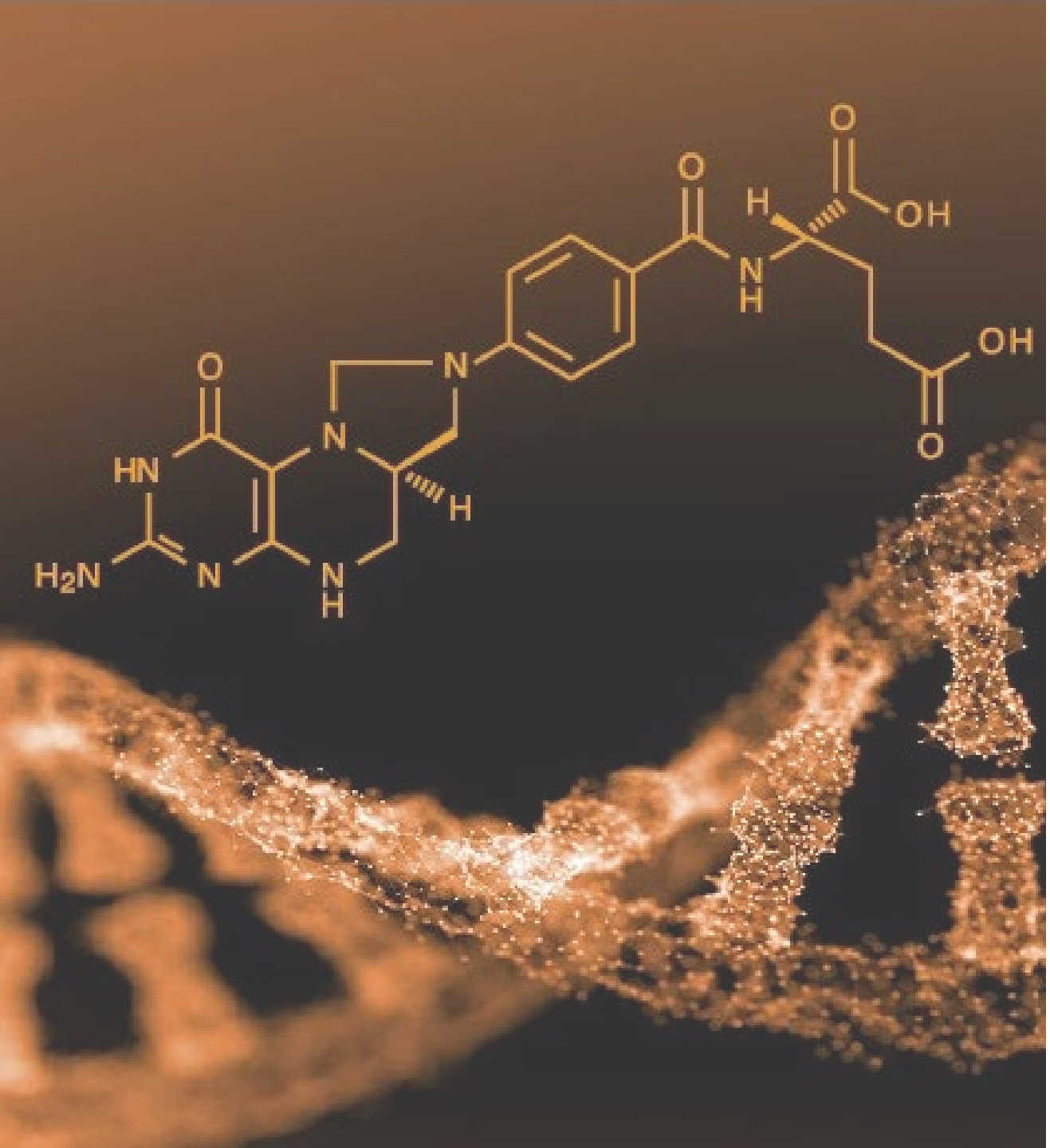


Shareholder meeting

March 19, 2024

ISOFOL

Disclaimer

Forward-looking statements

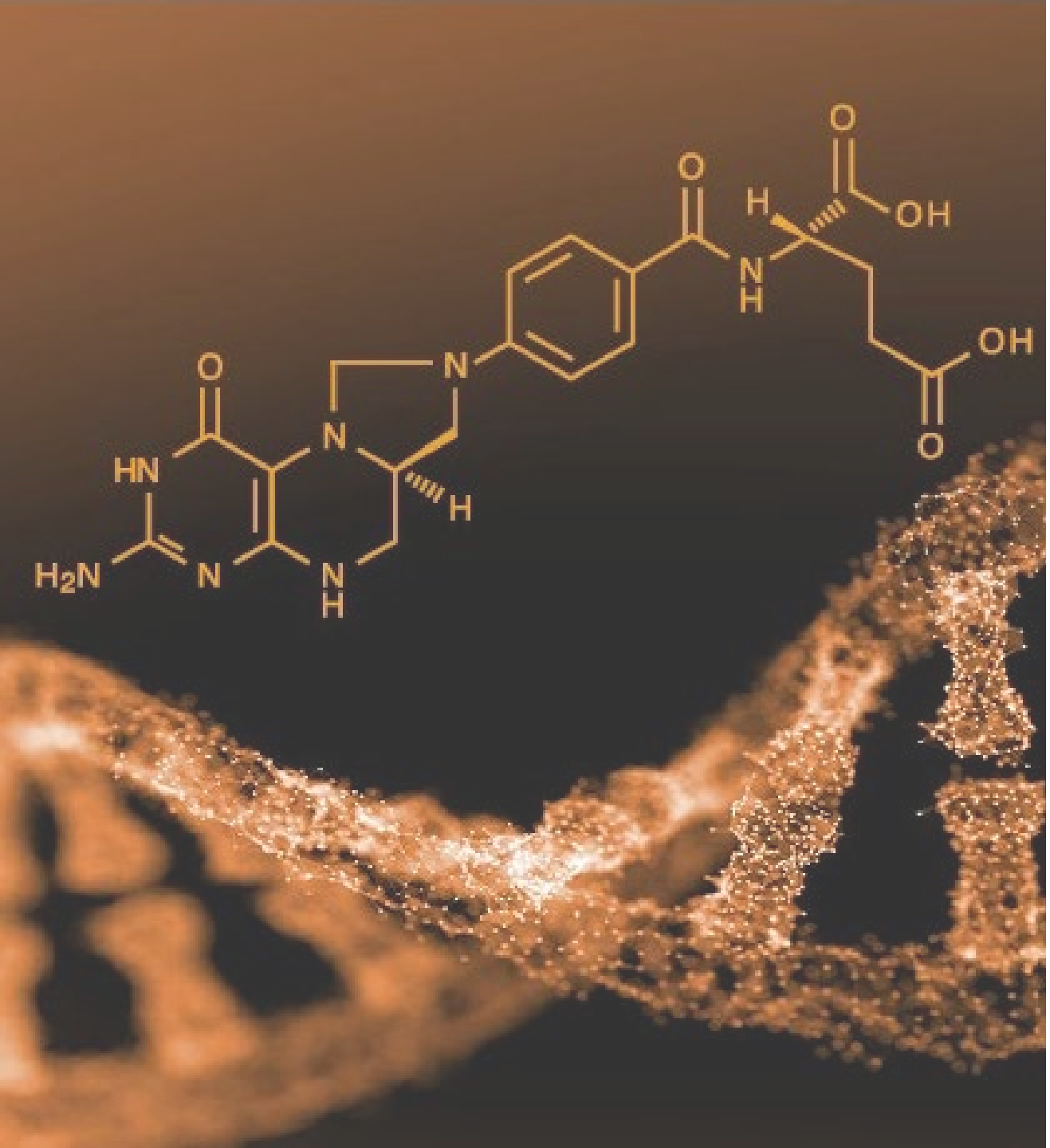
This presentation of Isofol Medical AB (publ) ("Isofol")contains certain forward-looking statements with respect to certain of the company's current expectations and projections about future events. These statements, which sometimes use words such as "intend," "proposed," "plan," "expect," and words of similar meaning, reflect management's beliefs and expectations and involve a number of risks, uncertainties and assumptions that could cause actual results and performance to differ materially from any expected future results or performance expressed or implied by the forward-looking statement. Statements contained in this presentation regarding past trends or activities should not be taken as a representation that such trends or activities will continue in the future. The information contained in this presentation is subject to change without notice and, except as required by applicable law, Isofol does not assume any responsibility or obligation to update publicly or review any of the forward-looking statements contained in it. You should not place undue reliance on forward-looking statements, which speak only as at the date of this presentation.

Not a prospectus

This presentation has been prepared for advertisement purposes. It is not a prospectus and has not been prepared in accordance with the prospectus requirements in the Swedish Financial Instruments Trading Act (lagen (1991:980) om handel med finansiella instrument) or the European prospectus regulation (809/2004/EC) (the "Prospectus Regulations"). This presentation is not subject to any registration or approval requirements under the Prospectus Regulations and has not been, and will not be, examined, approved or registered by the Swedish Financial