Paper Number: PD101-430

PhotoChemical Internalization: Current clinical trials in cholangiocarcinoma

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CMO, PCI Biotech

PCI Biotech

PCI TECHNOLOGY fimaCHEM

- ENABLING DRUGS TO REACH INTRACELLULAR THERAPEUTIC TARGETS
- LOCALIZES THE THERAPEUTIC EFFICACY WHERE MOST NEEDED

Enabling approved drugs to fulfil unmet local treatment need

Programme	Indications / Therapeutics	Preclinical	Phase I	Phase II	Pivotal	Status
fimaCHEM	*Bile duct cancer / gemcitabine*					- Encouraging early clinical results - Orphan designation in Europe and USA - Pivotal registration study initiated
fimaVACC	*Therapeutic cancer vaccines*					- Phase I in healthy volunteers completed - Proof of concept in man achieved - Highly sought after vaccination features
fimaNAc	*Nucleic acid therapeutics*					- Six research collaborations

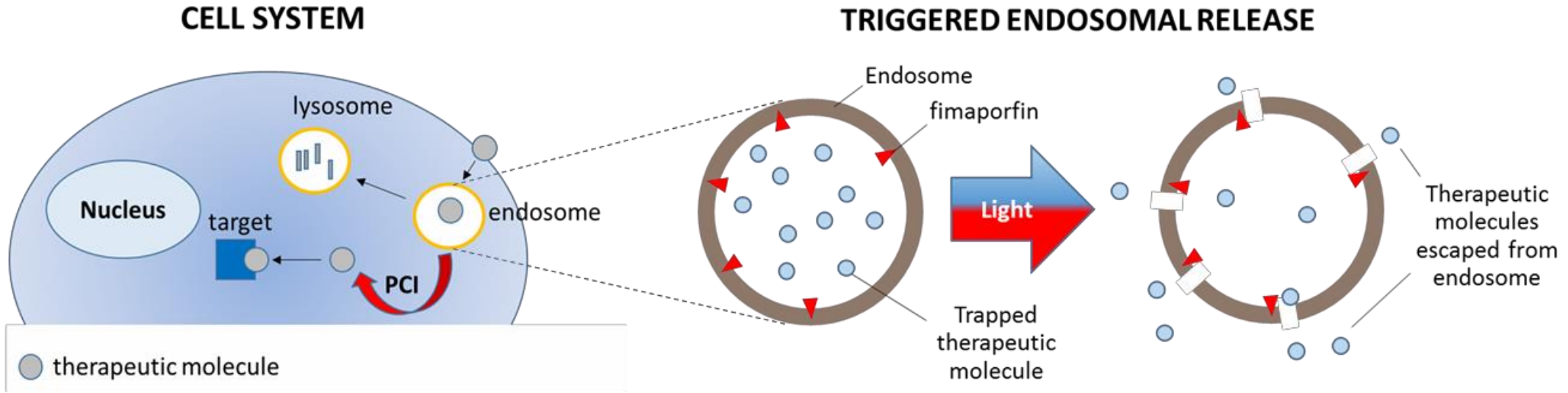
PCI TECHNOLOGY fimaCHEM

- ENABLING DRUGS TO REACH INTRACELLULAR THERAPEUTIC TARGETS
- LOCALIZES THE THERAPEUTIC EFFICACY WHERE MOST NEEDED

- **IV**
- **SC**
- **ID**
- **Intralesional**

- ✓**Chemotherapeutics**
- ✓**Vaccines**
- ✓**Nucleic acids**

Mode of action



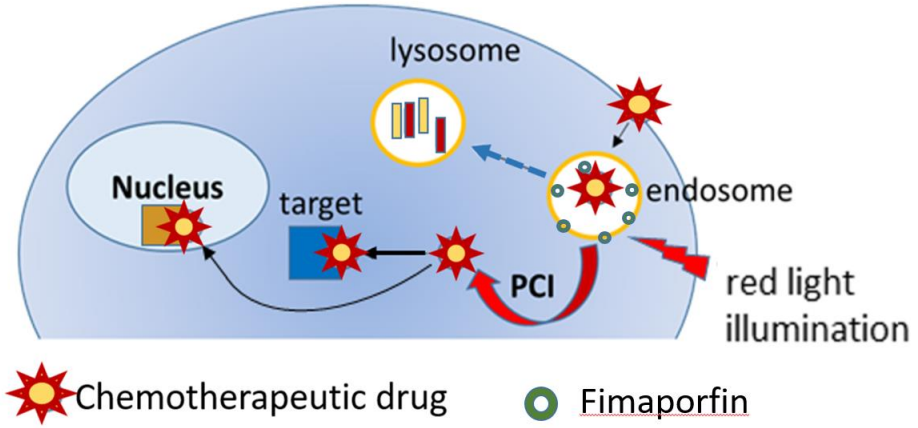
PCI TECHNOLOGY fimaCHEM

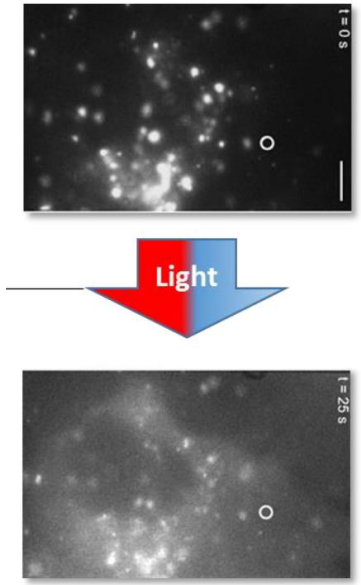
- ENABLING DRUGS TO REACH INTRACELLULAR THERAPEUTIC TARGETS
- LOCALIZES THE THERAPEUTIC EFFICACY WHERE MOST NEEDED

✓Chemotherapeutics

- ✓Many chemotherapeutics are entrapped in endosomes in tumor cells, ameliorating their full therapeutic potential
- ✓The PCI technology can induce an intra-cellular release - shown with a number of key chemotherapeutics

- *bleomycin*
- *docetaxel*
- *erlotinib*
- *doxorubicin*
- *topotecan*
- *gemcitabine*





