PledPharma

Capital Markets Day
26th March, 2019

Disclaimer

IMPORTANT: You must read the following before continuing. The following applies to this document, the oral presentation of the information in this document by PledPharma AB (the "Company") or any person on behalf of the Company, and any question-and-answer session that follows the oral presentation (collectively, the "Information"). In accessing the Information, you agree to be bound by the following terms and conditions.

The Information is confidential and may not be reproduced, redistributed, published or passed on to any other person, directly or indirectly, in whole or in part, for any purpose. This document may not be removed from the premises. If this document has been received in error it must be returned immediately to the Company.

The Information is not intended for potential investors and does not constitute or form part of, and should not be construed as an offer or the solicitation of an offer to subscribe for or purchase securities of the Company, and nothing contained therein shall form the basis of or be relied on in connection with any contractor commitment whatsoever. This document and its contents may not be viewed by persons within the United States or "U.S. Persons" (as defined in Regulation S under the Securities Act of 1933,asamended (the "Securities Act") unless they are qualified institutional buyers "QIBs" as defined in Rule 144A under the Securities Act. By accessing the Information, you represent that you are (i): a non-U.S. person that is outside the United States or (ii) a QIB. This document and its contents may not be viewed by persons within the United Kingdom unless they are persons with professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 as amended (the "Order"), or high net worth entities falling within Article 49(2)(a) to (d) of the Order (each a "Relevant Person"). By accessing the Information, you represent that you are: (i) outside the United Kingdom or (ii) a Relevant Person.

The Information has been prepared by the Company, and no other party accepts any responsibility whatsoever, or makes any representation or warranty, express or implied, for the contents of the Information, including its accuracy, completeness or verification or for any other statement made or purported to be made in connection with the Company and nothing in this document or at this presentation shall be relied upon as a promise or representation in this respect, whether as to the past or the future.

The Information contains forward-looking statements. All statements other than statements of historical fact included in the Information are forward-looking statements. Forward-looking statements give the Company's current expectations and projections relating to its financial condition, results of operations, plans, objectives, future performance and business. These statements may include, without limitation, any statements preceded by, followed by or including words such as "target," "believe," "expect," "aim," "intend," "may," "anticipate," "estimate," "plan," "project," "will," "can have," "likely," "should," "would," "could" and other words and terms of similar meaning or the negative thereof. Such forward-looking statements involve known and unknown risks, uncertainties and other important factors beyond the Company's control that could cause the Company's actual results, performance or achievements to be materially different from the expected results, performance or achievements expressed or implied by such forward-looking statements. Such forward-looking statements are based on numerous assumptions regarding the Company's present and future business strategies and the environment in which it will operate in the future.

No representation, warranty or undertaking, express or implied, is made as to, and no reliance should be placed on, the fairness, accuracy, completeness or correctness of the Information or the opinions contained therein. The Information has not been independently verified and will not be updated. The Information, including but not limited to forward-looking statements, applies only as of the date of this document and is not intended to give any assurances as to future results. The Company expressly disclaims any obligation or undertaking to disseminate any updates or revisions to the Information, including any financial data or forward-looking statements, and will not publicly release any revisions it may make to the Information that may result from any change in the Company's expectations, any change in events, conditions or circumstances on which these forward-looking statements are based, or other events or circumstances arising after the date of this document. Market data used in the Information not attributed to a specific source are estimates of the Company and have not been independently verified.

Agenda

PledPharma

1. Introduction, Company overview and drug candidates in development

2. PledOx® in Chemotherapy Induced Peripheral Neuropathy (CIPN)
   a. Unmet medical need
   b. Development of PledOx® in CIPN with oxaliplatin
   c. Commercial opportunity in CIPN with oxaliplatin
   d. Indication expansion – CIPN with taxanes

3. Aladote® in Paracetamol Overdose (POD)
   a. Unmet medical need
   b. Aladote® proof of principle study results
   c. Development of Aladote to prevent acute liver injury caused by POD
   d. Commercial opportunity in POD

4. Corporate Strategy
   a. Finance and up-listing
   b. Business development
   c. Direction and opportunities to enhance value

5. Summary & Closing remarks

Todays speakers and moderator

Nicklas Westerholm
CEO

Took office in June 2017. Previously worked in the AstraZeneca Group since 1996 in number of global leadership roles in various business areas such as R&D, Finance & Investor Relations, and Commercial Manufacturing and Supply, most recently as VP in Project & Portfolio Management, Cardiovascular and Metabolic Diseases, Global Medicines Development Unit. Prior, Nicklas has held positions such as Executive Officer & VP Japan Operations and Director of Investor Relations.

Christian Sonesson, Ph.D.
VP Product Strategy & Development

Appointed VP Product Strategy & Development in Aug 2017 following 13 years at Astra Zeneca. He has broad experience within drug development, including successfully leading products during Phase 3 (FORXIGA® in type 1 diabetes) and of regulatory submissions and defense, bringing new drug candidates to market in different regions (e.g. FORXIGA® in type 2 diabetes, MOVANTIK®, ONGLYZA®-SAVOR, BRILINTA®-PEGASUS and QTERN®). Christian has a Ph.D. in Biostatistics from Gothenburg University and an Executive MBA from Stockholm School of Economics.

Yilmaz Mahshid, Ph.D.
CFO

Joined Dec 2017. Dr Mahshid has a Ph.D. from department of Medical Biochemistry and Biophysics at Karolinska Institute and has previously been employed at Industrifonden as an Investment Manager & Controller. He also has previous experience as a healthcare analyst at Pareto Securities. He started his career as a researcher at Karolinska Institutet and later at the pharmaceutical companies Biolopox and Orexo

Prof Per Pfeiffer, PhD

Prof. Pfeiffer, MD, PhD, currently Professor at the University of Southern Denmark, Head of Clinical Research Unit and the Digestive Oncology Unit at department of Oncology, Odense University Hospital, Denmark.
Prof. Per Pfeiffer obtained his degree of MD and PhD at the University of Southern Denmark
His research interests include primarily clinical cancer research in patients with gastrointestinal cancer, primarily colorectal, gastric and pancreatic cancer.
He has published more than 170 peer-reviewed articles (H-factor 32) in prestigious journals.

James Dear, PhD

Dr James Dear: Medical training at University College London and a PhD in Pharmacology . Dr Dear spent 2 years at a research fellow at the National Institutes of Health, Bethesda, USA. Since 2005, Dr Dear has been at the University of Edinburgh. Current research interests are markers and mediators of paracetamol toxicity. In 2016 Dr. Dear won the British Pharmacological Societies Grahame-Smith Prize for Research Excellence in Clinical Pharmacology. Dr Dear has published 126 papers (H-index 32).

Lars Hevreng
Moderador

Lars is an equity research analyst focusing on the healthcare sector. He has a background from Roche, SEB Enskilda and Danske Bank, and is now at Vator Securities

PiedPharma

PledPharma

PledPharma is an **innovative**, **unique** and **integrated** pharmaceutical drug development company, focusing on improving treatments for diseases with substantial unmet medical need.

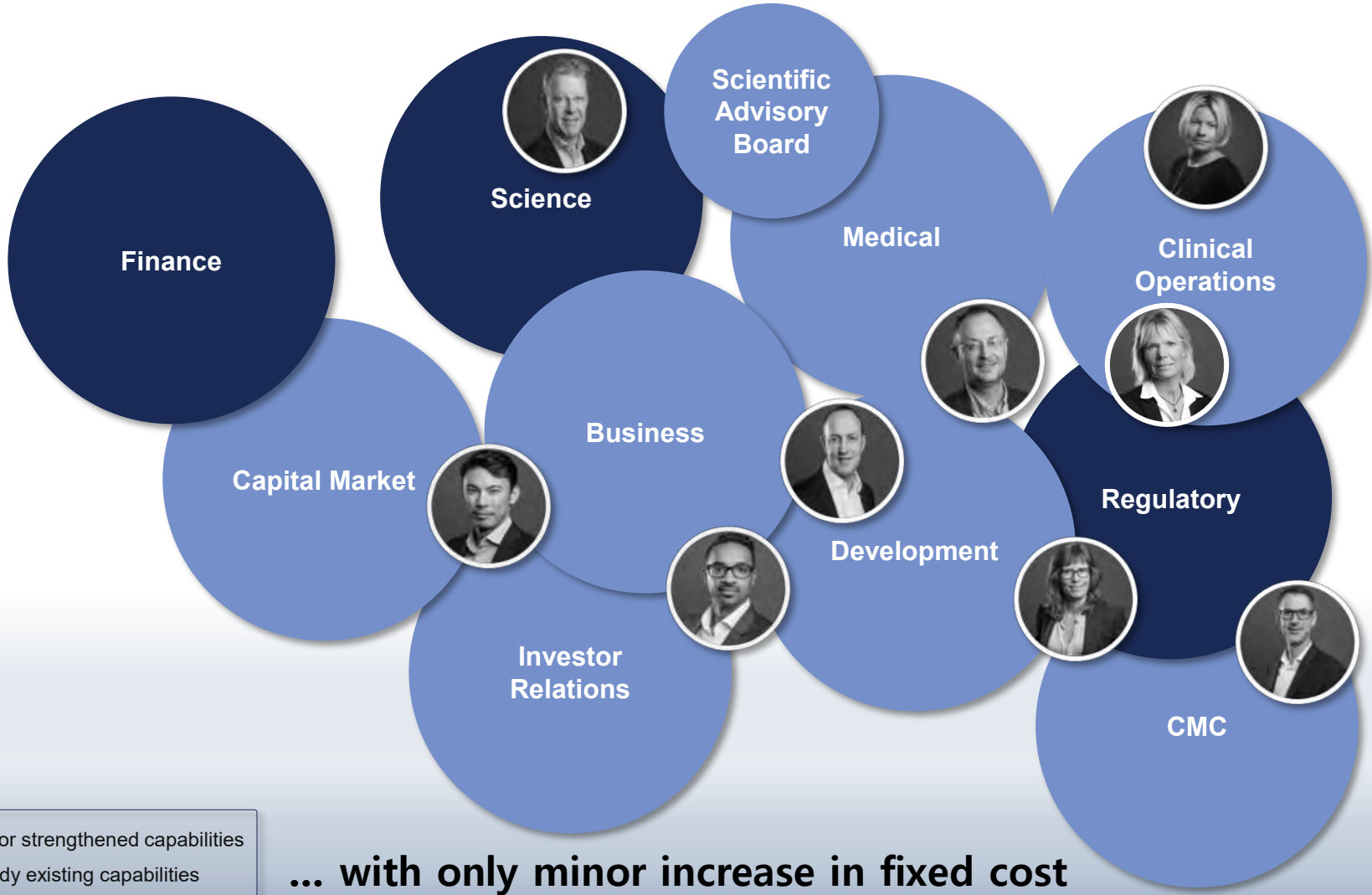
The company's most advanced project PledOx® is being developed to reduce nerve damage associated with chemotherapy. A global phase III program is ongoing.

The drug candidate Aladote® is being developed to reduce the risk of acute liver injury associated with acetaminophen poisoning. A proof of principle study has successfully been completed and will serve as the basis for the continued development.

Founded:	Listed:	Cash position[2]:
2006	**Nasdaq First North**	**SEK 230m**
Location:	**Market cap[1]:**	**FTE**
Stockholm	**SEK ~940m**	**10**

Note: (**1**) Market capitalization as per close of 20 March 2019. (2) Q4 2018 report

Transformation into an integrated drug development company 2017/18 with proven track-record of bringing new products to market…



… with only minor increase in fixed cost

Executive summary - PledOx®

Prevents nerve damage caused by chemotherapy treatment

Phase III

- Huge unmet medical need with **No** approved drug for prevention or treatment of Chemotherapy Induced Peripheral Neuropathy
- Global phase III studies approved in US, EU and JPN with recruitment ongoing - first patient included Nov, 2018
- License agreement with Solasia to develop and commercialize PledOx® in Asia territory
- Fully financed to top line results H2 2020
- Opportunity for indication expansion in taxanes

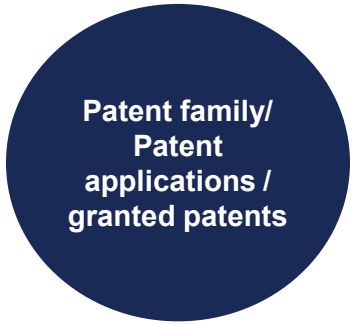
Executive summary - Aladote®

Prevents acute liver injury caused by paracetamol (acetaminophen) poisoning

Phase II

- Paracetamol (acetaminophen) poisoning is one of the most common overdose
- No adequate treatment for high risk patients
- Successful results from a Phase Ib/IIa study in paracetamol overdosed patients
- Orphan Drug Designation granted in March 2019 in the US
- Design of next study finalised - subject to regulatory interactions

Supported by a robust IP portfolio with composition of matter protection until end-2032



- **New chemical entity with composition of matter, manufacturing process and broad therapeutic use of calmangafodipir, with US, EU, China, Russia and Japan approved, end-2032**
- Application for a patent term extension of up to 5 years possible at product registration in major markets (e.g. EU, US and JP)
- Several additional “use” patents for PledOx® and Aladote® such as Cancer treatment methods, 2033, and acute liver failure, 2037.

Trademarks

PledOx® registered trademark in EU, US, Switzerland, Australia, Norway, China, Japan and Russia

Aladote® registered trademark in EU, US, China and Russia

PledPharma

2. PledOx® in Chemotherapy Induced Peripheral Neuropathy (CIPN)

a. Unmet medical need

b. Development of PledOx® in CIPN with oxaliplatin

c. Commercial opportunity in CIPN with oxaliplatin

d. Indication expansion – CIPN with taxanes

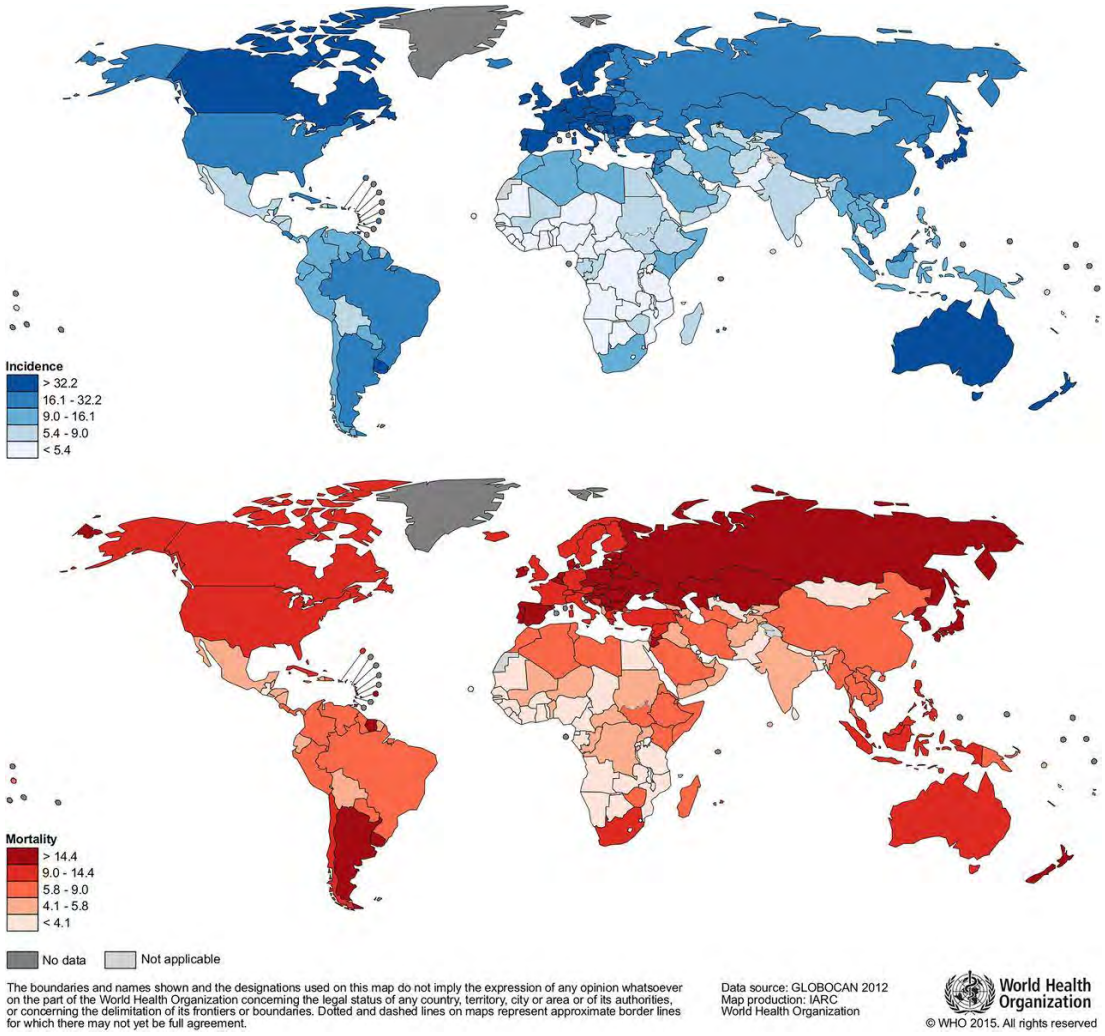
Phase III

Colorectal cancer

When we use oxaliplatin there is a medical need to prevent CIPN

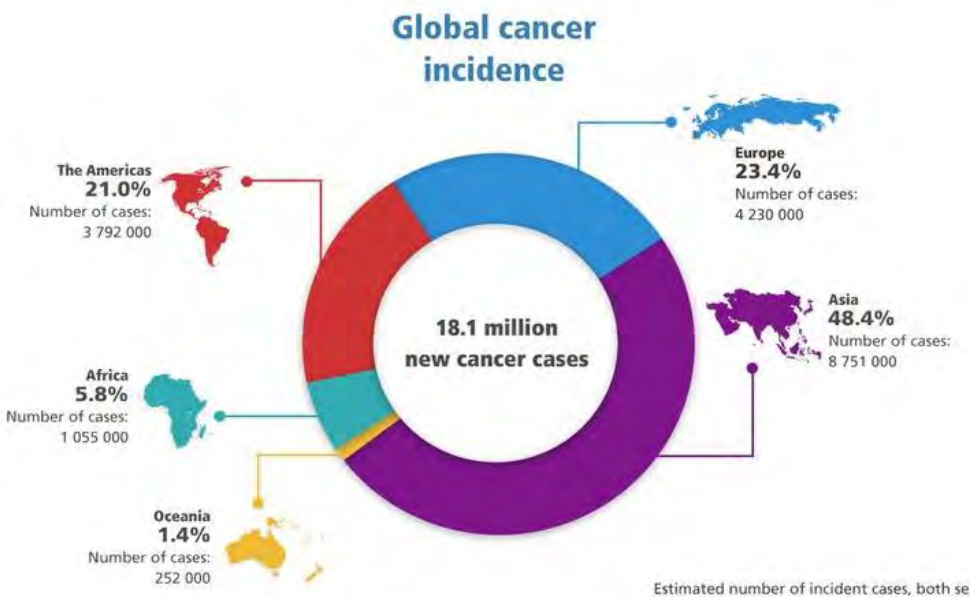
Per Pfeiffer, MD, PhD
Professor in Clinical Oncology
Dept of Oncology, OUH, Odense, Denmark
Institute of Clinical Research, USD, Odense, Denmark

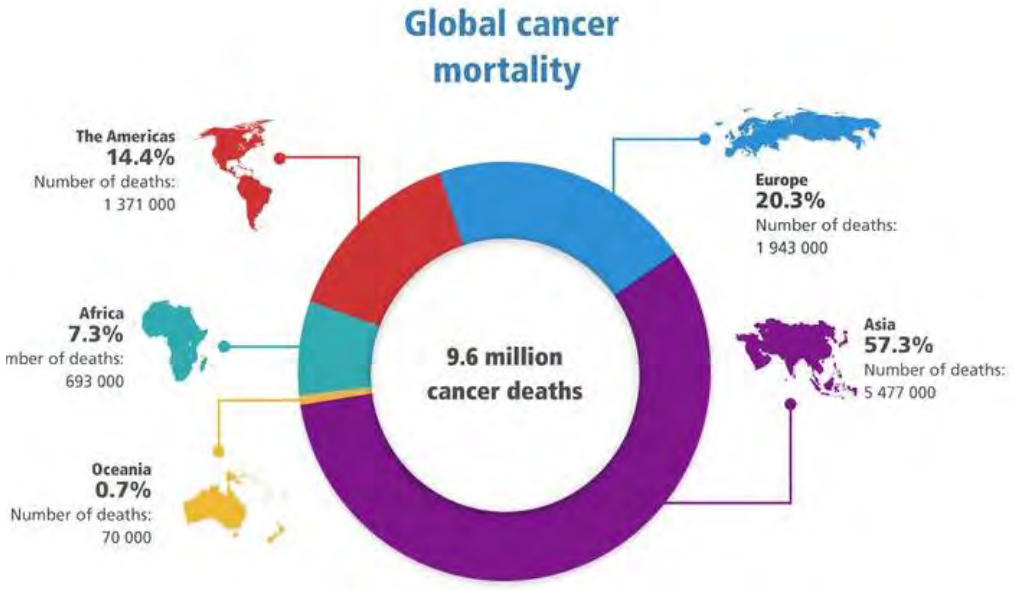
Colorectal cancer - GLOBAL CANCER DATA



Colorectal cancer

GLOBAL CANCER DATA



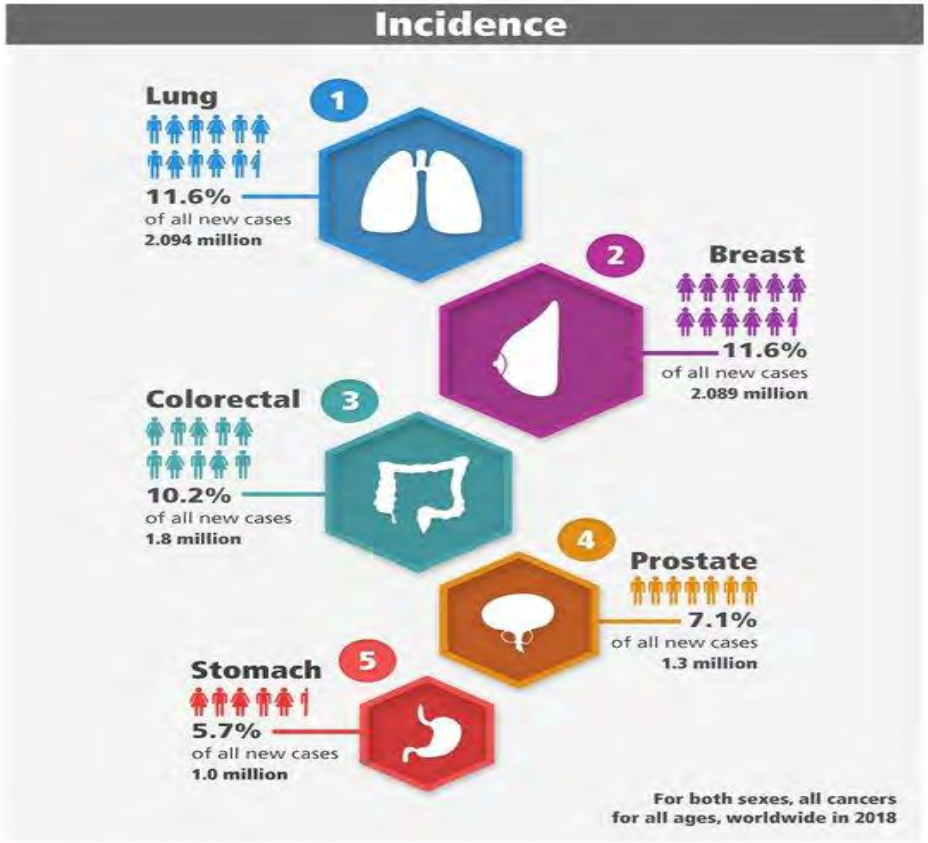


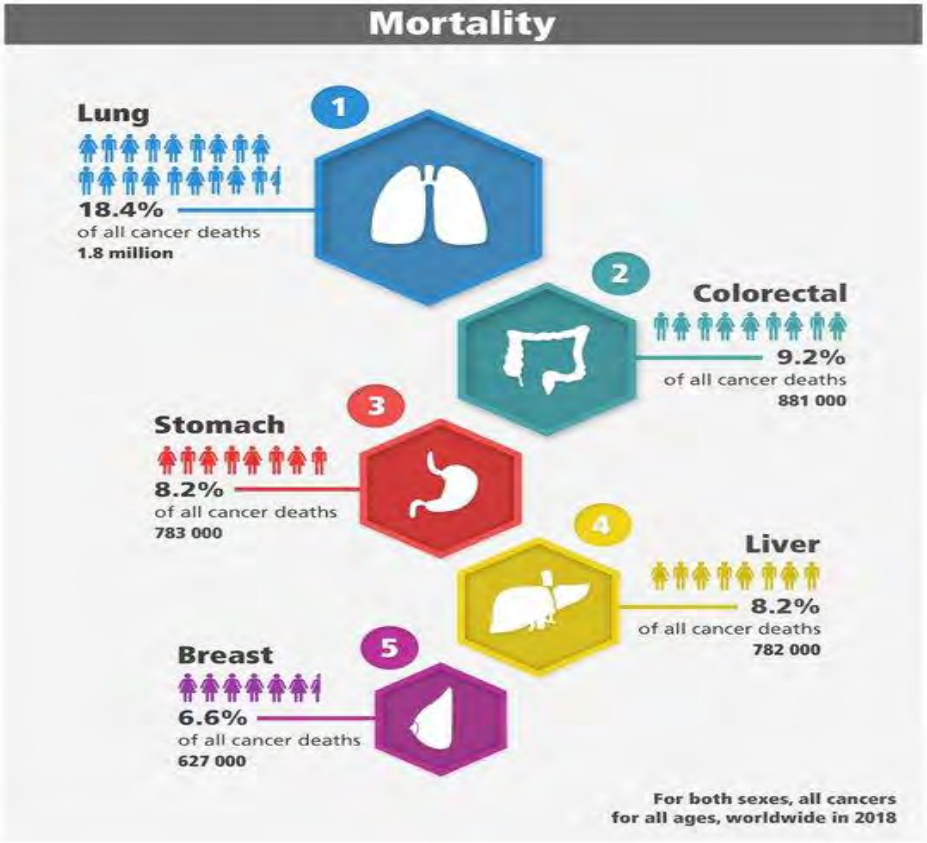
International Agency for Research on Cancer
World Health Organization

CANCER TODAY

The five most commonly diagnosed cancer types

Percentages of new cancer cases and cancer deaths worldwide in 2018





Data source: GLOBOCAN 2018

Colorectal cancer

Number of cases vs pathological stage - Denmark

	Total	%
Stage 1 +2	2,750	55
Stage 3, lymph node positive	1,500	30
Stage 4, metastatic disease	750	15
Total	~ 5,000	

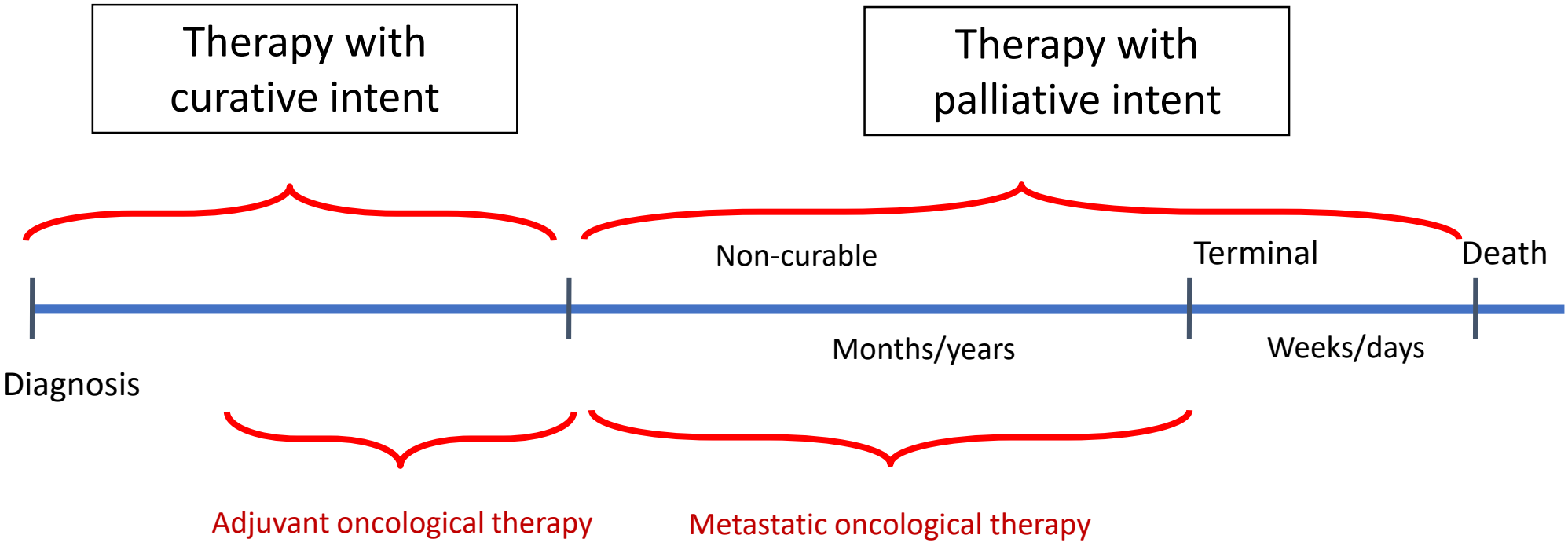
Colorectal cancer
Number of cases in Denmark