Supervisory Authority or any financial supervisory authority or other supervisory body within the EU. The presentation may not be forwarded, reproduced or made available in or into any jurisdiction in which such publication or distribution would require any additional documentation to be prepared or registration effected or that any measures are taken in addition to those required under Swedish law or where it would be in conflict with any law or regulation in such jurisdiction. Persons who come into possession of this presentation are required to inform themselves about, and to observe, such restrictions.

Jurisdiction

The courts of Sweden shall have exclusive jurisdiction over any dispute arising out of or in connection with this presentation and the City Court of Gothenburg, Sweden, shall be the court of first instance.



Introduction

Jan-Eric Österlund, Chairman of the Board

ISOFOL

Agenda

Introduction	Jan-Eric Österlund *Chairman of the Board*
The road ahead	Petter Segelman Lindqvist *CEO*
Clinical study	Roger Tell *CMO*
Why arfolitixorin?	Dr. Alain Herrera *Board Member*

How Isofol was created

ISOFOL

Our shareholders are a great asset

A unique and dedicated core group that has grown to more than 10,000 shareholders.

We value your commitment and input.

The stock market rules set the framework for our communication.

A board with a wide range of expertise

Jan-Eric Österlund
Chairman

Sten Nilsson

Helena Taflin

Alain Herrera

Lars Lind

Our guiding principles

Our information should be open, honest and transparent.

We are convinced of the potential of arfolitixorin.

We are responsive to input from experts.

ISOFOL

Arfolitixorin and the AGENT study

The AGENT study:

- Comprised of two arms, one with arfolitixorin and a control arm with leucovorin.
- Both showed similar results.
- However, the study was designed to show the superiority of arfolitixorin.