PCI TECHNOLOGY fimaCHEM

Preclinical	Phase I	Phase II	Pivotal

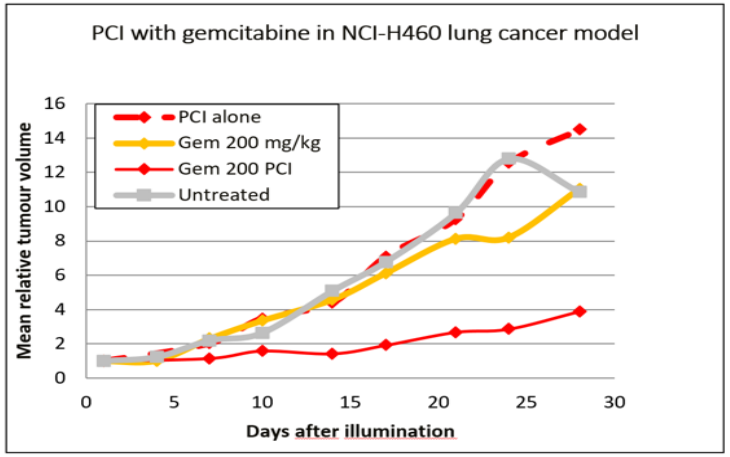
fimaCHEM — *Bile duct cancer / gemcitabine*

Phase I/II: Safety and dose finding, with encouraging efficacy in CCA
Currently initiating pivotal trial, US & EU

- ***bleomycin***
- *docetaxel*
- *erlotinib*
- *doxorubicin*
- *topotecan*
- ***gemcitabine***

✓**Bleomycin** was evaluated in a FIH trial with promising efficacy in solid tumors

✓**Gemcitabine** in preclinical models - solid, reproducible results with PCI

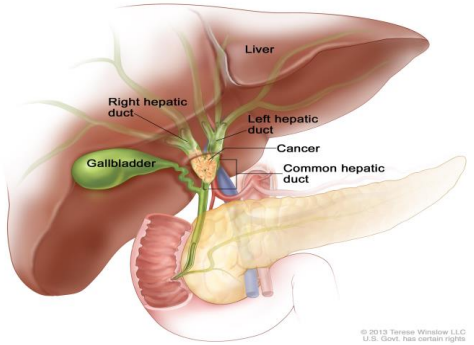


PCI Biotech – data on file

fima CHEM

EXTRAHEPATIC CHOLANGIOCARCINOMA

- **A rare cancer in need of new treatment approaches**
- ***Development largely focused on intrahepatic CCA***



- Orphan disease
- 5-year survival < 5%, avg. survival (inoperable) ≈ 12 mo
  - Intrahepatic tumours (10%*)
  - Perihilar tumours (60-70%*)
  - Distal tumours (20-30%*)
- Tumors tend to block the bile duct
  - Liver function is progressively affected
  - Palliative biliary drainage is key for patient treatment and survival
- Global Standard-of-Care (surgery < 25%):
  - Stenting (& maintenance) via ERCP or PTC
  - Gemcitabine + cisplatin

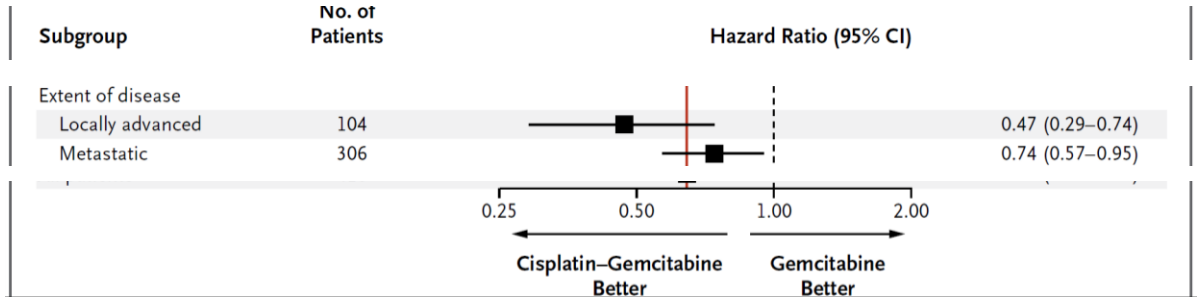
**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthoney, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iveson, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D., for the ABC-02 Trial Investigators*



* Bile duct cancer, Am Cancer Soc, 10/30/2013
** N Engl J Med 2010;362:1273-81.

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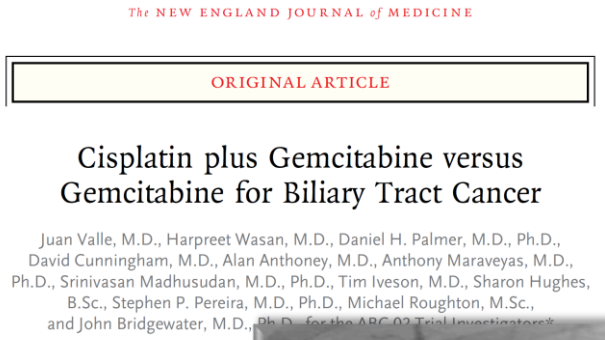
EXTRAHEPATIC CHOLANGIOCARCINOMA

