Where Science Becomes Hope

UPDATE ON INTRAPERITONEAL CHEMOTHERAPY FOR METASTATIC GASTROINTESTINAL CANCERS

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FINANCIAL DISCLOSURE
NONE

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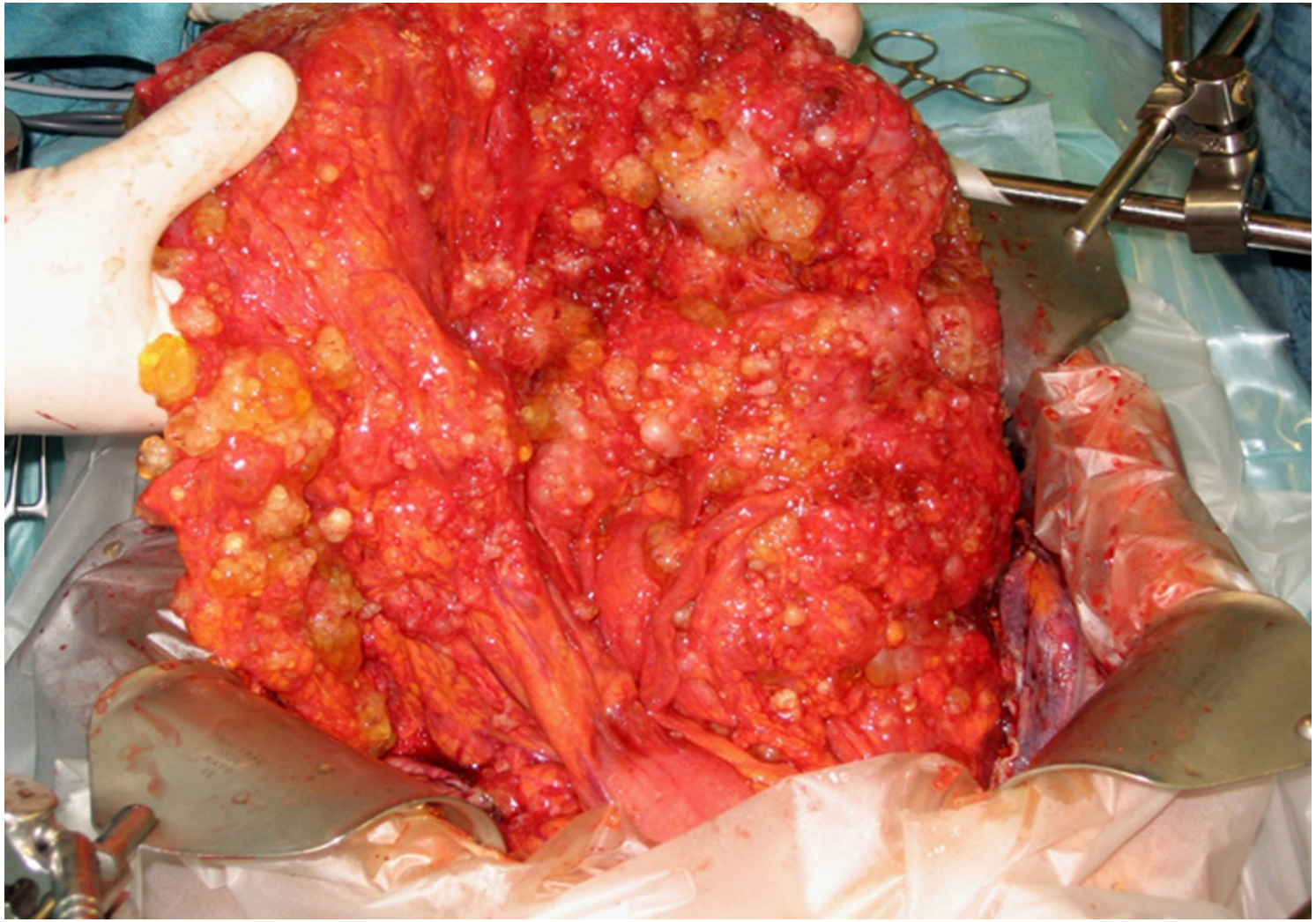
UPDATE AGENDA

- Cytoreductive Surgery and HIPEC for Colorectal Cancer
- Perioperative chemotherapy with HIPEC(Cairo 6)
- Pressurized Intraperitoneal Chemotherapy for Colorectal Cancer(PIPAC)
- Normothermic Iterative Intraperitoneal Chemotherapy for Gastric Cancer- Activating soon

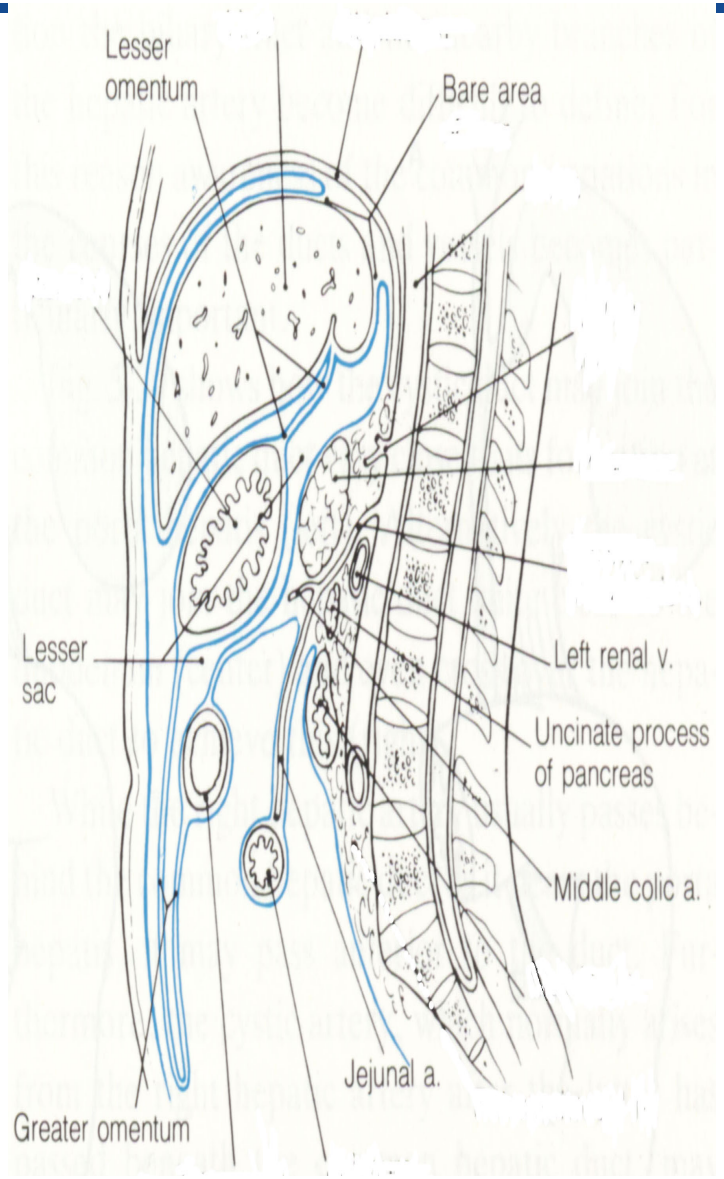
PERITONEAL CARCINOMATOSIS



RATIONALE FOR CYTOREDUCTION SURGERY

- **Consider the Peritoneum as Resectable, locoregional site of disease, not distant metastasis.**
- **Goal is to resect**

all macroscopic disease CC0 resection



Sugarbaker PH, et al. *Ann Surg.* 1995;221(2):124-132.