Why was arfolitixorin not shown to be superior?

- The effect of arfolitixorin is dose-dependent.
- Arfolitixorin is rapidly eliminated from the body.
- A peak of arfolitixorin should meet a peak of another drug, 5-FU, with which it interacts.

Our analyses indicates that:

- The dose of arfolitixorin was too low and the administration form was probably suboptimal.

ISOFOL

Size matters!

- A new study will use a higher dose of arfolitixorin
- Several studies have shown that a higher dose leads to better TS inhibition, which in turn leads to the death of more cancer cells.
- So why was not a higher dose used in the AGENT study?
  - The drug consists of 6R-5,10-MTHF (Bengt's discovery), but also of citrate which in large doses of the drug can lead to arrythmia.
  - It was considered that there was insufficient evidence for a higher dose.

A new study is needed to establish a safe and optimal dose of arfolitixorin.

ISOFOL

Focus on a new clinical study

- Laboratory tests or organoid studies cannot replace patient data.
- Only a new clinical trial can provide the evidence of good efficacy and safety that investors and pharmaceutical companies are looking for.

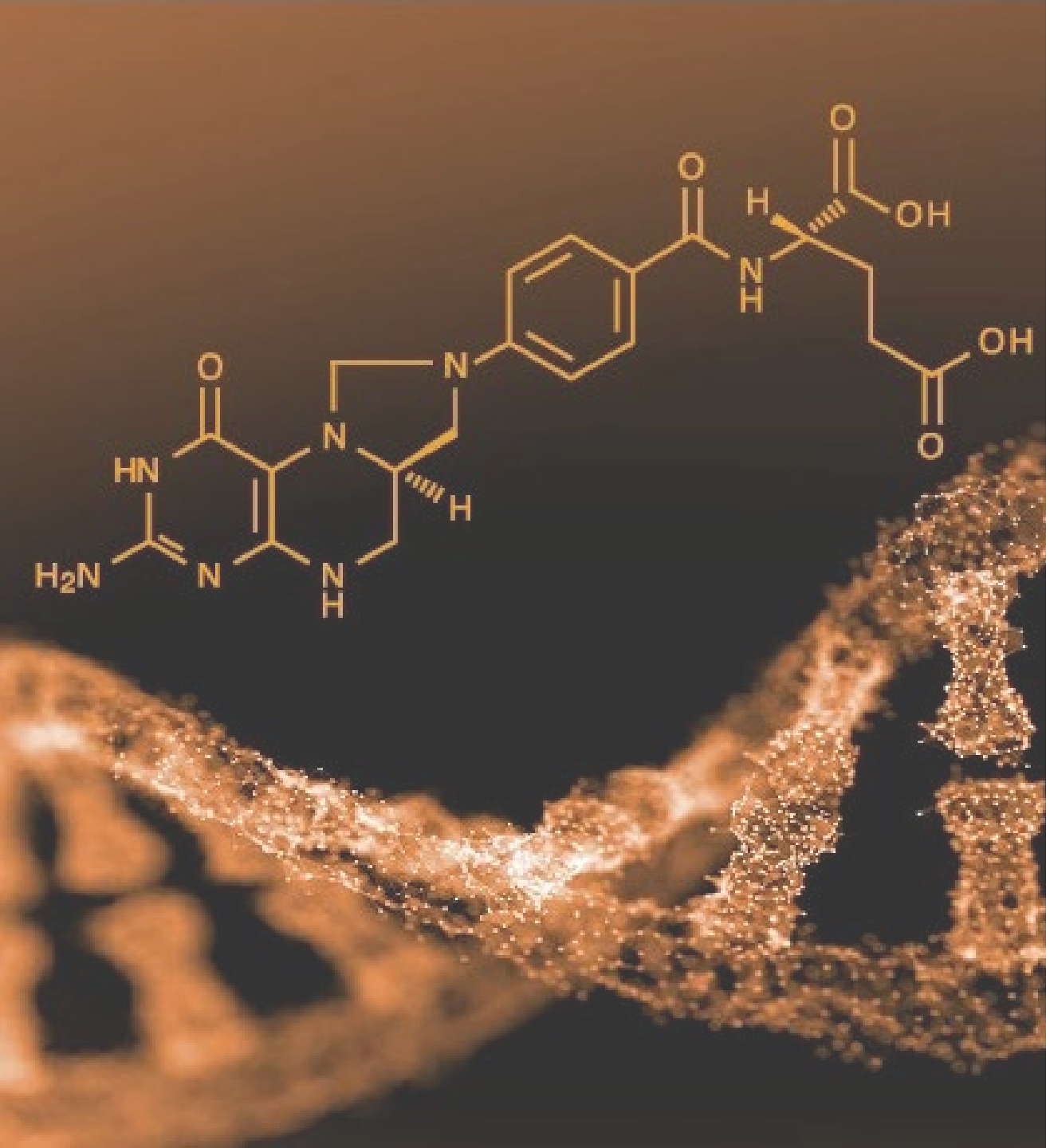
ISOFOL

Petter Segelman Lindqvist

CEO since January 9, 2024

Agenda

Introduction	Jan-Eric Österlund *Chairman*
Our way forward	Petter Segelman Lindqvist *CEO*
Clinical trial	Dr. Roger Tell *CMO*
Why arfolitixorin?	Dr. Alain Herrera *Board member*



The road ahead for Isofol

Petter Segelman Lindqvist, CEO

ISOFOL

New CFO and CMO since January

Magnus Hurst
Chief Financial Officer

Roger Tell
Chief Medical Officer

Colorectal cancer remains a major medical problem

154,000

people annually are affected in the USA alone

53,000

patient deaths per year in the USA alone

86 %

of patients with metastatic disease die within five years

Ref: American Society of Clinical Oncology (ASCO) Cancer.Net. Accessed 12 March 2024. https://www.cancer.net/cancer-types/colorectal-cancer/statistics.