- **A rare cancer in need of new treatment approaches**

Enhancing the active and recommended chemotherapy

Easy illumination through standard endoscopic methods

Boosting chemotherapy effect where it is most needed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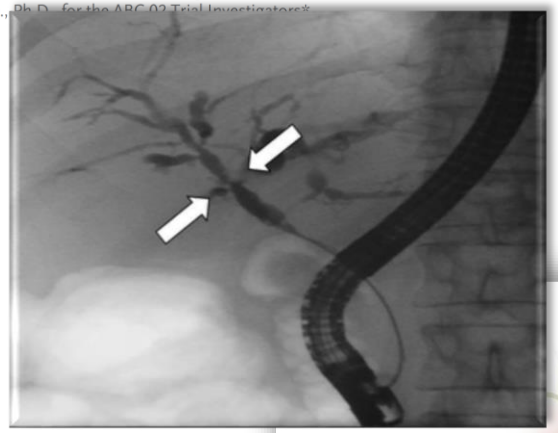
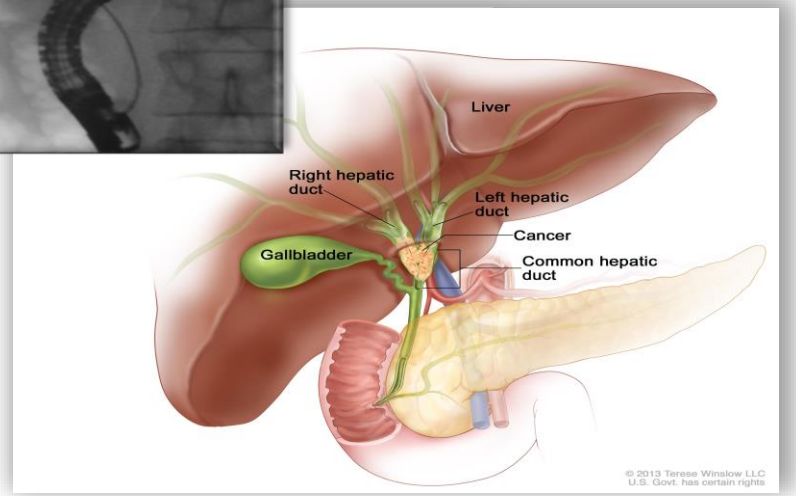
No approved therapy





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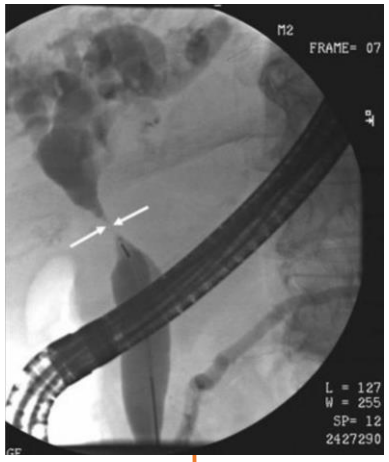
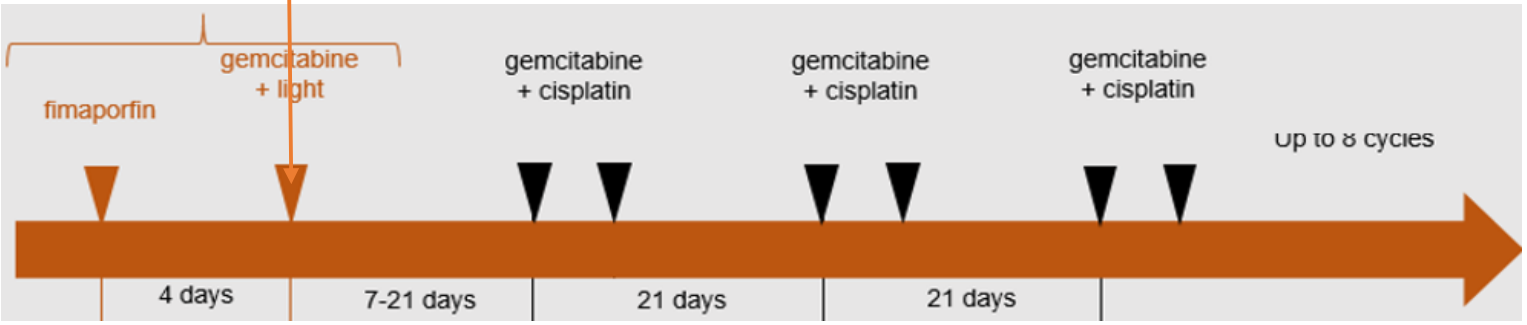
PCI IN EXTRAHEPATIC CHOLANGIOCARCINOMA

- A rare cancer in need of new treatment approaches
- **Clinical data – safety and dose established**

PCIA 202/12: A phase I, dose escalation trial of PCI with gemcitabine and SoC +Extension



- Multicenter trial in patients with advanced extrahepatic CCA
- Classical dose escalation 3+3 design
- One single PCI induction of gemcitabine at standard dose
- Followed by standard care gem/cis therapy for up to 8 cycles.
- Patients were on-study for 6 months, and thereafter followed OS



PCI IN EXTRAHEPATIC CHOLANGIOCARCINOMA

► Clinical data – safety and dose established

PCIA 202/12: A phase I, dose escalation trial of PCI with gemcitabine and SoC +Extension

- ►16 patients (13♂ & 3♀); avg. age 64 yrs
- ►Treatment-naïve with **histology confirmed**, locally advanced, **extrahepatic CCA**
- ►Baseline **ECOG <2** in all patients
- ►All patients were **stented**
- ►11/16 completed all 8 **gem/cis** cycles (avg, 6.4)

Cohort	1	2	3	4
Fimaporfin dose	0.06	0.06	0.12	0.25
Light dose J/cm	15	30	30	30
Total Pts / SAEs	3 / 5	3 / 2	4 / 14	6 / 10

- **Extension phase:** To evaluate the safety of 2 PCI procedures during chemo cycles (3+3)

PCI IN EXTRAHEPATIC CHOLANGIOCARCINOMA

► **Clinical phase I data – safety and dose established**

PCIA 202/12: RESULTS

Safety

- No Dose-Limiting Toxicity (DLT) were observed
- No unexpected safety concerns
- Serious Adverse Events (SAEs) were primarily cholangitis in approx. 50% of patients, but
  - ***not correlated in time to the PCI procedure***
  - ***similar to the frequency, severity and pattern reported in the literature for perihilar CCA***

- **Extension phase, 2 PCI procedures:**
  - 7 additional subjects: no new safety signals

Cohort	1	2	3	4
Fimaporfin dose	0.06	0.06	0.12	0.25
Light dose J/cm	15	30	30	30
Total Pts / SAEs	3 / 5	3 / 2	4 / 14	6 / 10
Serious Adverse Events by System Organ Class (# patients/SAE)				
Cardiac (pts/events)	0	0	0	1 / 2
Gastrointestinal	1 / 1	0	2 / 3	1 / 1
Hepatobiliary	1 / 3	2 / 2	3 / 11	3 / 3
Infections	1 / 1	0	0	1 / 1
Respiratory	0	0	0	1 / 1

