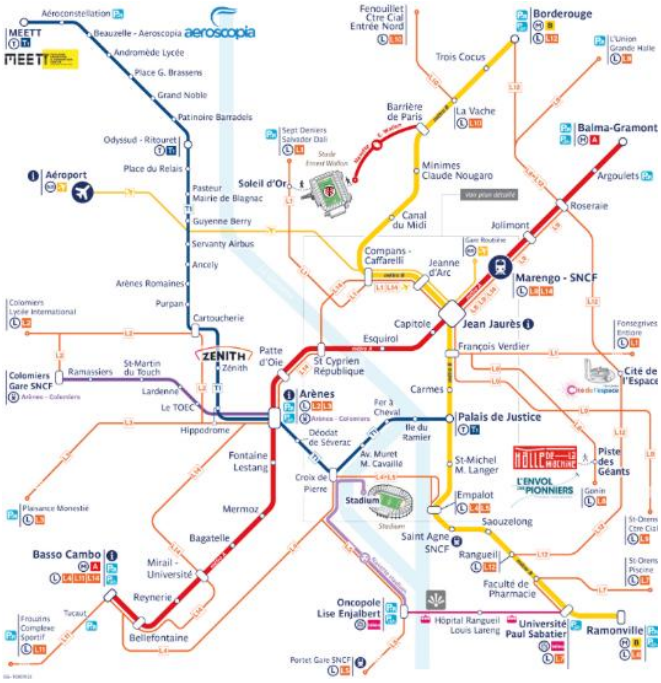
Friday, 27 March 2026

Time	Details
8:30	Welcome coffee & registration
[SESSION 4]	**Patient-Centred Endpoints**
9:00	The clinician's point of view *Frédéric Fiteni, CHU de Nîmes, Nîmes*
9:30	Quality of Life as a Primary or Composite Endpoint in De-escalation Trials: « Pros & Cons » *Amélie Anota, Centre Léon Bérard, Lyon*
10:00	Non-Inferiority Trials: Need for Improvement or a Paradigm Shift? *Marc Buyse, IDDI, One2Treat and University of Hasselt, Belgium*
10:30	Discussant
10:40	Coffee break
[SESSION 5]	**The Industry Perspective: Changing Paradigms in Oncology Drug Development**
11:00	Optimus: Shifting the paradigm, from maximum tolerated dose to optimal dose *David Jegou, Statistical Process Expert, Pierre Fabre*
11:30	The Role of AI in Optimizing Clinical Trials *Laurent-Philippe Albou, Institut Roche, France*
12:00	**Round Table** - *Muriel Dahan (Unicancer), Jean-Pierre Delord (Oncologist, Oncopôle Claudius Regaud, Toulouse), Pierre Dubois (Toulouse School of Economics), Laëtitia Gambotti (Agence Innovation Santé), Joachim Baba (Haute Autorité de Santé), Vincent Gazin (Agence Nationale de Sécurité du Médicament et des produits de santé)*
13:00	Closing & Lunch Buffet

Venue & Access

The 15th Annual Meeting of the SMAC Club will take place in the amphitheatre of IUCT-Oncopôle, Toulouse (1 Avenue Irène Joliot-Curie).
Public transport: Tisséo / Téléo
Bus stop: "Oncopole Lise Enjalbert"

→ *How to Get to IUCT-Oncopole*



Summary of Presentations from the 14th SMAC Club Conference

Claude Linassier, Institut National du Cancer, Paris, France
Title: The INCa Ten-Year Cancer Strategy: Focus on Therapeutic De-escalation
Abstract:
Therapeutic de-escalation consists in proposing modulated therapeutic strategies to limit sequelae and improve quality of life while maintaining equivalent efficacy. Surgeons were pioneers in this approach. The INCa ten-year cancer strategy (2021–2030) integrates therapeutic de-escalation as a priority axis, both in the 2021–2025 roadmap (Axis 2: limiting sequelae and improving quality of life) and in the 2026–2030 roadmap (Objective 10: promoting care relevance). The INCa has launched dedicated calls for projects (AAP) aiming to define organisational models for optimal access to de-escalation and to support deployment once efficacy is demonstrated. Therapeutic de-escalation is now a strong and recurrent axis of the national cancer strategy, supported by active involvement in research and care pathway innovation.

Gwenaelle Gravis, Institut Paoli-Calmettes, Marseille, France
Title: The clinician's point of view
Abstract:
Therapeutic de-escalation is a major challenge for patients and society in oncology. Immunotherapies currently approved are recommended until disease progression or unacceptable toxicity, with unknown optimal duration. Standard chronic administration leads to multiple medical visits, risk of chronic toxicity, impact on quality of life, and significant costs. The MOIO trial is an academic pragmatic phase III randomised non-inferiority trial comparing standard immunotherapy dosing versus reduced-intensity dosing every three months, in patients with locally advanced or metastatic cancer achieving complete or partial response after 6 months of standard immunotherapy. The primary endpoint is progression-free survival, with a non-inferiority margin of HR = 1.3. A total of 646 patients are expected, with an inclusion period of 36 months and a total study duration of 72 months. Secondary endpoints include overall survival, quality of life, anxiety, fear of relapse, safety profile, and cost-effectiveness. A translational study includes immune monitoring, pharmacokinetics, and circulating tumour DNA analysis.