	Total
Denmark, 2012-16	5,000
Denmark, 2032-36	8,200

Increase by 64%

Similar increase globally

Basic oncological concept



Adjuvant therapy - definition

- Adjuvant therapy = supplementary treatment for (apparently) radically treated patients (often after surgery)
- No signs of residual disease but high risk of recurrence (microscopic residual disease, locally or distant)
- Aim is cure (prolong survival)

Colorectal cancer

Stage vs cure

	Total	%	5 year OS (%)
Stage 1	1,250	25	75
Stage 2	1,500	30	65
Stage 3, lymph node positive	1,500	30	50
Stage 4, metastatic disease	750	15	< 10

Adjuvant treatment in colon cancer stage III
Lessons learned from randomized trials

One giant leap for mankind

- 12 months 5-FU (iv) increase 5 year OS

Other minor steps

- 6 months = 12 months

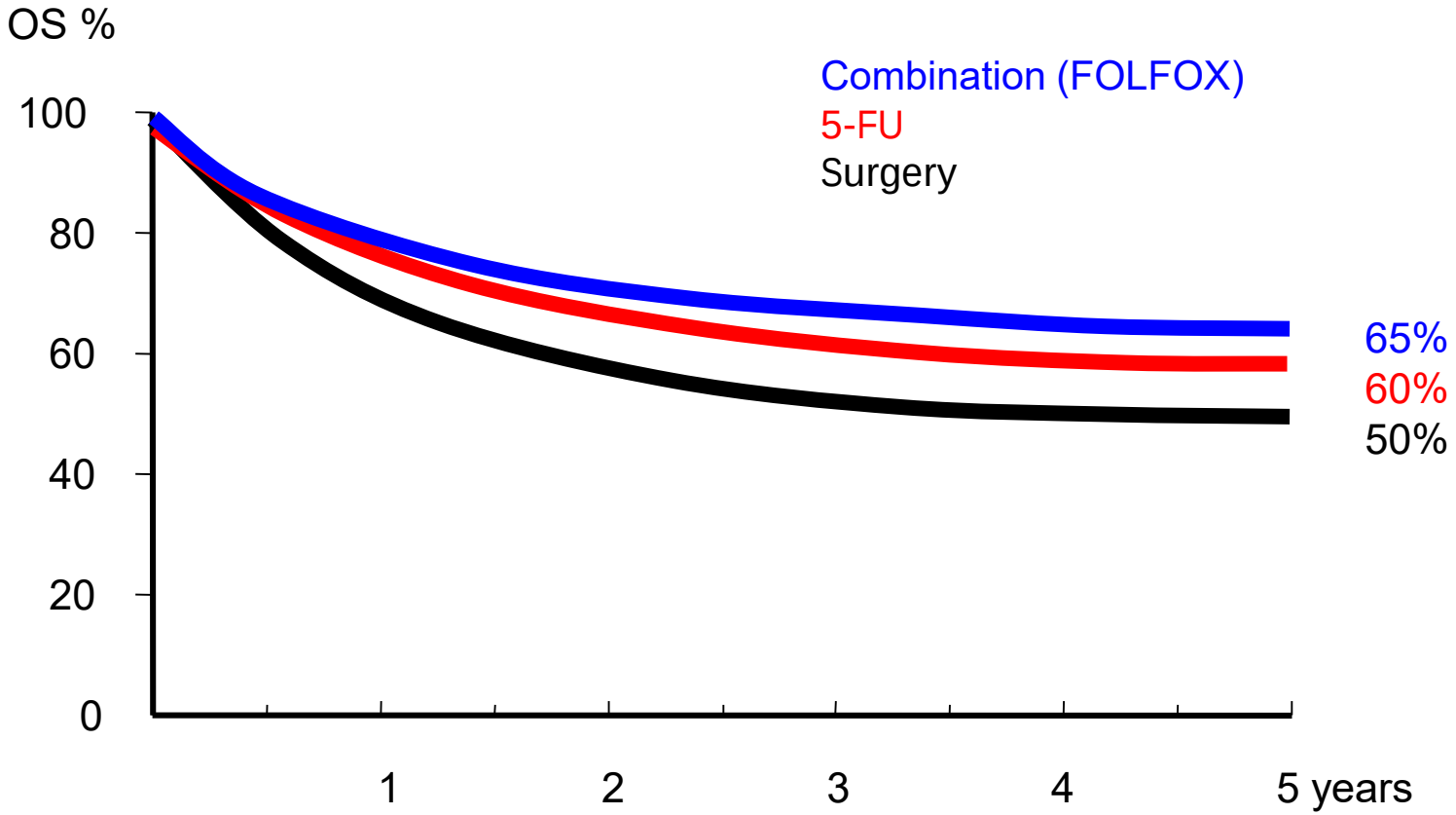
Second large step forward - oxaliplatin

- 5-FU + oxaliplatin (FOLFOX) better than 5-FU

Moertel, NEJM 1990; O'Connell; JCO 1998; Haller, JCO 2005; Twelves, NEJM 2005
Andre, NEJM 2004; Andre, JCO 2009; Andre JCO 2015; Kuebler, JCO 2007; Haller JCO 2011

Efficacy of adjuvant therapy

Colorectal cancer stage 3 (lymph node metastasis)



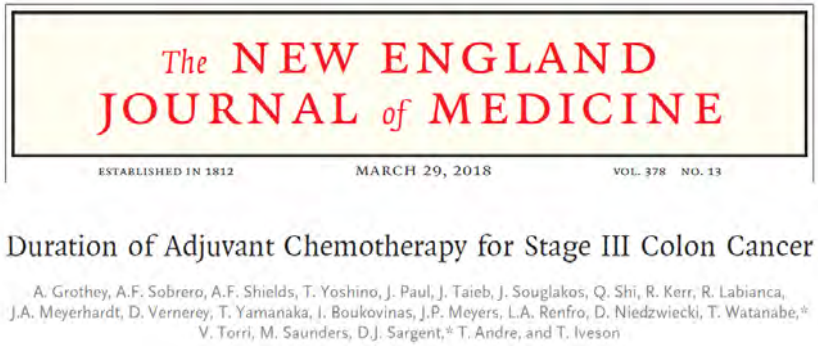
Adjuvant therapy in CRC

- Since 2004, FOLFOX has been standard adjuvant chemotherapy in patients with stage 3 colon cancer (lymph node +).
  - 3 randomized trials showed an improvement in overall survival

  - **Accordingly, 6 months of FOLFOX or CapOx became the standard**

    After IDEA (6 large phase III, 12,000+ patients)

    - **3 months in low risk stage III (~ 60%)**
    - **6 months in high risk stage III**



Andre et al, NEJM 2004 & JCO 2009; Kuebler et al., JCO 2007; Haller et al., JCO 2011; Grothey et al, NEJM 2018; Schilsky, NEJM 2018 (Editorial)

IDEA – neurotoxicity (CIPN) after 3 and 6 months

Table 3. Selected Adverse Events, According to Treatment and Duration of Therapy.*

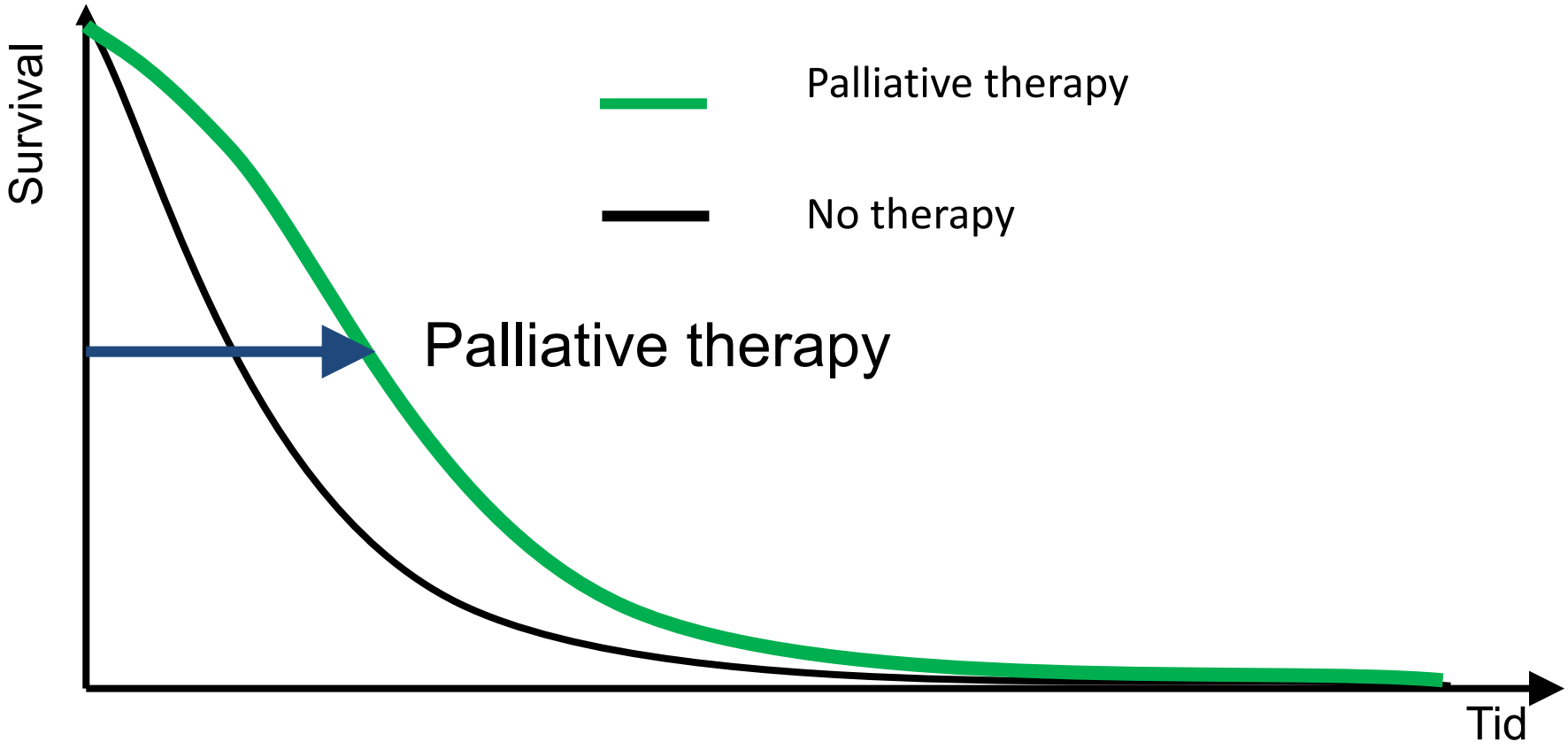
Adverse Event	FOLFOX				CAPOX			
	Grade 1	Grade 2	Grade 3 or 4	P Value	Grade 1	Grade 2	Grade 3 or 4	P Value
	number (percent)				*number (percent)*			
Any adverse event				<0.001				<0.001
3 mo	1008 (30.7)	1039 (31.6)	1236 (37.6)		496 (35.0)	578 (40.8)	342 (24.2)	
6 mo	363 (11.0)	1056 (32.1)	1874 (56.9)		203 (14.6)	674 (48.5)	512 (36.9)	
Peripheral sensory neurotoxicity†				<0.001				<0.001
3 mo	2661 (83.4)	450 (14.1)	80 (2.5)		1211 (85.8)	164 (11.6)	37 (2.6)	
6 mo	1700 (52.2)	1036 (31.8)	519 (15.9)		763 (55.0)	500 (36.0)	124 (8.9)	

	FOLFOX					CapOx				
	G1	G2	G3-4	G1-4	p	G1	G2	G3-4	G1-4	p
3 mo	83	14	17% 3	100	0.001	86	12	15% 3	100	0.001
6 mo	52	32	48%16	100		55	36	45% 9	100	

Grothey et al, NEJM 2018

Chemo-induced peripheral neuropathy (CIPN)

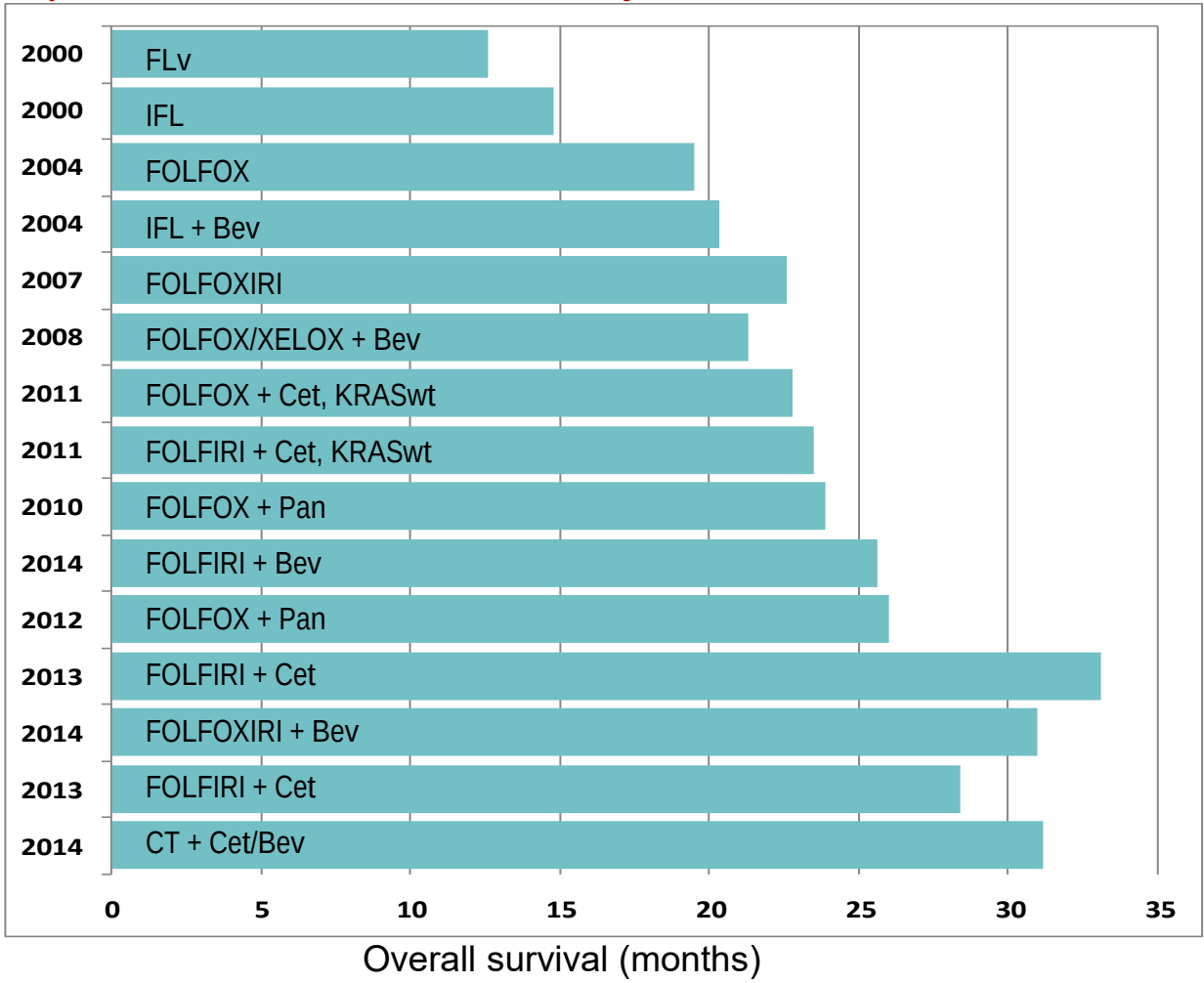
Palliative therapy



Small incremental steps and sequential use of many lines of therapy have led to major overall survival improvements in the last 15 years

PS 0	PS 1	PS 2	Age	
41	45	13	61	Saltz
39	46	15	62	Goldberg
50	43	5	61	Hurwitz
58	41	0	60	Falcone
61	37	2	62	Saltz
58	42	0	60	Bokemeyer
39	54	7	62	Van Cutsem
58	38	4	62	Douillard
50	44	6	62	Heinemann
52	47	1	65	Douillard
50	44	6	62	Heinemann
48	50	2	64	Cremolini
90	10	0	60	Van Cutsem
54	43	3	60	Lenz

PS: performance status



Systemic Therapy in mCRC

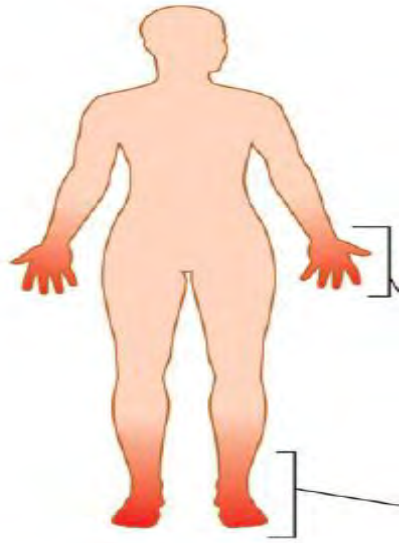
- 2 drugs better than 1
  - At least 50% of CRC patients will receive oxaliplatin-based
  - FOLFOX standard regimens in mCRC

- All available drugs should be used at some time

Van Cutsem et al, Ann Oncol 2016 (ESMO guidelines)

Neuropathy

- In general the symptoms of CIPN are sensory typically located in the hands and feet
  - Tingling
  - Numbness
  - Pain
- Motor symptoms may occur
  - Weakness, muscle cramps



- Patients with neuropathy report worse quality of life
- Future studies should focus on prevention of CIPN

Mols et al. JCO 2013

Oxaliplatin-Induced CIPN - Acute

- Acute form of CIPN (not seen with other platinums) characterized by peripheral nerve hyper-excitability triggered by exposure to cold
  - distal limb paraesthesias
    - sensory symptoms in the fingertips and toes
    - stocking and glove distribution
  - paraesthesias in the mouth and throat (laryngo-pharyngo dysesthesias - LPD) during or shortly after the infusion
    - muscle cramps with breathing problems may occur
  - sensed by all patients
  - usually transient and resolves within hours or days

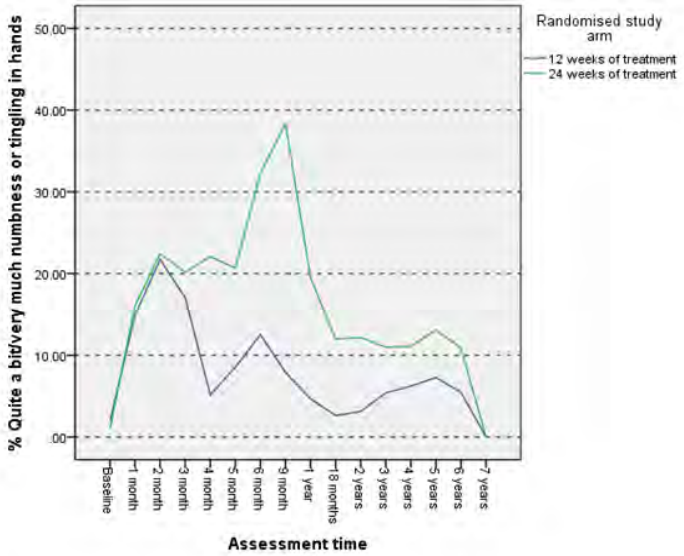
Oxaliplatin-Induced CIPN - Chronic

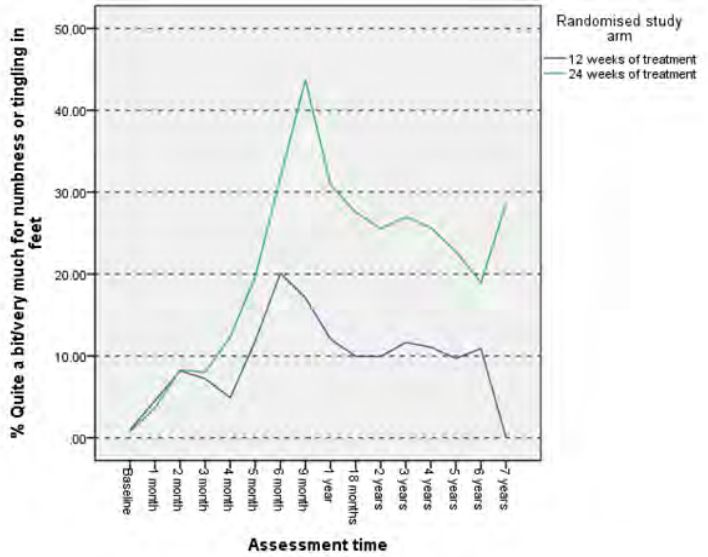
- Chronic form of CIPN characterized by
  - sensory paresthesias or dysesthesias
  - most often located in the extremities
  - persists between cycles
- The risk of severe neuropathy is dose dependent
  - 10 - 20% at cumulative doses of 750 – 850 mg/m^2
  - 50% of patients receiving cumulative doses of 1170 mg/m^2
  - Symptoms may continue to worsen even after treatment has ceased, a process referred to as the “coasting” phenomenon

Development of neurotoxicity over time - Persist for years

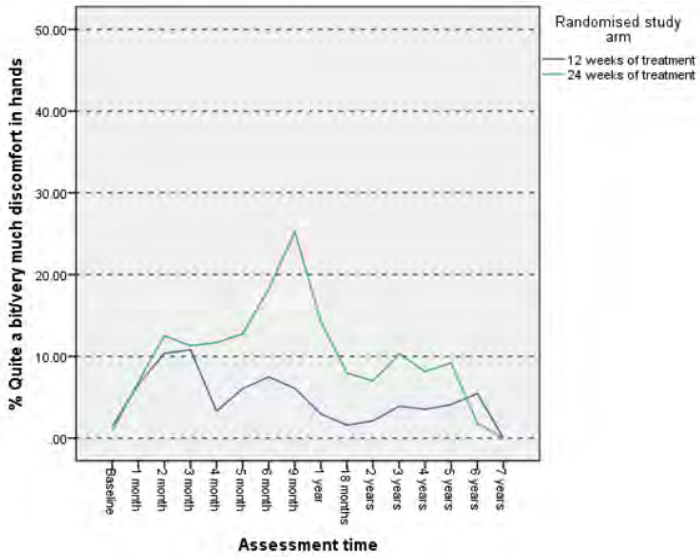
HANDS | **FEET**

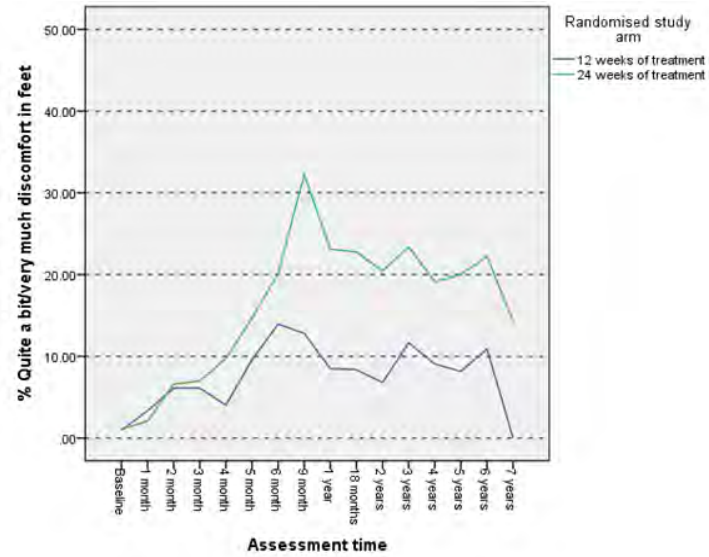
Numbness or tingling





Discomfort





Data from SCOT study - FACT/GOG-Ntx

Use of oxaliplatin in CRC

- How many patients will receive oxaliplatin?
  - At least 20% will receive adjuvant oxaliplatin
  - At least 30% of patients with mCRC will receive oxaliplatin for 1st line therapy
  - 20% of patients with mCRC will receive oxaliplatin as 2nd line therapy

  - 80% of all patients will receive oxaliplatin

Conclusions

- CIPN is a major problem in colorectal cancer
  - The use of oxaliplatin will continue for many years, presently no alternative
  - CIPN percist for years and reduce quality of life
  - Medical need to prevent CIPN, so far no effective treatment

PledPharma

VIDEO

https://vimeo.com/323561992

PledPharma

2. PledOx® in Chemotherapy Induced Peripheral Neuropathy (CIPN)

a. Unmet medical need

b. Development of PledOx® in CIPN with oxaliplatin

c. Commercial opportunity in CIPN with oxaliplatin

d. Indication expansion – CIPN with taxanes

Phase III

PledOx drives value by…

Development in CIPN/oxaliplatin

Expansion to CIPN/taxanes

Commercialization by strategic partnerships

Standard treatment of Colorectal Cancer cause CIPN

Numbness and Tingling

Burning pain

Cold sensitivity during oxaliplatin treatment

Problems with sensation

Impacts balance with risk of falling

Challenge to use computer and key board

Difficulty in buttoning buttons

Depression

Anxiety

Severe insomnia

Reduced quality of life

Loss of ability to work

Oxaliplatin is associated with dose limiting and debilitating toxicities

40-60 % of patients get peripheral neuropathy during and up to 3 months after chemotherapy

20-30% of patients with symptoms >7 years post chemotherapy

No approved drug for prevention or treatment of CIPN

PledOx® Target Product Profile in CIPN/oxaliplatin

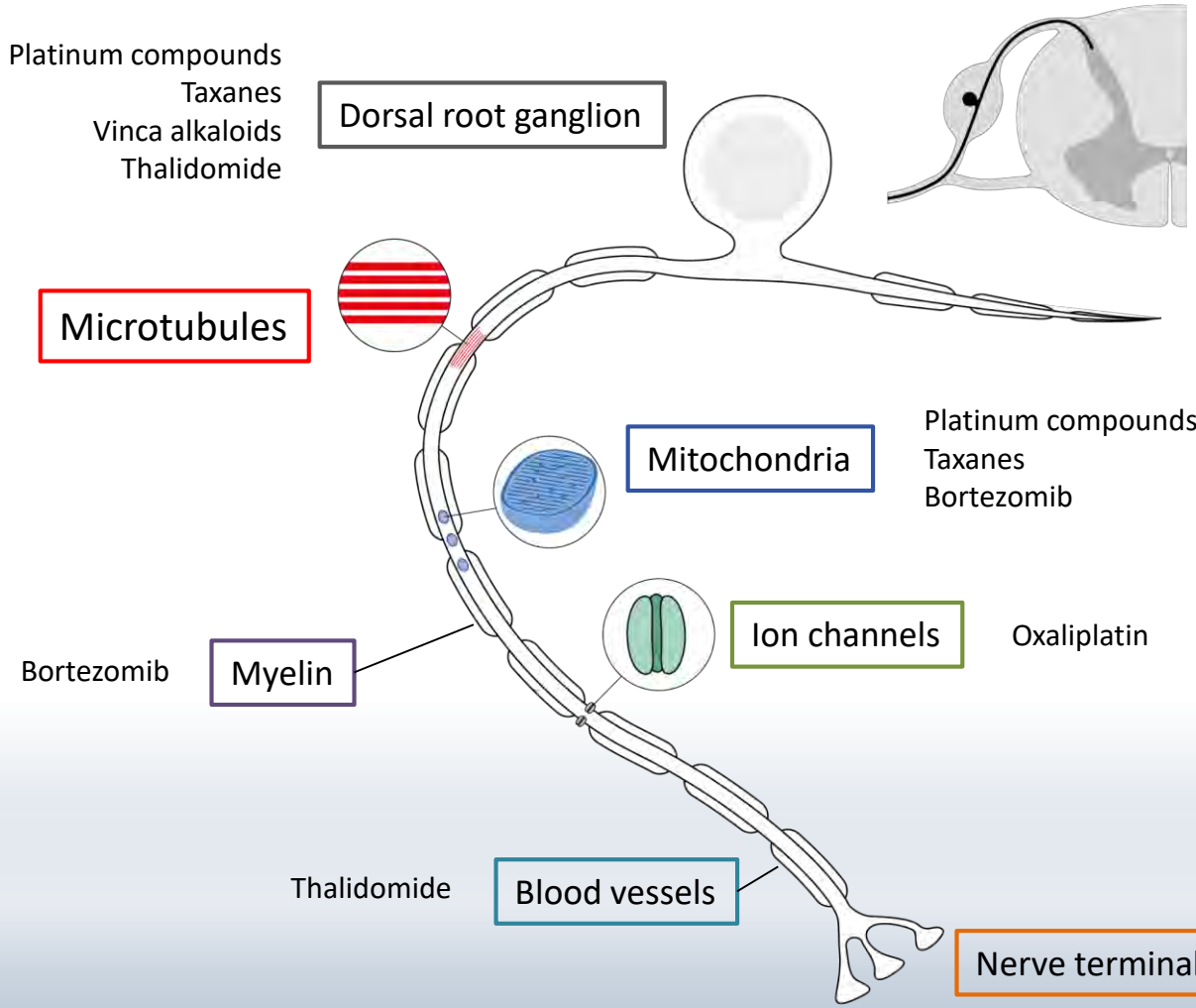
- Prevention of CIPN without negative impact on the efficacy of chemotherapy