ISOFOL

The same standard treatment for 50 years

5-FU-based chemotherapy

in combination with leucovorin is expected to remain the mainstay of treatment.

One of few innovations

Arfolitixorin

Potential to replace leucovorin and significantly enhance the efficacy of 5-FU therapy without compromising safety.

ISOFOL

The colorectal cancer market is large and growing

85

billion SEK

Current market size for pharmaceutical treatments[1]

105

billion SEK

Expected market size in the year of 2032[1]

1. Base year 2022. US, France, Germany, Italy, Spain, UK, Japan.
Garcìa, L, Webster, R. The colorectal cander drug market. Nature Reviews Drug Discovery. 09 Feb 2024. doi: https://doi.org/10.1038/d41573-024-00026-2.

ISOFOL

The basis for our value creation

Huge unmet medical need

Arfolitixorin has the potential to significantly improve patient outcomes.

Large and growing market

Comprehensive dataset as a basis for the next step

- ISO-CC-002 (Phase I/II)
- ISO-CC-005 (Phase I/II)
- ISO-MC-091 (Phase I/II)
- The AGENT study (Phase III)

- Preclinical studies at Sahlgrenska University Hospital
- Cell line experiments
- Studies on organoids
- The investigator-initiated Modelle study

▶ **Laboratory experiments, cell line and organoid studies, preclinical and clinical studies taken together clearly indicate arfolitixorin's efficacy**

ISOFOL

The AGENT study

Why were no differences in effectiveness seen between arfolitixorin and leucovorin?

- Too low dose: (120 mg/m^2) instead of the leucovorin equimolar one (200 mg/m^2)
  → unfair comparison.
- Suboptimal administration: (bolus 2 x 60 mg/m^2)
  → the concentration of the drug candidate was too low.
- **Despite this, arfolitixorin showed comparable safety and efficacy to leucovorin.**

Can it be assumed that a higher dose of arfolitixorin would lead to a better effect?

- Overall, the previously conducted studies indicate a dose-response relationship.

ISOFOL

The dosing and administration regiment could be optimized aiming at further improving arfolitixorin's efficacy.

We have a responsibility to patients, shareholders, and society at large to move arfolitixorin forward.

ISOFOL

Focus on a new phase I/II clinical trial

In parallel, we are conducting further analyses and laboratory studies to optimize the study design and facilitate the dialogue with regulatory authorities.

Key components of our strategic plan for value creation

Continued clinical development

Leverage on our partnerships

Proper cost control

Continued clinical development

Initiate a phase I/II study in colorectal cancer to identify an optimal dose regime, safety profile and efficacy.

Perform a **time- and cost-effective study** within our financial framework with the aim of starting the study (FPI) before the end of 2024/25.

The aim is to conduct the study in collaboration with a **world-leading academic institution** and key opinion leaders.

Leverage on our partnerships

MERCK

Strategic development partner and manufacturer.

Solasia

Partner for development and commercialization in Japan.

KEY OPINION LEADERS

Close collaboration with leading clinical expertise.

ISOFOL

Proper cost control

Cost control allows the current cash position to take us to interim and top-line read-outs of study data.

Full focus on value-adding activities → *clinical study*.

Collaborating with consultants and subcontractors provides flexibility.