Xavier Paoletti, Institut Curie / Université de Versailles-St Quentin, INSERM U1331, Paris, France
Title: Designing a non-inferiority trial according to best practice
Abstract:
Non-inferiority trials aim to demonstrate that a new treatment is not unacceptably worse than a reference treatment. The key methodological challenge lies in the definition of the non-inferiority margin. Using the PHARE trial as a case study, comparing 6 versus 12 months of trastuzumab in HER2-positive breast cancer, this presentation illustrates the step-by-step design of a non-inferiority trial. The non-inferiority margin was derived from the lower bound of the control effect estimated from the HERA trial (HR = 0.54, 95% CI: 0.43–0.67), yielding .

The presentation highlights the complexity of interpreting results based on double negation logic, and reflects on the real-world impact of such trials on healthcare practice, 20 years after the first patient was enrolled.

Clémence Leyrat, Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom
Title: Non-Inferiority Trials: Handling Non-Adherence and Defining Estimands
Abstract:
Non-adherence in clinical trials refers to intercurrent post-randomisation events such as treatment discontinuation, modification or switching. In non-inferiority trials, non-adherence carries specific risks of artificially making treatment arms appear more similar, potentially leading to false conclusions of non-inferiority. This presentation introduces the estimand framework as a tool to clarify the research question of interest. A key distinction is made between trial-specific and non-trial-specific intercurrent events. The choice of estimand depends on the underlying mechanism of intercurrent events: treatment policy estimands are analysed using intention-to-treat, while hypothetical estimands require inverse probability weighting (IPW) or instrumental variable (IV) methods. A review of 57 non-inferiority trials for which EMA scientific advice was requested illustrates the gap between estimands proposed in protocols and those recommended by the EMA. Simulation results confirm the importance of aligning the choice of estimand and estimator to avoid misleading conclusions.

Muriel Dahan, Unicancer, Paris, France
Title: The sponsor's point of view
Abstract:
Therapeutic de-escalation trials aim to reduce the use of costly treatments when not strictly necessary, while guaranteeing optimal efficacy and reducing adverse effects. From a sponsor's perspective, these trials represent a dual challenge: generating immediate savings for the health insurance system from trial initiation, and multiplying long-term benefits if results are positive. However, academic de-escalation trials face major funding difficulties. The main obstacles are the absence of commercial interest, the limited budget of public programmes such as PHRC-K, increased competition between high-quality projects, and the lack of complementary funding mechanisms. Despite their strong societal impact, reducing healthcare costs and improving patient quality of life, these trials struggle to secure sufficient funding. Existing academic funding sources in France include PHRC-K, the Plan Cancer/INCa, ANR, and foundations, but these remain insufficient to cover the full needs of academic research in this field.

Luc Cabel, Institut Curie, Paris, France
Title: Therapeutic Escalation and De-escalation in Breast Cancer: The Clinician's Perspective
Abstract:
Therapeutic escalation in breast oncology has been driven by the arrival of new molecules, with a tendency to add treatments. In parallel, academic de-escalation trials face major challenges: limited funding, large sample size requirements, and few events in many good-

prognosis situations. This presentation reviews the current landscape of de-escalation strategies in early breast cancer, across three subtypes: HER2-positive, triple-negative, and hormone receptor-positive tumours. For HER2-positive breast cancer, a continuum of de-escalation options is presented, ranging from anthracycline omission to chemotherapy omission, illustrated by the APT trial (paclitaxel + trastuzumab for pT1N0). For triple-negative breast cancer, examples include the WISH-DIAMOND trial (anthracycline de-escalation in BRCA1-2 mutated tumours) and the OMIRCHIR trial (surgery omission after predicted complete pathological response). New tools to guide de-escalation, including dynamic MRI (TRAIN-3 trial), genomic signatures, and circulating tumour DNA, are presented. Detection of circulating tumour DNA after neoadjuvant chemotherapy and before surgery is emerging as a promising ultrasensitive tool to identify patients at very low risk of relapse and potentially guide de-escalation decisions.

Stefan Michiels, Gustave Roussy, Université Paris-Saclay, INSERM U1018, Villejuif, France

Title: Complementary Approaches in Non-Inferiority Trials: Pragmatic Trials and Single-Arm Trials

Abstract:

Pragmatic trials and single-arm trials represent complementary approaches to randomised controlled trials in the context of therapeutic de-escalation. Pragmatic trials are characterised by broad eligibility criteria, simple protocols, limited monitoring, and primary intention-to-treat analyses. The HypoG-01 trial a phase III randomised non-inferiority trial comparing hypofractionated (40 Gy/15 fractions/3 weeks) versus normofractionated (50 Gy/25 fractions/5 weeks) radiotherapy for regional nodes in breast cancer, illustrates this approach. The primary endpoint is 3-year cumulative incidence of arm lymphedema. Results published in *Lancet* (Rivera et al., 2026) are presented, along with a planned prospective meta-analysis with the international Skagen01 trial. Single-arm trials with external controls are also discussed, using the OPT-PEMBRO trial as an example: a de-escalation trial of pembrolizumab in triple-negative breast cancer after pathological complete response, with a planned prospective meta-analysis with the OptimICE-PCR trial. The MyPebs pragmatic non-inferiority trial on mammography de-escalation is also presented, illustrating sample size challenges specific to low event rate settings.