PCI IN EXTRAHEPATIC CHOLANGIOCARCINOMA

► Clinical phase I data – safety and dose established

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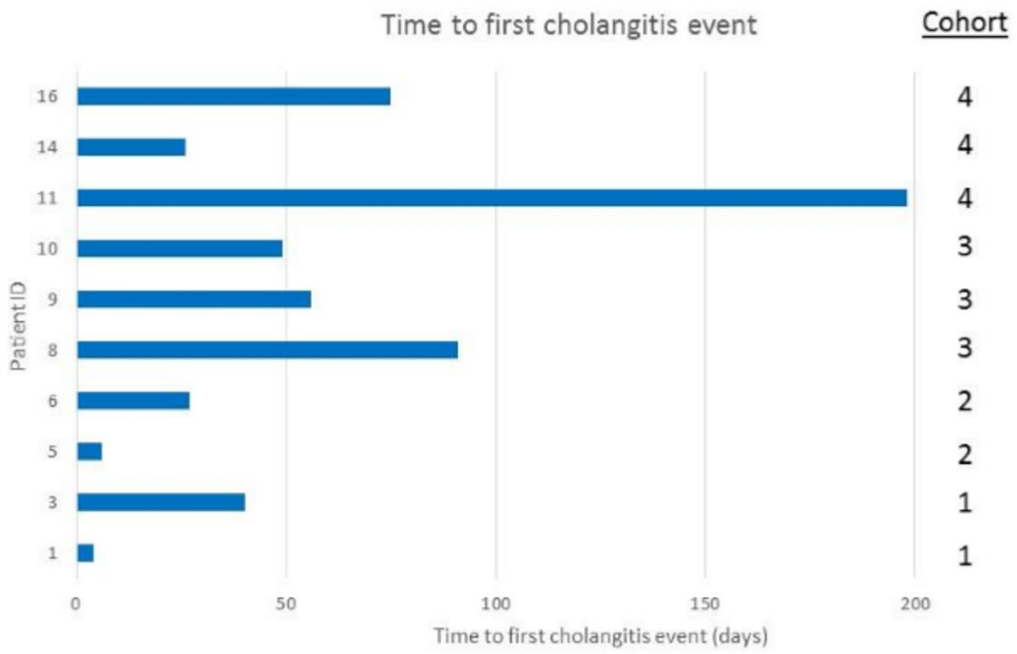
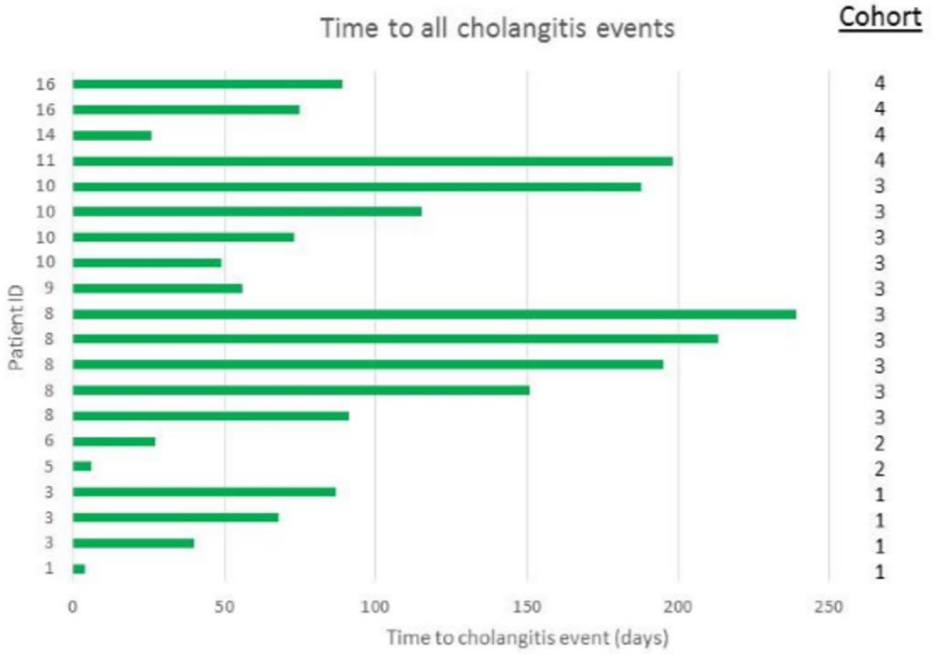
Hepatobiliary	1 / 3	2 / 2	3 / 11	3 / 3
Infections	1 / 1	0	0	1 / 1
Respiratory	0	0	0	1 / 1

PCIA 202/12: RESULTS

Safety – cholangitis

- Cholangitis timing did not indicate a relation to the PCI procedure:
  - Avg. 57 days after PCI endoscopy
- Trended to occur sooner in the two lowest dose cohorts (however, low N)
- A comprehensive literature review of Gem/Cis treatment trials in perihilar CCA with endoscopic procedures showed a similar rate of cholangitis episodes to this trial





PCI IN EXTRAHEPATIC CHOLANGIOCARCINOMA

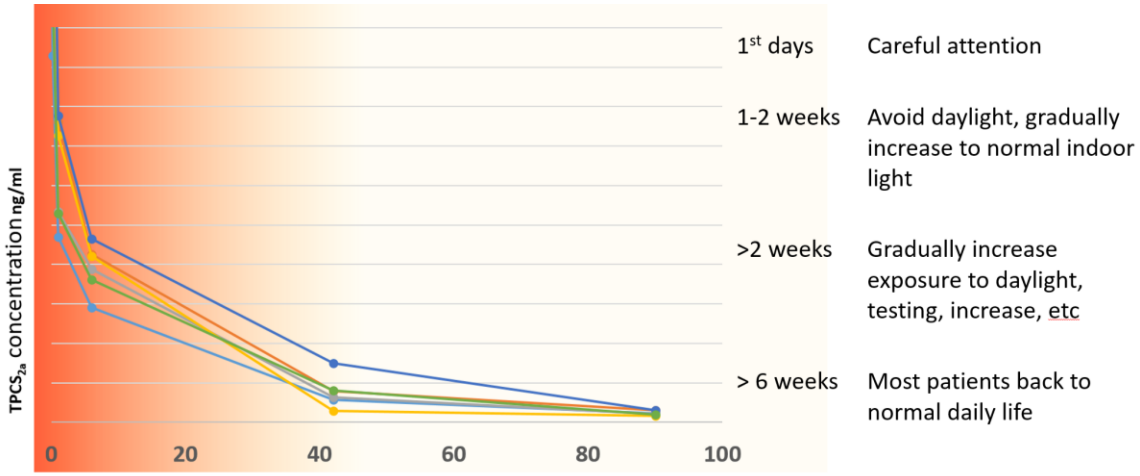
► Clinical phase I data – safety and dose established