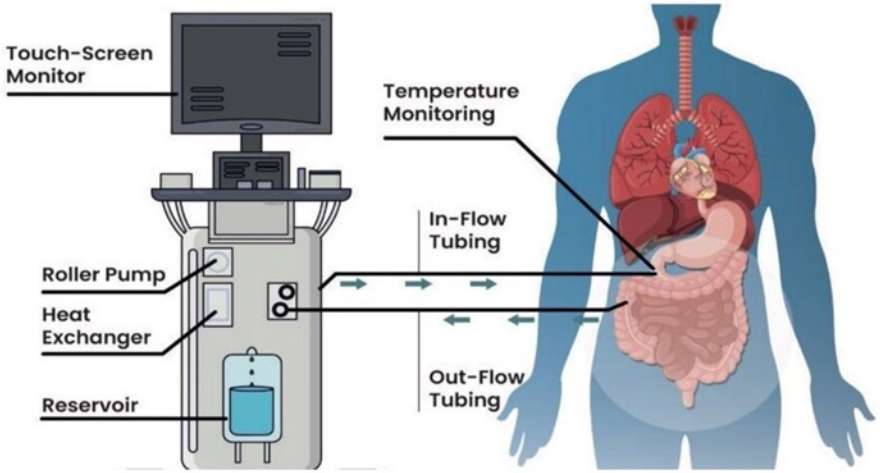
RATIONALE FOR HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

1-4mm of direct tumor absorption

Plasma-peritoneal barrier **high** intraperitoneal concentrations-**low** systemic concentrations

Tumor tissue more sensitive to heat than normal tissue

Hyperthermia synergistically enhances the chemosensitivity of tumor cells to Mitomycin C



CRS/HIPEC FOR CRC[1]

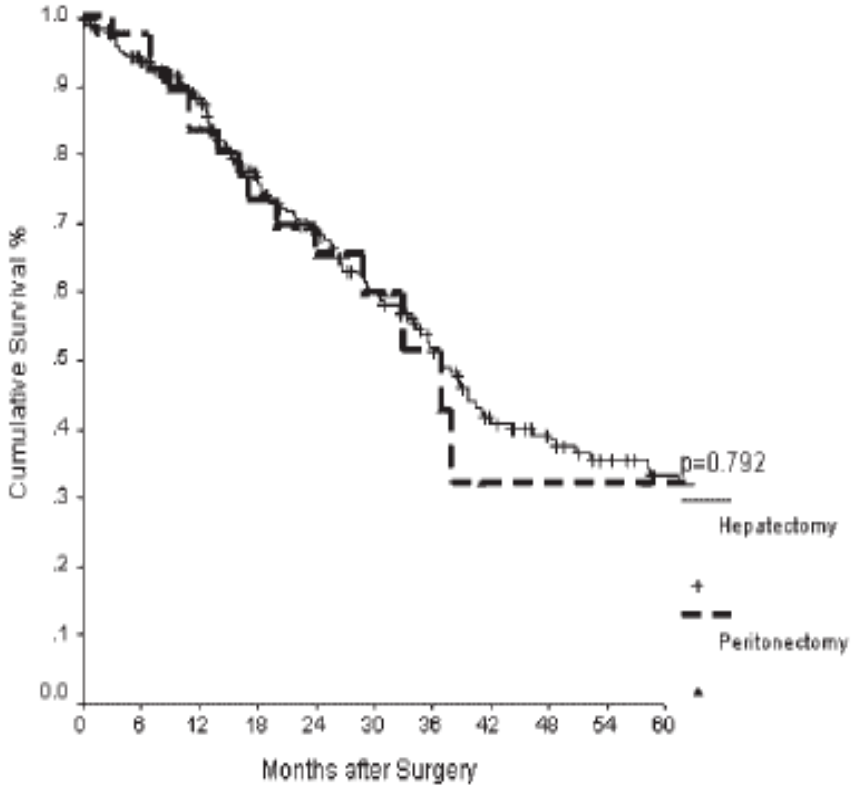


Fig. 1. Overall survival of patients with liver metastasis who underwent hepatectomy versus patients with peritoneal carcinomatosis who underwent peritonectomy.

Table 1

Survival outcome of patients with CRC-PM undergoing CRS + HIPEC

Author	Year	N	Overall survival (mo)	Five-year survival (%)
Glehen (10)	2004	377	32	40
da Silva (11)	2006	70	33	32
Shen (12)	2008	121	34	26
Chua (13)	2009	54	33	NR
Franko (14)	2010	67	34	26
Elias (15)	2010	523	32	30
Elias (16)	2011	146	41	42
Ung (17)	2013	211	47	42
Chua (9)	2013	722	33	43
Esquivel (4)	2014	705	41	NR