Jérôme Lambert, Université Paris Cité, Service de Biostatistique et Information Médicale, Hôpital Saint-Louis, AP-HP, INSERM U1342, Paris, France

Title: External Control Arms and Non-Inferiority Trials

Abstract:

External controls, also referred to as historical controls or synthetic controls can serve as the control arm of a single-arm trial or supplement the control arm of a randomised trial. Their use is frequent in reimbursement dossiers submitted by industry for superiority trials. The main methodological approaches for population-adjusted indirect comparisons (PAIC) include matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC), both applicable when only aggregate data are available from the comparator study. When individual patient data are available from both studies, methods include propensity score

matching, inverse probability of treatment weighting, and outcome regression. A key prerequisite is the exchangeability of internal and external control populations, as defined by Pocock's six criteria (1976). The presentation discusses the specific challenges of applying external controls in the non-inferiority context: unlike superiority trials, de-escalation requires demonstrating that outcomes are not worse, which demands particularly rigorous control of confounding and selection biases. Current applications remain of limited quality and are rarely taken into account by HTA agencies. The randomised clinical trial remains and must remain the gold standard for therapeutic evaluation, including for non-inferiority.

Raphaël Porcher, Université Paris Cité, INSERM U1153, Hôpital Hôtel-Dieu, AP-HP, Paris, France

Title: Target Trial Emulation for Non-Inferiority Studies

Abstract:

Target trial emulation is a framework for designing and analysing observational studies by explicitly emulating the protocol of a randomised trial that would answer the causal question of interest. The key components of a target trial protocol include eligibility criteria, treatment strategies, assignment procedures, follow-up period, outcomes, causal contrasts, and analysis plan. The main sources of bias in observational studies confounding, immortal time bias, and depletion of susceptibles can be addressed through this framework. The presentation illustrates the application of target trial emulation to non-inferiority questions, using the example of rivaroxaban versus warfarin for stroke prevention in atrial fibrillation (emulation of the ROCKET-AF trial). Specific challenges of non-inferiority target trial emulation are discussed, including the definition of the non-inferiority margin, the choice of analysis population (ITT, per-protocol, as-treated), and the risk that residual confounding may artificially inflate or deflate treatment differences. The conditions under which observational data can reliably support non-inferiority conclusions remain an open and active area of methodological research.

Nicolas Savy, Institut de Mathématiques de Toulouse, Université Paul Sabatier, Toulouse, France

Title: Reinforcement Learning and Dynamic Treatment Regimes

Abstract:

Reinforcement learning (RL) is a branch of machine learning in which an agent learns an optimal decision rule by interacting with an environment. At each decision step , the agent observes a state , selects an action , and receives a reward . The objective is to learn an optimal policy that maximises the long-term discounted reward , where is a discount parameter. The theoretical framework relies on Markov decision processes, the Bellman equation, and the value-action function . Key milestones in RL development include Bellman's dynamic programming (1957), Q-learning and Temporal Difference methods (1989), Deep Q-Networks achieving human-level performance on 49 Atari games (DeepMind, 2013), AlphaGo/AlphaZero (2016), and reinforcement learning from human feedback (RLHF) for large language models (2022). In the clinical research context, RL provides a natural framework for Dynamic Treatment Regimes (DTR), where the Q-function can be interpreted as the expected causal effect of treatment for a patient in state . DTR algorithms are primarily based on backward Q-learning, estimating . The medical context imposes specific adaptations, and key open challenges include model trust and clinical implementation.

Frédéric Fiteni, CHU de Nîmes, Nîmes, France

Title: The clinician's point of view

Abstract:

Patient-centred endpoints in oncology clinical trials include overall survival (OS), health-related quality of life (QoL), and patient-reported outcomes (PRO). Tumour-centred endpoints include progression-free survival (PFS), relapse-free survival (RFS), and disease-free survival (DFS). Overall survival remains the gold standard for marketing authorisation. PFS, RFS and DFS are not always validated as surrogates for OS and their use should be limited. QoL is increasingly used as an endpoint, particularly when OS is not achievable, in de-escalation settings, or when a new treatment carries significant toxicity. Its importance increases with later lines of treatment. A review of phase III oncology trials shows that OS is the primary endpoint in 35% of trials and QoL in only 3%. The conclusion drawn from Sherry et al. (JAMA, 2025) is that modern phase III oncology RCTs are severely underachieving in improving outcomes that matter to patients. QoL measurement tools include generic instruments such as the EQ-5D and disease-specific instruments such as the EORTC QLQ-C30 and FACT-G. Statistical analysis methods include time-to-deterioration survival models and linear mixed models for repeated measures. Recommendations for QoL analysis and reporting in clinical trials are provided by the SISAQOL initiative.