PCIA 202/12: RESULTS

Safety – photosensitivity

- Like other photosensitizers: transient light sensitivity
- Did not induce any SAEs
- Among AE reports, chemotherapy effects may have contributed to skin reactions
- A variability in reported light sensitivity seems to correlate to PK of fimaporfin (Amphinex®)
- PK of Amphinex® influenced by concomitant medications and potentially the degree of liver dysfunction
- Patients are advised to follow precautions to prevent skin and eye photosensitivity reactions - counselling and information is of key importance for compliance and motivation

Illustrative photosensitivity pattern with eliminiation curves in 6 patients depicted. Days after IV fimaporfin



fima CHEM

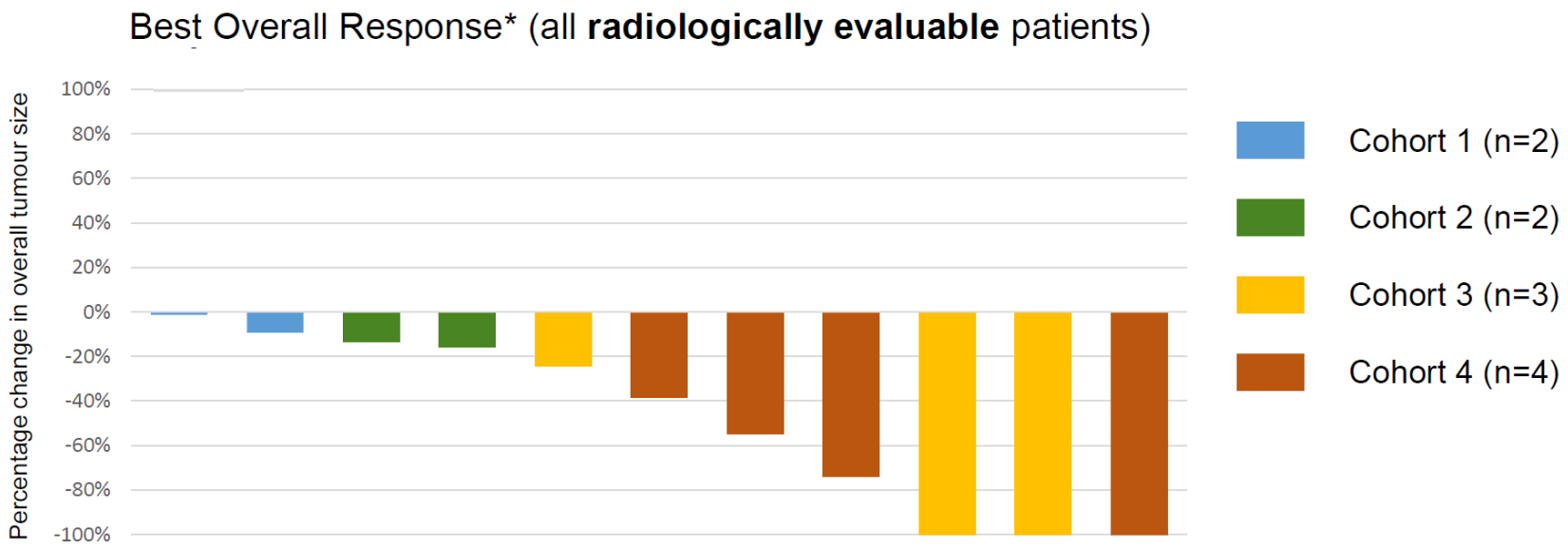
PCI IN EXTRAHEPATIC CHOLANGIOCARCINOMA

- Clinical phase I data – safety and dose established

PCIA 202/12: Safety and early efficacy results paves the way for a pivotal trial

Efficacy – dose escalation cohort

- A >20% reduction in tumor size was observed in 17/19 target lesions in the *two highest dose cohorts at 6 months*
- Of these,12 lesions became undetectable (independent reading)
- ⅓ of the patients alive >30 months after PCI x 1 at initiation of standard gem/cis therapy



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PCI IN EXTRAHEPATIC CHOLANGIOCARCINOMA

- Clinical phase I data – safety and dose established

PCIA 202/12: Safety and early efficacy results paves the way for a pivotal trial

Efficacy – mOS of 21.7 months in cohort IV = RP2D

Parameters, Oct 2018	Phase I, full study (N=16) (0.06-0.25mg/kg)	Cohort IV (N=6) (0.25mg/kg, RP2D for pivotal)
Avg. # of gem/cis cycles	6.4 (range: 0 - 8)	**6.0 (range: 0 - 8)**
Pts with measurable lesions	12/16 (75%)	**5/6 (83%)**
Avg. overall tumour size	4.1 cm (range: 1.5 - 7.8 cm)	**5.2 cm (range: 2.1 - 7.8)**
Objective Response Rate	4/12 patients (33%) (2 PR; 2 CR)	**3/5 patients (60%) (2 PR; 1 CR)**
Interim avg. Duration of Response	≥ 12.4 months (range: 6.5 – 20.2)	**≥ 15.4 months (range: 8.0 – 20.2)**
Overall Survival (OS)	median OS: 14.4 months interim avg OS: 18,9 months	**median OS: 21.7 months interim avg OS: 19.8 months**

PCI IN EXTRAHEPATIC CHOLANGIOCARCINOMA

► Clinical phase I data – safety and dose established

PCIA 202/12: RESULTS FROM THE EXTENSION COHORT WITH REPEAT fima*CHEM*

An extension cohort was recommended, purposed to explore safety of repeated treatment
Summary of characteristics and interim results