Indication: Prevention of oxaliplatin-induced chronic peripheral neuropathy

Patients treated with PledOx® report…	
Efficacy	Safety & Tolerability
… less numbness, tingling and discomfort compared to placebo	…similar PFS/OS/DFS outcomes as patients treated with placebo
… less cold sensitivity during chemotherapy compared to placebo	… similar adverse event profile as patients treated with placebo
… no functional loss compared to placebo	
… less dose-modifications of oxaliplatin compared to placebo	

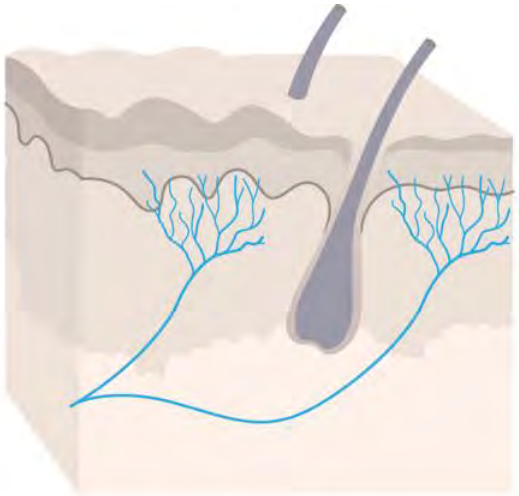
PledPharma

Mechanisms underlying CIPN are diverse and complex

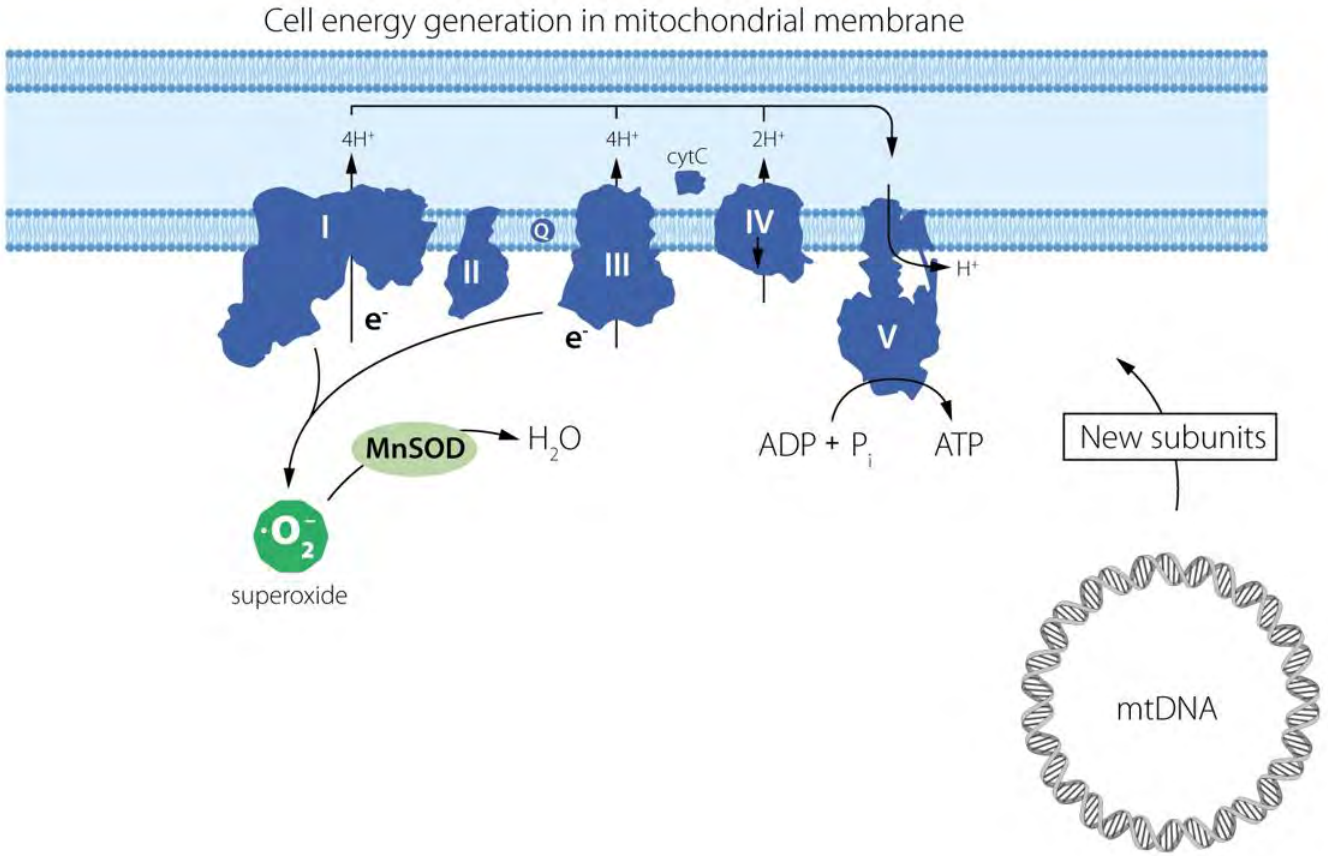


Kerckhove et.al (2017) Long-Term Effects, Pathophysiological Mechanisms, and Risk Factors of Chemotherapy-Induced Peripheral Neuropathies: A Comprehensive Literature Review
Park et al (2008) Mechanisms underlying chemotherapy-induced neurotoxicity and the potential for neuroprotective strategies

In healthy cells, mitochondrial homeostasis is maintained by MnSOD

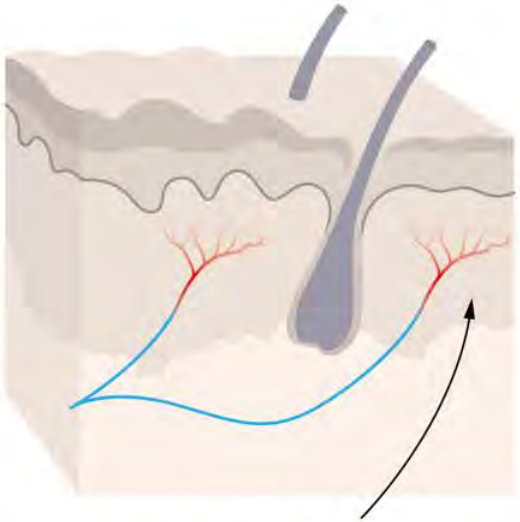


Functional sensory peripheral nerve

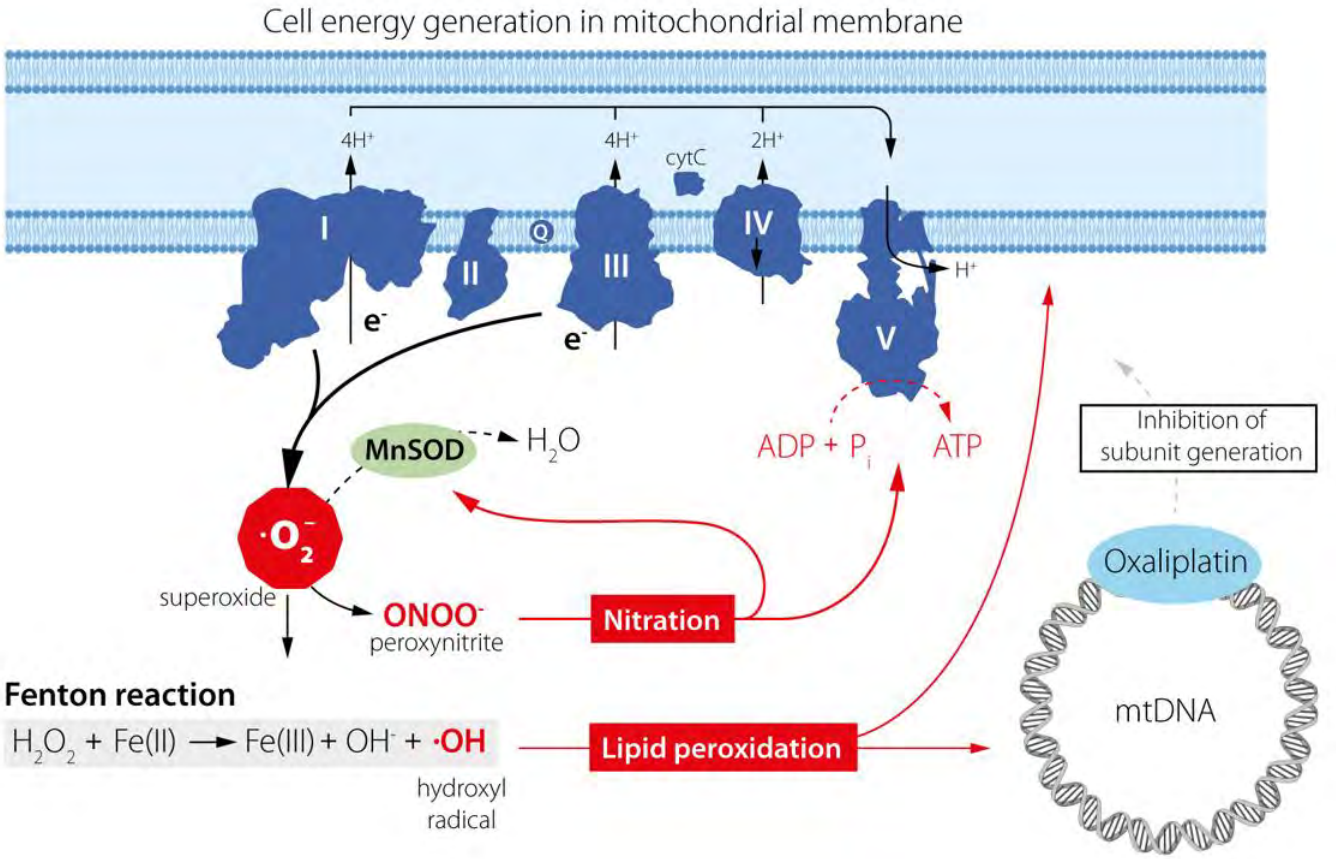


- Superoxide is generated as a by-product of energy production in the mitochondria
- MnSOD is an enzyme catalysing the degradation of superoxide

Chemotherapy leads to mitochondrial dysfunction and CIPN



Nerve ending degeneration, due to lack of energy generated in mitochondria, leads to chronic CIPN



- Oxaliplatin binds to mtDNA, leading to inefficient energy generation and more superoxide
- More superoxide radicals drive harmful nitration and lipid peroxidation pathways

PledOx® prevents mitochondrial dysfunction

- Being a MnSOD mimetic, PledOx® supports superoxide regulation

- PledOx® binds free iron, inhibiting the Fenton reaction and thus lipid peroxidation

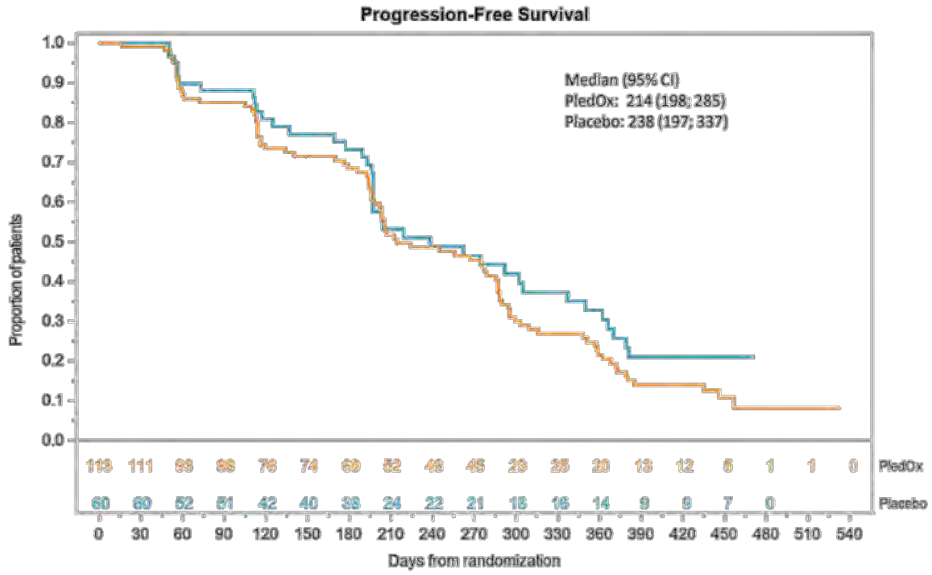
Summary of key neuropathy efficacy endpoints in Phase IIb PLIANT study

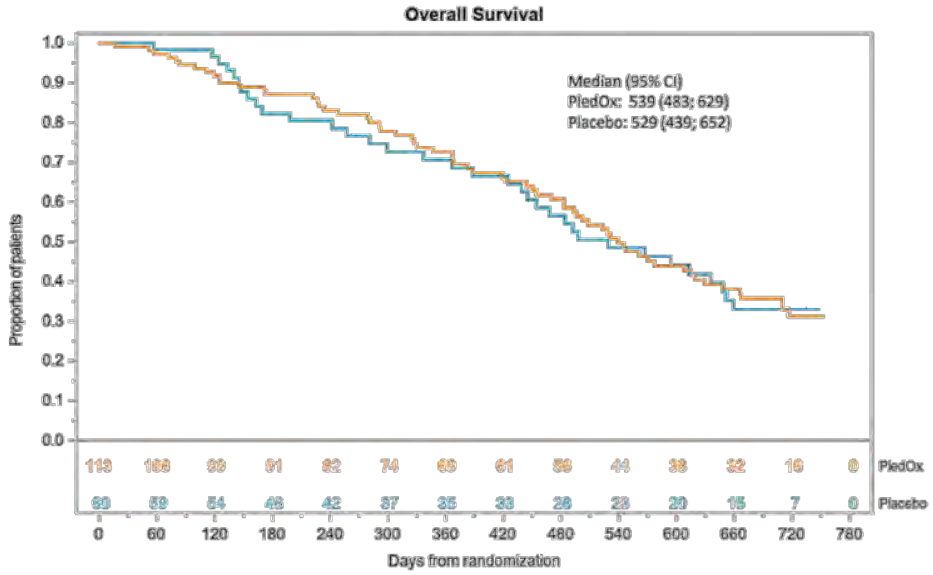
PLIANT study: 173 patients with metastatic CRC treated with PledOx® or placebo together with chemotherapy FOLFOX (oxaliplatin)

Type of CIPN assessment	Dose vs Placebo (Study Part†)	2 µmol/kg (2a+2b)	5 µmol/kg (2b)	2+5+10 µmol/kg (2a+2b)
Physician reported (primary endpoint)	**OSSS odds ratio over cycle 1 to 8§ (nominal p-value)**	0.78 (p=0.31)	0.68 (p=0.25)	0.62 (p=0.16)
Patient reported	**Leonard PRO, odds ratio at FU2* (exploratory analysis; nominal p-value)**	0.38 (p=0.15)	0.12 (p=0.018)	0.23 (p=0.014)

† In the initial part of the study, Part 2a, randomized patient to Placebo, 2 µmol/kg or 10 µmol/kg. After changing the high dose from 10 µmol/kg to 5 µmol/kg, the majority of patients were randomized to Placebo, 2 µmol/kg or 5 µmol/kg in Part 2b.
§ Investigator reported neuropathy grade 2 or higher vs. placebo
* Proportion of patients scoring 3 or more on either numbness, tingling or burning pain/discomfort with cold in hands or feet at FU2 (6 months after last dose), which is approximately 10 months after first dose for the majority of patients that reported follow-up 2.

Progression free survival (PFS) and Overall survival (OS) in Phase IIb PLIANT study





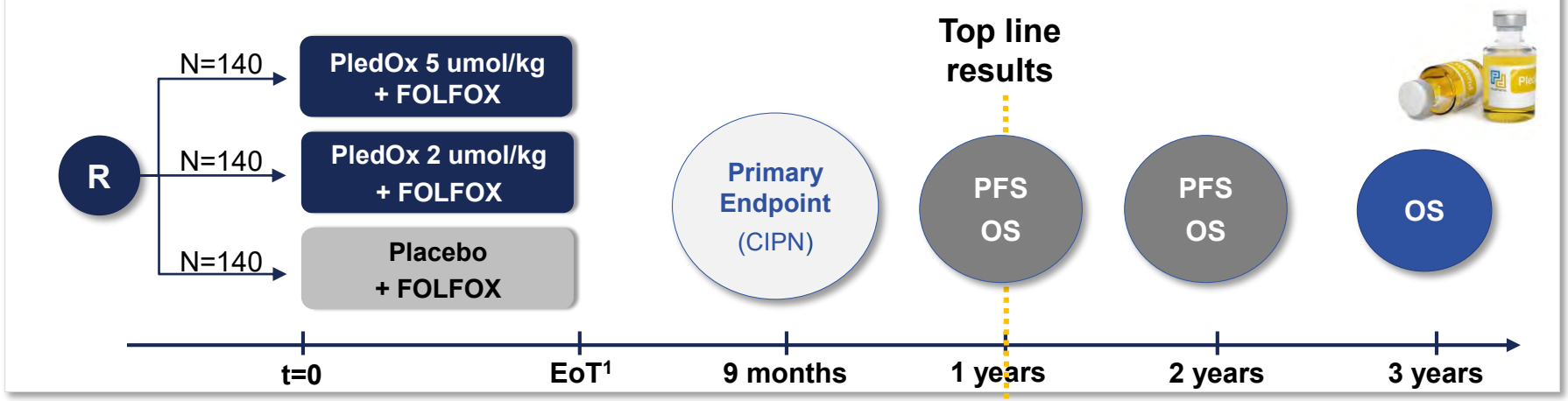
No apparent negative effect on the efficacy of the chemotherapy treatment

PiedPharma

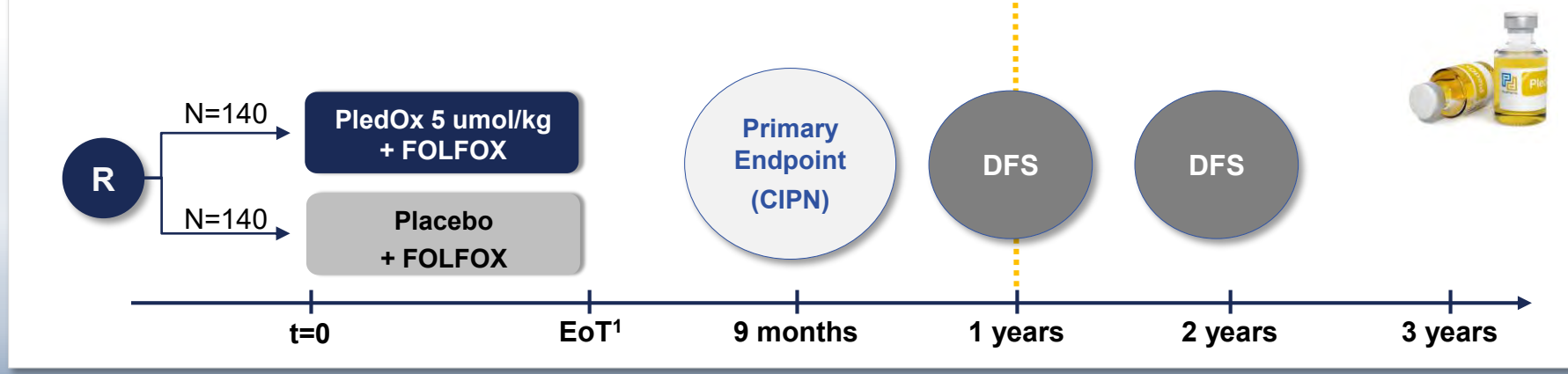
PledOx® Global Phase III program – the POLAR studies

Scientific Advisory Board

POLAR-M (US, EU & Asia)



POLAR-A (EU & Asia)



 Note: (**1**) End of treatment.

POSTER BOARD
Q7

POSTER BOARD
Q6

PledPharma

TPS722

The Global POLAR program: Calmangafodipir used on top of modified FOLFOX6 (5-FU/FA and oxaliplatin) to prevent chemotherapy induced peripheral neuropathy (CIPN)

Solasia

Per Pfeiffer[*], Camilla Qvortrup[**], Kei Muro[#], Maryam B Lustberg[##], Fumiko Nagahama[^], Yusuke Sonehara[^], Marie Bengtson[%], Malin Nittve[%], Christian Sonesson[%], Stefan Carlsson[%]

[*]Department of Oncology, Odense University Hospital, Odense, Denmark; [**] The Finsen Center – Rigshospitalet, Department of Oncology, Copenhagen, Denmark; [#] Aichi Cancer Center Hospital, Nagoya, Japan; [##] The Ohio State Comprehensive Cancer Center, Columbus, OH, USA; [^] Solasia Pharma K.K.Tokyo, Japan; [%] PledPharma AB, Stockholm, Sweden. Contact person: Per Pfeffer, per.pfeffer@rsyd.dk

The POLAR program is a phase 3, double-blinded, multicenter, placebo-controlled program of calmangafodipir used on top of modified FOLFOX6 (5-FU/FA and oxaliplatin) to prevent chemotherapy induced peripheral neuropathy (CIPN) A total of 700 patients will be randomized in 110 sites distributed across US, Europe and Asia. The program consists of two studies POLAR M (metastatic) and POLAR A (adjuvant).

Background:

Oxaliplatin (OXA), is approved in combination with 5-FU/FA (5-fluorouracil/ folinic acid; FOLFOX) for metastatic as well as in adjuvant colorectal cancer (CRC) treatment.

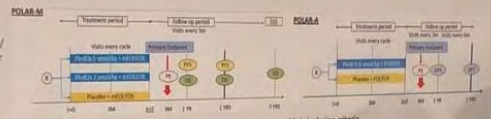
CIPN is a common adverse event, after OXA treatment. The incidence of severe CIPN is approximately 15% after a cumulative dose of 780 to 850 mg/m² and 50% after a cumulative dose of 1170 mg/m² and peaks after 6 months of OXA at 9 months after first dose of OXA, see Fig 1 (Iveson et al. 2018).

OXA induced neuropathy, results in greatly reduced nitrated manganese superoxide dismutase (MnSOD) activity. Treatment with a superoxide dismutase mimetic, such as calmangafodipir (CAL), prevents and reverses oxaliplatin-induced neuropathies. This has been demonstrated in the randomized PLIANT study (Glimelius et al. Acta Oncol 2017).

Fig. 1.FACT-GOG Ntx4 questionnaire (SCOT trial)

Peripheral neuropathy, as reported via a patient questionnaire FACT/GOG Ntx4 (numbness, tingling and discomfort in hands and feet) , was significantly worse in the 6-month group and persisted for at least 5 years. Peak neuropathy occurred at 9 months in the 6-month group and at 6 months in the 3-month group. ACT/GOG-Ntx4 data were available from 2871 patients.

References: Iveson et al. Lancet Oncol 2018; 19: 562–78. Glimelius et al. Acta Oncol. 2017; 15: 1–10.



Main inclusion criteria

- Metastatic colorectal cancer (mCRC)
- Planned first-line modified FOLFOX6 (mFOLFOX6) chemotherapy for at least 3 months

Therapy

Patients will be randomized in a 1:1:1 ratio:

Arm A: calmangafodipir (2 µmol/kg) + mFOLFOX6 chemotherapy. n=140

Arm B: calmangafodipir (5 µmol/kg) + mFOLFOX6 chemotherapy. n=140

Main inclusion criteria

- Stage III or high-risk Stage II colorectal cancer
- Planned adjuvant modified FOLFOX6 (mFOLFOX6) chemotherapy for 3- 6 months.

Therapy

Patients will be randomized in a 1:1 ratio

Arm A: calmangafodipir (5 µmol/kg) + mFOLFOX6 chemotherapy. n=140

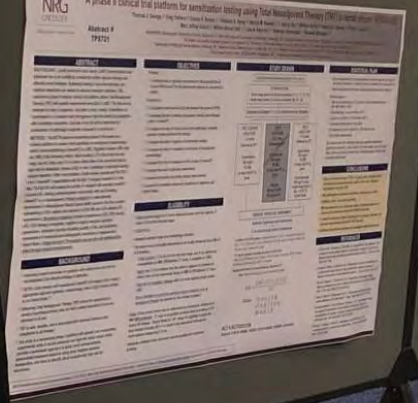
Arm B: Placebo + mFOLFOX6 chemotherapy. n=140

- **Primary objective** is to compare calmangafodipir vs placebo with respect to the proportion of patients with moderate or severe chronic CIPN
- **Primary endpoint:** Patient reported symptoms as proportion of patients (with moderate or severe chronic CIPN) scoring 3 or 4 in at least 1 of the first 4 items of the FACT/GOG-NTX-13 (i.e., FACT/GOG-NTX-4), targeting numbness, tingling or discomfort in hands and/or feet, assessed 9 months after the first dose of chemotherapy
- **Secondary endpoints:** Progression Free Survival and Overall Survival in the POLAR M study, whilst Disease Free Survival is one safety endpoint assessed in the POLAR A study
- **Results are expected during second half 2020**

NRG ONCOLOGY

A phase II clinical trial platform for sensitization testing using Total Neoadjuvant Therapy (TNT)

Abstract #
TPS721

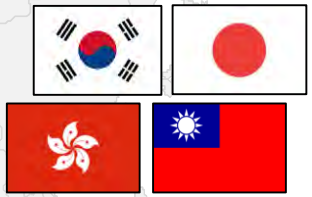


Design of POLAR program presented at Gastrointestinal Cancer Symposium (ASCO GI), San Fransisco, Jan, 2019

POLAR program – a global program across three regions

US
1 country
25 sites

Europe
7 countries
60 sites



Asia
4 countries
21 sites

The basis for evaluation of CIPN in the POLAR program

Primary Endpoint	Description
FACT/GOG-NTx-4	4-question PRO instrument addressing key CIPN symptoms of numbness, tingling and discomfort in hands and feet

Secondary & Exploratory Endpoints	Description
FACT/GOG-NTx-13	13-question PRO instrument addressing CIPN broadly
Graduated tuning fork	Objective measure of CIPN
Grooved PEG board	Functional measure of CIPN
Cold sensitivity questionaire	4-question PRO instrument adressing acute CIPN symptoms during chemotherapy
Numeric rating scale of pain	3-question PRO instrument of pain
EQ-5D-5L	General Quality-of-Life PRO instrument

Primary endpoint based on FACT/GOG-Ntx-4 is clinically relevant and interpretable

FACT/GOG-Ntx (4 item)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4

Primary endpoint targeting a percentage of patients with 3 or 4 in any of the NTx-4 questions is clinically interpretable. Broad consensus on clinical relevance of the two response options 3 and 4.