Amélie Anota, Centre Léon Bérard, Lyon, France

Title: Quality of Life as a Primary or Composite Endpoint in De-escalation Trials: « Pros & Cons »

Abstract:

Quality of life (QoL) can be used as a primary endpoint, a composite endpoint, or a co-primary endpoint in de-escalation trials. When used as a primary endpoint, QoL offers the advantage of

being patient-centred and of providing results earlier than overall survival. However, its use faces several limitations: missing data, the multidimensional nature of QoL requiring a choice of dimension, lack of validation of the minimal important difference (MID) for some instruments, and lack of established hypotheses for time-to-deterioration (TTD) analyses. Statistical methods for longitudinal QoL data include mixed models for repeated measures (MMRM) and time-to-deterioration models. When used as a composite endpoint, combining QoL with OS produces a patient-centred criterion (quality-adjusted survival without QoL deterioration), whereas combining QoL with PFS produces a tumour-centred criterion that is poorly correlated with QoL. When QoL and PFS are both of interest, preferred approaches include co-primary non-inferiority on PFS and superiority on QoL, hierarchical endpoints, QoL as a key secondary endpoint, or joint models. Recommendations for QoL integration in clinical trials are provided by COSMIN, SPIRIT, SISAQOL, and CONSORT PRO guidelines. QoL results are often not reported in the primary publication of clinical trials, or published years later, limiting their relevance and impact.

Marc Buyse, IDDI, One2Treat and University of Hasselt, Belgium
Title: Non-Inferiority Trials: Need for Improvement or a Paradigm Shift?
Abstract:
Non-inferiority trials present several well-documented issues: very large sample sizes are required, the choice of the non-inferiority margin is problematic, impossible to achieve based on FDA guidance and driven by subjective clinical considerations for EMA poorly conducted trials are more likely to show equivalence, and even large NI trials may fail to conclude. In de-escalation trials specifically, non-inferiority designs do not address the real clinical question of interest, which is the evaluation of the benefit-risk balance. An alternative approach is proposed: reframing de-escalation trials as superiority trials asking whether dose reduction improves the benefit-risk balance. This requires the use of multiple hierarchical endpoints (survival, toxicity) and the estimation of the Net Treatment Benefit (NTB) via Generalized Pairwise Comparisons (GPC). For each pair of patients, one from the experimental arm and one from the control arm, the highest priority outcome is compared first; if the pair is neutral, the comparison moves to the next prioritized outcome, until all outcomes have been compared. NTB is defined as the percentage of favorable pairs minus the percentage of unfavorable pairs. This approach offers reduced sample sizes at equivalent power and a transparent and pragmatic analysis. Its main current limitation is that interpretation of NTB is not yet well established. Two examples are presented: designing a dose de-escalation trial for ATRA in acute promyelocytic leukemia, and analysing benefit-risk in a completed trial of chemotherapies for HER2-positive early breast cancer.

David Jegou, Statistical Process Expert, Pierre Fabre
Title: Optimus: Shifting the paradigm, from maximum tolerated dose to optimal dose
Abstract:
The FDA's Project Optimus represents a fundamental paradigm shift in oncology drug development, moving away from the traditional maximum tolerated dose (MTD) approach toward optimal dose selection. Historically, dose selection has been based on a "turn the volume to MAX" mentality, focusing on a single toxicity endpoint. The new approach uses an

"equalizer" metaphor, integrating benefit-risk balance and patient-reported outcomes earlier in development.

The sotorasib case study illustrates the problem with MTD-based approval: approved at 960 mg (MTD) based on CodeBreak 100 phase 2 trial with ORR 37.1%, no early multi-dose exploration was conducted. The FDA mandated a post-approval dose comparison study (VP4-2023), which should have been done before pivotal trials. CodeBreak 200 (Phase 3 vs. docetaxel, n=345, 2L NSCLC) showed: median PFS 5.6 mo (sotorasib) vs 4.5 mo (docetaxel), median OS 10.6 mo vs 11.3 mo, ORR 28.1% vs 13.2%, Grade ≥3 TRAEs 33.1% vs 40.4%. The FDA ruled PFS results unreliable due to methodological flaws, mandating a new confirmatory study by 2028.

Project Optimus key features include: integrated patient-reported outcomes earlier in development, limiting dose expansion cohorts to maximum 40 patients to prevent unnecessary exposure to ineffective therapies, advanced statistical designs (BOIN = Bayesian Optimal Interval Design, BLRM = Bayesian Logistic Regression Model), replacing one-size-fits-all approaches with personalized benefit-risk assessment. This represents a critical evolution toward more rational, patient-centered oncology drug development.