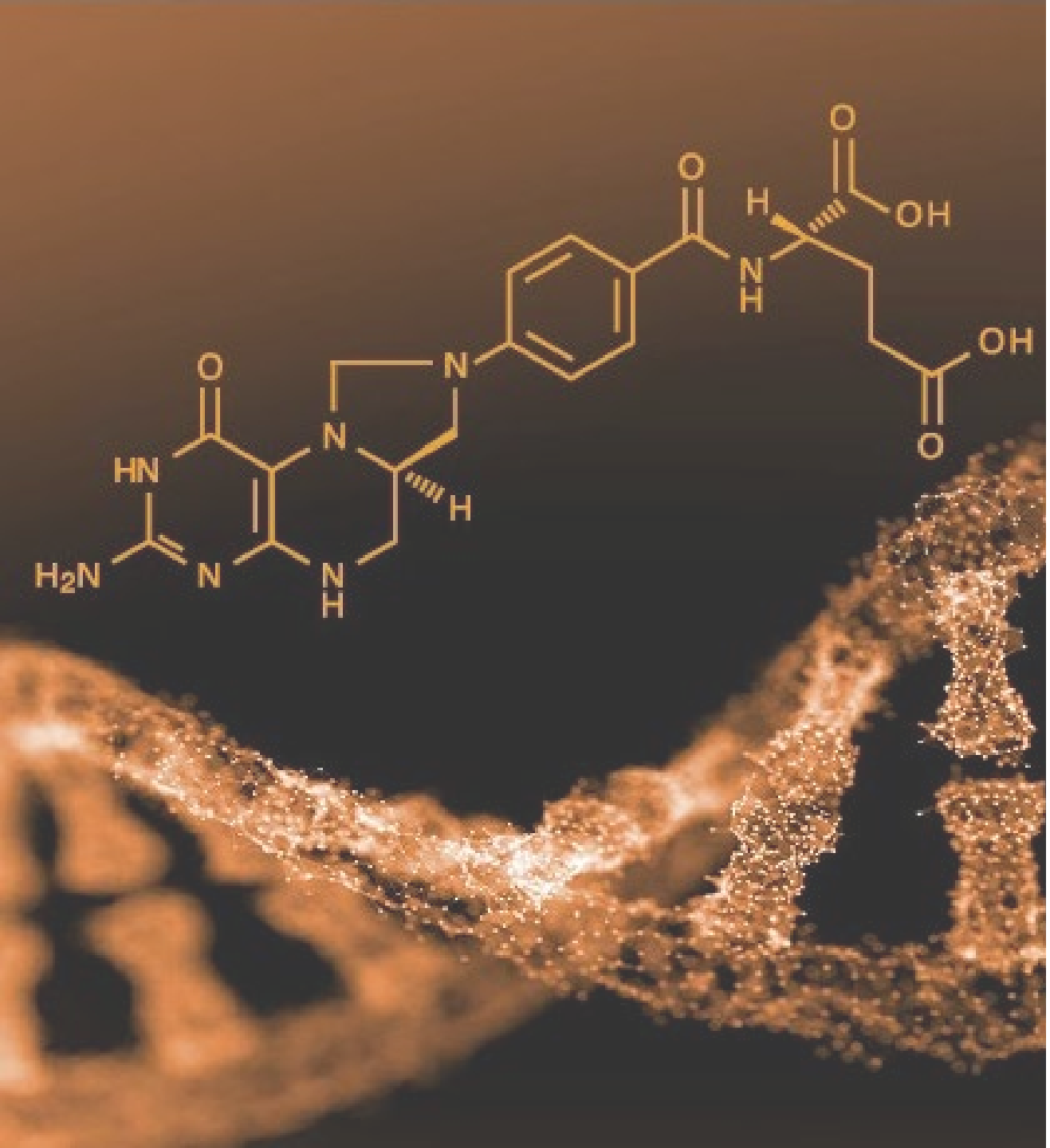
We are convinced that arfolitixorin has the potential to revolutionize the treatment of colorectal cancer.

Now the journey continues.

ISOFOL

Agenda

Introduction	Jan-Eric Österlund *Chairman*
Our way forward	Petter Segelman Lindqvist *CEO*
Clinical trial	Dr. Roger Tell *CMO*
Why arfolitixorin?	Dr. Alain Herrera *Board member*



Next step in the clinical development of arfolitixorin

Dr Roger Tell, Chief Medical Officer

ISOFOL

A phase I/II clinical study

A study in treatment-naïve patients with metastatic colorectal cancer.

Arfolitixorin is used in addition to 5-FU-based chemotherapy treatments.

Optimized dose and administration based on previously generated data.

ISOFOL

Dose level and administration

The AGENT study

2 x 60 mg/m^2

Intravenous bolus injection

The new study

Up to 1 x 400 mg/m^2

Intravenous bolus injection / short infusion

Preliminary study plan

Phase I – dose escalation

Three dose levels
up to 400 mg/m²

Intravenous bolus injection / short infusion

(6–30 patients)

Phase II – dose optimization

Maximum tolerated dose
(20 patients)

Second highest tolerated dose
(20 patients)

Interim data
(10+10 patients)