- 7 patients were included – 5 of these received two fima*CHEM* treatments (C1 + C5)
- Safety endpoint reached – a pivotal study can be initiated with up to two treatments
- 4/7 included patients had radiologically measurable disease
  - The average tumour burden (overall target tumour diameter) was about twice the average tumour burden in the dose escalation
  - None of the measurable local treated tumours showed progression during the six months follow-up period, but 2 patients had progression due to appearance of new lesions
- 3/7 patients alive at last censoring (March – May), all having received two treatments – the emerging mOS in this cohort was approx. 14 months at the time

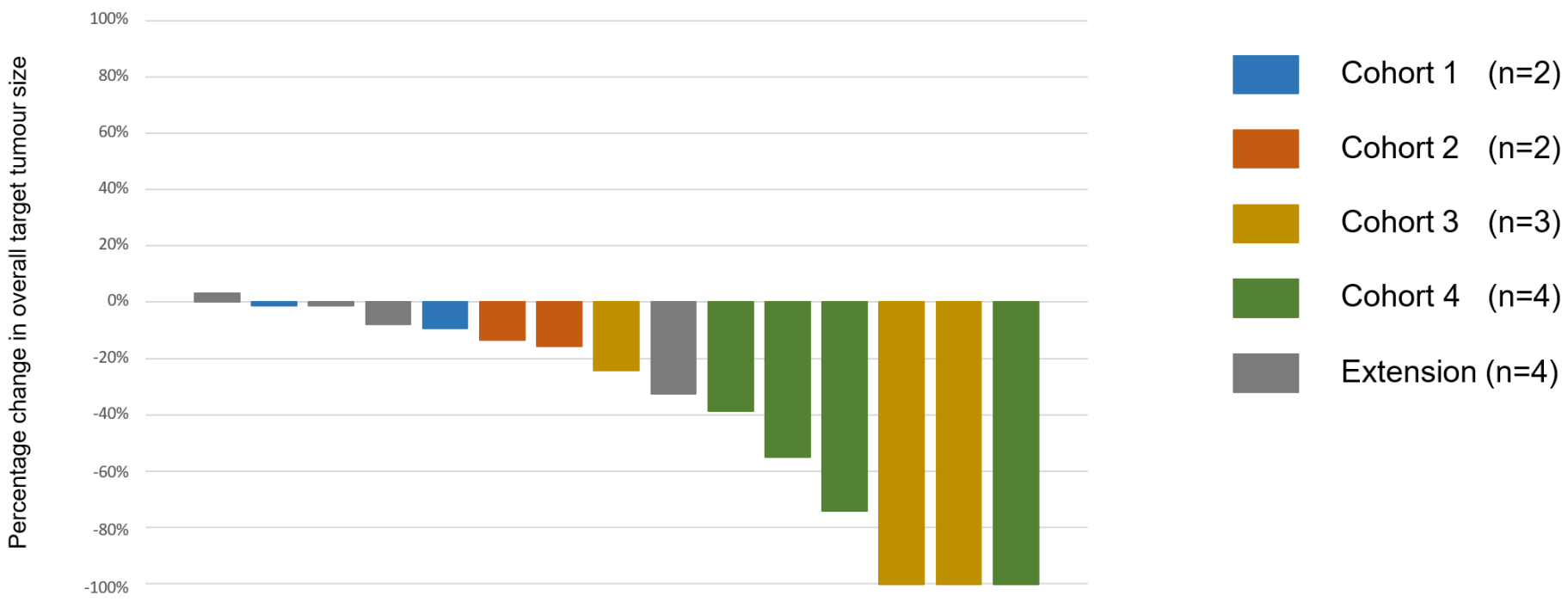
PCI IN EXTRAHEPATIC CHOLANGIOCARCINOMA

► Clinical phase I data – safety and dose established

PCIA 202/12: Safety established, and the median OS was 21.7 months in cohort IV = RP2D

Cohort IV (N=6) (0.25mg/kg, RP2D for pivotal)
6.0 (range: 0 - 8)
5/6 (83%)
5.2 cm (range: 2.1 - 7.8)
3/5 patients (60%) (2 PR; 1 CR)
≥ 15.4 months (range: 8.0 – 20.2)
median OS: 21.7 months **interim avg OS: 19.8 months**

All patients in dose escalation and extension part (measurable)



PCI IN EXTRAHEPATIC CHOLANGIOCARCINOMA

- Clinical data – safety and dose established

PCIA 202/12 RESULTS IN PERSPECTIVE

- Meta-analysis of (only Gem-Cis studies, n=15):
- Pooled ORR 20.0 (95% CI 15.8-24.6)