Laurent-Philippe Albou, Institut Roche, France

Title: The Role of AI in Optimizing Clinical Trials

Abstract:

Therapeutic de-escalation represents a major challenge for patient quality of life. De-escalation requires better understanding of our treatments and data. Several de-escalation strategies are illustrated: protocol simplification (Phesgo: IV 2-4h → SC 10min; Ocrevus: IV 2-4h → SC 10min), dose spacing (Vabysmo: 4/8 weeks → 16 weeks), and treatment duration. Duration of treatment has historically been limited by the duration of clinical trials and data access constraints. Digital twins emerge as a potential solution. The presentation introduces RAGnarok, a semantic GraphRAG tool developed by Roche for improved AI-assisted search in clinical documents, emphasizing auditability and open-source distribution. The EPAR corpus tested contains 852 documents spanning 59,330 pages (from January 2020 onwards). RAGnarok enables citation of referenced pages, supporting evidence-based decision-making in clinical optimization. The tool represents an important step toward leveraging AI for enhanced data accessibility and clinical trial optimization, ultimately serving the principle: "Doing now what patients need next."

Replay of the 15th SMAC Club Conference

All sessions of the SMAC Club have been recorded. Replays are being published progressively on the Cancéropôle Grand Sud-Ouest YouTube channel, as they become available:
→ *Watch the replay of the 15th SMAC Club Meeting on our YouTube channel*

Each presentation is accompanied by the speaker's corresponding slides. Access to this content is limited to those with the playlist link.

Participants' Register

Surname	First Name	Profession	Unit / Laboratory / Company Name	City
ALACHRAM	Yassine	Clinicien	CHU de Toulouse	Toulouse
ALBOU	Laurent-Philippe (Speaker)	Biostatisticien	Institut Roche	Boulogne-Billancourt
ANOTA	Amélie (Speaker)	Biostatisticien	Centre Léon Bérard	Lyon
ASSEMAT	Pauline	Chercheur / Ingénieur	Institut de Mécanique des Fluides de Toulouse	Toulouse
BABA	Joachim (Speaker)	Autre	Direction de l'Évaluation et de l'Accès à l'Innovation (DEAI) - HAS	Saint-Denis La Plaine
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BEN NASR	Nesrine	Autre	Direction de la Recherche de l'EH - Institut Curie	Paris
BEN-ROUMMANE	Hasnae	Biostatisticien	CHU de Toulouse	Toulouse
BERARD	Emilie	Clinicien	CHU de Toulouse	Toulouse
BERGER	Frédérique	Biostatisticien	Institut Curie - Service de Biométrie	Paris
BLANC-LAPIERRE	Audrey	Biostatisticien	Institut de Cancérologie de l'Ouest	Nantes
BOHER	Jean-Marie	Biostatisticien	Unité de Biostatistique et Méthodologie / DRCI / Institut Paoli Calmettes	Marseille
BOUSSARI	Olayide	Chercheur / Ingénieur	Fédération Francophone de Cancérologie Digestive, EPICAD, Inserm U1231	Dijon

BRINGUIER-BRANCHEREAU	Sophie	Clinicien	CHU Montpellier	Montpellier
BUYSE	Marc (Speaker)	Biostatisticien	One2Treat	Ottignies-Louvain-la-Neuve, Belgique
CABARROU	Bastien	Biostatisticien	IUCT Oncopole	Toulouse
CABEL	Luc (Speaker)	Clinicien	Institut Curie	Paris
CAROFF	Juliette	ARC / TEC	IUCT Oncopole	Toulouse
CAUNES-HILARY	Nathalie	Clinicien	Oncopole Claudius Regaud	Toulouse
CAVILLON	Ana	Biostatisticien	IUCT Oncopole	Toulouse
CHABARDES	Hugo	Communication	IUCT Oncopole	Toulouse
CHAILLOL	Isabelle	Biostatisticien	LYSARC	Lyon
CHAPDELAINE	Kévin	Biostatisticien	AXIODIS CRO	Toulouse
CHARLES	Hugo	Biostatisticien	GORTEC	Tours
CHOUQUET	Cécile	Chercheur / Ingénieur	Institut de Mathématiques de Toulouse	Toulouse
COLIN	Rémi	Biostatisticien	Institut du Cancer de Montpellier	Montpellier
CORNIC	Renaud	Biostatisticien	Unité de Recherche Clinique/DEBRC - hôpital Bichat, APHP	Paris
CROPET	Claire	Biostatisticien	Centre Léon Bérard	Lyon
DAHAN	Muriel (Speaker)	Chercheur / Ingénieur	Unicancer	Paris
DASSÉ	Emilie	Chercheur / Ingénieur	Unicancer	Paris
DELATTRE	Alexis	Biostatisticien	FFCD	Dijon
DELORD	Jean-Pierre (Speaker)	Clinicien	IUCT Oncopole	Toulouse
DESACHY	Guillaume	Industrie / Biotech	Institut de Recherche Pierre Fabre	Toulouse
DEVLAMYNCK	Laure	Biostatisticien	USMR - CHU de Toulouse	Toulouse
DI MÉGLIO	Emma	Etudiant	Institut Desbrest d'Épidémiologie et de Santé Publique	Montpellier
DIALLO	Mamadou Hassimiou	Biostatisticien	Institut Curie	Paris
DIAZ	Fabienne	Biostatisticien	HORIANA	Bordeaux