Throughout the Phase III studies, data on the full FACT/GOG-NTx-13 questionaire is collected

FACT/GOG-NTx-4 captures the majority of relevant chronic CIPN symptoms

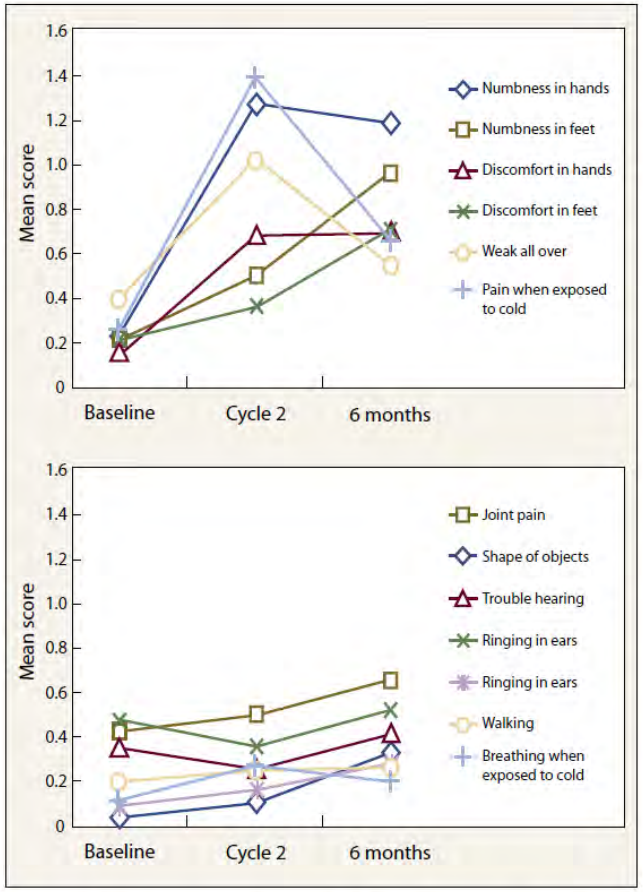


Figure 1 Response Patterns to Neurotoxicity Scale Items

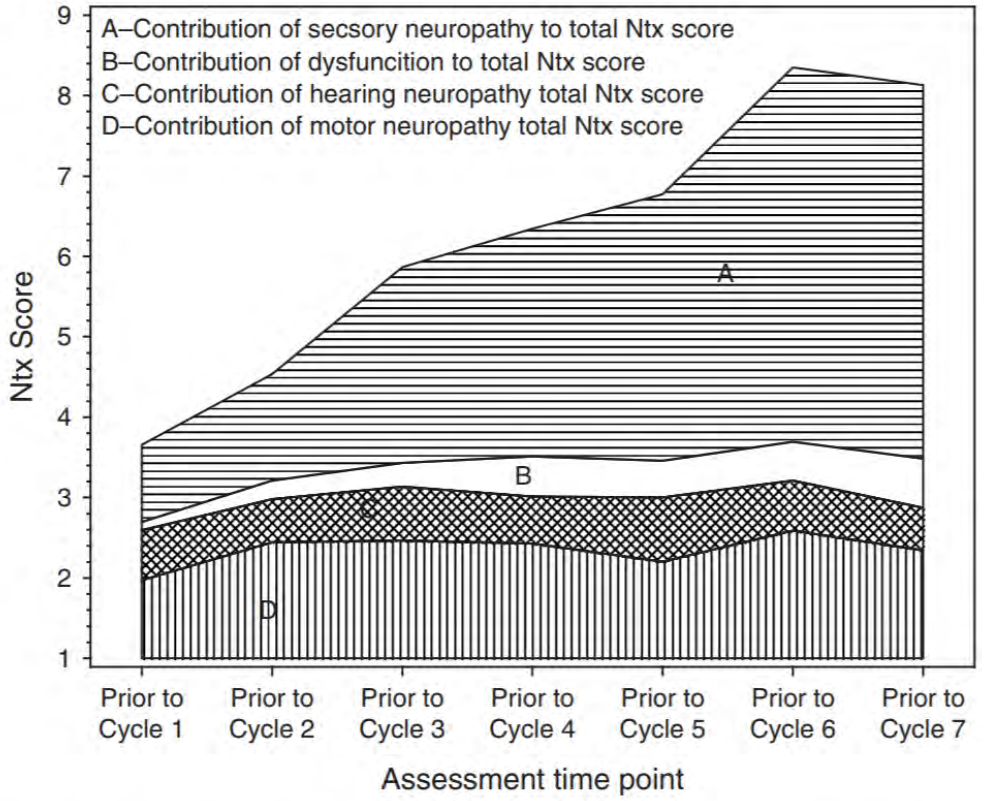


Figure 3. Responsiveness of Ntx scores to TAP cycles received.

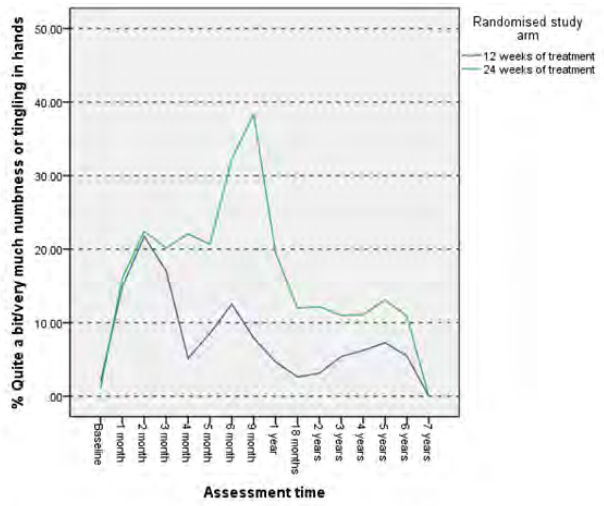
Note: “A” in Figure refers to the questions in Ntx-4

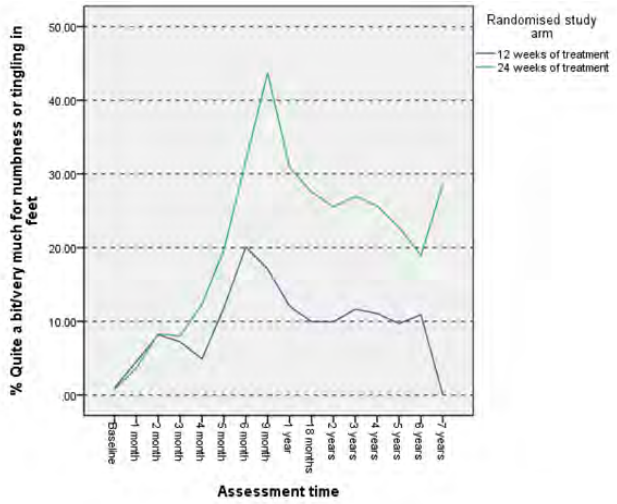
(1) Kopec et.al (2006) Validation of a self-reported neurotoxicity scale in patients with operable colon cancer receiving oxaliplatin
(2) Huang et al. (2007) Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study

Results in SCOT study confirm the sensitivity of FACT/GOG-Ntx-4 in CRC patients treated with oxaliplatin

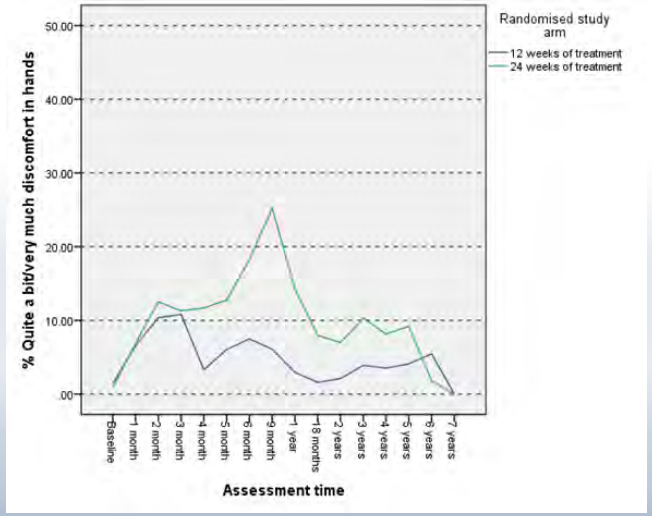
HANDS | **FEET**

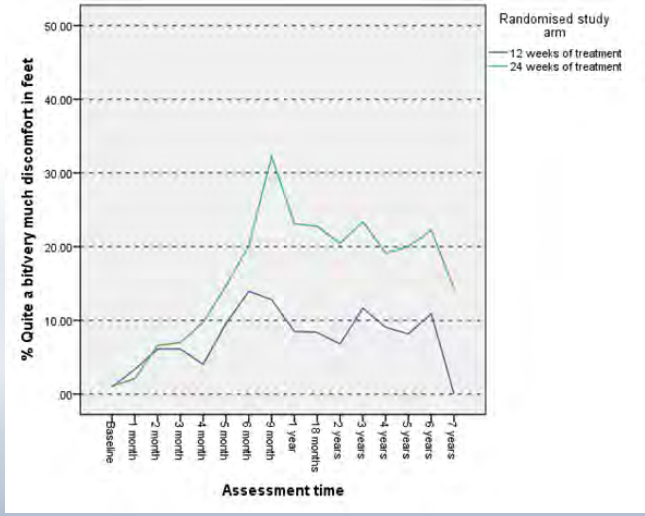
Numbness or tingling





Discomfort



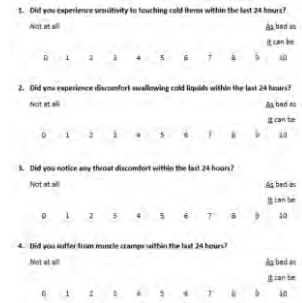


PiedPharma

Other endpoints build a robust characterization of efficacy

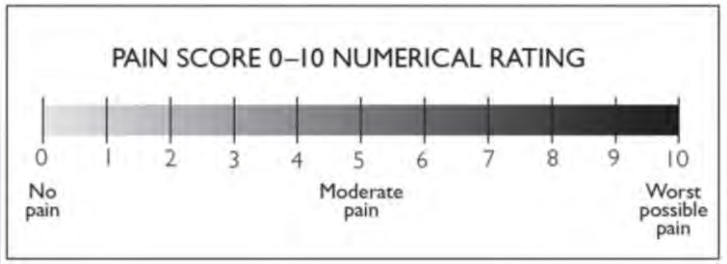
Graduated tuning fork
(objective measure of chronic CIPN)

Grooved PEG board
(functional measure of chronic CIPN)



Cold sensitivity questionnaire
(measure of acute CIPN symptoms during chemotherapy)

EQ-5D-5L
Quality of Life questionaire



Numeric rating scale of Pain

PiedPharma

PledOx® – development timeline

2018

- ✓ Results Ph.1 Study JPN
- ✓ Asian expansion of POLAR studies
- ✓ POLAR CTAs approved in US,JPN, UK, Spain, Italy, France & Belgium
- ✓ First Patient In (POLAR studies)

2019

- ✓ Further CTA approvals
- All patients randomized
- Initiate Indication expansion

2020

Top line results of primary endpoint (CIPN) and key safety endpoints (1 year PFS/OS/DFS)

2021

Regulatory submissions start

2022

First launch

2032

Calmangafodipir composition of matter patent expires

PledPharma

2. PledOx® in Chemotherapy Induced Peripheral Neuropathy (CIPN)

a. Unmet medical need

b. Development of PledOx® in CIPN with oxaliplatin

c. Commercial opportunity in CIPN with oxaliplatin

d. Indication expansion – CIPN with taxanes

Phase III

Epidemiology - Colorectal cancer (CRC) is the third most commonly diagnosed cancer

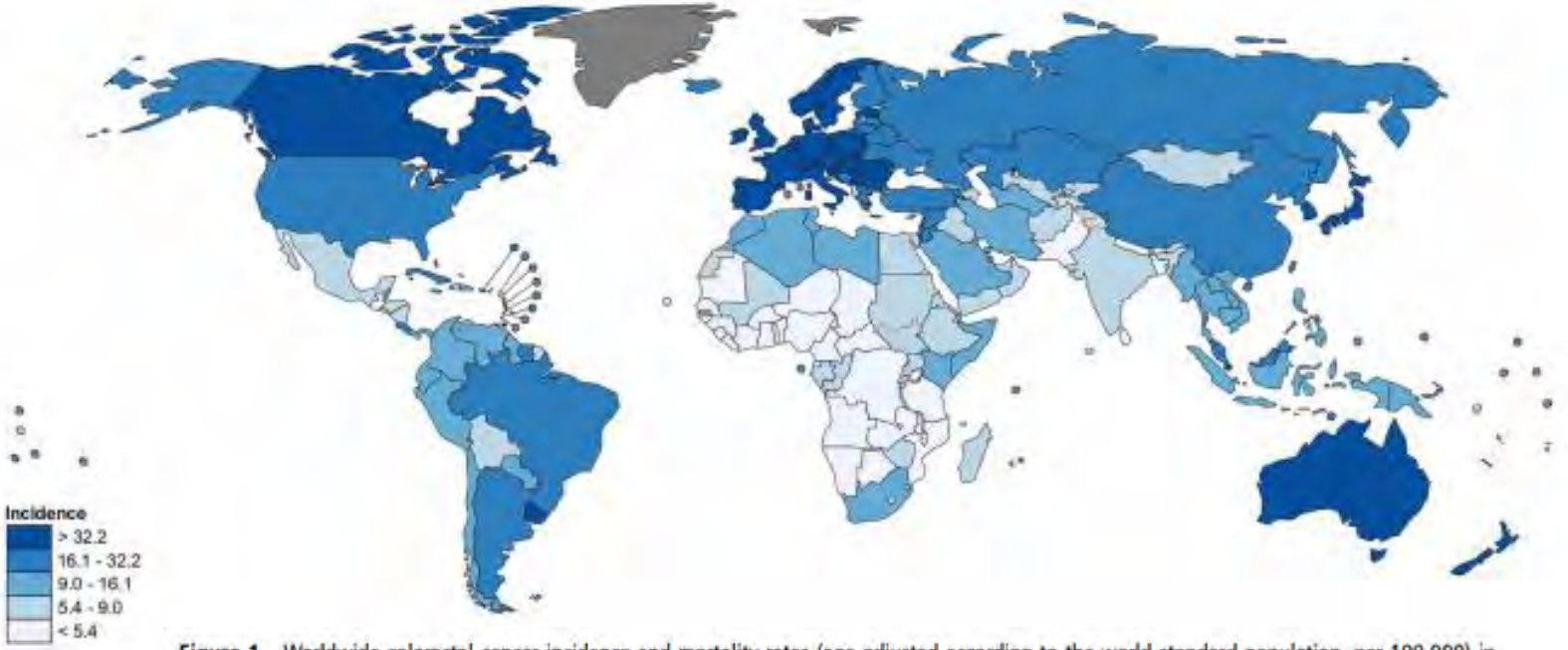


Figure 1 Worldwide colorectal cancer incidence and mortality rates (age adjusted according to the world standard population, per 100 000) in males in 2012 (GLOBOCAN 2012[1]).

"…and its burden is expected to increase by 60% by 2030"

 BMJ: Arnold M, et al. Gut 2016

Colorectal Cancer – Common treatment approaches

Stage I & II

- Surgery +/- RT
- Surgery + systemic therapy +/- RT (high-risk patients)

In early stages of disease, surgery has a high cure rate; many patients do not require additional systemic therapy

Stage III (adjuvant)

- Surgery + systemic therapy +/- RT

Common Systemic Therapies:

- FOLFOX
- CAPOX
- Capecitabine

Stage IV (metastatic)

- Systemic therapy +/- RT
- Surgery + systemic therapy +/- RT (resectable disease)

1L:

- FOLFOX + bevacizumab
- FOLFIRI + bevacizumab
- FOLFOX

2L (dictated by 1L therapy):

- FOLFIRI or FOLFOX + bevacizumab
- FOLFIRI
- FOLFIRI + cetuximab (KRAS+) or aflibercept
- KEYTRUDA (MSI-H or dMMR)

3L:

- Regorafenib
- Capecitabine
- Panitumumab (KRAS+)

While markets vary, FOLFOX +/- targeted therapy is the most commonly used first-line cytotoxic regimen for the systemic treatment of both Stage III and Stage IV CRC

- CAPOX, capecitabine + oxaliplatin
- FOLFOX, 5-FU + leucovorin + oxaliplatin
- FOLFIRI, 5-FU + leucovorin + irinotecan

CRC Stage IV (and III) Phase 3 Clinical development landscape

1L mCRC

KEYTRUDA [pembrolizumab]
(PD-1; Merck)

- Active, Not Recruiting: 1L dMMR or MSI-H mCRC; n=308 (May 2018)
- Primary completion: August 2019
- Treatment: Keytruda vs. Investigator Choice SOC (SOC regimens may include [FOLFOX or FOLFIRI] +/- targeted tx)

KEYTRUDA granted FDA accelerated approval for 2L mCRC in 2017

TECENTRIQ [atezolizumab]
(PD-L1; Roche)

- Recruiting: 1L dMMR or MSI-H mCRC
- Primary completion: April 2022
- Treatment: Tecentriq vs. Tecentriq + FOLFOX + Avastin vs. FOLFOX + Avastin

Trial sponsored by National Cancer Institute

2L mCRC

Masitinib
(MEK; AB Science)

- Terminated: 2L mCRC
- Terminated due to Sponsor portfolio prioritization
- Treatment: Masitinib + FOLFIRI vs. FOLFIRI

Encorafenib +/- Binimetinib
(Raf Kinase +/- MEK; Array)

- Active, Not Recruiting: 2L or 3L BRAF V600E+ mCRC
- Primary completion: July 2019
- Treatment: Encorafenib + Erbitux +/- binimetinib vs. Investigator's Choice SOC (SOC may be [FOLFOX + Erbitux] or [Erbitux + irinotecan])

Napabucasin
(STAT3; Boston Biomedical)

- Recruiting: 2L mCRC
- Primary completion: June 2020
- Treatment: Napabucasin + FOLFIRI +/- Avastin vs. FOLFIRI +/- Avastin

3L mCRC

TECENTRIQ (atezolizumab) +/- COTELLIC (cobimetinib)
(PD-L1 +/- MEK; Roche)

- Completed: 3L mCRC
- Primary completion: March 2018. Study completion in Dec 2018, with results March 2019
- Treatment: Tecentriq +/- Cotellic vs. Stivarga

Other

Adjuvant

TECENTRIQ (atezolizumab)
(PD-L1; Roche)

- Recruiting: Adjuvant Stage III dMMR CRC
- Primary completion: December 2020
- Treatment: Tecentriq + FOLFOX vs. FOLFOX

Trial sponsored by National Cancer Institute

Maintenance

Lefitolimod
(TLR9; Mologen AG)

- Active, Not Recruiting: Maintenance mCRC
- Primary completion: March 2019
- Treatment: Lefitolimod vs. Investigator's Choice SOC Maintenance Tx

Chemotherapy Induced Peripheral Neuropathy - Competitive landscape

COMMON TREATMENT APPROACHES FOR CIPN

Prevention

No approved drug for prevention or treatment of Chemotherapy Induced Peripheral Neuropathy

Treatment of Symptoms

Duloxetine (Cymbalta®)

Tricyclic Antidepressants

Gabapentin

Pregabalin (Lyrica®)

CIPN EMERGING TREATMENTS

MN-166
(Inflammation target)
Medicinova
Ph I study start announced in Mar-2018

APX-3330
(APE1/Ref1)
Apexian
Ph I SAD study start in Jan-2018

E-52862
(Sigma-1 Receptor)
Mundipharma
Ph II results published in Sept-2017

ART-123
(Thrombin [Coagulation Factor IIa])
Asahi Kasei Pharma
Japanese development

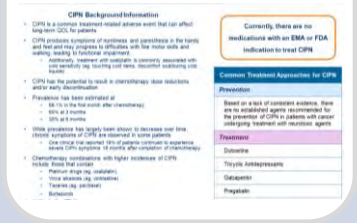
PledOx®
PledPharma

Phase I → Phase II → Phase III

PledOx® – Market Research, Pricing & Reimbursement

CIPN market research with US and EU Oncologists and Payers to gain insight into Unmet needs in the management of CIPN, validate Target Product Profile and Pricing & Reimbursement

CIPN Background



TPP & IDI Guide Development

Efficacy vs Safety Options and Key Questions for Insight

Testing

12 Physicians and 12 Payers

Team Expertise

Market Research Overview:

1:1, blinded, in-depth interviews

Physicians and Payers were recruited as follows:

- 6 Physicians, 6 Payers
- 2 Physicians, 2 Payers
- 2 Physicians, 2 Payers
- 2 Physicians, 2 Payers

Physician Requirements:

- Medical Oncologists or GI specialists involved in the management of metastatic colorectal cancer (CRC)

Payer Requirements:

- Working knowledge of oncology, specifically CRC
- Participated in 2 formulary reviews in last 12 months

 Note: (**1**) Oncologists from US and EU3. Payers from US (National MCO, Regional HMO, Medicare, Academic/Integrated System) and EU3.

Physician Insight – confirms the unmet medical need and verifies TPP

- All Oncologists interviewed stated CIPN has a major impact on the appropriate treatment of patients with various forms of cancer
  - Of the various chemotherapeutic regimens available, oxaliplatin was identified as one of the major culprits for development of CIPN
  - All respondents stated that CIPN symptoms, decreasing the number of cycles, treatment discontinuation, and/or changing to a less efficacious regimen
- Oncologists interviewed felt the incidence was higher than that stated in clinical publications

'Oxaliplatin CIPN incidence is higher than seen in publications. In many cases it arises after chemotherapy, especially in the adjuvant setting where patients can have unpleasant neuropathy for the rest of their lives. Overall, 50% of patients have long-term problems with CIPN'

'For 15-20% of patients with chronic problems, their new baseline will be where they are at 12 months – I don't see much change in symptoms between 12 and 18 months'

'For oxaliplatin in adjuvant therapy, we dose reduce in 70–80% of patients and have to stop treatment in about 10%'

'For a lot of patients there is a small decrease in the symptoms over time, but for the majority there is not recuperation is irreversible. It impacts QOL and patients may have trouble writing or walking'

Note: (**1**) interviews with Oncologists from US and EU3.

Payer Insight & combined EMA Scientific & Payer Advice

- clarifies data collection in Phase 3 to build robust pricing arguments

- With PledOx being first-in-class
  - Important to provide information of disease burden, unmet need, and costs of not treating or inadequately treating CIPN

'You're pushing an unopen door with CIPN in that Oncs are aware of its existence and how troublesome it can be, but nothing has been assessed in this space previously'

Pricing assumption based on base-case target product profile[1]

1,000 USD/cycle

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

NICE National Institute for Health and Care Excellence

Statens legemiddelverk

- Collection of data in POLAR studies extended to capture key variables associated with CIPN costs: hospital visits, medicines, medical procedures and events
- Draft cost-effectiveness model developed to be updated with POLAR efficacy study data and included in Payer dossier

Note: (**1**) interviews with Oncologists from US and EU3; price comparators branded Lyrica and Cymbalta.

CIPN associated with high health care costs in the US

Research Article

Healthcare Costs and Workloss Burden of Patients with Chemotherapy-Associated Peripheral Neuropathy in Breast, Ovarian, Head and Neck, and Nonsmall Cell Lung Cancer

Crystal T. Pike,[1] Howard G. Birnbaum,[1] Catherine E. Muehlenbein,[2] Gerhardt M. Pohl,[2] and Ronald B. Natale[3]

- Privately insured administrative claims database study (Ingenix Employer db, 4.7 million people)
- Patients with qualifying tumors, and claims for chemotherapy and services indicative of CIPN
- Patients <65 years of age
- Cases were matched 1:1 to controls with no CIPN-related claims based on demographics, diabetes history and propensity for having a diagnosis of PN during the study period

Increased health care costs for CIPN patient:

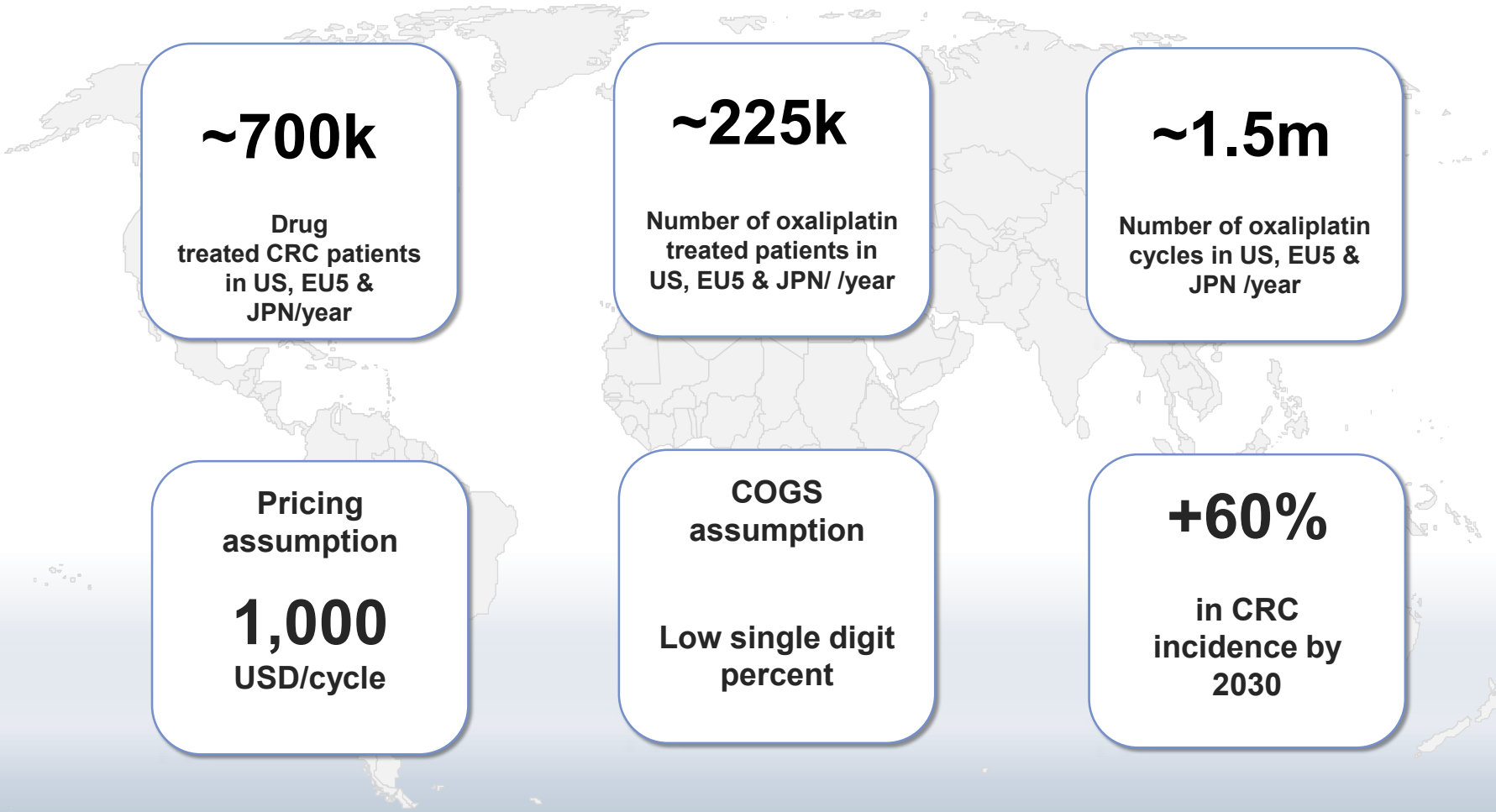
17,344 USD

during first year after chemotherapy

On average, each CIPN case had 12 more outpatient visits than controls, and spent more days in the hospital

Pike et al (2012) Healthcare Costs and Workloss Burden of Patients with Chemotherapy-Associated Peripheral Neuropathy in Breast, Ovarian, Head and Neck, and Nonsmall Cell Lung Cancer.