1. Esquivel J. *J Gastrointest Oncol.* 2016;7:72-78.

DISEASE SPECIFIC SURVIVAL

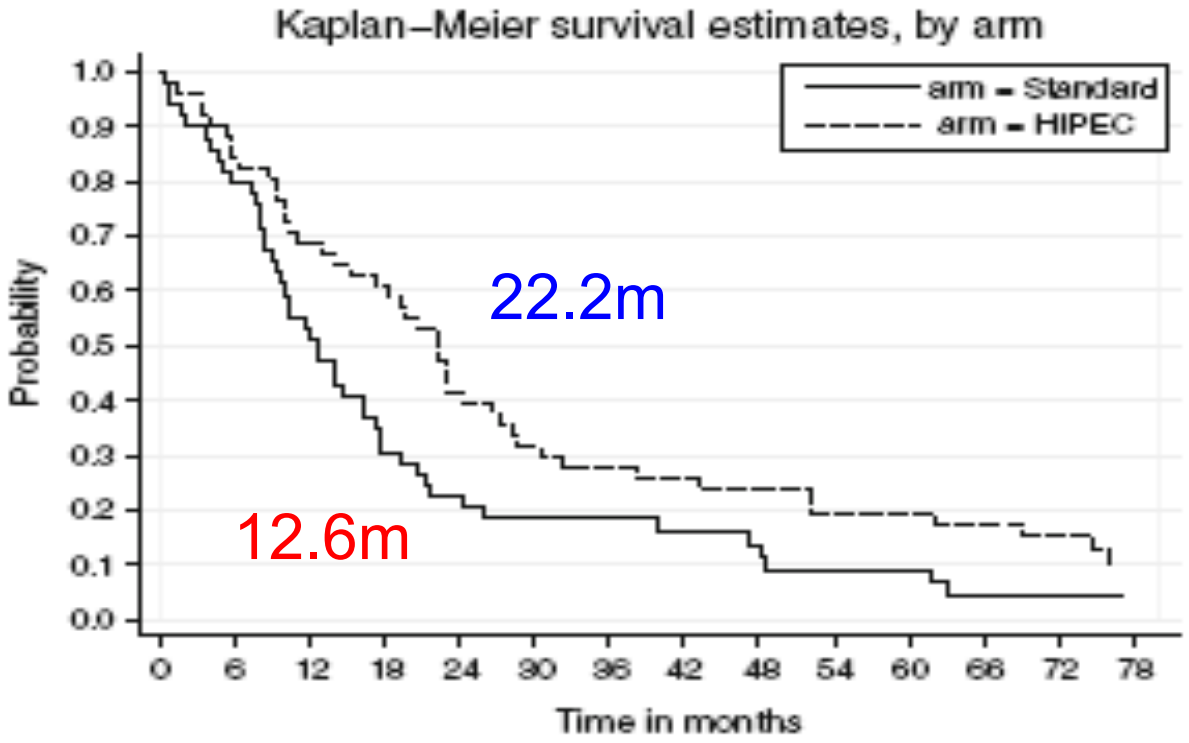


FIG. 2. Disease-specific survival of patients treated for peritoneal carcinomatosis, divided by treatment.

Both Intraperitoneal and systemic treatments are important for colon cancer

Verwaal ASO 2008

Results

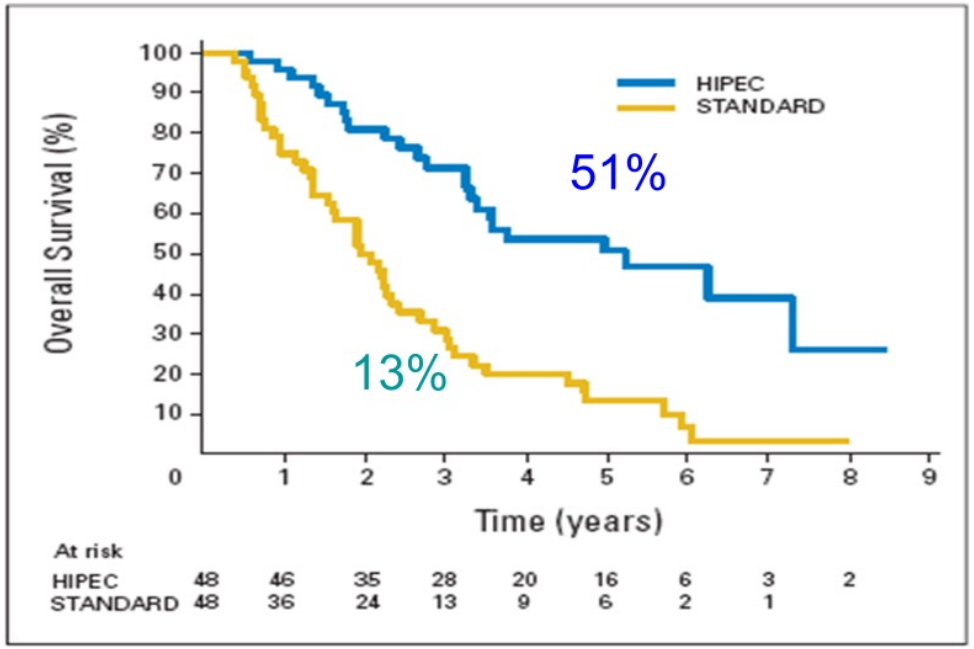


Fig 1. Overall survival of group receiving cytoreductive surgery, hyperthermic intraperitoneal chemotherapy (HIPEC), and systemic treatment versus those receiving standard treatment.