ISOFOL

Preliminary endpoints

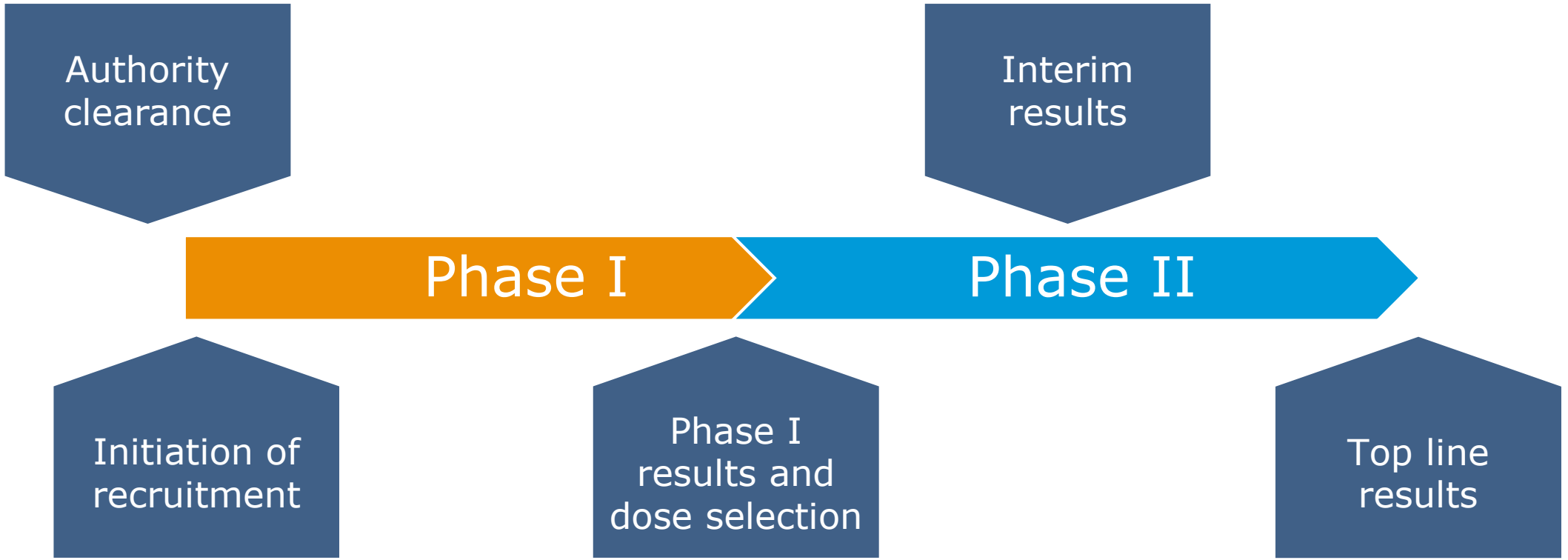
Phase I – dose escalation

- **Safety and tolerability**
- Efficacy read-out

Phase II – dose optimization

- **Objective response**
- Progression-free survival
- Overall survival
- Pharmacokinetics
- ctDNA
- Biopsy analyses

Value creating milestones



Agenda

Introduction	Jan-Eric Österlund *Chairman*
Our way forward	Petter Segelman Lindqvist *CEO*
Clinical trial	Dr. Roger Tell *CMO*
Why arfolitixorin?	Dr. Alain Herrera *Board member*

Is there still a need to improve the effectiveness of 5-FU chemotherapy?

Patients with mCRC (stage IV) are seldom curable, with a 5-year survival rate of less than 10 percent.

April 20, 2019 • Volume 41, Number 8

oncology-times.com

ONCOLOGY TIMES®

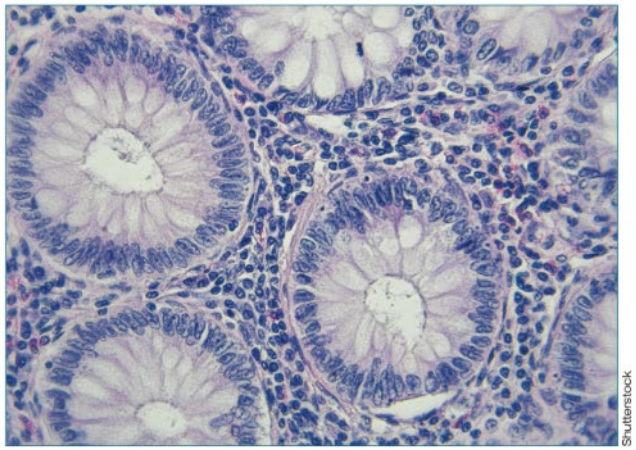
Independent News on HEMATOLOGY / ONCOLOGY

Increasing Effectiveness of Chemo for Metastatic Colorectal Cancer

BY JOSEP TABERNERO, MD, PHD, MSC

Colorectal cancer (CRC) is the third most common cancer in men (10% of the total) and the second in women (9.2%), with more than 1.8 million new cases identified every year globally accounting for about one in 10 cancer cases and deaths (*CA Cancer J Clin* 2011;61(2):69-90, *CA Cancer J Clin* 2018;68(6):394-424). Approximately 40-50 percent of the affected patients develop metastatic colorectal cancer (mCRC) and more than half a million deaths are reported annually worldwide as a consequence of CRC (*CA Cancer J Clin* 2011;61(2):69-90). Patients with mCRC (stage IV) are seldom curable, with a 5-year survival rate of less than 10 percent (*Eur J Cancer* 2013;49:(11)2476-2485). This creates a great need for advancements

Continued on page 3



Shutterstock

Genomic Analysis Guides Diagnosis & Treatment of High-Risk Leukemia

Acute erythroid leukemia (AEL) is a high-risk cancer with a dismal prognosis, uncertain genetic basis, and controversy surrounding the diagnosis. That is changing, thanks to research led by St. Jude Children's Research Hospital that recently published in *Nature Genetics* (2019; doi:10.1038/s41588-019-0375-1).

The researchers completed the largest, most comprehensive genomic analysis yet of AEL and identified six age-related subgroups with distinct mutations and patterns of gene expression as well as treatment outcomes.

The analysis revealed that 45 percent of patients had mutations in signaling pathways that help drive uncontrolled cell growth. Investigators

ISOFOL

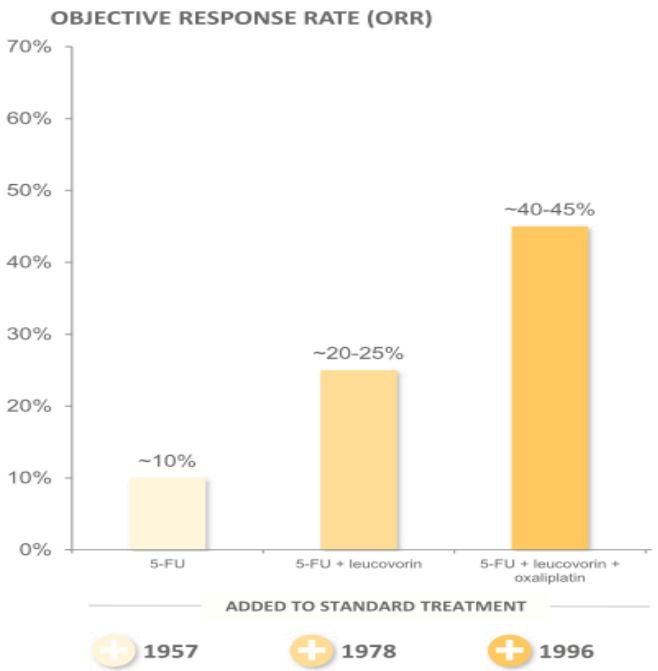
Is there still a possibility to improve the effectiveness of 5-FU chemotherapy?

in the standard of care (SoC) for patients and families affected by mCRC.