PledOx® – Commercial potential in CRC patients



~700k

Drug treated CRC patients in US, EU5 & JPN/year

~225k

Number of oxaliplatin treated patients in US, EU5 & JPN/ /year

~1.5m

Number of oxaliplatin cycles in US, EU5 & JPN /year

Pricing assumption

1,000
USD/cycle

COGS assumption

Low single digit percent

+60%

in CRC incidence by 2030

10 years pattern protection assuming launch 2022 (without any patent extension)

PledPharma

PledOx® Summary and Opportunities in CIPN with oxaliplatin

PREVENTS NERVE DAMAGE CAUSED BY OXALIPLATIN TREATMENT

DEVELOPMENT STATUS

- Phase II data provide reason to believe in Phase III
- Global Phase III POLAR studies approved in US, EU and Japan and first patient included – November, 2018
- Asian expansion of Phase III supported by Japanese PMDA. First patient in January 2019
- Milestone payment of 600 MJPY (c.49 MSEK) was triggered due to the inclusion of the first patient in Japan to the global Phase III program for PledOx®
- Top-line results in POLAR-studies expected 2020 with regulatory submissions starting in 2021

BUSINESS OPPORTUNITY

- CRC 3rd most diagnosed cancer
- ~1.5M cycles of oxaliplatin yearly (US, EU5, JPN)
- 60% growth in CRC incidence by 2030
- High incidence of CIPN (40-60%) in CRC patients.
- 20-30% of patients with symptoms >7 years later
- No available prevention or treatment of CIPN
- Limited competition
- Pricing and Reimbursement Research suggests a base-case pricing of 1,000 USD/cycle

PledPharma

2. PledOx® in Chemotherapy Induced Peripheral Neuropathy (CIPN)

a. Unmet medical need

b. Development of PledOx® in CIPN with oxaliplatin

c. Commercial opportunity in CIPN with oxaliplatin

d. Indication expansion – CIPN with taxanes

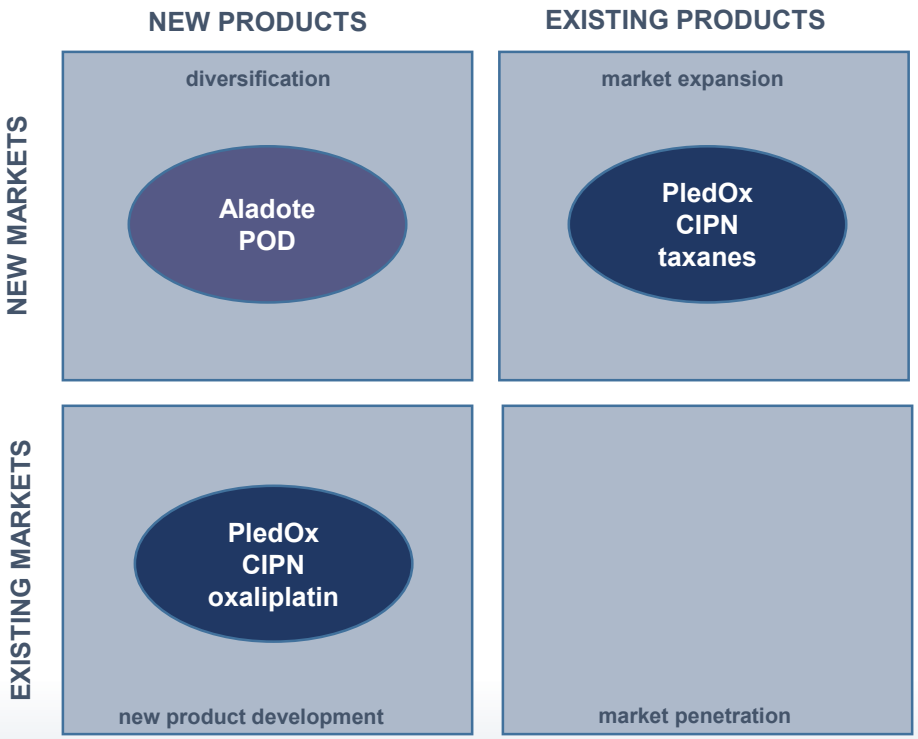
PledOx drives value by…

Development in CIPN/oxaliplatin

Expansion to CIPN/taxanes

Commercialization by strategic partnerships

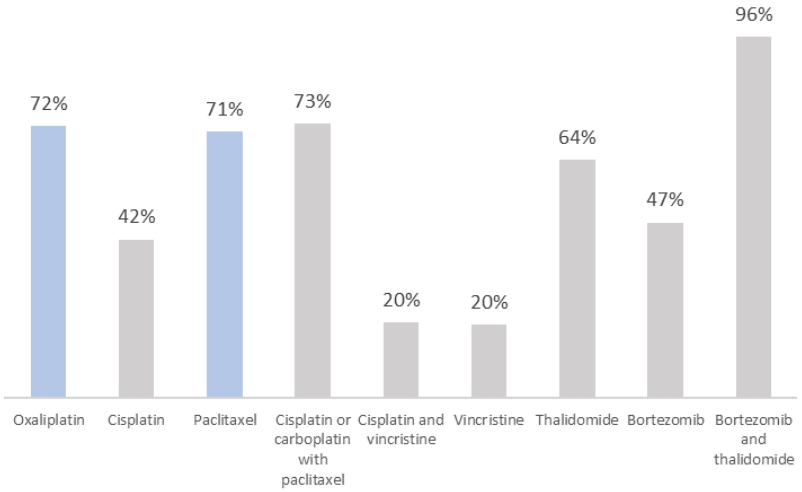
CIPN/taxanes a strategic opportunity for PledOx®



Ansoff's matrix of PledPharma portfolio with PledOx in CIPN/oxaliplatin as frontrunner to Aladote & PledOx LCM

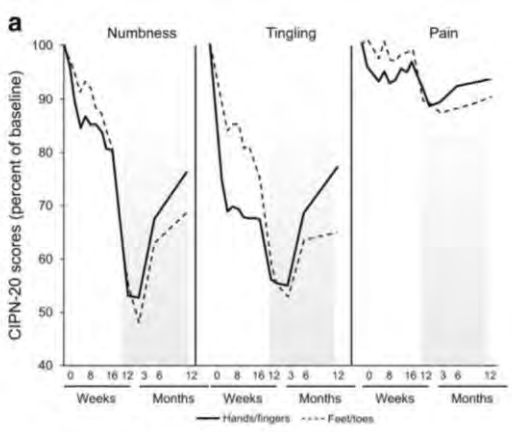
- Good strategic fit in PledPharma portfolio
- Most attractive commercial opportunity with huge unmet medical need
- Safety database generated in POLAR program of value in CIPN/taxanes
- Positive data from POLAR program further increases likelihood of success
- Learnings from regulatory & clinical experience in CIPN/oxaliplatin can be leveraged to CIPN/taxanes

Unmet medical need for CIPN with taxanes is similar to that for oxaliplatin

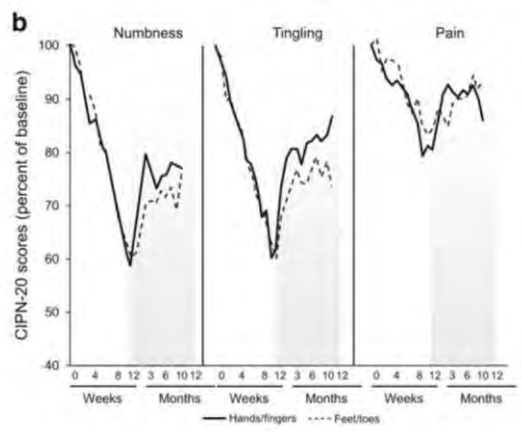


- Similar percentage of patients experience CIPN with oxaliplatin and paclitaxel(1)

Oxaliplatin



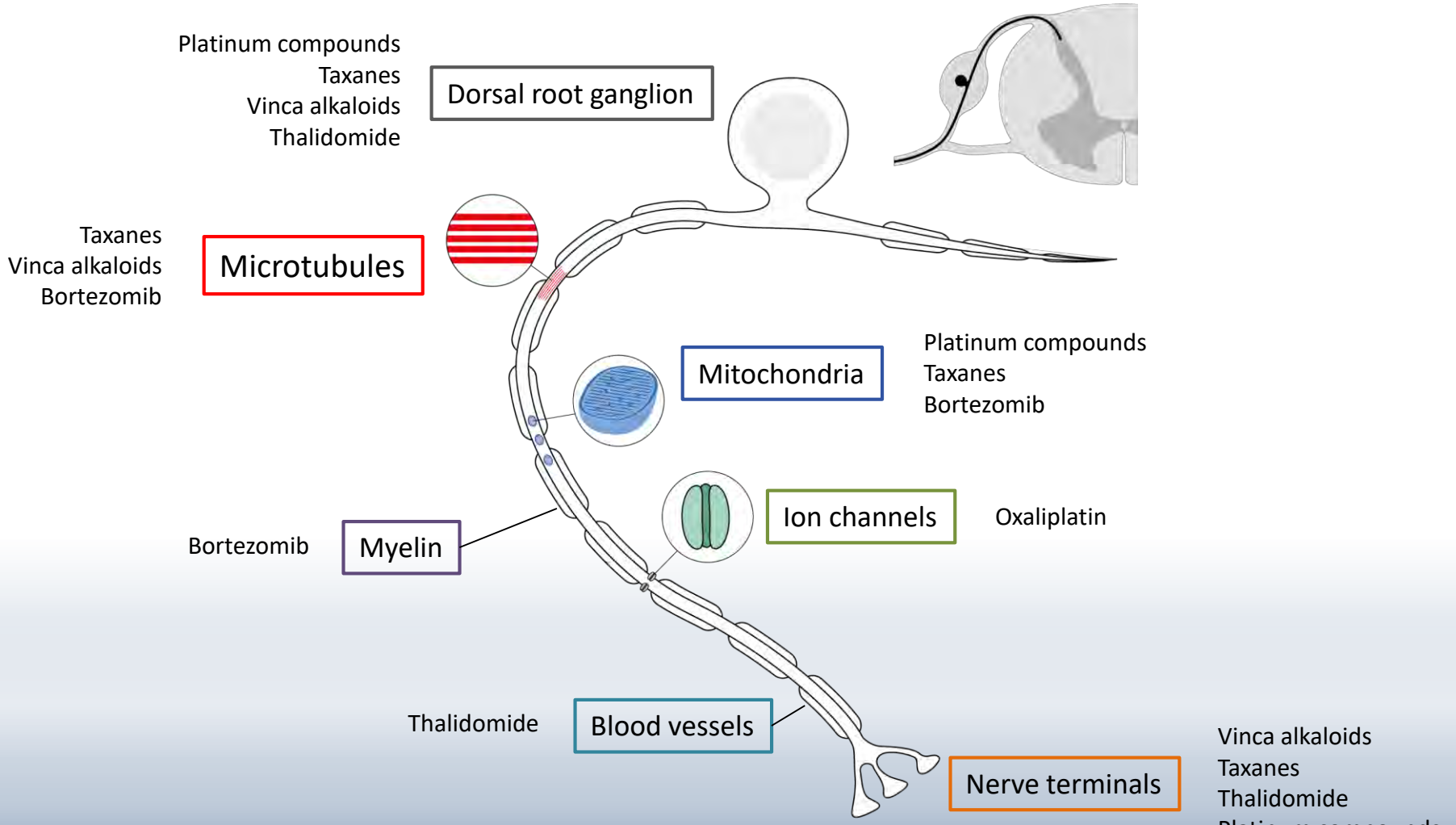
Paclitaxel



- Similar type of chronic CIPN symptoms are experienced, i.e numbness, tingling in hands and feet(2)
- Coasting pronounced with oxaliplatin, not with paclitaxel(2)
- Acute symptoms with paclitaxel include aching pain, for oxaliplatin cold sensitivity(2)

(1) Seretny et.al (2014) Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis
(2) Pachman et.al (2017) Comparison of oxaliplatin and paclitaxel-induced neuropathy

Mitochondrial dysfunction a contributing factor to CIPN by taxanes give reasons to believe in PledOx®

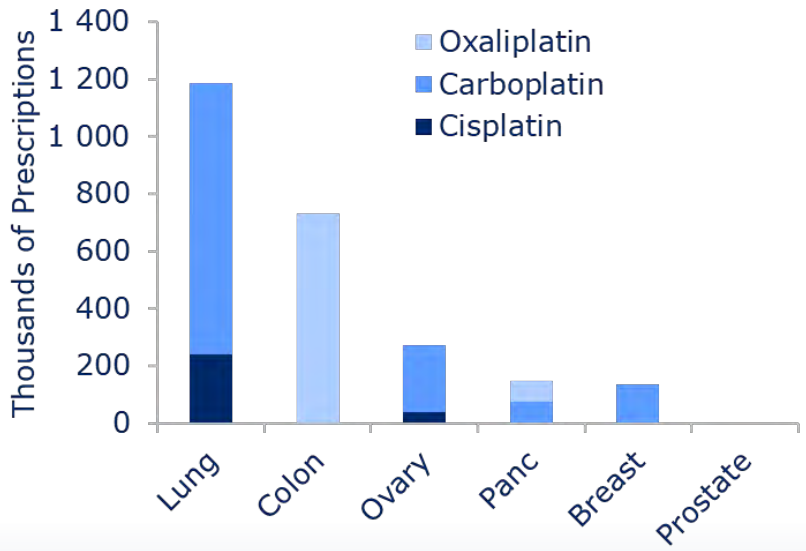


Kerckhove et.al (2017) Long-Term Effects, Pathophysiological Mechanisms, and Risk Factors of Chemotherapy-Induced Peripheral Neuropathies: A Comprehensive Literature Review
Park et al (2008) Mechanisms underlying chemotherapy-induced neurotoxicity and the potential for neuroprotective startegies

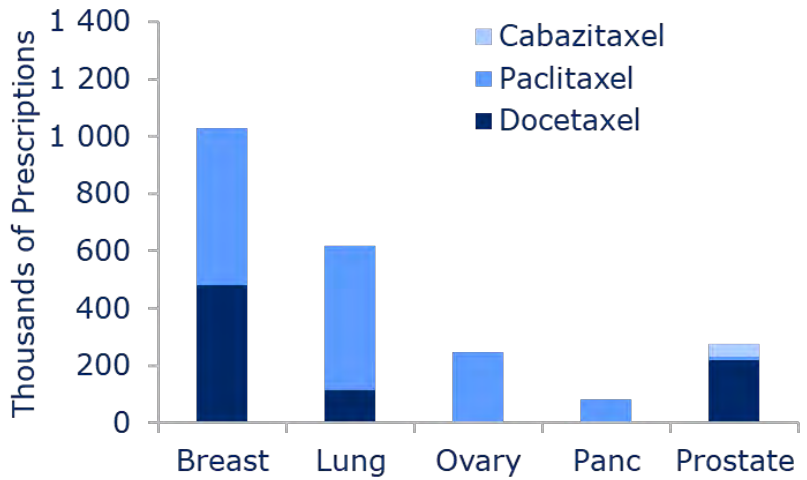
Attractive commercial opportunity in CIPN/taxanes

Market size

Use of platinum-based chemotherapy by tumor type



Use of taxane-based chemotherapy by tumor type



Competitive landscape

No competitor clinical trials registred on clinicaltrials.gov

IMS Health (2015); US data

Next steps in development path for CIPN/taxanes

Pre-clinical studies (2019)

In collaboration with Prof Cavaletti, Univ Milano-Biocca

1) Preliminary dose-ranging study with PledOx®

2) Efficacy of PledOx® will be evaluated vs placebo on top of paclitaxel (taxane) alone or in combination with carboplatin

Regulatory interactions (2019-2020)

Clarify development path, including

a) Requirements for clinical efficacy & safety data for sNDA/MAA – how to leverage POLAR study data?
b) Design of clinical study incl endpoints, sample size etc
c) Dose selection in CIPN/taxanes

PledOx drives value by…

Development in CIPN/oxaliplatin

Expansion to CIPN/taxanes

Commercialization by strategic partnerships

PledPharma

Capital Markets Day
26th March, 2019

Agenda

PledPharma

1. Introduction, Company overview and drug candidates in development

2. PledOx® in Chemotherapy Induced Peripheral Neuropathy (CIPN)
    a. Unmet medical need
    b. Development of PledOx® in CIPN with oxaliplatin
    c. Commercial opportunity in CIPN with oxaliplatin
    d. Indication expansion – CIPN with taxanes

3. Aladote® in Paracetamol Overdose (POD)
    a. Unmet medical need
    b. Aladote® proof of principle study results
    c. Development of Aladote to prevent acute liver injury caused by POD
    d. Commercial opportunity in POD

4. Corporate Strategy
    a. Direction and opportunities to enhance value
    b. Business development
    c. Finance and up listing

5. Summary & Closing remarks

PledPharma

VIDEO

https://vimeo.com/325159064

Phase II

PledPharma

3. Aladote in Paracetamol Overdose (POD)

a. Unmet medical need

b. Aladote® proof of principle study results

c. Development of Aladote to prevent acute liver injury caused by POD

d. Commercial opportunity in POD

Phase II

Paracetamol overdose:
- epidemiology and management
- results from Aladote POP study

Dr James Dear
University of Edinburgh


Paracetamol is the world's most used drug

Hospital Episode Statistics 2017/18

Reason for admission	Emergency admissions (England)
Paracetamol overdose	**41,898**
Fracture of neck of femur	47,334
Pulmonary embolism	29,541
Appendicitis	44,149
Acute pancreatitis	42,672

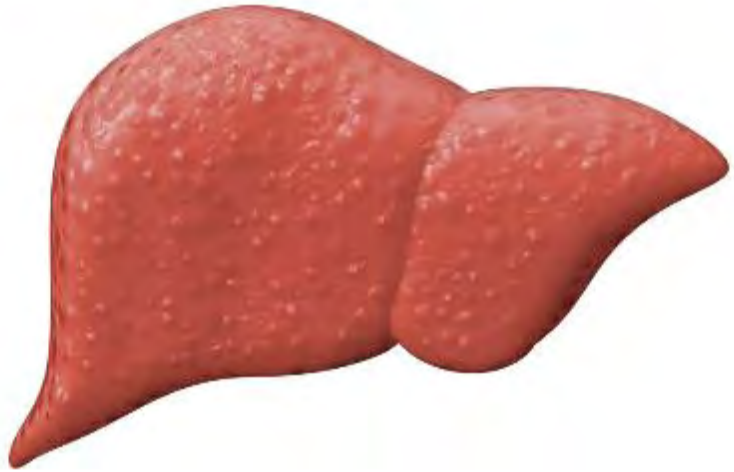
Epidemiology in UK every year:

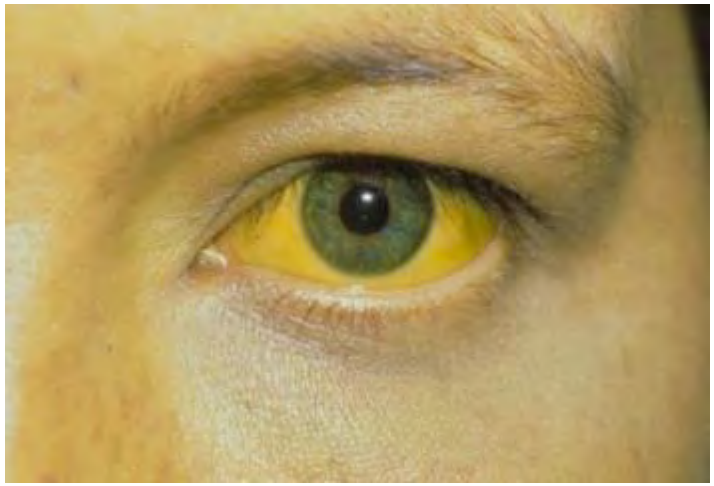
- 100,000 hospital attendances per year
- 50,000 emergency admission for treatment
- At least 12,500 lack an effective treatment (25%)
- 112,000 hospital bed days occupied
- 350 people registered for liver transplant
- 225 deaths

POD Healthcare costs in US:

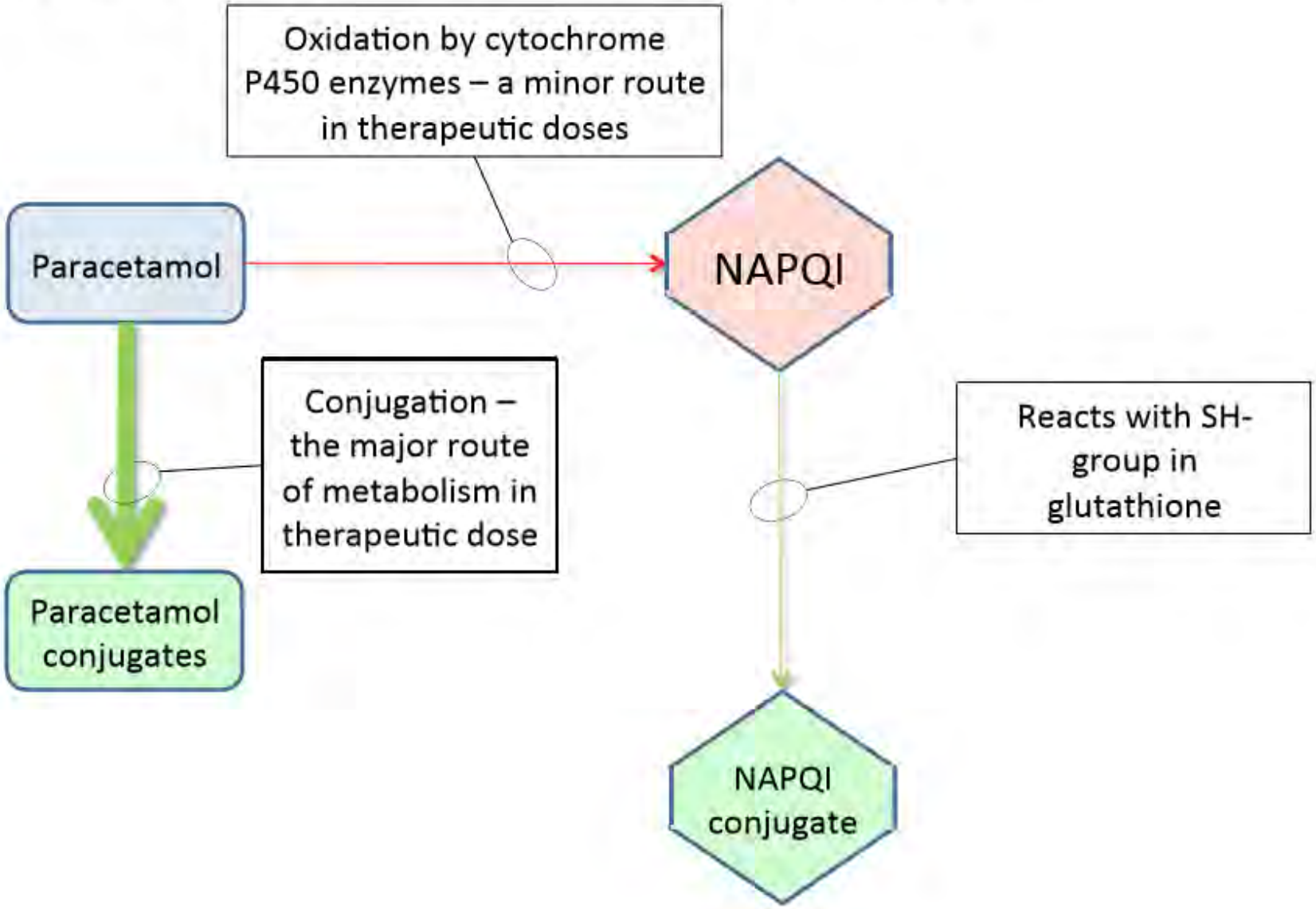
- Healthcare costs were $1bn in 2010
- Average inpatient length of stay was 3.1 Days
- Liver Transplant Costs between $125k - $473k

Problem is liver damage

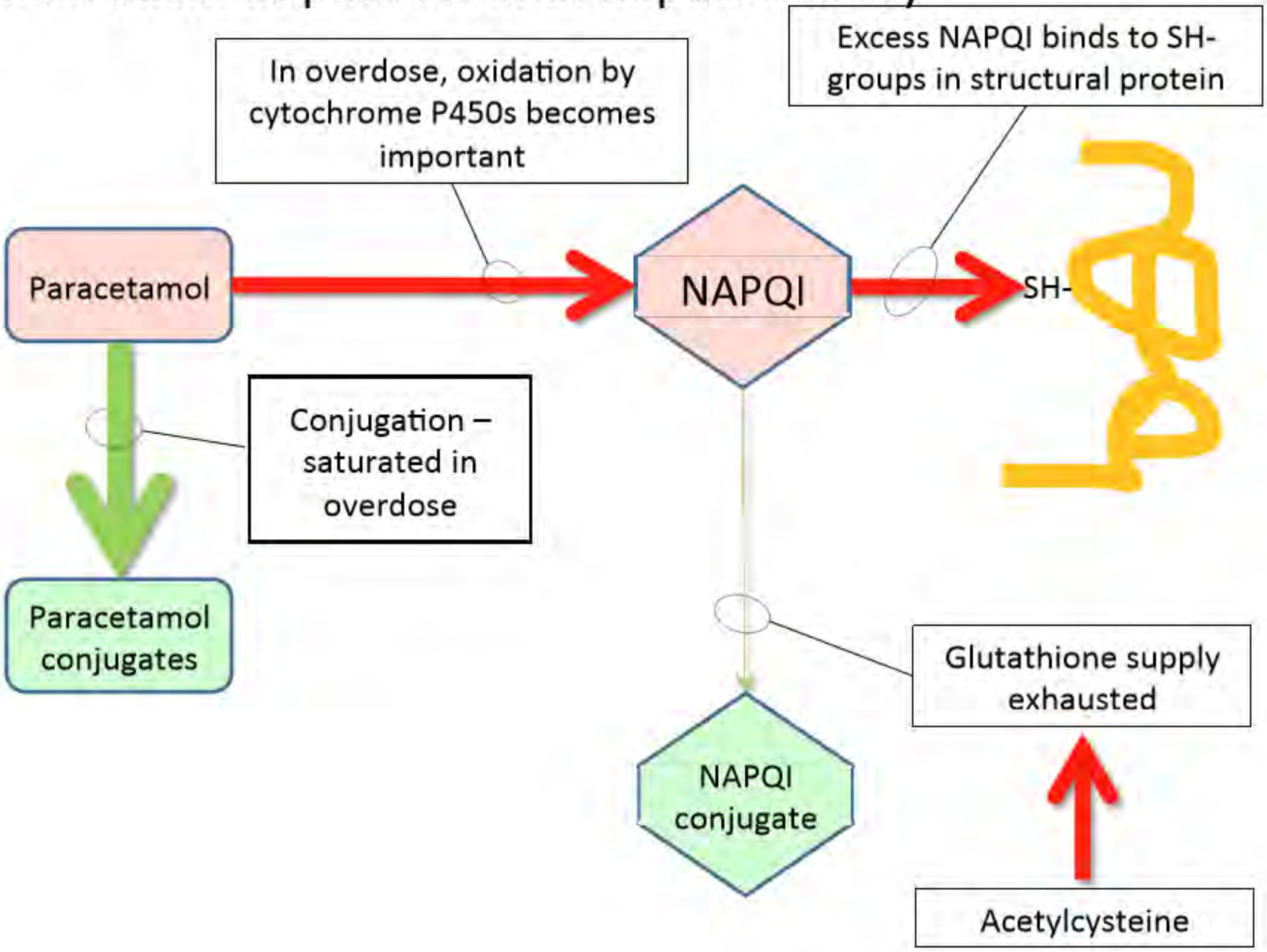




Mechanism of paracetamol hepatotoxicity



Mechanism of paracetamol hepatotoxicity

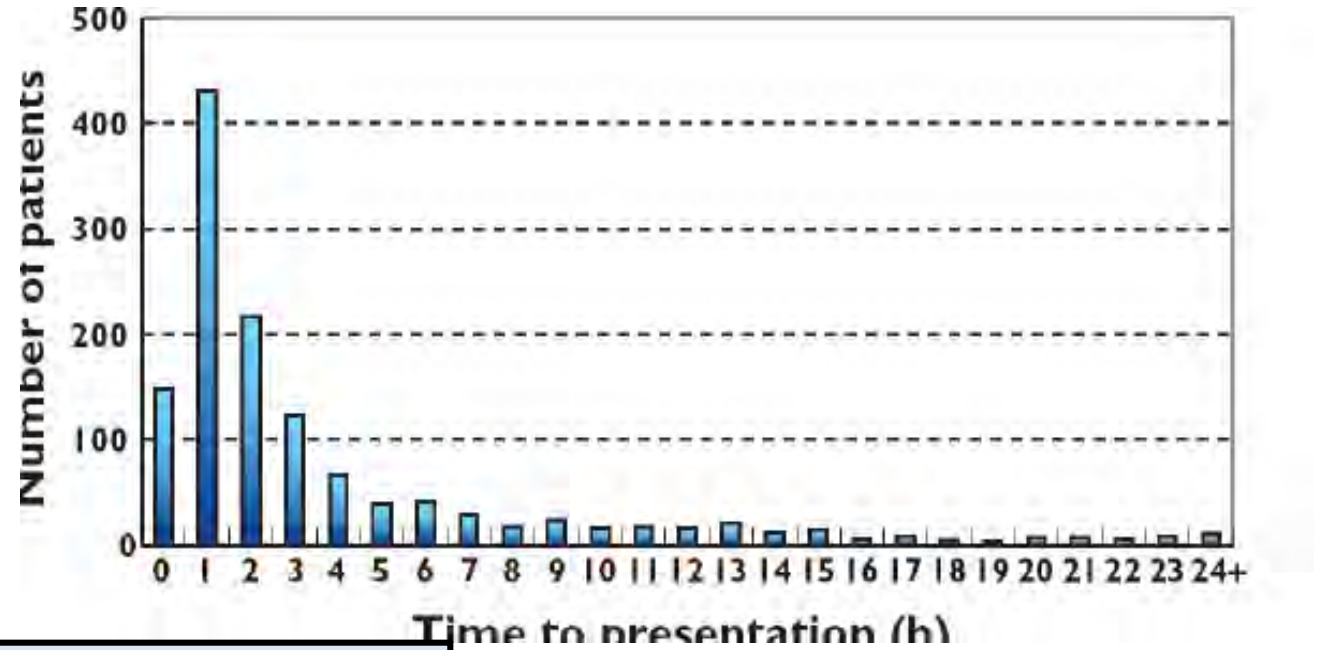


PARACETAMOL QUESTION 1:

Who gets treatment after overdose?