Median Survival 23.9 months systemic chemo

62.7 months for CRS and HIPEC

Elias JCO 2009

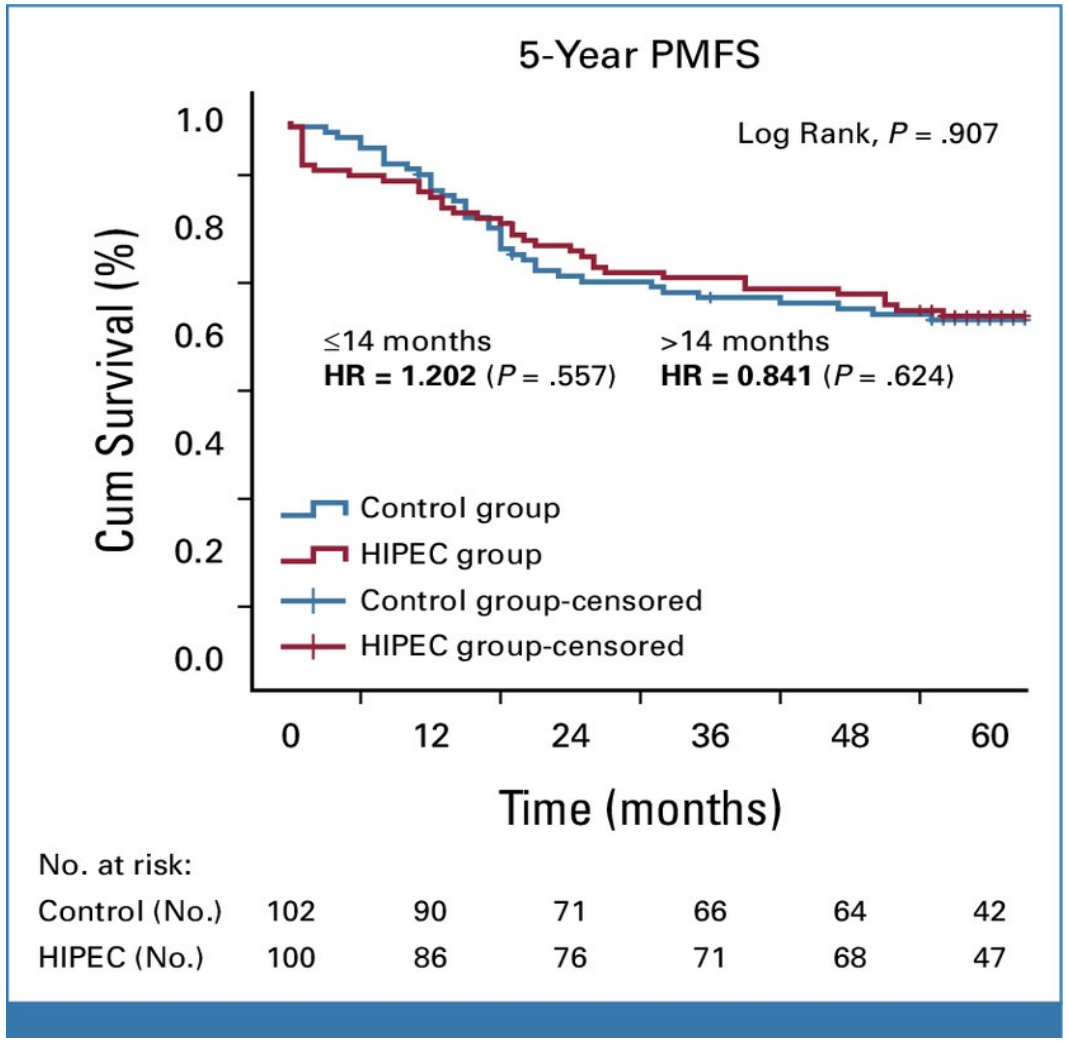
Prodige 7
Colopec
Prophylochip

Oxali with 30 min hyperthermia

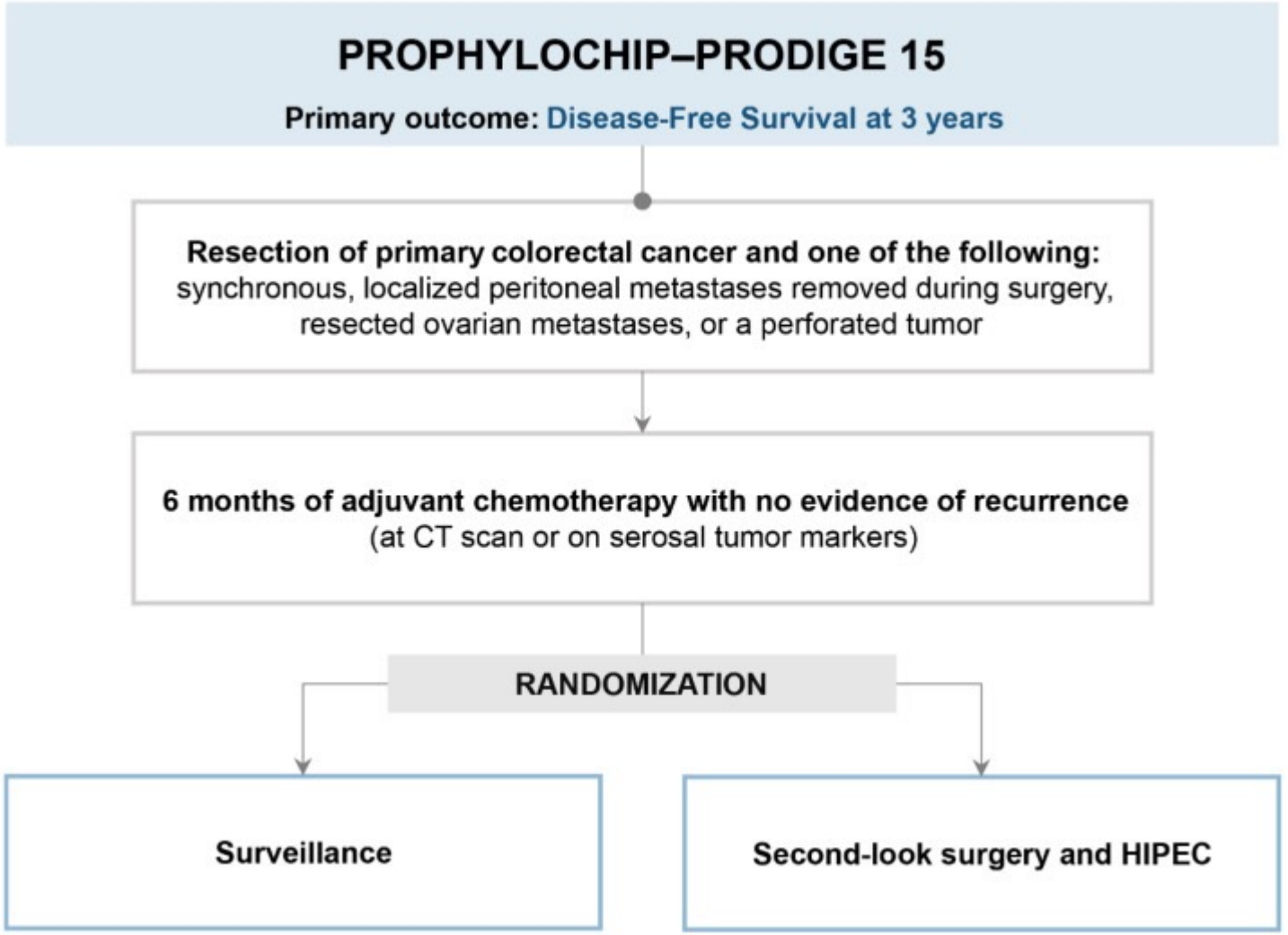
COLOPEC-2024

T4N0-2M0 resectable tumors
N=204 pts
Oxaliplatin 460 mg/m2

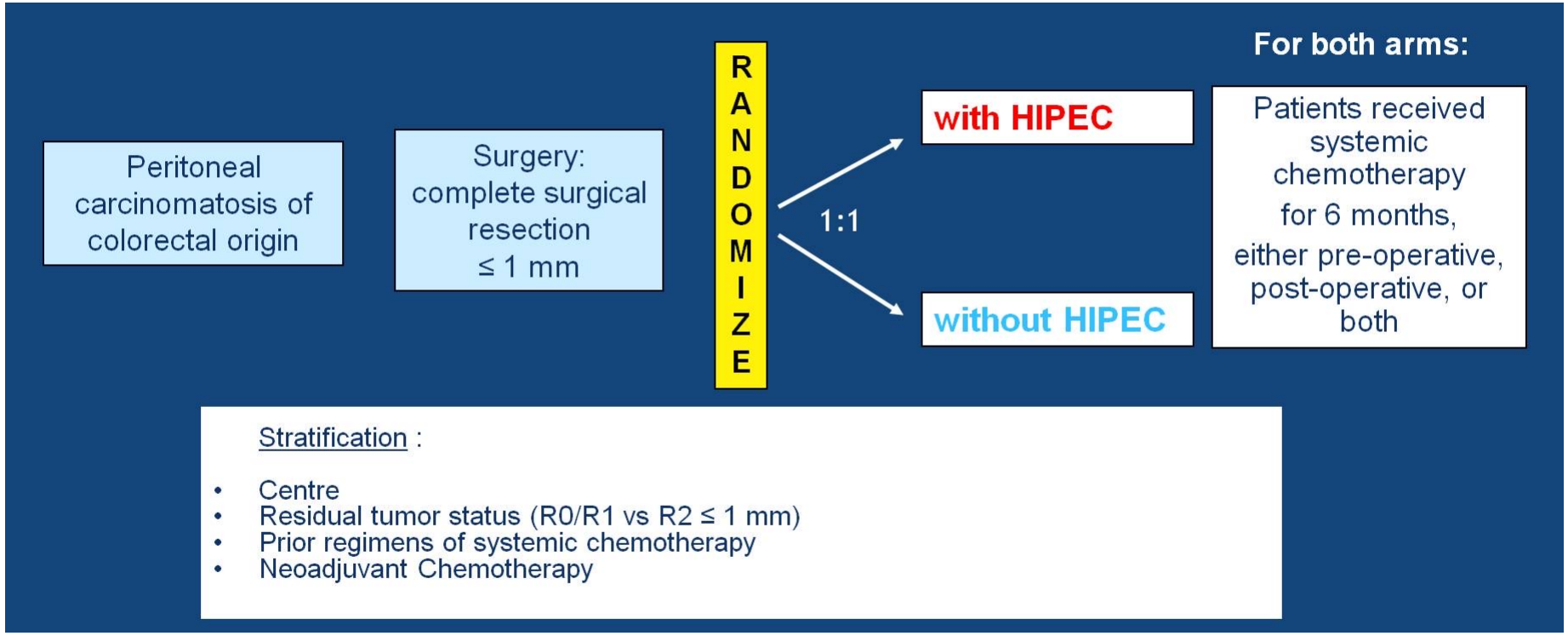
No benefit of adjuvant HIPEC



Second look surgery Detecting early recurrence did not change overall survival compared to routine surveillance