DUBOIS	Pierre (Speaker)	Autre	Toulouse School of Economics	Toulouse
DUPONT	Axelle	Biostatisticien	AP-HP	Paris
DUPUIS	Maeva	Biostatisticien	MDSTAT Consulting	Lyon
DUPUY	Elena	Biostatisticien	Institut de Recherche Pierre Fabre	Toulouse
FILLERON	Thomas (Speaker)	Biostatisticien	IUCT Oncopole	Toulouse
FITENI	Frederic (Speaker)	Clinicien	CHU de Nîmes	Nimes
FOURNIER	Marguerite	Biostatisticien	LYSARC	Pierre-Bénite cedex
FRISON	Eric	Clinicien	CHU de Bordeaux / CIC1401 de Bordeaux	Bordeaux
GAL	Jocelyn	Biostatisticien	IHU RespirERA	Nice
GAMBOTTI	Laetitia (Speaker)	Autre	Agence de l'Innovation en Santé (AIS)	Paris
GAZIN	Vincent (Speaker)	Autre	Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM)	Saint-Denis
GOURGOU	Sophie	Biostatisticien	Institut du Cancer de Montpellier	Montpellier
GRAND	Anaïs	Pharmacien	IUCT Oncopole	Toulouse
GRAVIS	Gwenaelle (Speaker)	Clinicien	Institut Paoli-Calmettes	Marseille
GROC	Mélanie	Biostatisticien	Institut de Recherche Pierre Fabre	Toulouse
GUILHOT	François	Clinicien	INSERM CIC 1402	Périgny
GUILLOTIN	Sophie	Pharmacien	CHU de Toulouse	Toulouse
HARDOUIN	Jean-Benoit	Chercheur / Ingénieur	Methods in Patient Centered Outcomes and Health Research	Nantes
HASNAOUI	Manel	Management / Administration	IUCT Oncopole	Toulouse
HAURET-CLOS	Louanne	Biostatisticien	CHU de Toulouse	Toulouse
HERNALSTEEN	Marianne	Etudiant	Université de Toulouse	Toulouse
HOMMAIS	Antoine	Responsable de projet chez INCa	Institut National du Cancer	Boulogne Billancourt
JEGOU	David (Speaker)	Industrie / Biotech	Institut de Recherche Pierre Fabre	Toulouse

JUZYNA	Béata	Autre	UNICANCER R&D	Paris
KAMMER	Michael	Chercheur / Ingénieur	Université Toulouse 1 Capitole	Toulouse
KELLER	Laura	Pharmacien	Laboratoire de biologie médicale oncologique	Toulouse
KLEIN	Segolene	Autre	Bureau des Essais Cliniques, Oncopole Claudius Regaud	Toulouse
KOSOROK	Michael (Speaker)	Chercheur / Ingénieur	Department of Biostatistics, University of North Carolina	Chapel Hill (distanciel)
LAJOINIE	Audrey	Autre	RCTs	Lyon
LAMBERT	Jérôme (Speaker)	Biostatisticien	Université Paris Cité	Paris
LANGLAIS	Alexandra	Biostatisticien	Intergroupe Francophone de Cancérologie Thoracique (IFCT)	75009
LANGLOIS-JACQUES	Carole	Biostatisticien	Service de biostatistiques HCL	Lyon
LAUWERS CANCES	Valérie	Clinicien	CHU de Toulouse	Toulouse
LE GUEN	Louis	Chercheur / Ingénieur	IUCT Oncopole	Toulouse
LE GUILLOUX	Adèle	Biostatisticien	CIC 1436 Toulouse	Toulouse
LE MERDY	Maelle	Etudiant	Toulouse Business School	Toulouse
LEBEAU	Prisca	ARC / TEC	Oncopole Claudius Regaud	Toulouse
LELLOUCHE	Lionel	Biostatisticien	Institut du Cancer de Montpellier	Montpellier
LENOIR	Thomas	Etudiant	Université Toulouse 3 Paul Sabatier	Toulouse
LEPAGE	Benoit	Biostatisticien	Centre d'épidémiologie et de recherche en santé des populations	Toulouse
LESCOUZERES	Marianne	Chef de projet en recherche clinique	CHU de Toulouse	Toulouse
LEYRAT	Clémence (Speaker)	Biostatisticien	London School of Hygiene and Tropical Medicine	London