Of note, the small N in PCIA 202/12 does not allow for comparative conclusions

Juan Valle et al (ABC02). N Eng J Med 2010; 362:1273-82
Juan Valle et al (ABC03). The Lancet Oncology 2015; 16: 967-978
Thongprasert et al. Ann Oncol 2005; 16:279
Giuliani et al. Ann Oncol2006; 17 Suppl 7:vii73
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Meyerhardt et al. DigDis Sci 2008; 53:564
Kim et al. Cancer 2006;106:1340-1346
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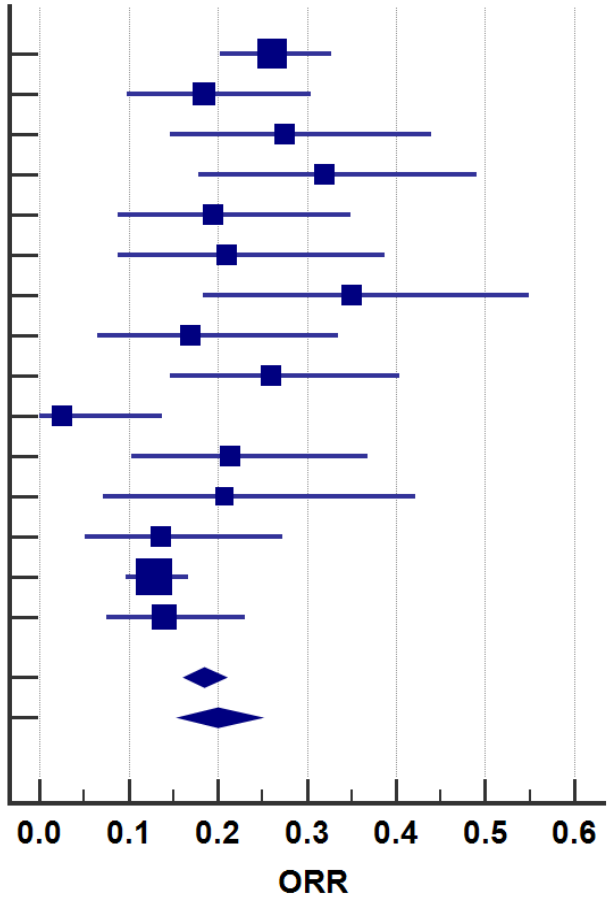
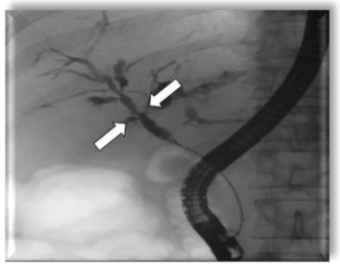
Goldstein et al 2011
Croitoru et al 2012
Charoentum et al 2007
Lee et al 2006
Heo et al 2017
Kim et al 2017
Takahara et al 2017

Total (fixed effects)
Total (random effects)



THE *RELEASE* TRIAL

A pivotal trial of **fimaCHEM** in gem/cis SoC regimen in inoperable extrahepatic CCA



- A pivotal randomized study with an interim analysis for potential accelerated/conditional approval

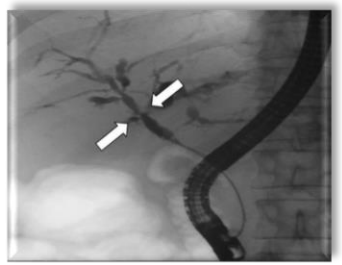
- Based on 1st line SoC treatment inoperable extrahepatic bile duct cancer
- Approx. 40 key centers (Europe & USA)
- Approx. 36 months to interim and 50 to final analysis
- Randomization (1:1) of 186 patients
- Primary endpoint: PFS, with OS as key secondary
- Interim analysis primary endpoints: PFS followed by ORR (at 60 events)

- **Safety endpoint in extension study achieved – pivotal study with up to two treatments**
- **Orphan designation granted in both the US and EU**
- **Design based regulatory interactions with EMA and FDA**
- **Ongoing regulatory and ethics approvals and site initiations progressing well**
- **First site opened in March and first patient enrolled in May**

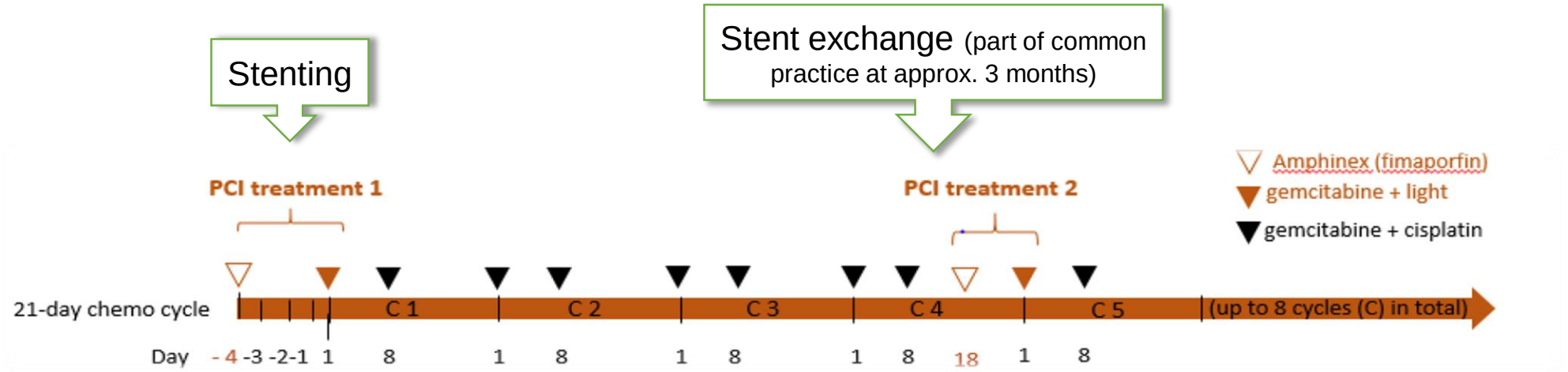
fima CHEM

THE *RELEASE* TRIAL

A pivotal trial of **fima*CHEM*** in gem/cis SoC regimen in inoperable extrahepatic CCA



► A pivotal randomized study with an interim analysis for potential accelerated/conditional approval

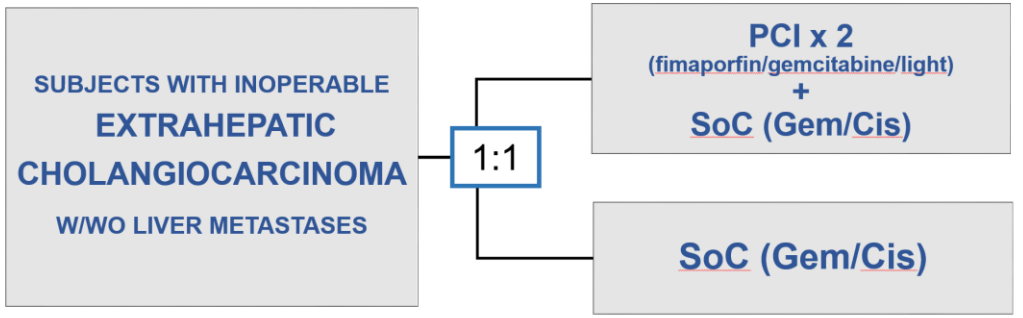


✓*In the management of extrahepatic CCA, the endoscopic (or transhepatic) stenting is easily adapted to include also light delivery as part of treatment (3 minutes of illumination) at 1-2 occasions*