PRODIGE 7 TRIAL DESIGN- PHASE 3 RCT

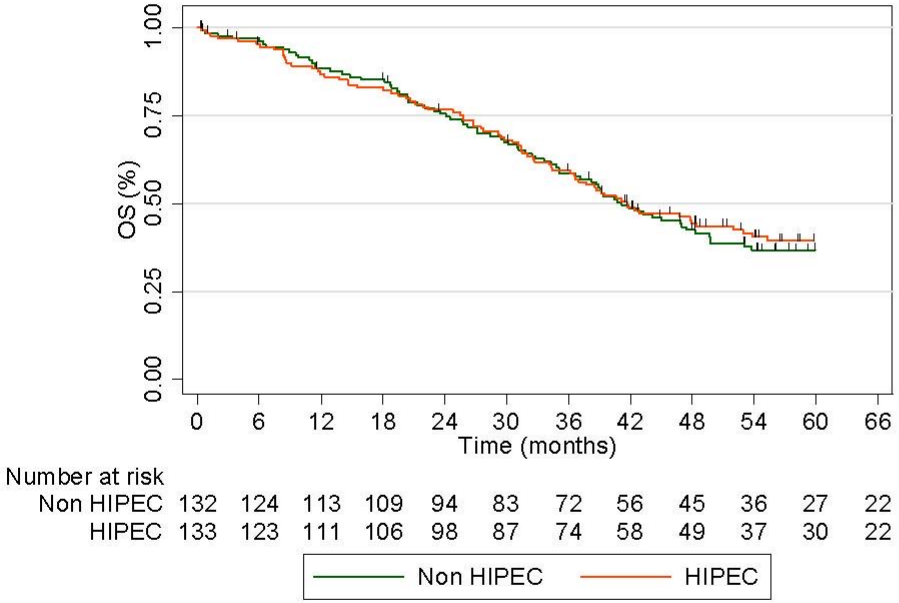


HIPEC- Oxaliplatin

1. Quenet F, et al. *J Clin Oncol.* 2018;36:LBA3503.

OVERALL SURVIVAL (ITT)

Median follow-up: 64 months (95% CI 58.9-69.8)



	HIPEC	Non-HIPEC	P value
Median Survival, months [95% CI]	41.7 [36.2-52.8]	41.2 [35.1-49.7]	0.995
1-year Survival	86.9%	88.3%	
5-year Survival	39.4%	36.7%	

HR = 1.00, 95% CI [0.73-1.37], *P* = 0.995

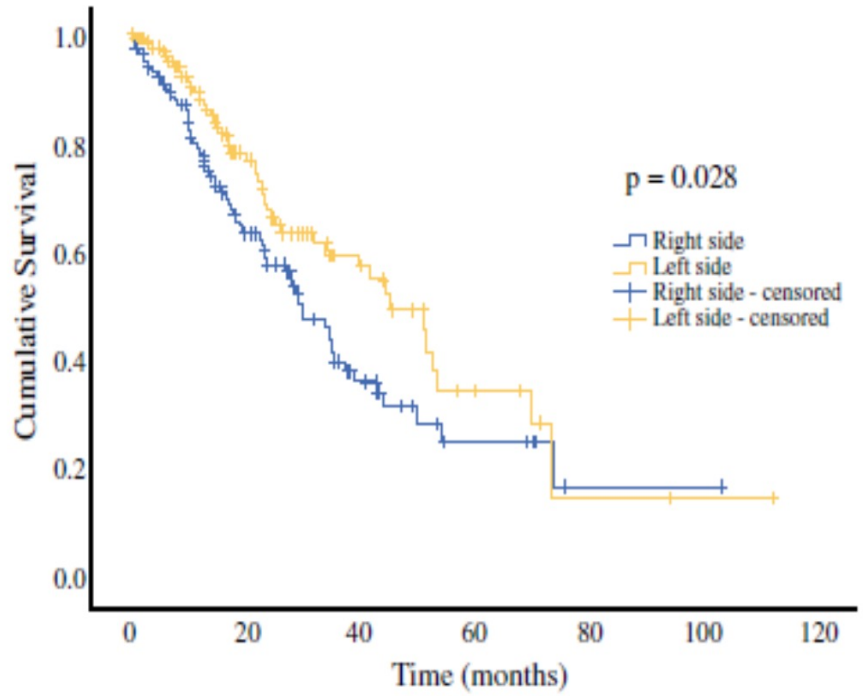
1. Quenet F, et al. *J Clin Oncol.* 2018;36:LBA3503.