LINASSIER	Claude (Speaker)	Autre	Institut National du Cancer	Boulogne-Billancourt
LODIN	Sabrina	Management / Administration	IUCT Oncopole	Toulouse
LUSQUE	Amélie	Biostatisticien	IUCT Oncopole	Toulouse
MARINESCU	Elena	Etudiant	Toulouse School of Economics	Toulouse
MARTIN	Elodie	Biostatisticien	Institut de Cancérologie de l'Ouest	St Herblain
MATOSES	Daphné	Etudiant	Institut de Mathématiques de Toulouse	Toulouse
MERCIER	Sabine	Chercheur / Ingénieur	Université Toulouse 2 Jean Jaurès	Toulouse
MICHIELS	Stefan (Speaker)	Biostatisticien	Gustave Roussy	Villejuif
MOLLEVI	Caroline	Biostatisticien	CHU de Montpellier	Montpellier
MONNEREAU	Matthias	Biostatisticien	IUCT Oncopole	Toulouse
MONTEIRO	Claudio	Chercheur / Ingénieur	Nova In Silico	Lyon
MORISSEAU	Mathilde	Biostatisticien	Oncopole Claudius Regaud	Toulouse
MOUNIER	Muriel	Autre	IUCT Oncopole	Toulouse
NACIRI	Meryem	Etudiant	IUCT Oncopole	Toulouse
PAJIEP	Marie	Biostatisticien	CHU de Toulouse	Toulouse
PAOLETTI	Xavier (Speaker)	Biostatisticien	Institut Curie	Paris
PERETTI	Lou-Anne	Etudiant	U1018	Villejuif
PICOT	Marie-Christine	Clinicien	CHU de Montpellier	Montpellier
PIZOT	Cécile	Biostatisticien	LYSARC	Pierre-Bénite cedex
PORCHER	Raphaël (Speaker)	Biostatisticien	Centre de Recherche Épidémiologie et StatistiqueS, APHP	Paris
POUBLANC	Muriel	Management / Administration	IUCT Oncopole	Toulouse
RICHERT	Laura	Chercheur / Ingénieur	CHU de Bordeaux	Bordeaux
RIOUAL	Jonathan	Biostatisticien	CHU de Toulouse	Toulouse
ROCA	Lise	Biostatisticien	Institut du Cancer de Montpellier	Montpellier
ROLS	Marie-Pierre	Chercheur / Ingénieur	Laboratoires Chimie-Biologie de Toulouse	Toulouse

ROSIER	Lore	Chercheur / Ingénieur	IUCT Oncopole	Toulouse
ROUSSEAU	Vanessa	Biostatisticien	CHU de Toulouse	Toulouse
ROUX	Flavien	Autre	RCTs	Lyon
ROYE	Sandrine	Biostatisticien	Institut de Recherche Pierre Fabre	Toulouse
RÉGNIÉ	Gwénaël	Autre	Université - IUT	Castres
SAINT PIERRE	Philippe	Chercheur / Ingénieur	Institut de Mathématiques de Toulouse	Toulouse
SANSAS	Benoit	Industrie / Biotech	Institut de Recherche Pierre Fabre	Toulouse
SAVY	Nicolas (Speaker)	Chercheur / Ingénieur	Institut de Mathématiques de Toulouse	Toulouse
SEEGERS	Valérie	Biostatisticien	Institut de Cancérologie de l'Ouest	Angers
SHOURICK	Jason	Biostatisticien	Centre d'épidémiologie et de recherche en santé des populations	Montberon
TARDIVON	Coralie	Biostatisticien	Unité de Recherche Clinique / DEBRC - hôpital Bichat	Paris
TEBBAL	Sara	Pharmacien	CHU Bejaia	Bejaia
TENSAOUTI	Fatima	Chercheur / Ingénieur	IUCT Oncopole	Toulouse
TERUEL	Eva	Biostatisticien	Institut du Cancer de Montpellier	Montpellier
TRAN	Maylis	Etudiant	ARAMIS LAB - Inria Paris	Paris
VERA	Carine	Biostatisticien	Institut de Recherche Pierre Fabre	Toulouse
WILSON	Lydia	Biostatisticien	UMS 54 MART	Bordeaux

The SMAC Club seminar brought together 125 participants, including 22 speakers.

Financial report

TABLE 1 - EXPENSES

Category	Details	Total (VAT incl.)
Venue	Amphitheatre – IUCT-Oncopôle (1.5 days)	€ 0.00
Subtotal Venue		€ 0.00
Catering	Welcome coffee	€ 654.55
	Morning break 1	€ 490.91
	Lunch 1	€ 3,054.55
	Afternoon break	€ 490.91
	Evening event – Pierre Fabre	€ 0.00
	Dinner in town – Speakers & CoPil	€ 955.00
	Welcome coffee	€ 654.55
	Morning break 2	€ 545.45
	Lunch 2	€ 2,850.91
Subtotal Catering		€ 9,616.00
Accommodation	Speakers - nights 25/03 - 27/03	€ 1,841.10
Subtotal Accommodation		€ 1,841,10
Travel	Speaker travel reimbursements	€ 4,222.56
Subtotal Travel		€ 4,222.56
GRAND TOTAL EXPENSES		€ 15,679.66

TABLE 2 - REVENUE

Funding Body	Amount (VAT incl.)
Ligue contre le Cancer	€ 5,000.00
Fondation ARC	€ 1,000.00
ANITI / IA pour la Santé	€ 1,000.00
AMIES	€ 1,600.00
SFC	€ 2,000.00
Registrations	€ 2,070.00
GSO Management Fees	€ 3,009.66
GRAND TOTAL REVENUE	€ 15,679.66

The grants received were used to support the organization of the Club SMAC meetings: to cover researchers' travel, accommodation, and meal expenses during these events.