Hugo Dear

Risk assessment

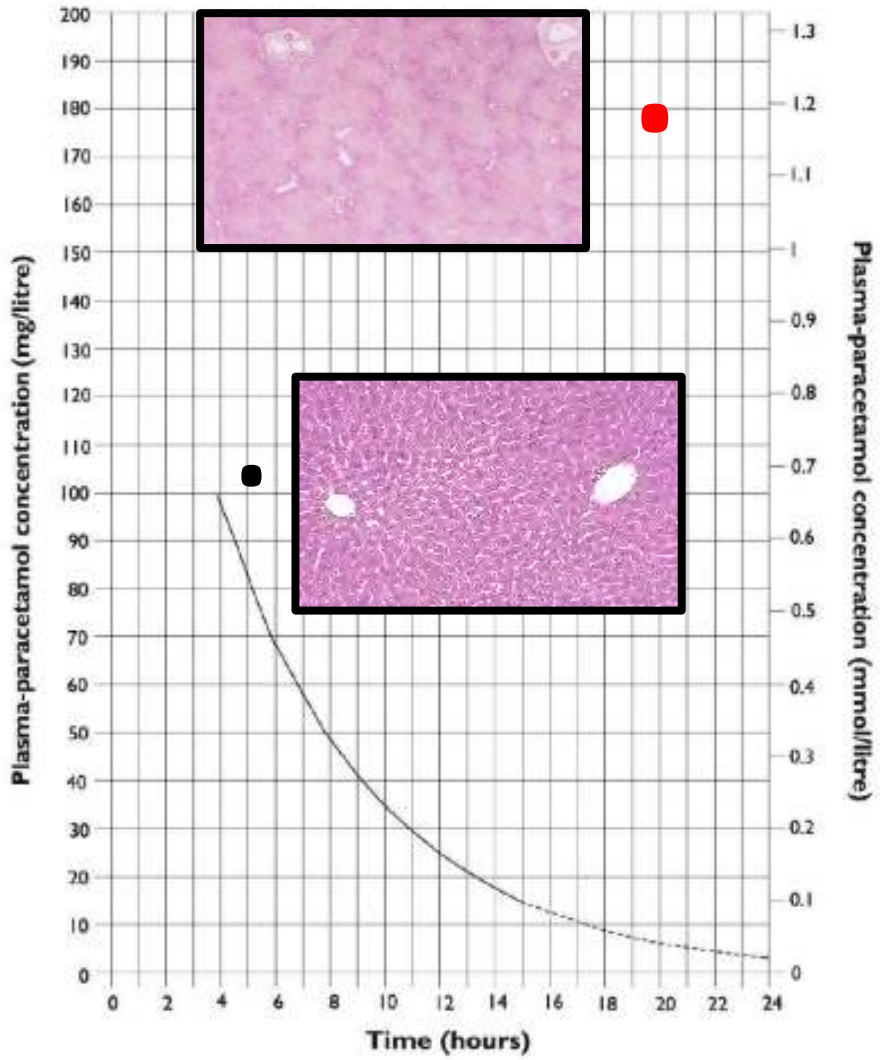


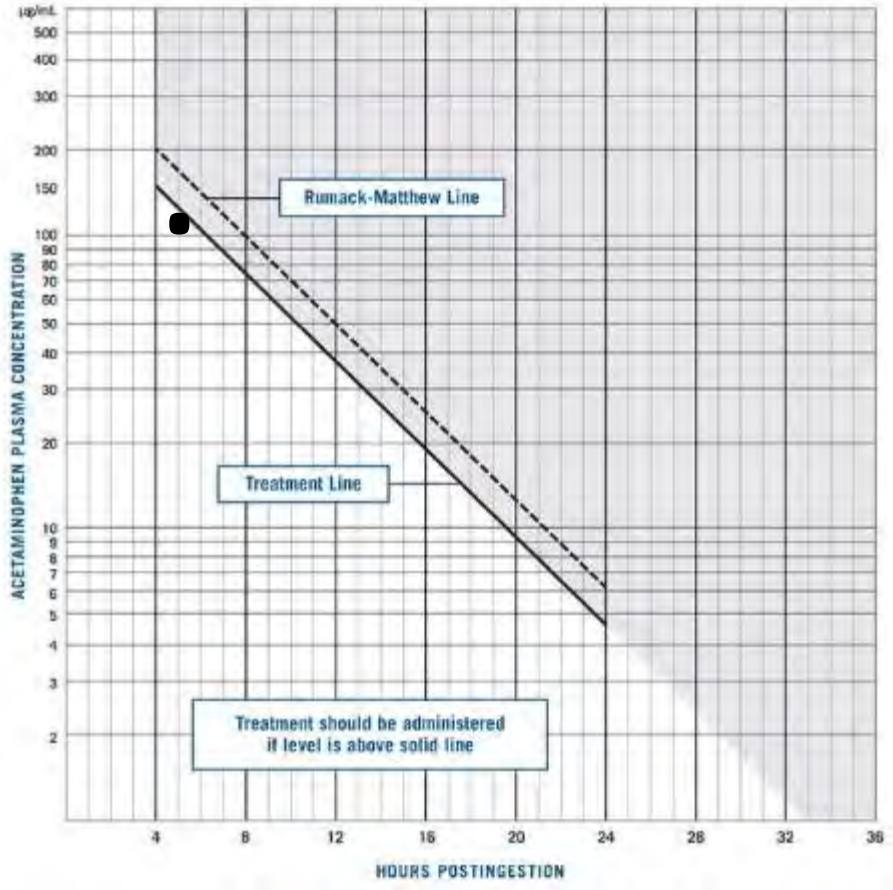
***BJCP* 2009 68 260 - 268**

- Majority of patients present soon after OD before liver injury can be diagnosed using current tests such as ALT
- Therefore, use surrogate marker
- **Blood paracetamol concentration**

Risk assessment – paracetamol concentration

UK





Early, diagnostic markers …
Paracetamol OD …

Now …

Presenting complaint

Risk stratify

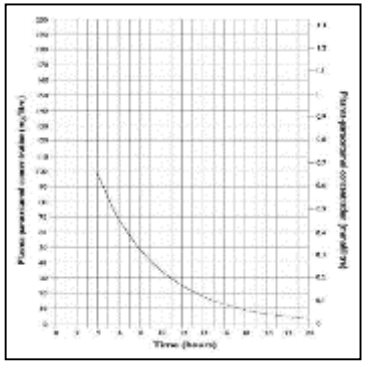
Detect cell death

time

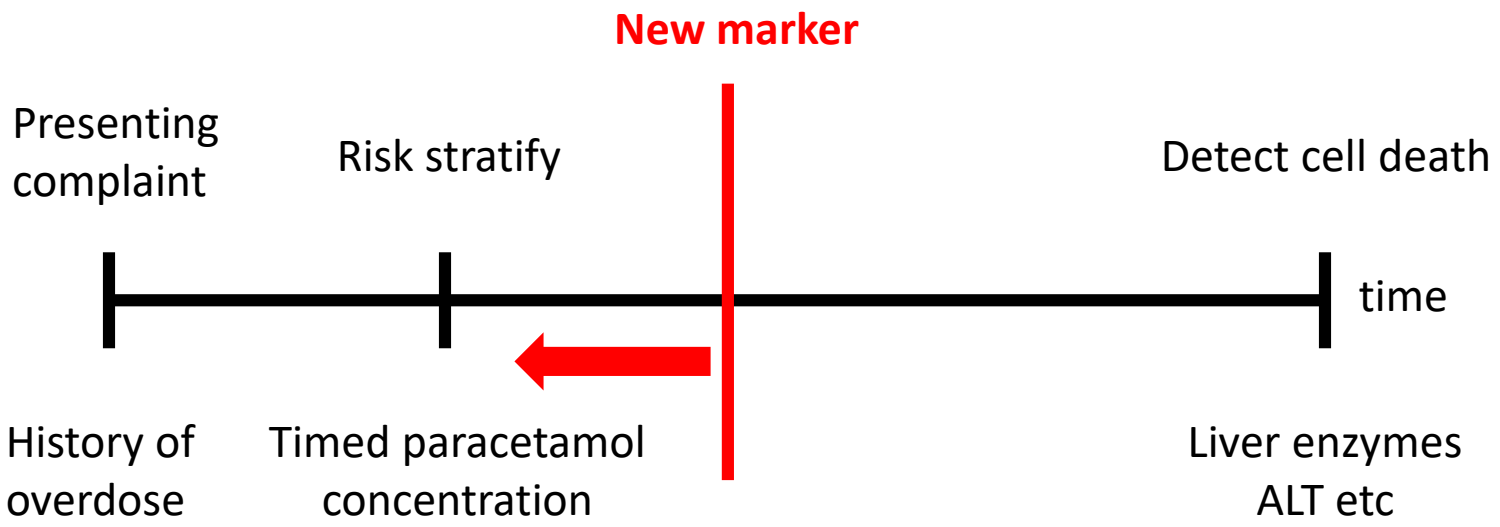
History of overdose

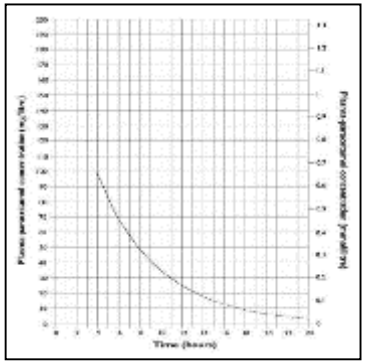
Timed paracetamol concentration

Liver enzymes ALT etc



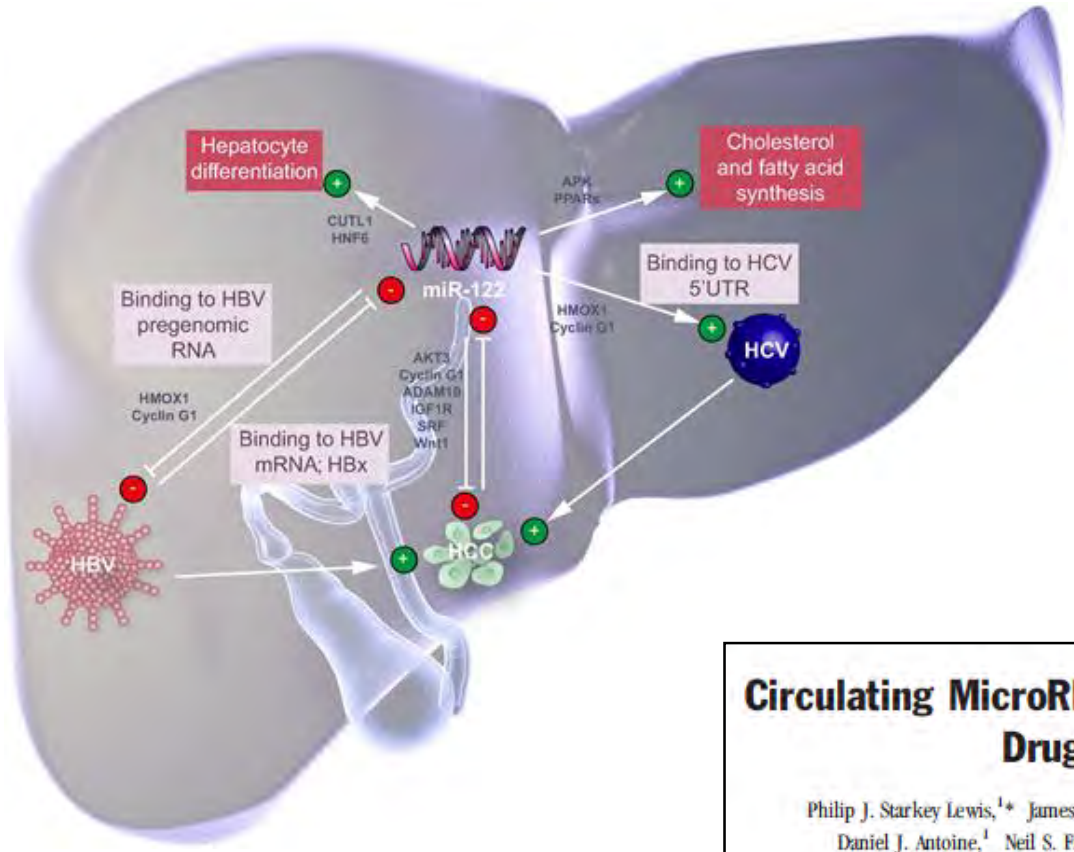
Early, diagnostic markers …
Paracetamol OD …





Biomarker

microRNA-122 (miR-122)

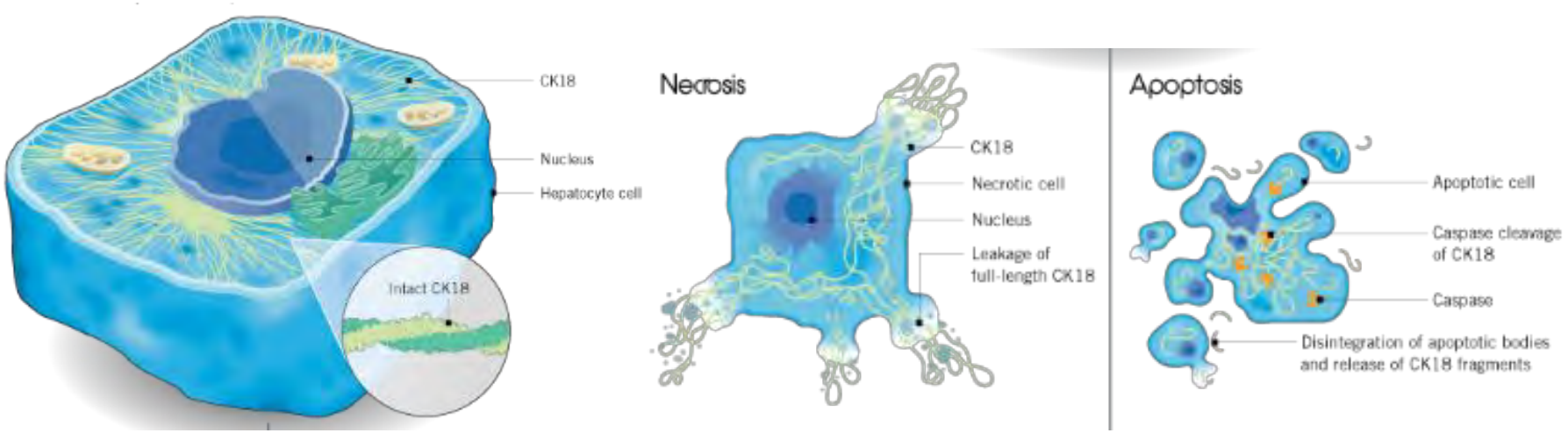


Circulating MicroRNAs as Potential Markers of Human Drug-Induced Liver Injury

Philip J. Starkey Lewis,[1*] James Dear,[2*] Vivien Platt,[1] Kenneth J. Simpson,[3] Darren G.N. Craig,[3] Daniel J. Antoine,[1] Neil S. French,[1] Neeraj Dhaun,[4] David J. Webb,[4] Eithne M. Costello,[5] John P. Neoptolemos,[5] Jonathan Moggs,[6†] Chris E. Goldring,[1†] and B. Kevin Park[1†]

***Hepatology* 2011: no of citations 364**

Mechanism of Cell Death - Biomarkers



Molecular forms of HMGB1 and keratin-18 as mechanistic biomarkers for mode of cell death and prognosis during clinical acetaminophen hepatotoxicity

Daniel J. Antoine[1,*], Rosalind E. Jenkins[1], James W. Dear[2], Dominic P. Williams[1], Mitchell R. McGill[3], Matthew R. Sharpe[4], Darren G. Craig[5], Kenneth J. Simpson[5], Hartmut Jaeschke[3], B. Kevin Park[1]

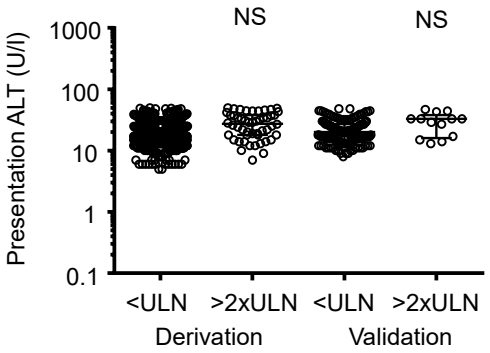
***J Hepatol* 2012: no of citations 223**

Risk stratification after paracetamol overdose using mechanistic biomarkers: results from two prospective cohort studies

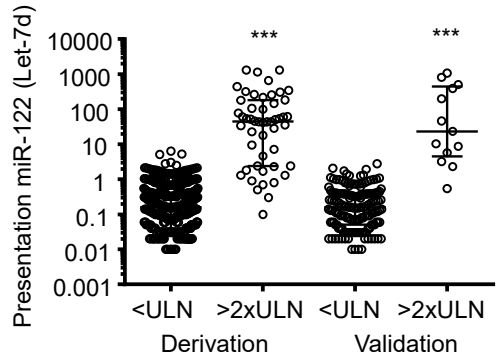
NORMAL ALT ON PRESENTATION

MAPP N=875

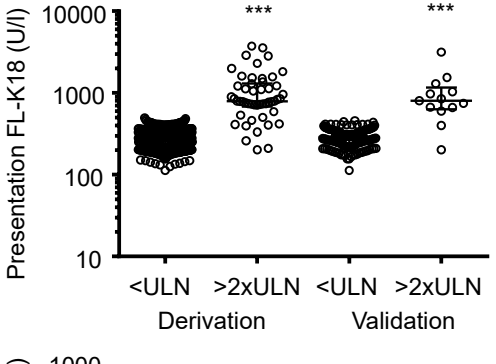
BIOPAR N=176



ALT



miR-122



Necrosis K18

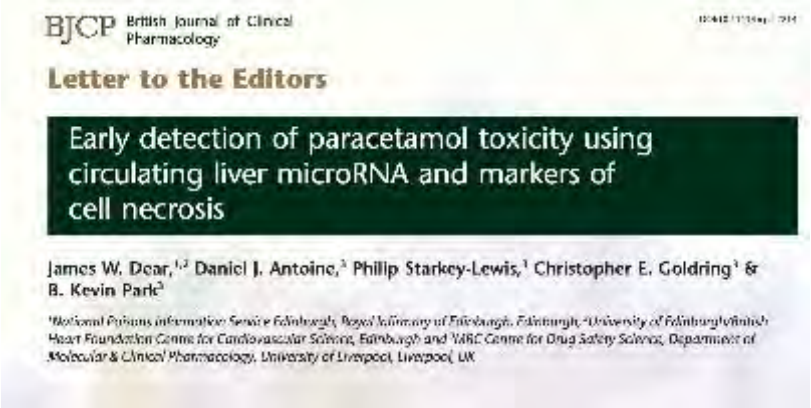
GDLH

miR-122 and K18 are higher in patients who develop ALI

Study	ROC-AUC (95%CI)	P value	Sens at 95% Spec (95%CI)
miR-122			
MAPP	**0.96 (0.93-0.99)**	<0.0001	0.84 (0.71-0.92)
BIOPAR	**0.97 (0.94-1.00)**	<0.0001	0.92 (0.63-0.99)
K18			
MAPP	**0.94 (0.89-0.99)**	<0.0001	0.88 (0.76-0.95)
BIOPAR	**0.93 (0.81-1.00)**	<0.0001	0.85 (0.55-0.98)

***Lancet Gastroenterol Hepatol* 2018**

CASE REPORT:
25 year old male
Single overdose of 35g paracetamol at 02:30
(timing supported by Facebook message)
Assessed 4.5h after OD
No risk factors for hepatotoxicity. Paracetamol level 107 mg/L (below nomogram)
Normal biochemical evidence of liver injury
Assessed by senior doctor and not treated
Discharged after psychiatry review



BJCP British Journal of Clinical Pharmacology

Letter to the Editors

Early detection of paracetamol toxicity using circulating liver microRNA and markers of cell necrosis

James W. Dear,[1,2] Daniel J. Antoine,[3] Philip Starkey-Lewis,[1] Christopher E. Goldring[1] & B. Kevin Park[3]

[1]National Poisons Information Service Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, [2]University of Edinburgh/British Heart Foundation Centre for Cardiovascular Science, Edinburgh and [3]MRC Centre for Drug Safety Science, Department of Molecular & Clinical Pharmacology, University of Liverpool, Liverpool, UK

Time from OD (h)	4.5	
Paracetamol (mg/L)	107	
ALT (U/L) (ULN 50)	34	
INR	1.0	

***BJCP* 2014;77:904-5**

CASE REPORT:
25 year old male
Single overdose of 35g paracetamol at 02:30
(timing supported by Facebook message)
Assessed 4.5h after OD
No risk factors for hepatotoxicity. Paracetamol level 107 mg/L (below nomogram)
Normal biochemical evidence of liver injury
Assessed by senior doctor and not treated
Discharged after psychiatry review

Represented to hospital 43h after OD
Lethargic and vomiting
Tender abdomen


BJCP British Journal of Clinical Pharmacology

Letter to the Editors

Early detection of paracetamol toxicity using circulating liver microRNA and markers of cell necrosis

James W. Dear,[1,2] Daniel J. Antoine,[3] Philip Starkey-Lewis,[3] Christopher E. Goldring[3] & B. Kevin Park[3]

[1]National Poisons Information Service Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, [2]University of Edinburgh/British Heart Foundation Centre for Cardiovascular Science, Edinburgh and [3]MRC Centre for Drug Safety Science, Department of Molecular & Clinical Pharmacology, University of Liverpool, Liverpool, UK

Time from OD (h)	4.5	43
Paracetamol (mg/L)	107	9
ALT (U/L) (ULN 50)	34	11314
INR	1.0	2.1

***BJCP* 2014;77:904-5**

CASE REPORT:
25 year old male
Single overdose of 35g paracetamol at 02:30
(timing supported by Facebook message)
Assessed 4.5h after OD
No risk factors for hepatotoxicity. Paracetamol level 107 mg/L (below nomogram)
Normal biochemical evidence of liver injury
Assessed by senior doctor and not treated
Discharged after psychiatry review

Represented to hospital 43h after OD
Lethargic and vomiting
Tender abdomen

miR-122 and K18 CORRECTLY IDENTIFIED LIFE THREATENING HEPATOTOXICITY MISSED BY CURRENT TESTS

Time from OD (h)	4.5	43
Paracetamol (mg/L)	107	9
ALT (U/L) (ULN 50)	34	11314
INR	1.0	2.1
miR-122 (/ let-7d) (ULN 5.2*)	**261 (x50)**	
K18 (U/L) (ULN 480*)	**4018 (x8)**	

*95% prediction interval – no liver injury after overdose n=82 *Hepatology* 2013

Qualification as tool in drug development

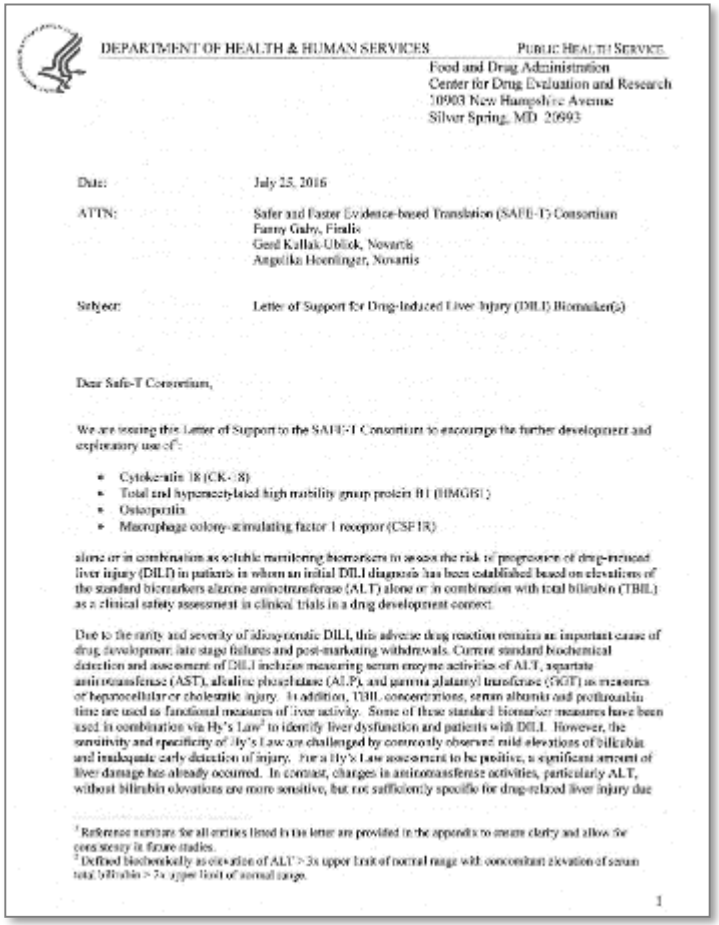
Regulatory endorsement for miR-122 and K18 as a DILI biomarker

SAFE-T

DILIN
Drug-Induced Liver Injury Network

TransBioLine Consortium

imi innovative medicines initiative



DEPARTMENT OF HEALTH & HUMAN SERVICES — PUBLIC HEALTH SERVICE

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: July 25, 2016

ATTN: Safer and Faster Evidence-based Translation (SAFE-T) Consortium
Fanny Gaby, Finalis
Gerd Kullak-Ublick, Novartis
Angelika Hoenlinger, Novartis

Subject: Letter of Support for Drug-Induced Liver Injury (DILI) Biomarker(s)

Dear Safe-T Consortium,

We are issuing this Letter of Support to the SAFE-T Consortium to encourage the further development and exploratory use of[1]:

- Cytokeratin 18 (CK-18)
- Total and hyperacetylated high mobility group protein B1 (HMGB1)
- Osteopontin
- Macrophage colony-stimulating factor 1 receptor (CSF1R)

alone or in combination as soluble monitoring biomarkers to assess the risk of progression of drug-induced liver injury (DILI) in patients in whom an initial DILI diagnosis has been established based on elevations of the standard biomarkers alanine aminotransferase (ALT) alone or in combination with total bilirubin (TBIL) as a clinical safety assessment in clinical trials in a drug development context.

Due to the rarity and severity of idiosyncratic DILI, this adverse drug reaction remains an important cause of drug development late stage failures and post-marketing withdrawals. Current standard biochemical detection and assessment of DILI includes measuring serum enzyme activities of ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT) as measures of hepatocellular or cholestatic injury. In addition, TBIL concentrations, serum albumin and prothrombin time are used as functional measures of liver activity. Some of these standard biomarker measures have been used in combination via Hy's Law[2] to identify liver dysfunction and patients with DILI. However, the sensitivity and specificity of Hy's Law are challenged by commonly observed mild elevations of bilirubin and inadequate early detection of injury. For a Hy's Law assessment to be positive, a significant amount of liver damage has already occurred. In contrast, changes in aminotransferase activities, particularly ALT, without bilirubin elevations are more sensitive, but not sufficiently specific for drug-related liver injury due

[1] Reference numbers for all entities listed in the letter are provided in the appendix to ensure clarity and allow for consistency in future studies.
[2] Defined biochemically as elevation of ALT > 3x upper limit of normal range with concomitant elevation of serum total bilirubin > 2x upper limit of normal range.

1

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Letter of support for drug-induced liver injury (DILI) biomarker

Summary

The Drug-Induced Liver Injury (DILI) work package 3 (WP3) of the SAFE-T consortium specifically aimed to address the current lack of sensitive and specific clinical tests to diagnose, predict and monitor drug induced injury to the liver, which is a major hurdle in drug development.

The objectives of DILI WP3 were to qualify one or a set of new biomarkers with respect to:
- an early or earlier diagnosis of DILI as compared to current diagnostic rules
- the ability to predict DILI outcome, with particular emphasis on severe DILI/acute liver failure
- the prognosis and monitoring of progression and regression of DILI
- the differentiation between patients who incur true drug-induced liver injury from those who recover from the initial injury despite ongoing drug treatment (adaptors)

Originally, the overall strategy for biomarker selection was ambitious with regard to the initial selection, further exploration, and final confirmation within a variety of clinical trials.

However, given time constraints and the limited number of patients available by the end of 2014, the DILI WP decided to investigate 10 new biomarkers selected largely from the first stage gate analysis in one subsequent analysis using all available datasets and to no longer separate an exploratory from a confirmatory phase. True confirmatory data which could support a Qualification Opinion are therefore currently not available. All results submitted now are considered exploratory in nature.

Scientific discussion

During the development, the applicant have conducted or evaluated (1) protocols that recruited patients diagnosed with DILI and (2) protocols that recruited patients without a diagnosis of DILI but who were on treatment with potentially hepatotoxic drugs and were prospectively monitored for several months. For all studies, cases with suspected DILI were ascertained by clinical judgment of the investigators and subsequently, by the evaluation of an adjudication committee. All cases meeting the trial enrollment criteria were adjudicated, the great majority of those fulfilled the consensus criteria for

PARACETAMOL QUESTION 2:

How should patients be treated?

Pediatrics. 1978 Nov;62(5 Pt 2 Suppl):898-903.

Acetaminophen Overdose: Incidence, Diagnosis, and Management in 416 Patients

Barry H. Rumack, M.D., *and* Robert G. Peterson, M.D., Ph.D.

From the Departments of Pediatrics, Medicine, and Pharmacology, and the Division of Clinical Pharmacology, University of Colorado Medical Center, Denver, and the Rocky Mountain Poison Center, Denver General Hospital

Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning

L F PRESCOTT, R N ILLINGWORTH, J A J H CRITCHLEY, M J STEWART, R D ADAM, A T PROUDFOOT

British Medical Journal, 1979, **2**, 1097-1100

Pediatrics. 1978 Nov;62(5 Pt 2 Suppl):898-903.