Early-stage CRC patients are treated surgically with the intent of curing the condition by removing all cancerous tissue. As the stage of the tumor advances, in terms of depth of penetration and lymph node involvement, the chance of cure with surgery alone diminishes and the rate of local recurrence increases.

More advanced CRC is treated using standard first-line systemic therapy in accordance with current European Society for Medical Oncology (ESMO) guidelines: chemotherapy with 5-fluorouracil (5-FU) + leucovorin + oxaliplatin/irinotecan ± bevacizumab or cetuximab/panitumumab, depending on clinical factors and *RAS* mutation status (*Ann Oncol* 2016;27:1386-1422).

Figure 1: Response Rates of Patients With mCRC to Historic SoC First-Line Treatments



JOSEP TABERNERO, MD, PHD, MSC, is Head of the Medical Oncology Department of Vall d'Hebron University Hospital, Barcelona, Spain, and Global Coordinating Investigator of the global pivotal phase III AGENT study.

One of the oldest and most widely used chemotherapy agents, 5-FU, was first identified in 1957 as a potent inhibitor of DNA synthesis and has been given to cancer patients for over 50 years (*Nature* 1957;179(4561):663-666). In 1978, leucovorin was found to greatly increase the efficacy of 5-FU and fast became adopted as an integral component of palliative chemotherapy regimens for cancers, including CRC (*NCI Monogr* 1987:165-170, *Cancer Res* 1981;41:3288-3295). However, even with the addition of leucovorin, only about 20 percent of mCRC patients respond to treatment, compared to approximately 10 percent response to 5-FU alone (*J Clin Oncol* 1989;7:1419-1426) (**Figure 1**).

More recently, oxaliplatin was found to have synergistic effects when combined with 5-FU + leucovorin therapy, called FOLFOX therapy, raising the response rate in mCRC patients to approximately 38-45 percent (*Semin Oncol* 1999;26(6):647-662, *J Clin Oncol* 2008;26:2013-2019) (**Figure 1**). With the exception of biologic agents that can help increase overall survival when paired with FOLFOX treatment (*Oncology* 2008;75(3-4):215-223), there have been no significant advances to therapies for mCRC for decades.

Rationale for Arfolitixorin

Arfolitixorin is a new drug that has the potential to increase the efficacy of first-line standard of care treatment for mCRC (FOLFOX therapy). The hypothesis for arfolitixorin is well-supported by preclinical models and research on the mechanism of 5-FU-based inhibition of the normal cellular process of DNA synthesis.

In normal cells, deoxythymidine monophosphate (dTMP) is a critical substrate necessary for DNA synthesis (**Figure 2, left**). To produce dTMP, a ternary complex is formed between enzyme thymidylate synthase, and its substrates deoxyuridine monophosphate (dUMP) and methylene-tetrahydrofolic acid (MTHF). When administered, 5-FU metabolite 5-FdUMP competes with dUMP while forming the ternary complex. Incorporation of 5-FdUMP to the ternary complex blocks the formation of dTMP, effectively inhibiting DNA synthesis required for cancer cell replication (**Figure 2, right**).

Leucovorin, which can be converted to MTHF through a complex set of metabolic steps, helps stabilize 5-FdUMP-containing ternary complexes, thereby increasing the effectiveness of 5-FU in blocking DNA synthesis (**Figure 2, right**). However, only a fraction of CRC patients are able to fully metabolize leucovorin to MTFH, greatly limiting

Continued on page 4

…even with the addition of leucovorin, only about 20% of mCRC patients respond do treatment, compared to approximately 10% response to 5-FU alone.

…there have been no significant advances to therapies for mCRC for decades.

ISOFOL

Is arfolitixorin a good potential candidate to improve the effectiveness of 5-FU chemotherapy?

Cancer Treatment Reviews 98 (2021) 102218

Contents lists available at ScienceDirect

Cancer Treatment Reviews

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

New Drugs

Metastatic colorectal cancer: Advances in the folate-fluoropyrimidine chemotherapy backbone

Bengt Glimelius [a,*], Sebastian Stintzing [b], John Marshall [c], Takayuki Yoshino [d], Aimery de Gramont [e,*]

[a] Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden
[b] Department of Hematology, Oncology, and Tumor Immunology (CCM) Charité, University Medicine Berlin, Berlin, Germany
[c] Georgetown University Medical Center, Washington, DC, USA
[d] National Cancer Center Hospital East, Kashiwa, Japan
[e] Hôpital Franco-Britannique, Lavallois-Perret, France