PRODIGE 7 CONCLUSIONS

The addition of oxaliplatin-HIPEC compared to cytoreductive surgery alone does not influence OS and RFS

The curative management of PC from colorectal cancer by cytoreductive surgery alone shows unexpected excellent survival results

<u>Limitations</u>: heterogeneous group, prognostic factors- Ras, BRAF, sidedness, chemo resistance using same drug, HIPEC factors- 30 vs 90 min perfusion, poor chemotherapy choice, short hyperthermia

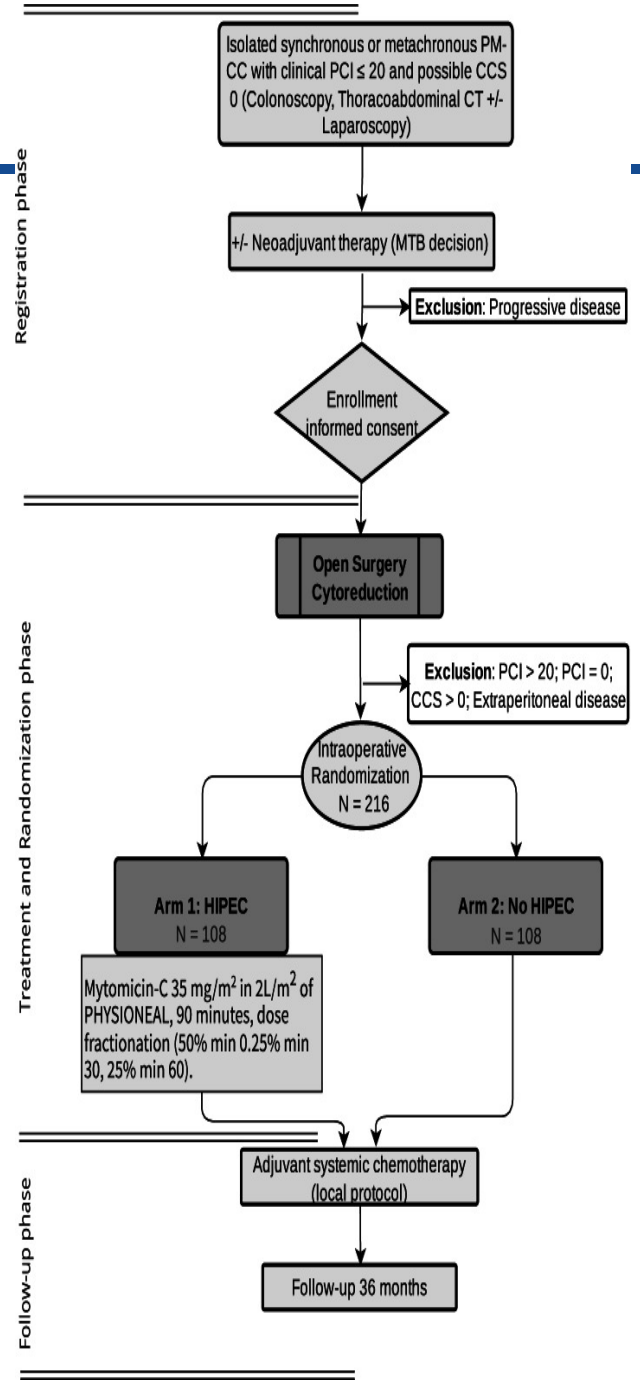


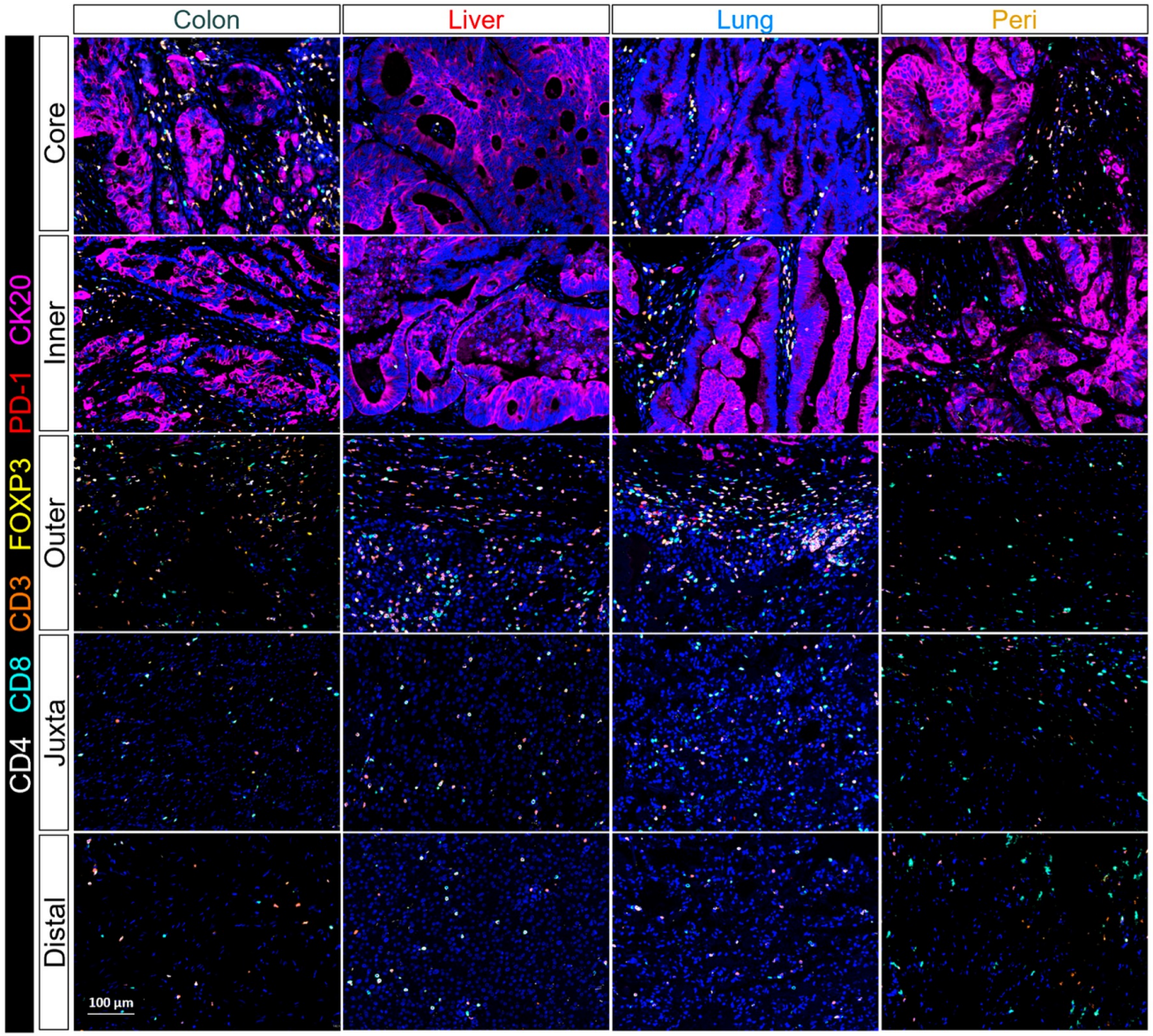
1. Quenet F, et al. *J Clin Oncol.* 2018;36:LBA3503.