Acetaminophen Overdose: Incidence, Diagnosis, and Management in 416 Patients

Barry H. Rumack, M.D., *and* Robert G. Peterson, M.D., Ph.D.

From the Departments of Pediatrics, Medicine, and Pharmacology, and the Division of Clinical Pharmacology, University of Colorado Medical Center, Denver, and the Rocky Mountain Poison Center, Denver General Hospital

Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning

L F PRESCOTT, R N ILLINGWORTH, J A J H CRITCHLEY, M J STEWART, R D ADAM, A T PROUDFOOT

British Medical Journal, 1979, **2**, 1097-1100

Clinical Toxicology (2009) **47**, 81–88

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650802665587

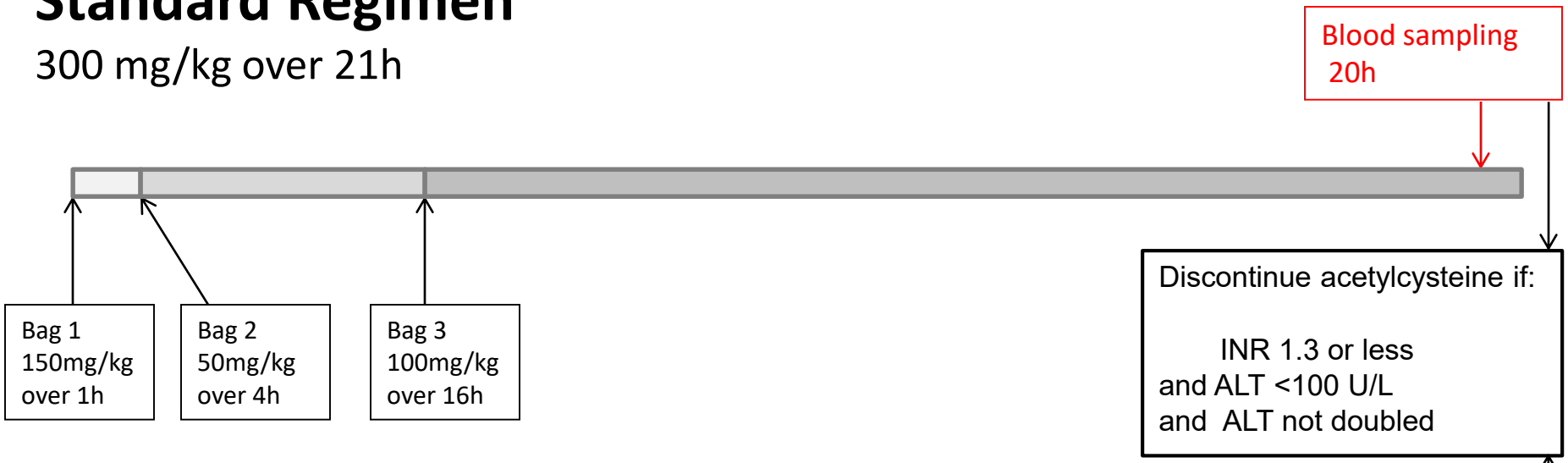
REVIEW ARTICLE

Adverse reactions associated with acetylcysteine

E.A. SANDILANDS and D.N. BATEMAN

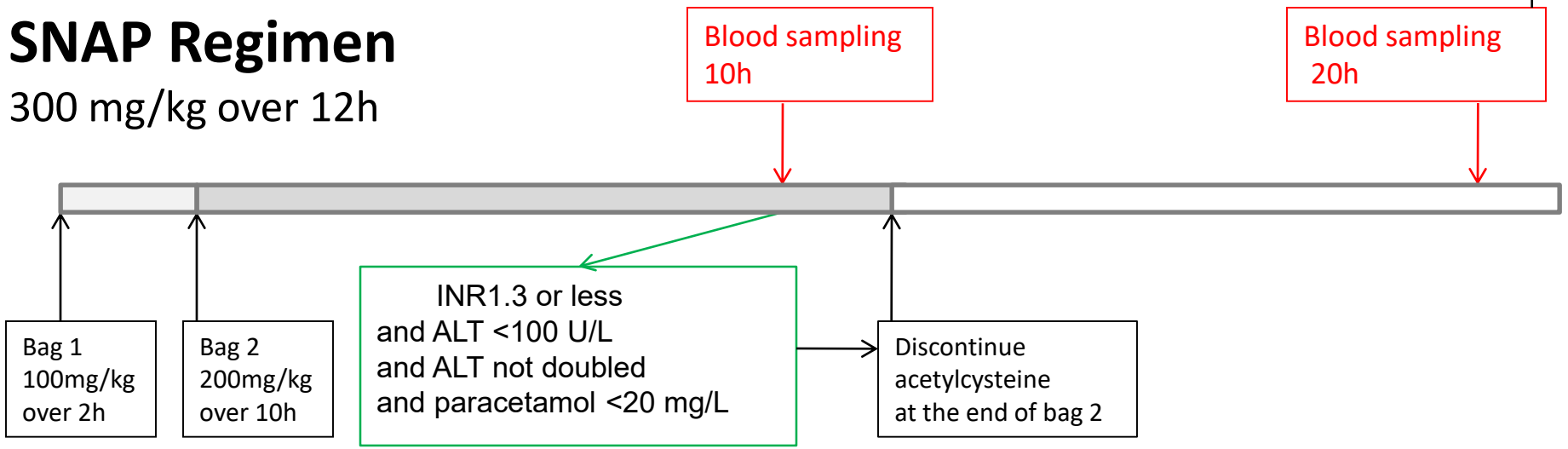
Standard Regimen

300 mg/kg over 21h



SNAP Regimen

300 mg/kg over 12h

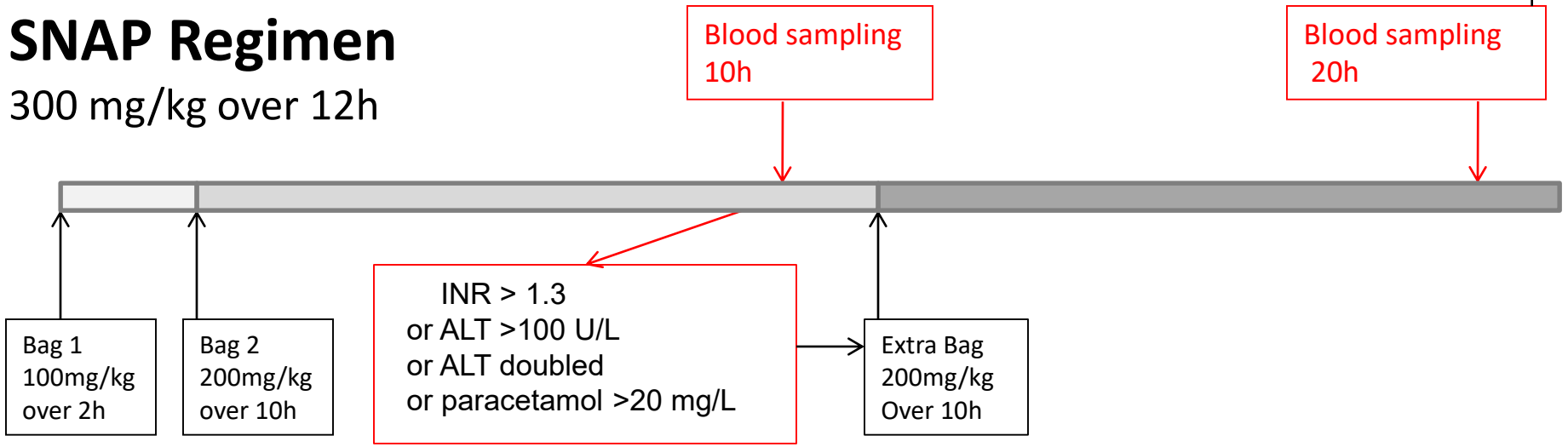


Standard Regimen

300 mg/kg over 21h

SNAP Regimen

300 mg/kg over 12h



Real clinical case

Mr AB

25 year old man
Suffers from depression
Took 70 paracetamol tablets
(35g – **500mg/kg** body weight) **around 20 hours ago**
Wants to die but happy to stay in hospital and receive treatment

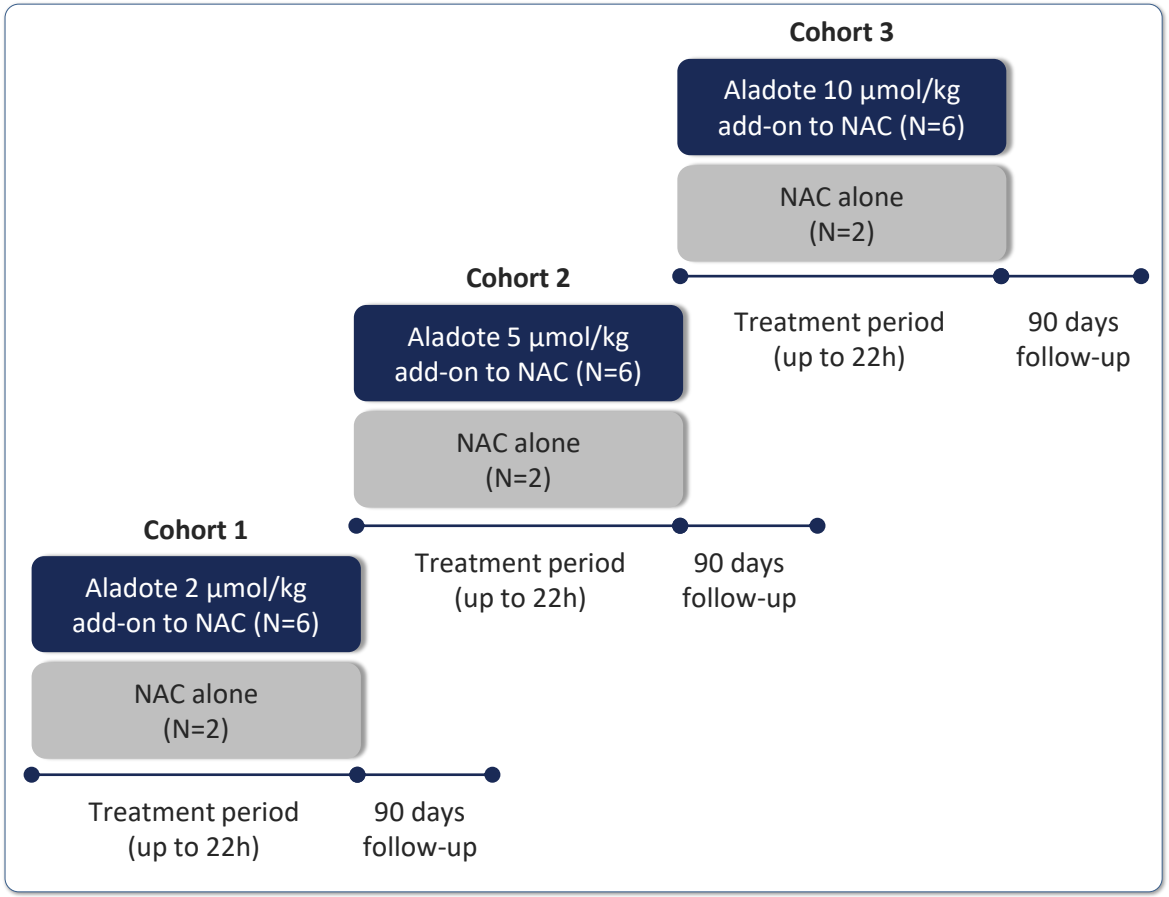
Agrees to take part in a clinical study (MAPP2 Study)

Blood results: ALT **3340** U/L (ULN 50 U/L)
INR 1.9
Started on acetylcysteine at dose
based on body weight even though **minimal effectiveness**

THERE IS NO TREATMENT FOR MR AB
EXCEPT LIVER TRANSPLANTATION

Results from first clinical study with Aladote

Design of Aladote clinical study



Design

- Single ascending dose study in 3 dosing cohorts of 8 patients (N=24) as add-on to NAC regime

Patients

- Admitted to hospital within 24h of paracetamol overdose requiering NAC treatment

Treatment

- Aladote/Placebo administered 2 hrs after NAC loading dose

Endpoints

- Safety and tolerability
- Biomarkers[1] of liver status

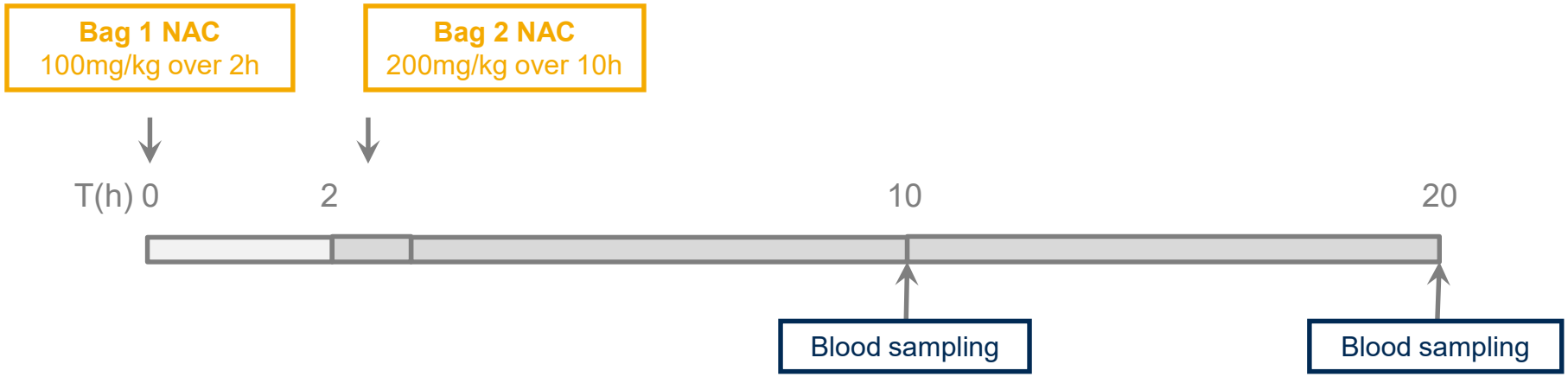
Explored safety and efficacy of NAC and Aladote (calmangafodipir)

Inclusion Criteria:

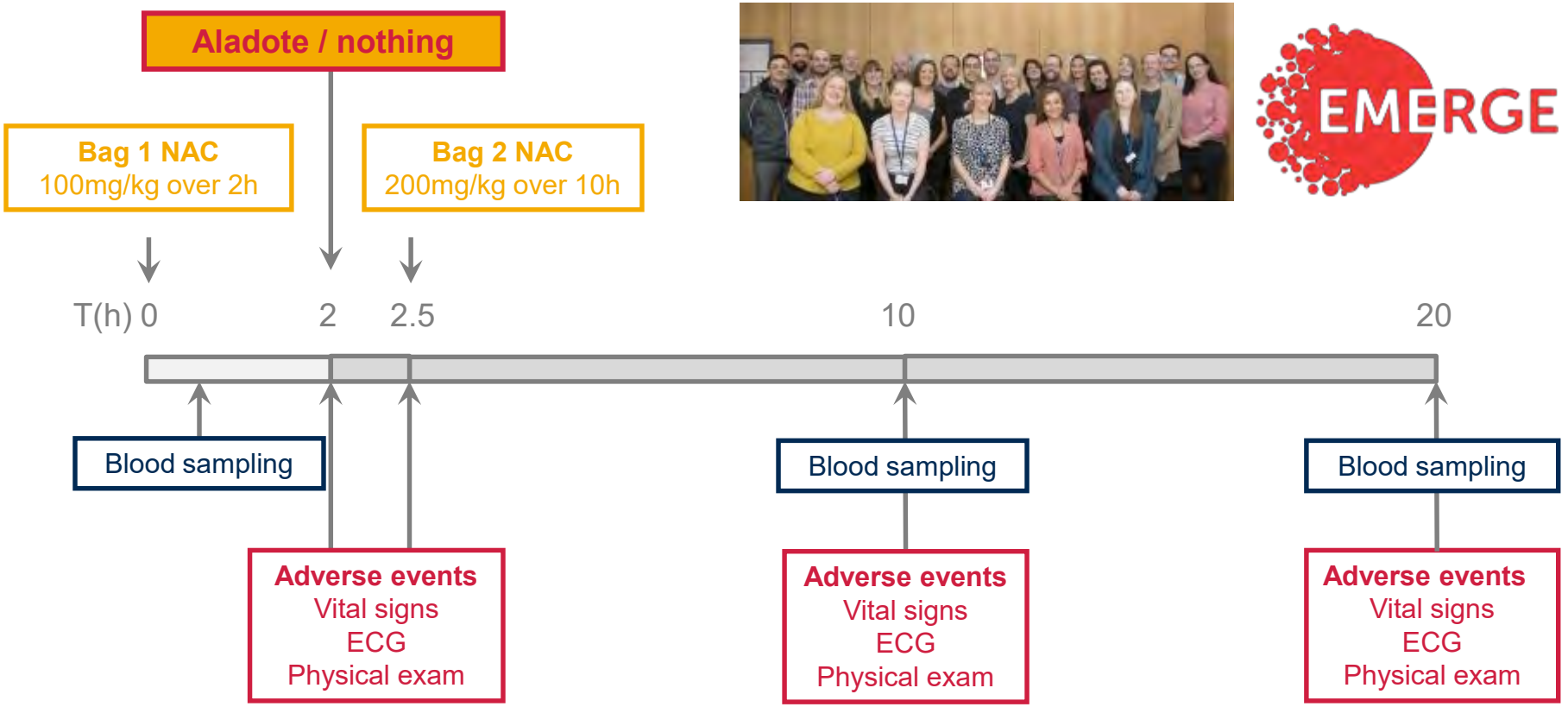
1. Any patient with capacity admitted to hospital within 24 hrs either a single acute POD or more than one dose of paracetamol (staggered) and deemed to require treatment with NAC.
2. Provision of written informed consent
3. Males and females of at least 16 years of age

Note: (**1**) Conventional biomarker ALT and experimental biomarkers such as microRNA-122 (miR-122) and Keratin-18 (K18)

Aladote (Calmangafodipir) for Overdose of Paracetamol (POP) (NCT03177395)



Aladote (Calmangafodipir) for Overdose of Paracetamol (POP) (NCT03177395)



EMERGE

POP

Primary outcome

Event	NAC alone	NAC + 2 µmol/kg Aladote	NAC + 5 µmol/kg Aladote	NAC + 10 µmol/kg Aladote
Any adverse event	6 (100%)	6 (100%)	6 (100%)	6 (100%)
Any serious adverse event	2 (33%)	4 (67%)	2 (33%)	3 (50%)
Serious adverse event starting within 7 days	1 (17%)	1 (17%)	1 (17%)	2 (33%)

No AE or SAE probably or definitely related to Aladote

Met the primary endpoint of safety and tolerability in the combination of Aladote® and NAC

Real clinical case

Mr AB

25 year old man
Suffers from depression
Took 70 paracetamol tablets
(35
Wa

Ag

Aladote represents a new treatment for patients like Mr AB

Blood results: ALT **3340** U/L (ULN 50 U/L)
INR 1.9

Started on acetylcysteine at dose
based on body weight even though **minimal effectiveness**

KEY POINTS

- **Paracetamol overdose is very common**
- **Current treatment is not effective in at least a quarter of patients (12,500/year in UK)**
- **We can deliver clinical trials in this clinical space galvanised by new biomarkers**
- **Aladote is safe and may reduce liver injury when added to standard of care**

PledPharma

3. Aladote® in Paracetamol Overdose (POD)

a. Unmet medical need

b. Aladote® proof of principle study results

c. Development of Aladote to prevent acute liver injury caused by POD

d. Commercial opportunity in POD

Phase II

Paracetamol (acetaminophen) poisoning … no adequate treatment for high risk patients

19bn units of paracetamol packages sold every year in the US.

Minimum toxic dose of paracetamol in adults – only 7.5g

~50 % of overdoses are unintentional

Could lead to acute liver failure, liver transplant or death

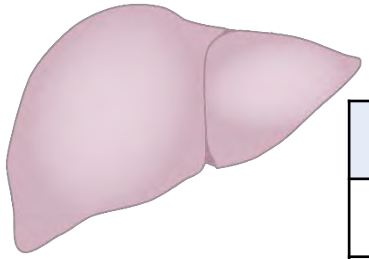
89,000 cases of paracetamol overdose in US per year

105,000 cases of paracetamol overdose in UK per year

No adequate treatment for high risk patients

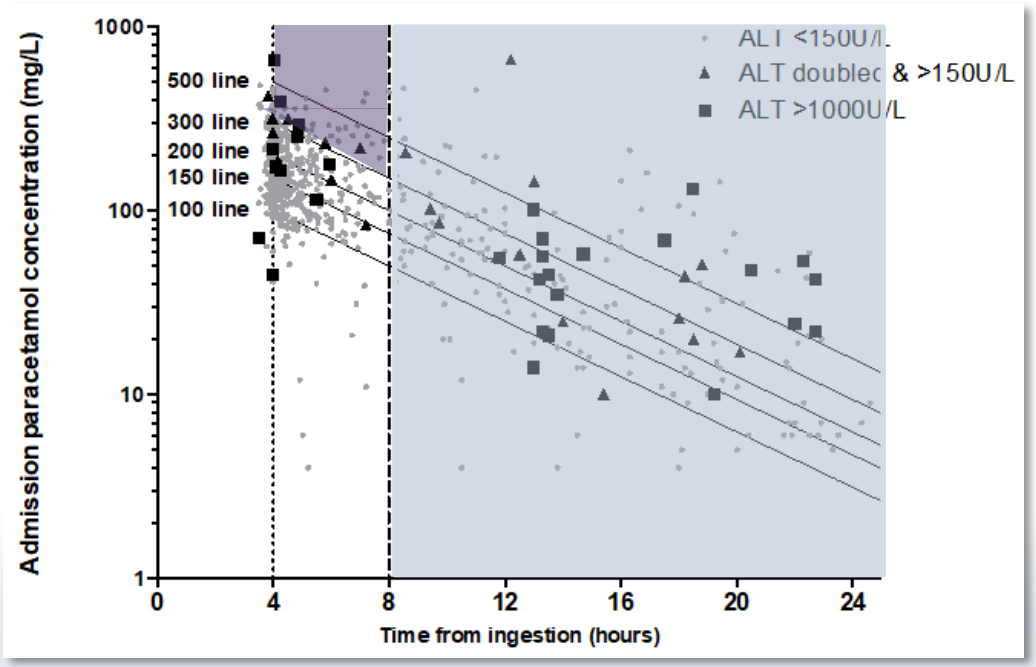
Aladote Target Product Profile in high-risk paracetamol overdose patients

Indication: To reduce hepatic injury in high-risk patients



Patients treated with Aladote (in combination with NAC) has …	
Efficacy	Safety & Tolerability
… lower risk of requiring additional bags of NAC (beyond planned NAC treatment) and associated prolonged hospital stay compared to placebo (in combination with NAC)	… similar adverse event profile as patients treated with placebo (in combination with NAC)
… lower risk of ALT>100 or doubling of ALT compared to placebo (in combination with NAC)	

Early presenters with high paracetamol levels and late presenters are both at high risk of liver damage



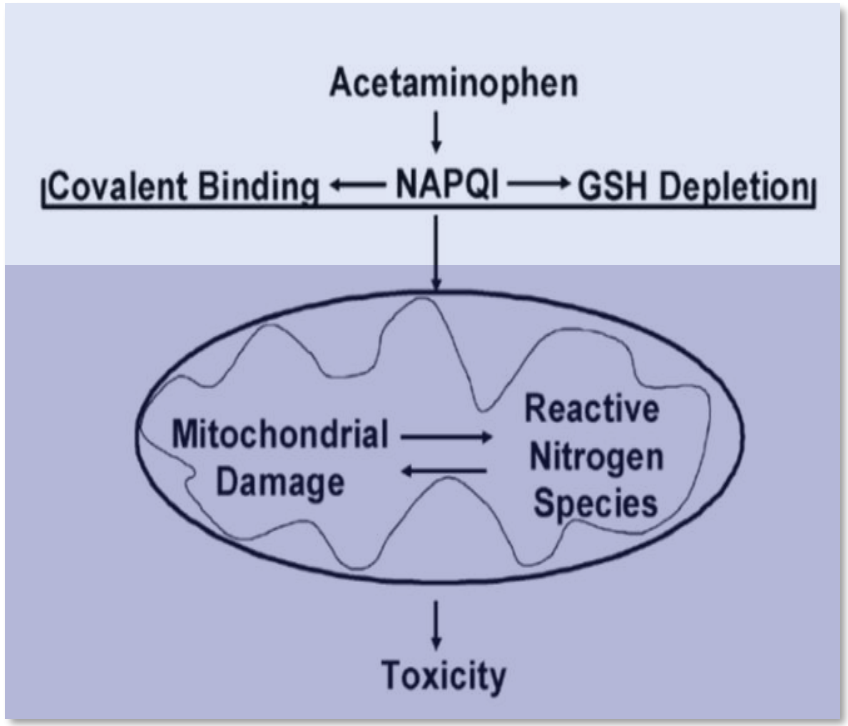
Paracetamol level (by nomogram line)	Number of patients	% of pts with ALT>150	% of pts with ALT>1000
0-100	70	7%	4%
101-150	195	7%	4%
151-200	149	9%	5%
201-300	186	12%	6%
301-500	82	18%	10%
>500	45	27%	18%

Early presenters with high risk

Late presenters with high risk

 Note: Cairney et.al (2016) Plasma paracetamol concentration at hospital presentation has a dose-dependent relationship with liver injury despite prompt treatment with intravenous acetylcysteine

Aladote® has potential for reducing APAP-induced acute liver injury in high risk patients

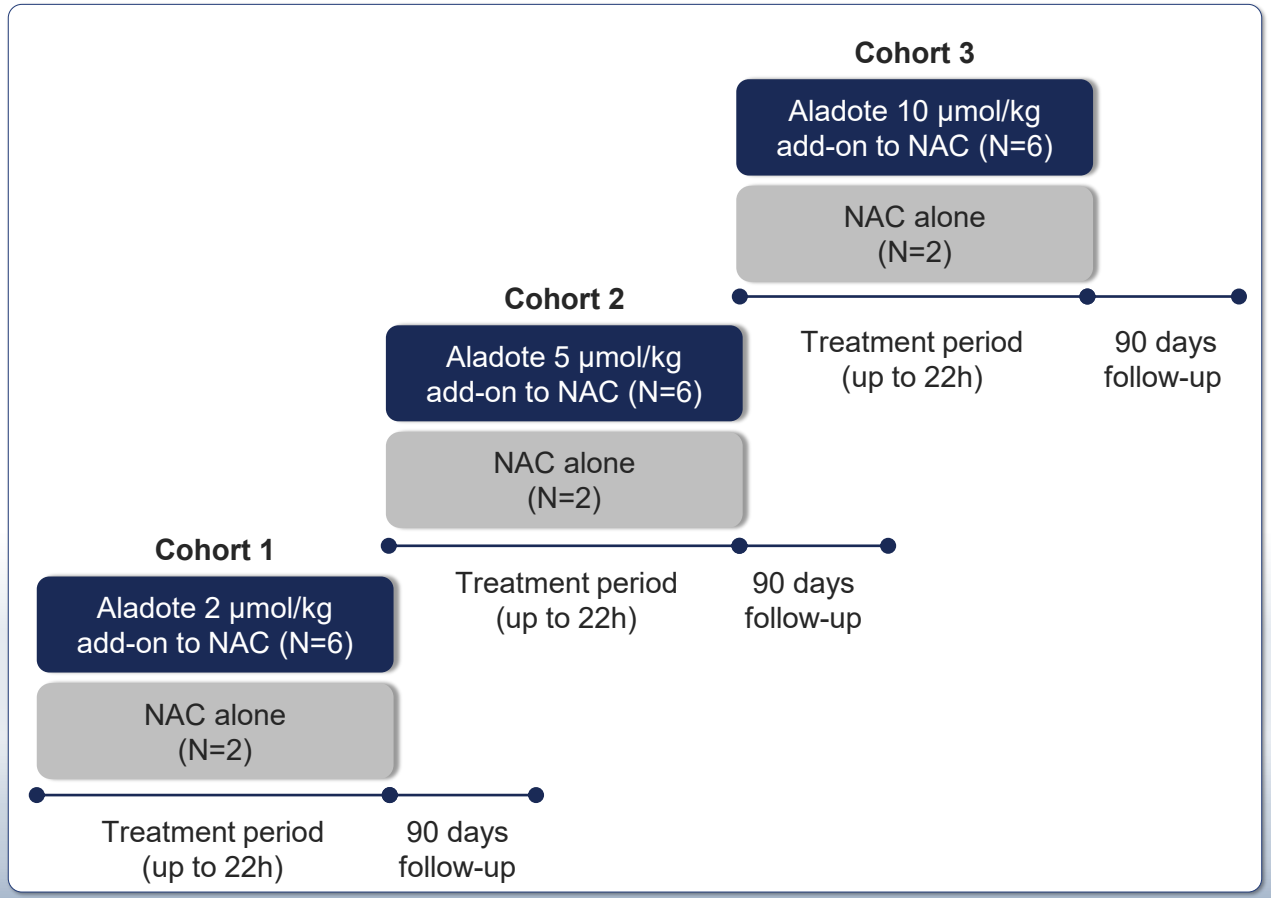


Source: Burke et al. 2010

- APAP overdose leads to formation of the toxic metabolite NAPQI
- In the metabolic phase, this leads to depletion of reduced glutathione (GSH) and binding of NAPQI to liver proteins
  - NAC is effective in this phase by replenishing GSH
  - However, the effectiveness depends on the amount of APAP overdose and timing of NAC
- In parallel, the oxidative phase occurs in the mitochondria, leading to subsequent cell death when GSH is significantly depleted
  - NAC is ineffective in this phase once GSH is significantly depleted
  - Aladote can inhibit oxidative pathways and thereby potentially preventing Acute Liver Injury

Design and results of Aladote® POP study

Randomised Open Label Exploratory, Safety and Tolerability Study with Calmangafodipir in Patients Treated with the 12-hour Regimen of N-Acetylcysteine (NAC) for Paracetamol Overdose



Phase Ib/IIa Study – Positive results

- In total 24 patients, were recruited to three Aladote® doses as add-on to NAC regime versus NAC alone
- Met the primary endpoint of safety and tolerability in the combination of Aladote® and NAC
- Results indicate that Aladote® may have the potential to reduce liver injury

 Note: (**1**) Conventional biomarker ALT and experimental biomarkers such as microRNA-122 (miR-122) and Keratin-18 (K18)

PiedPharma

P242

Principal Results of a Randomised Open Label Exploratory, Safety and Tolerability Study with Calmangafodipir in Patients Treated with a 12h Regimen of Acetylcysteine for Paracetamol Overdose (POP Trial)

Abstract no 1216

The POP Trial Investigators – Chief Investigator Dr James Dear - james.dear@ed.ac.uk

University of Edinburgh, Edinburgh Clinical Trials Unit , Emergency Medicine Research Group & NHS Lothian, Scotland & PledPharma AB, Stockholm, Sweden

P243

Key messages

Calmangafodipir:

- was safe and tolerated in patients treated with acetylcysteine (NAC) for acetaminophen overdose
- may reduce liver toxicity

Background

- Acetaminophen (paracetamol) overdose is a common cause of acute liver failure
- Calmangafodipir is a superoxide dismutase mimetic

Methods

Patients were recruited in the Emergency Department of the Royal Infirmary of Edinburgh from 8th June 2017 to 10th May 2018. The inclusion criterion was: adults within 24h of an acetaminophen overdose that required NAC. Within one of 3 sequential dosing cohorts, patients were randomly assigned, with concealed allocation, to NAC+calmangafodipir (n=6) or NAC alone (n=2). The doses of calmangafodipir were 2, 5 or 10μmol/kg, administered IV between NAC bags 1 & 2.The study was unblinded. The primary outcome was the safety and tolerability of calmangafodipir combined with NAC. Pre-defined secondary outcomes included alanine transaminase (ALT), keratin-18 (K18), caspase cleaved K18 (ccK18) and microRNA-122 (miR-122) (Figure 1).