ARTICLE INFO

Keywords:
Metastatic colorectal cancer
5-fluorouracil
Leucovorin
Chemotherapy

ABSTRACT

Notwithstanding recent treatment advances in metastatic colorectal cancer (mCRC), chemotherapy with a combination of a fluoropyrimidine and a folate agent, often 5-fluorouracil (5-FU) and leucovorin, remains the backbone of treatment regimens for the majority of patients with mCRC. This is despite a recent focus on molecular-targeted treatments and patient stratification according to mutational status or expression levels of specific genes. Intracellular folate concentration was discovered to be pivotal in the cytotoxic efficacy of 5-FU, paving the way to the current standard combination therapy approach. Subsequent discovery that systemic chemotherapy agents, such as irinotecan and oxaliplatin, can further increase the efficacy of 5-FU-based treatments led to the development of several combination chemotherapy regimens, including FOLFOX, FOLFIRI and FOLFOXIRI. Subsequent efforts to optimise 5-FU-based treatments have focused on 5-FU analogues, initially capecitabine and the combination drug tegafur/gimeracil/oteracil (S-1) and then TAS-102, which has recently been evaluated in phase 3 clinical trials for refractory colorectal cancer. Further approaches taken to improve the efficacy of 5-FU chemotherapy regimens have focused on optimising the route and dosing schedules and regulating folate metabolism. Pharmacokinetic variability caused by the requirement for metabolic conversion of leucovorin has been central to recent research, and the development of agents such as arfolitixorin which bypass the need for metabolic conversion remains promising for future therapeutic candidates. In this review, we summarise the evidence leading to the current treatment regimens employing 5-FU and leucovorin, focusing on recent approaches taken to optimise and refine treatments to improve clinical outcomes in patients with mCRC.

…the development of agents such as arfolitixorin which bypass the need for metabolic conversion remains promising for future therapeutic candidates.

If so, why did the AGENT study fail?

Link to Publisher's site

Cancer Res Commun. 2024 Jan; 4(1): 28–37.
Published online 2024 Jan 4. doi: 10.1158/2767-9764.CRC-23-0361
PMCID: PMC10765772
PMID: 38059497

A Randomized Phase III Study of Arfolitixorin versus Leucovorin with 5-Fluorouracil, Oxaliplatin, and Bevacizumab for First-Line Treatment of Metastatic Colorectal Cancer: The AGENT Trial

Josep Tabernero,[1] Takayuki Yoshino,[2] Sebastian Stintzing,[3] Aimery de Gramont,[4] Peter Gibbs,[5] Derek J. Jonker,[6] Peter Nygren,[7] Christos Papadimitriou,[8] Gerald W. Prager,[9] Roger Tell,[10] and Heinz-Josef Lenz[11]

If so, why did the AGENT study fail?

A Randomized Phase III Study of Arfolitixorin versus Leucovorin with 5-Fluorouracil, Oxaliplatin, and Bevacizumab for First-Line Treatment of Metastatic Colorectal Cancer: The AGENT Trial

Josep Tabernero[1], Takayuki Yoshino[2], Sebastian Stintzing[3], Aimery de Gramont[4], Peter Gibbs[5], Derek J. Jonker[6], Peter Nygren[7], Christos Papadimitriou[8], Gerald W. Prager[9], Roger Tell[10], and Heinz-Josef Lenz[11]

ABSTRACT

Purpose: Suboptimal treatment outcomes with 5-fluorouracil (5-FU)/folate, the standard of care for metastatic colorectal cancer (mCRC), have generated interest in optimizing the folate. Arfolitixorin ([6R]-5,10-methylene-tetrahydrofolate) is an immediately active folate and may improve outcomes over the existing standard of care (leucovorin).

Experimental Design: AGENT was a randomized, phase III study (NCT03750786). Patients with mCRC were randomized to arfolitixorin (120 mg/m^2 given as two intravenous bolus doses of 60 mg/m^2) or leucovorin (400 mg/m^2 given as a single intravenous infusion) plus 5-FU, oxaliplatin, and bevacizumab. Assessments were performed every 8 weeks. The primary endpoint was the superiority of arfolitixorin for overall response rate (ORR).

Results: Between February 2019 and April 2021, 490 patients were randomized (245 to each arm). After a median follow-up of 266 days, the primary endpoint of superiority for ORR was not achieved (48.2% for arfolitixorin vs. 49.4% for leucovorin, $P_{superiority} = 0.57$). Outcomes were not achieved for median progression-free survival (PFS; 12.8 and 11.6 months, $P = 0.38$), median duration of response (12.2 and 12.9 months, $P = 0.40$), and median overall survival (23.8 and 28.0 months, $P = 0.78$). The proportion of patients with an adverse event of grade ≥3 severity was similar between arms (68.7% and 67.2%, respectively), as was quality of life. *BRAF* mutations and *MTHFD2* expression were both associated with a lower PFS with arfolitixorin.

Conclusions: The study failed to demonstrate clinical benefit of arfolitixorin (120 mg/m^2) over leucovorin. However, it provides some useful insights from the first-line treatment setting, including the effect of gene expression on outcomes.

Significance: This phase III study compared arfolitixorin, a direct-acting folate, with leucovorin in FOLFOX plus bevacizumab in mCRC. Arfolitixorin (120 mg/m^2) did not improve the ORR, potentially indicating a suboptimal dose.

Arfolitixorin (120 mg/m²) did not improve the ORR, potentially indicating a suboptimal dose.

ISOFOL

ISOFOL


O
OH
H
N
H
OH
O
N
HN
N
H
H2N
N
N
H


"Nous avons perdu une bataille mais pas la guerre"
CHARLES DE GAULLE

So,

We may have lost a battle

We will win the war

ISOFOL

Q&A

ISOFOL

We are convinced that arfolitixorin has the potential to revolutionize the treatment of colorectal cancer.

Now the journey continues.

ISOFOL