✓*The phase I trial (PCIA 202/12) demonstrate that targeted illumination can be safely conducted during standard ERCP*

✓*The 2nd treatment, scheduled to C5, may be postponed due to intercurrent disease events that delays treatment, or other patient factors*

In both arms, subjects will receive SoC background treatment with gem/cis



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THE *RELEASE* TRIAL

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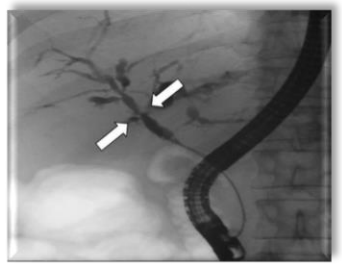

► A pivotal randomized study with an interim analysis for potential accelerated/conditional approval

STUDY POPULATION

- Subjects with inoperable, previously untreated **extrahepatic** CCA ≥18 years
- Biliary obstruction requiring **stenting**
- **If metastatic**, metastatic disease **confined** to the liver, and/or restricted only to local lymph nodes and/or with peritoneal engagement locally
- No previous anti-tumor treatment for CCA
- At least 1 radiological lesion (measurable and/or non- measurable but evaluable)
- Adequate biliary drainage (at least 50% of the liver volume, or at least 2 sectors)
- ECOG 0-1
- Histology verified CCA

PRIMARY OJECTIVE

- ***Progression-Free Survival (PFS)* with PCI-induction of gemcitabine + gem/cis chemotherapy**

  VS

- **Gem/cis therapy alone**

SECONDARY OJECTIVES

- **Overall Survival (key 2:ary)**
- RECIST 1.1 endpoints
  - Best Overall Response (BOR), Objective Response Rate (ORR), Duration of Response (DoR), Disease Control Rate (DCR) at 6 and 12 months, and change in tumor size
- To further asses the safety of PCI, including loco-regional tumor and biliary tract related events, and the overall safety profile
- To assess Health-Related Quality of Life (HRQoL) and Patient Reported Outcome (PRO) in the two study arms

- ***A formal interim analysis of PFS will be performed after approximately 60 progression events (per RECIST 1.1, estimated at 120 patients)***

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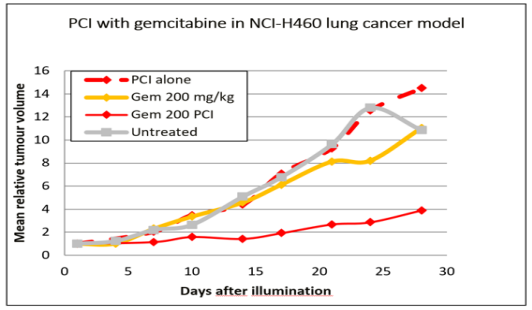
CONCLUSIONS



PCI Biotech – data on file

► The translation of PoP of PhotoChemical Internalization with gemcitabine from preclinical data to clinical PoC data was secured in the PCIA 202/12 trial

► There is a huge unmet need in the majority of CCA patients, i.e. extrahepatic

► The fimaCHEM PCI procedure can safely be incorporated in SoC treatment, also with two procedures

► The promising RP2D dose taken into the pivotal trial, with a mOS of 21.7 months, and the safety profile of PCI has triggered the now initiated pivotal trial in Europe, and is soon to be expanded to the US

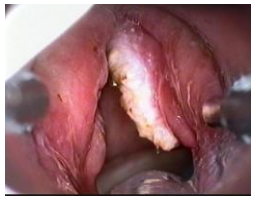
► The pivotal trial, with an interim analysis that may lead to an expedited approval, was designed in alignment with the expectations of RAs

► First site opened in March and first patient enrolled in May

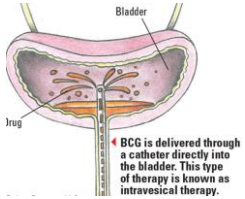
THE PCI PLATFORM

Future PCI opportunities – small molecules, vaccines, nucleotides

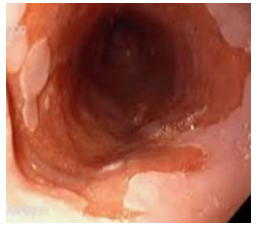
- Early lesions, aim at **cure**
- Surface illumination



Larynx



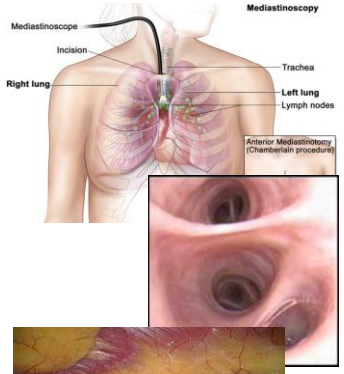
Bladder



Esophagus

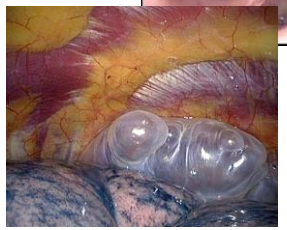
Penile, vulvar

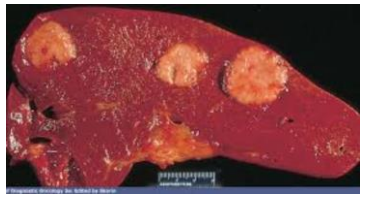
- ..or, **downstaging**
- Endoscopic or interstitial



Lung (PD-1 resistant)

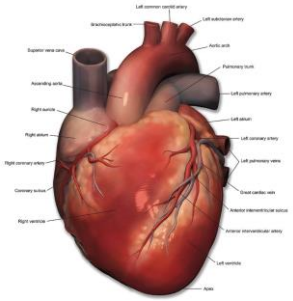
- Mediastinoscopy
- Bronchoscopy
- Thoracoscopy





Liver metastases, pancreatic
Aim: resectability
Approach: transhepatic, US guided or laparoscopic

- **Palliatiation**
- Endoscopic, interstitial
  - Irresectable tumours with PCI applicable therapies/vaccines
  - Decrease pain or obstruction, other local tumour effects
  - Glioblastoma
  - Spinal tumours
  - Esophagus
  - GI
  - Heart




THANK YOU!