Photos of the Event

Credit_HugoChabarges-IUCT-Oncopole


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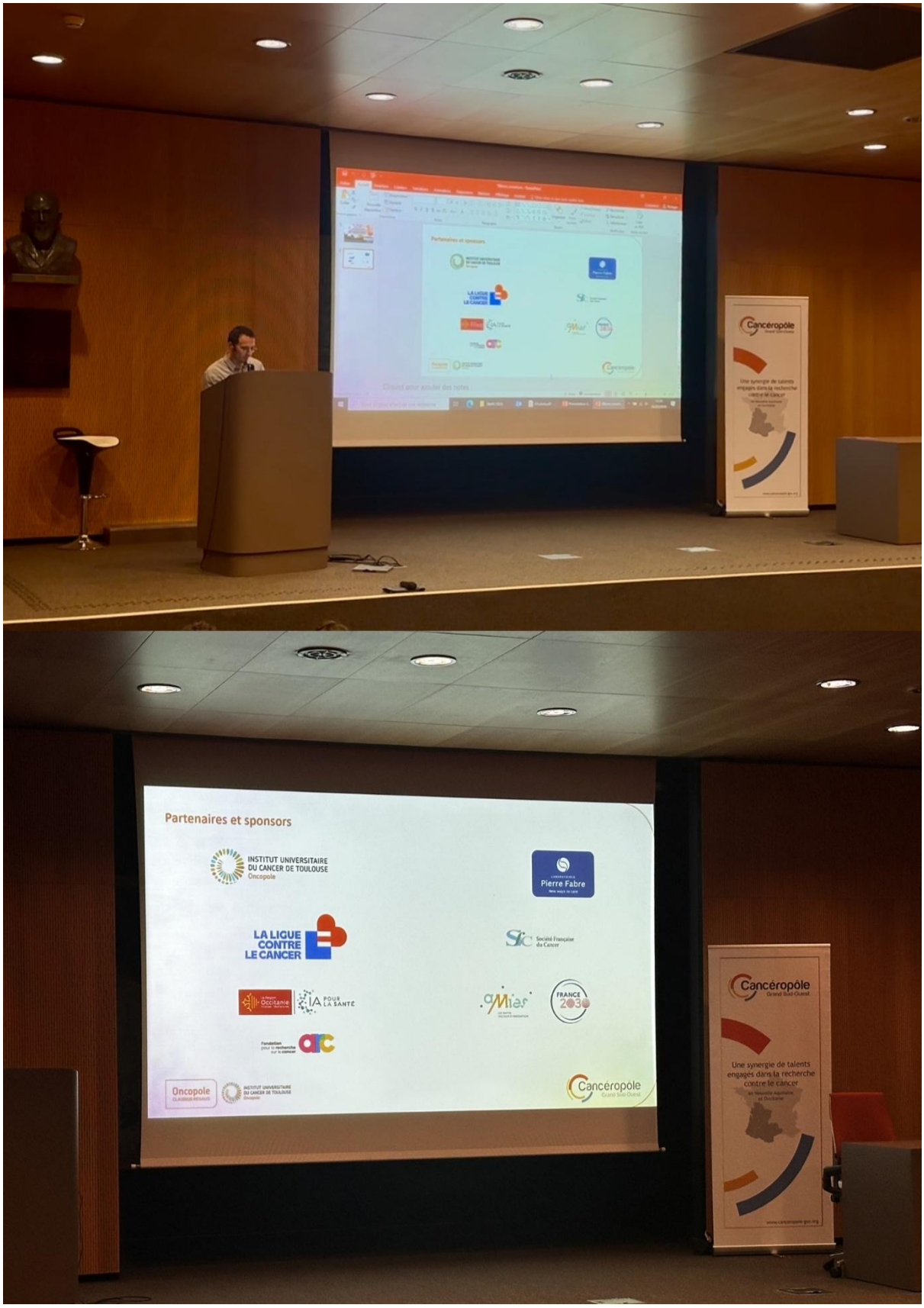
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Communication materials : event samples

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3 mois •

👏 Dernier jour des Journées du Club SMAC 2026

Cette deuxième journée a permis de mettre en avant plusieurs thématiques autour des critères de jugement en oncologie et des enjeux associés.

🔬 Session 4 : Critère de jugement centré sur le patient
Avec les interventions de : Frédéric Fiteni (CHU, Nîmes), Amélie Anota (Centre Léon Bérard, Lyon) ainsi que Marc Buyse (Hasselt University ; One2Treat, Belgique).

💊 Session 5 : Le point de vue des pharmas : comment ne pas en arriver à ce point ?
Avec les interventions de David Jegou (Laboratoires Pierre Fabre) et Laurent Philippe Albou (Institut Roche).

Enfin la matinée s'est conclue par une table ronde avec Muriel Dahan (Unicancer), Jean-Pierre Delord (Oncopôle Claudius Regaud, Toulouse), Pierre Dubois (Toulouse School of Economics), Laëtitia Gambotti (Agence Innovation Santé), Joachim Baba (Haute Autorité de Santé) et Vincent Gazin (Agence Nationale de Sécurité du Médicament et des produits de santé).

Cette table ronde a permis de croiser les points de vue des différents acteurs et de prolonger les échanges avec les participants.

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👏 Retour sur l'après-midi des Journées SMAC 2026 !

Après une matinée riche en échanges, l'après-midi s'est poursuivie avec les ... plus