Study Design

(Clinicaltrials.gov NCT03177395)

A phase 1, open label, rising dose, randomised study which explored the safety & tolerability of calmangafodipir with acetylcysteine for acetaminophen overdose

Results

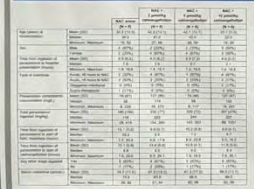


Table 1. Patient demographics for 4 treatment groups

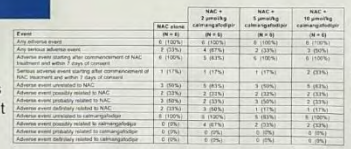


Table 2. Primary outcomes Adverse events and serious adverse events

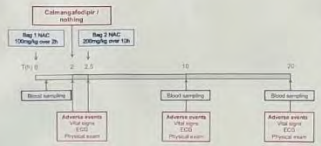


Figure 1. Trial design.

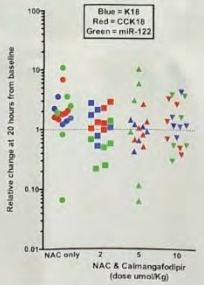


Figure 2. Secondary outcomes Fold change in keratin-18 (K18), caspase cleaved keratin-18 (ccK18) and microRNA-122 (miR-122) from baseline to 20 hours after starting NAC for the treatment groups

Results

All 24 participants received their allocated dose of calmangafodipir/NAC **(Table 1).** All participants experienced at least 1 adverse event (AE). The numbers experiencing at least 1 serious adverse event (SAE) are listed in **Table 2.** There were no AEs or SAEs probably or definitely related to calmangafodipir.

In the NAC alone group 2/6 patients had an ALT activity >100U/L, a clinically-relevant value used to indicate need for more NAC (secondary outcome pre-defined in trial protocol). No patients in the calmangafodipir treated groups reached this value

K18 at 20h was:

NAC alone, geometric mean	**347U/L** (SD 3.18)
NAC+calmangafodipir (2μmol/kg)	**229U/L** (1.94)
NAC+calmangafodipir (5μmol/kg),	**172U/L** (1.45)
NAC+calmangafodipir (10μmol/kg)	**181U/L** (1.73).

K18: For the relative fold increase from baseline to 20h the ratio of geometric group means for NAC +calmangafodipir to NAC alone was:

2μmol/kg,	**0.7** (95%CI 0.35 to 1.37)
5μmol/kg,	**0.48 (0.28 to 0.83)**
10μmol/kg,	**0.76** (0.40 to 1.46)

ccK18 and miR-122 had a similar pattern to K18. miR-122 had greater variability **(Figure 2).**

Trial protocol paper:
Trials. 2019 Jan 8;20(1):27
Sponsor: PledPharma AB

Results of the PoP study presented at the 58th Annual Meeting of the Society of Toxicology Baltimore, March 2019

Aladote® granted Orphan Drug Designation by the FDA (March 18, 2019)

PledPharma

PRESSRELEASE

PledPharma's drug candidate Aladote® granted Orphan Drug Designation

Stockholm, March 18, 2019. PledPharma AB (publ) today announces that the U.S. Food and Drug Administration (FDA) has granted an Orphan Drug Designation (ODD) to the drug candidate Aladote®, in development for reducing liver damage due to paracetamol overdose.

Today's treatment for overdose of paracetamol, N-acetylcysteine (NAC), is most effective if given within eight hours of the overdose. Patients arriving later to the hospital, and for those with a severe overdose, there is a need for more efficacious treatment options. Aladote® is a first-in-class drug candidate in development to reduce liver damage due to paracetamol overdose.

The scientific rationale as well as clinical results from the completed proof-of-principle study indicate that Aladote® in combination with NAC has the potential to reduce liver damage in the specified patient population. PledPharma intends to conduct regulatory interactions to determine the next step in development of Aladote®.

ODD benefits

- Lowered development cost – driven by patient safety and efficacy requirements (typically < 300 patients in Phase II / III studies)
- Shortened development time
- Commitment of the regulators to support development
- Early exposure of a drug to regulators
- 7-year Marketing Exclusivity if first approved
- Tax credits (-50%) for qualified clinical trial cost
- Waiver of NDA user fees (– over US$2 million)

Tentative study design for next clinical study - pending finalization after regulatory interactions

Design item	
Patient population	High risk POD patients (Early >300 nomogram OR Late (>8h) with >20mg/L paracetamol) requiring treatment with NAC
NAC regims	12 hr or 21 hr regims
Initiation of randomized treatments	IV (bolus) as soon as possible after randomization and after starting NAC (but no later than 4 hours after starting NAC)
Treatment arms	3 arms Aladote high-dose; Aladote low-dose; Placebo
Sample size	TBD
Key efficay endpoints	% change from baseline to end of first NAC regime in K18 Number (%) of patients that need further NAC after 12h/21h ALT >100 IU/L or doubled at end of treatment Experimental biomarkers for liver injury (miR-122 and GLDH) Length of hospital stay
Study countries	EU, US (4-8 sites)

Aladote® – timeline

2018

- ✓ Ph Ib/IIa study fully recruited
- ✓ Initial Results Ph Ib/IIa study
- ✓ Established Scientific Advisory Board
- ✓ Full results Ph Ib/IIa study
- ✓ Submission of Orphan Drug Designation

2019

- ✓ Orphan Drug Designation granted
- ✓ Presentation of study results at Society of Toxicology
- Presentation of study results EASL ILC
- Regulatory interactions – development program
- Initiate next study - subject to regulatory interactions

2023

- Regulatory submissions start

2032

- Calmangafodipir composition of matter patent expires

PledPharma

3. Aladote® in Paracetamol Overdose (POD)

a. Unmet medical need

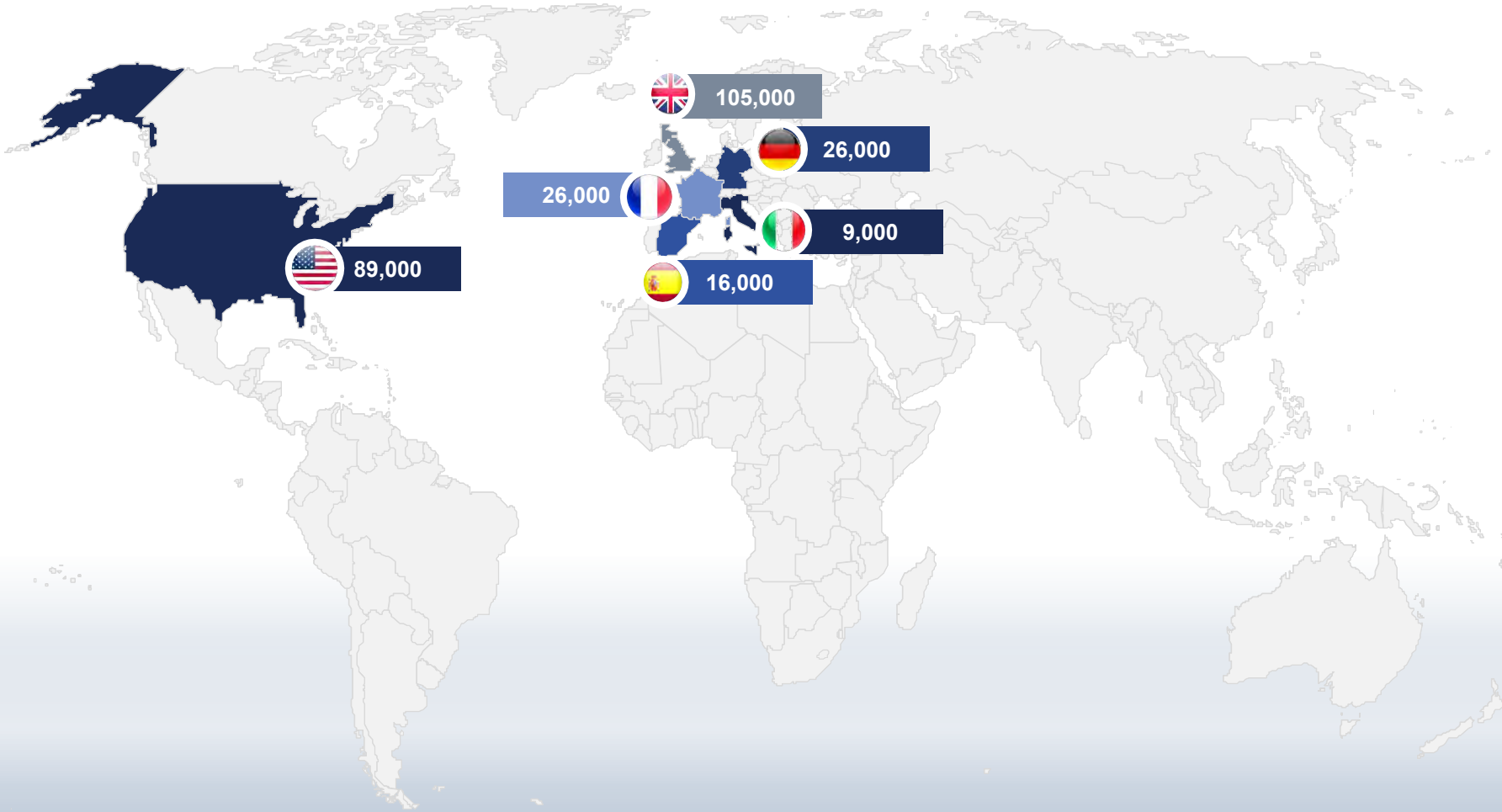
b. Aladote® proof of principle study results

c. Development of Aladote to prevent acute liver injury caused by POD

d. Commercial opportunity in POD

Phase II

POD incidence in EU5 and US – Hospital visits 2018



 Note: Paracetamol (acetaminophen) Overdose 2018 estimate Epidemiology.

Burden on society - POD US Healthcare Costs were $1bn in 2010

In the US the annual cost in 2010 was estimated at $1,059 million to treat Patients with POD

The POD Emergency Department and inpatient cost is around $13K-40K

The average POD inpatient length of stay was 3.1 Days, with a variance of + 4.4 Days for the most severe cases

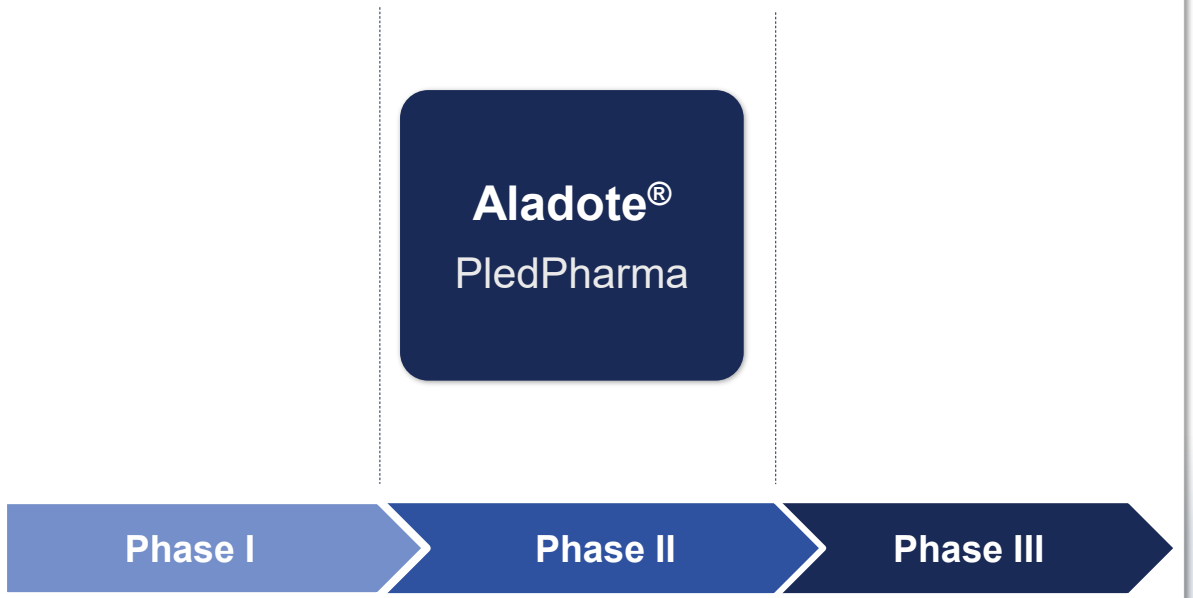
US liver transplant costs $125-473K

 Note: Adapted from: Altyar A. Clinical and economic characteristics of emergency department visits due to acetaminophen toxicity in the USA BMJ Open 2015;5

No competitor in development

TREATMENT APPROACHES FOR POD
Active Charcoal
N-Acetylcysteine (NAC)
Liver transplant

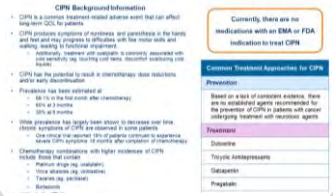
POD EMERGING TREATMENTS



Aladote® – Initial Market Research, Pricing & Reimbursement

Market research with US and EU Physicians and Payers to gain insight into unmet needs, validate Target Product Profile and Pricing & Reimbursement

POD Background



TPP & IDI Guide Development

Efficacy vs Safety Options and Key Questions for Insight

Testing

12 Physicians and 12 Payers

Team Expertise

24 qualitative interviews comprised

- 6 US payers, 6 EU3 (2 from each of D, F, UK)
- 6 US physicians, 6 EU3 (2 from each of D, F, UK)

PiedPharma

Physician & Payer Insight

– confirms the unmet medical need and verifies TPP

- Patients as defined in study design (ie early high level /late presenters) confirmed as being high risk
- Unmet Need Ultimately Prevention Of Liver Failure Requiring Transplant And Death
- Unmet Need Is Unanimously A Reduction In Infusion Time And Therefore Reduced Hospital Stay

'Overdose - especially acute, is not a matter of priority, but is a matter of an obligation for the hospital'

"To have the same efficacy in the patients 8-24 hours as in the patients 1-4 hours - that would be good'

'What do we do if we don't give this…it is the only drug available'

"Whatever you use the limitation is effectiveness, when you are aware of an overdose too late'

'The problem with this type of treatment, is that it is the only one'

'If it's an intentional overdose then it's to psychiatric care'

'If they have a mental issue we refer them to the psych team. They need a risk assessment'

 Note: (1) interviews with Oncologists from US and EU3.

Physician & Payer Insight

– time in hospital a major driver of value in a cost-benefit analysis

'Really working in, for us, a primary endpoint of 'time for readiness for discharge'. That would speak volumes about the efficacy of the drug'

'That is very important to invest in identification of the resource consumption for managing the disease - to have a reference cost of what you do. And not just reduced to the cost of the drug to which you compare, in order to advocate that your drug is maybe costly, but saves consumption of resources. "

"If it is possible to reduce the hospitalisation for the patients (e.g. 5 days to 2 days), the sickness funds will save money - so the pharmaceutical company can ask for more price"

'In France we are going to move to downsize the number of beds in the hospital'

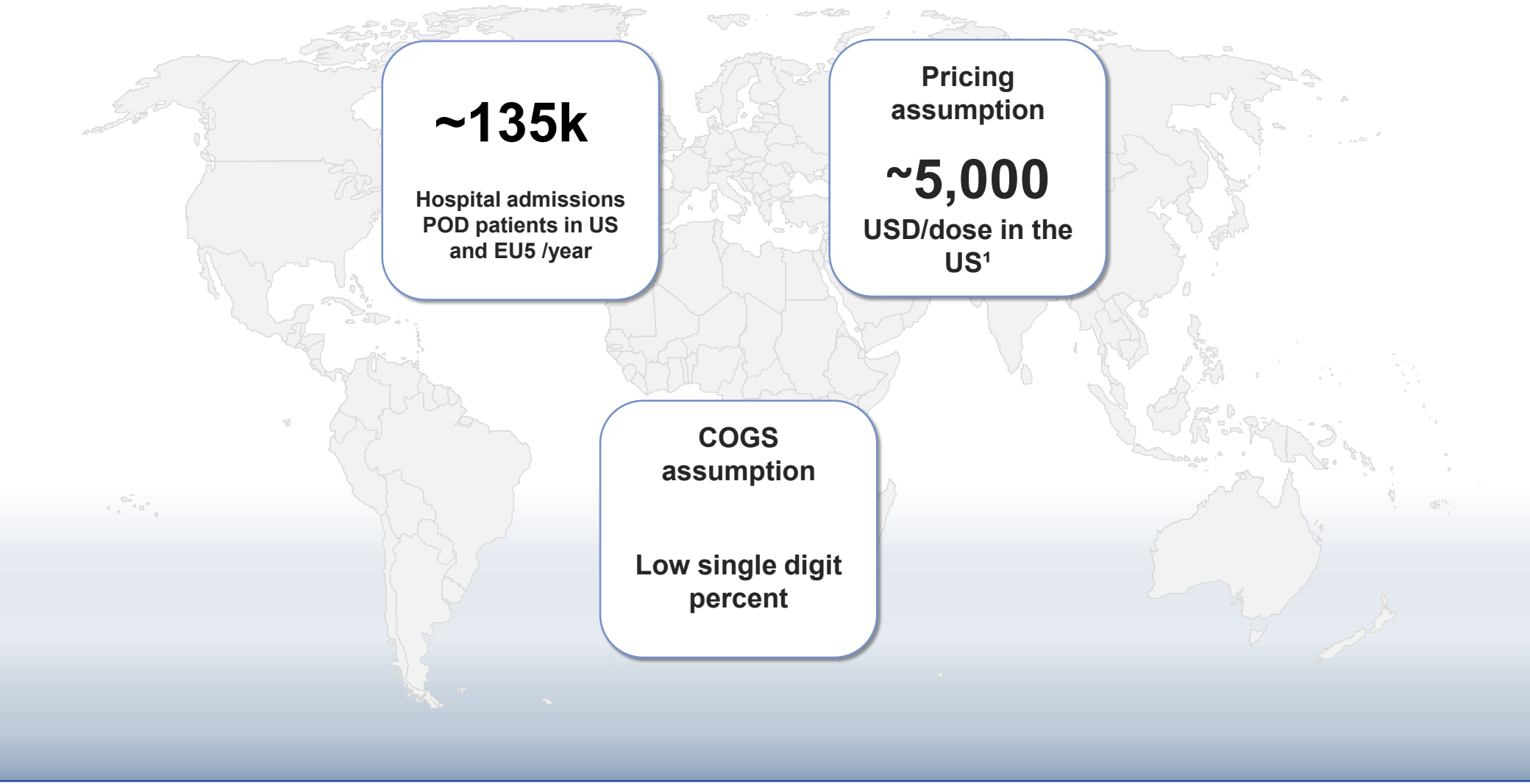
'As just outlined {21 hours, 3 infusions} it's a bit difficult the administration of the drug and the timeframe'

'The hospital stay is very interesting in terms of having a new treatment that modifies hospital stay - as that is a huge driver obviously'

"Even if it was a lower level of care - ITU to a Med surg - would be significant. So if that could be proved that could be factored into overall reflecting a decreasing care cost. It is often difficult to prove - but if there is data there it is a great endpoint. "

'Avoid downstream longer term liver and kidney impairment and treatment costs of that'

Aladote® – Commercial potential in POD patients



~135k

Hospital admissions POD patients in US and EU5 /year

Pricing assumption

~5,000

USD/dose in the US[1]

COGS assumption

Low single digit percent

 Note: **(1)** Up to $5000 based on initial and limited research

PiedPharma

Aladote® - Summary and Opportunities

PREVENTS ACUTE LIVER FAILURE CAUSED BY PARACETAMOL (ACETAMINOPHEN) POISONING

DEVELOPMENT STATUS

- Positive study results Ph Ib/IIa announced in September 2018 – presented at the 58th Annual Meeting of the Society of Toxicology
- Study results Ph Ib/IIa to be presented at EASL ILC April, 2019
- Orphan Drug designation granted March 2019 in the US
- Design of next study finalised together with Scientific Advisory Board - subject to regulatory interactions

BUSINESS OPPORTUNITY

- Paracetamol (acetaminophen) poisoning is one of the most common sorts of overdoses
- No adequate treatment for high risk patients
- ~135K Hospital admissions POD patients in US and EU5 /year
- Price assumption, ~5,000 USD/dose[1] in the US based on initial market research

 Note: **(1)** Up to $5000 based on initial and limited research

PledPharma

4. Corporate Strategy

a. Finance and up listing

b. Business development

c. Direction and opportunities to enhance value

Finance

Finance

- 2018 operating results were SEK -92.5M
- Q4-2018 Cash position was reported at SEK 230M
- Milestone payment from Solasia of c.SEK 49M (JPY 600M) in Q1-2019 due to continued progress of the POLAR-studies in Asia
- Cash position is sufficient to top-line for the POLAR-studies
- Intensive recruitment period during 2019

Income statement

SEKk	2018 Jan-Dec	2017 Jan-Dec
Revenue		
Sales	28,211	13,585
Other operating income	2	302
	28,212	**13,886**
Operating expenses		
Project costs	-83,855	-76,974
Other external costs	-11,324	-12,849
Employee benefit costs	-20,034	-10,895
Depreciation and impairment	-	-
Other operating expenses	-5,511	-1,266
Operating result	**-92,513**	**-88,097**
Financial items		
Interest income and similar items	7,510	163
Interest expense and similar items	-1	0
Result after financial net	**-85,003**	**-87,935**
Result before tax		
Tax	-	-
Result after tax	**-84,350**	**-85,851**
Statement of comprehensive income		
Other comprehensive income	-	-
Comprehensive income for the period	**-84,350**	**-85,851**

Cash position sufficient until top-line results from the POLAR study

PledPharma

Nasdaq main market

Up-listing

- Up-listing process ongoing
- Listing of shares on Nasdaq main market estimated to Q4 2019
- Aligned with the maturity level of the company
- PledPharma shares will be accessible and visible to a global investor base

PledPharma

4. Corporate Strategy

a. Finance and up listing

b. Business development

c. Direction and opportunities to enhance value

Proactively purse Business development

Business development

- Commercialize PledOx through strategic partnership
  - PledPharma is open for license agreement/s for major regions before read-out, if the terms are attractive
- Opportunistic approach to partnering during development for Aladote
- Ambition to optimize deals for PledPharma shareholders

License agreement develop and commercialize PledOx®in Asia

PledPharma

Solasia

PRESS RELEASE
PledPharma AB
Stockholm, November 20, 2017

PledPharma and Solasia enter license agreement to develop and commercialize PledOx® in Asia

Stockholm, Sweden / Tokyo, Japan, [November 20th 2017] - PledPharma AB ("PledPharma") (STO: PLED) and Solasia Pharma K.K. ("Solasia") (TSE: 4597) today jointly announce that they have entered a license agreement pertaining to the clinical development and commercialization of PledOx® in Japan, China, Hong Kong, Macau, South Korea and Taiwan.

Under the terms of this agreement, PledPharma grants exclusive development and commercialization rights to PledOx® in the territories mentioned and Solasia will pay upfront, development, regulatory and sales milestones of up to ~USD 83 million (SEK 700 million)*. In addition, Solasia will pay industry standard royalty rates on sales applicable for a deal pertaining to an in-licensed asset in Phase III development. Solasia will also fully finance an expansion of the Phase III program to include Asian patients subject to regulatory consultations.

PledPharma

Key value drivers of Asia licensing agreement

Solasia

Partnership with Solasia and its capabilities

3-4 years of accelerated development in Asia

Milestones & Royalties

Expansion of Phase 3 program will further enhance robustness

PiedPharma

PledOx® Asia deal structure & Expansion of Phase III to Asia

1

- PledOx® for Chemotherapy Induced Peripheral Neuropathy (CIPN) – Colorectal cancer.
- License to develop and commercialize PledOx® in Japan, China, Hong Kong, Macau, South Korea, and Taiwan.

2

- Solasia will pay upfront, development, regulatory and sales milestones of up to 83 MUSD (approximately 700 MSEK)[1]. Upfront milestone of ~ USD 1m received in Dec-17. Development milestone of ~ USD 5.5m received in Jan-19.
- Solasia will pay industry standard royalty rates on sales applicable for an in licensed asset in Phase III development.

3

- Solasia will also **fully finance an expansion** of the Phase III program (POLAR-A and POLAR-M) to include Asian patients, supported by Japanese PMDA.
- The Phase I study in Japanese and Caucasian Healthy Volunteers with focus on safety, tolerability and pharmacokinetics showed positive results. Fully financed by Solasia.

 Note: (**1**) JPY 9.3 billion.

PledPharma

4. Corporate Strategy

a. Finance and up listing

b. Business development

c. Direction and opportunities to enhance value

Summary - Direction, opportunities and enablers to enhance value

1 PledOx®

- Huge unmet medical need with no treatment approved today
- Ongoing global phase III program in CIPN with oxaliplatin
- Expand into CIPN with taxanes

2 Aladote®

- Substantial unmet medical for patient where NAC not adequate
- Exciting results from first clinical study motivates further development
- Granted ODD by US FDA

3 Business development

- Strategic partnerships
- Maximise PledOx value
- Enhance value to the development of Aladote in an orphan setting

4 Financial

- Listing of shares on Nasdaq main market
- Cash position sufficient to top-line for the POLAR-studies

5 People & Organisational

- Transformed organisation
- Proven track record in bringing products to the market

 Note: (**1**) JPY 9.3 billion.

Closing remarks

Chairman of the Board – Håkan Åström