GECOP-MMC

PHASE 4 TRIAL

216 patients
Activated 2022





42 patients with resected MSS CRC (primary, liver, lung, peritoneum) at City of Hope

Multiplex IF of FFPE specimens

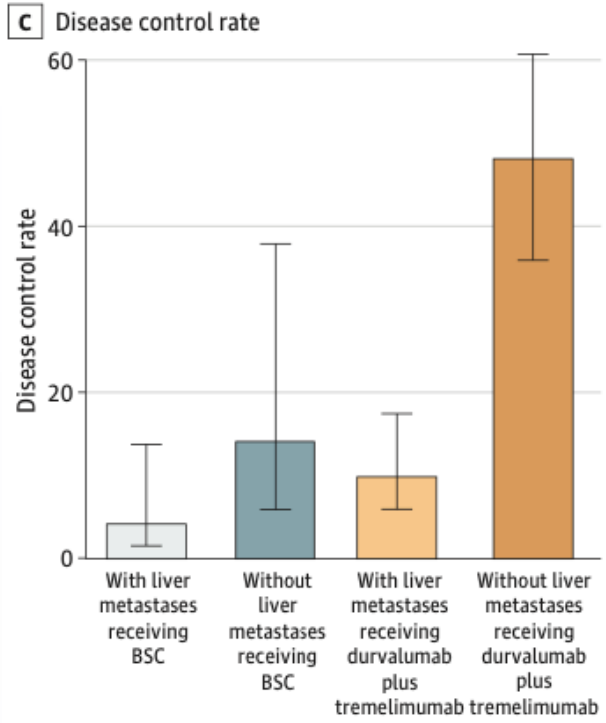
>> T cell and NK cell activation and suppression markers **similar** between peritoneal and lung metastases

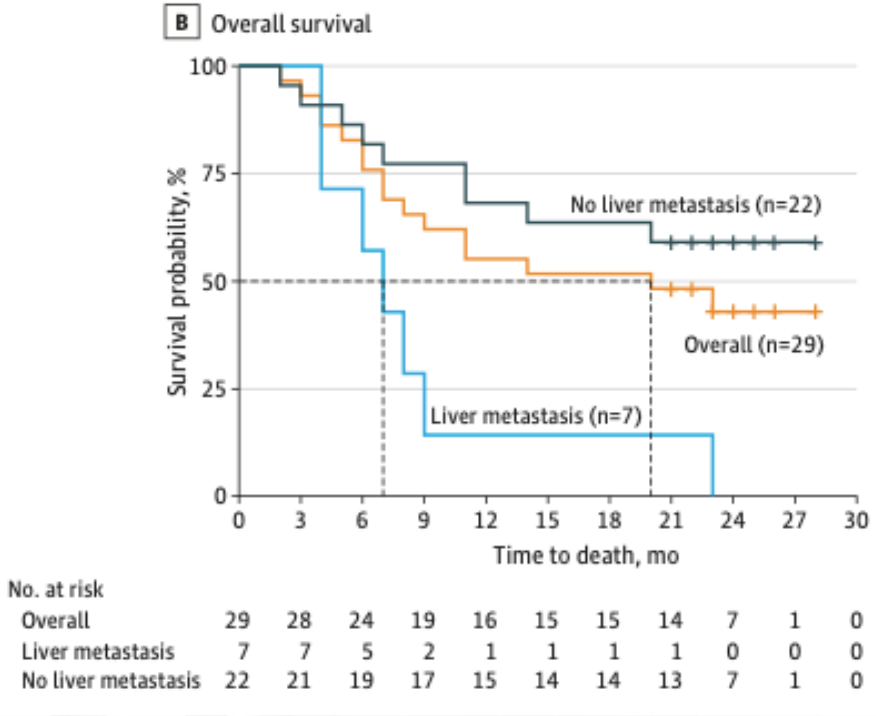
>> peritoneal metastases distinct from other metastatic sites: **high levels of PD-1 receptor and ligands, and fibrosis-related proteins**

Key
Cancer cell: CK20+
CD4 T cell: CD3 CD4+
T reg cell: CD3 CD4 FOXP3+
CD8 T cell: CD3 CD8+

Ye J et al. Cancer Res Commun; 3(10) October 2023

Dual ICI Effective for Metastatic pMMR CRC <u>in Absence of LM</u>





CCTG CO.26 – Durva/treme vs BSC
Without LM:

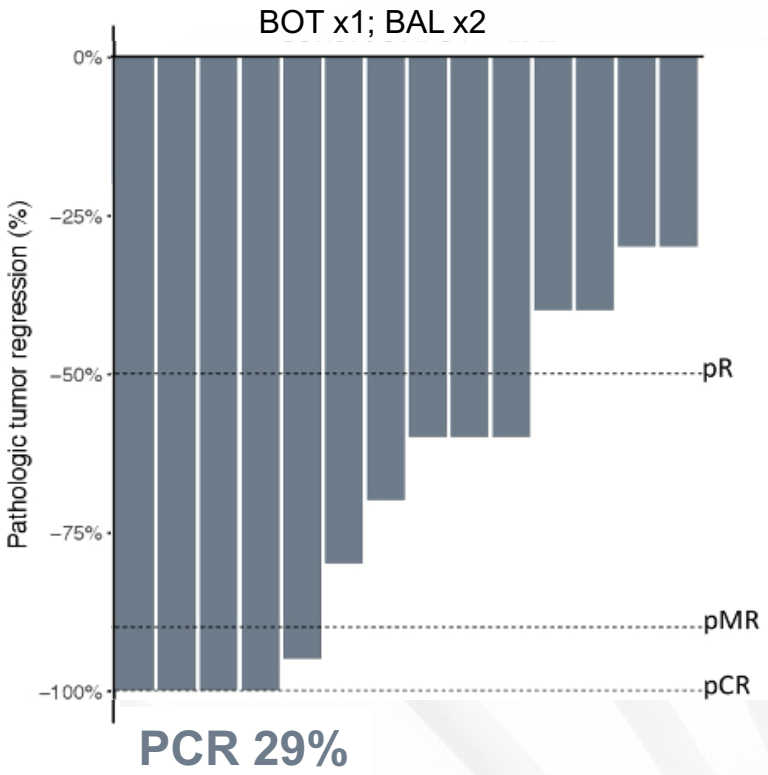
- RR *(not published)*
- DCR 49%
- Median OS 9.4 months
- (HR 0.69, 90% CI 0.51-0.94)

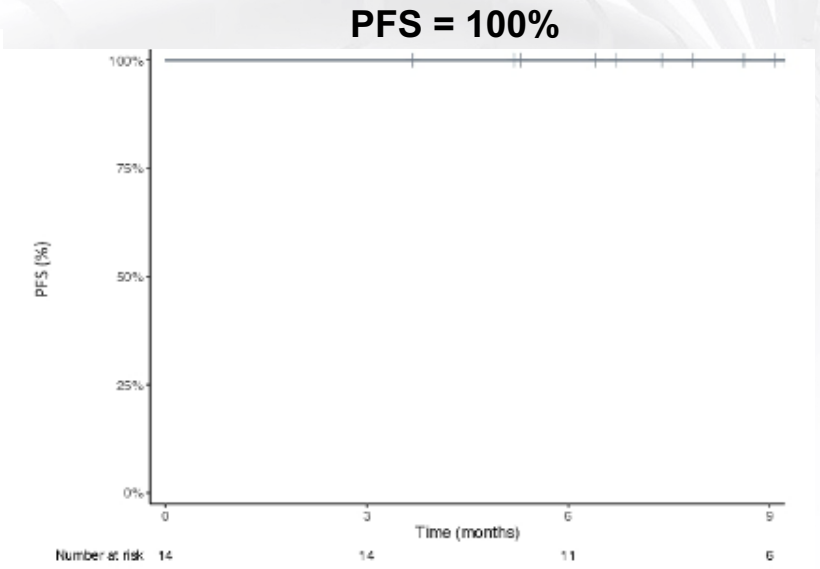
RIN – Regorafenib, ipi, nivo
Without LM:

- RR 36%
- DCR 68%
- Median OS >22 months

Chen EX. JAMA Network Open. 2023
Fakih. JAMA Onc. 2023

Second-Gen Dual ICI with Improved Responses in Resectable pMMR CRC





UNICORN (NCT05845450)

Response Rate:
BOT/BAL: 10/14 (71%)

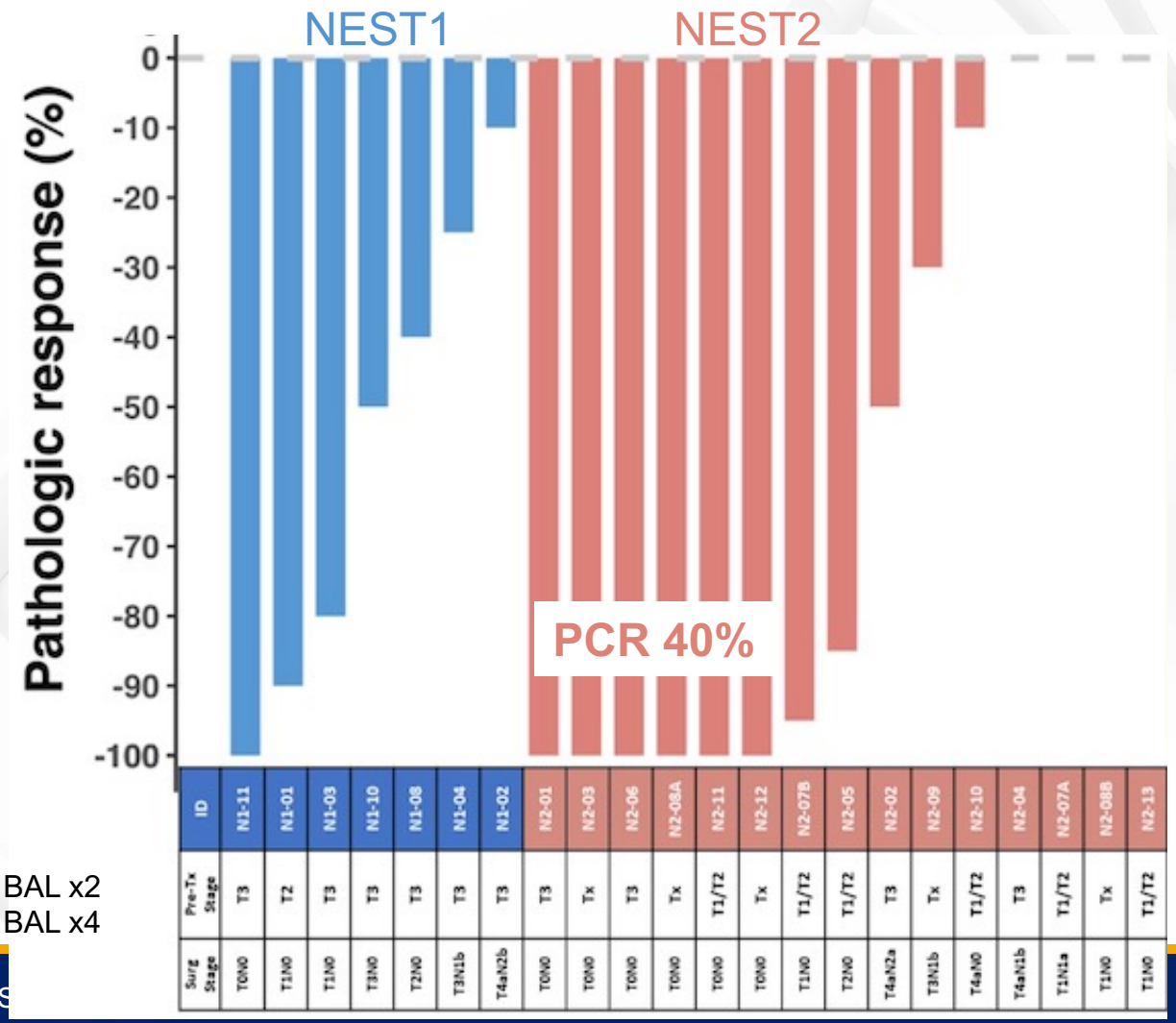
Unresolved irAE:
0%

imCD:
2/56 (4%)
(0% grade 3)

Delays to OR > 4 weeks:
0/56 (0%)

Chelardi F et al. ASCO GI 2025

Second-Gen Dual ICI with Improved Responses in Resectable pMMR CRC



NEST1 BOT x1; BAL x2
NEST2 BOT x1; BAL x4

Response Rate:
NEST2: 9/15 (60%)

Unresolved irAE:
0/24 (0%)

imCD:
6/24 (25%)
NEST2: 5/14 (36%)
(14% grade 3)

Delays to OR:
0/24 (0%)

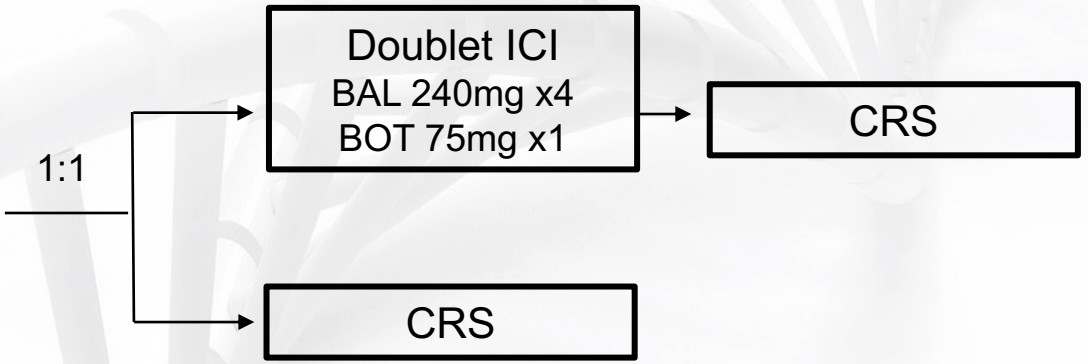
Kasi P et al. ESMO GI. 2024
Hissong K et al. ASCO GI. 2025

Hypothesis:

Preoperative Bot/Bal can overcome T-cell exhaustion of the peritoneal niche to improve PFS for oligometastatic resectable peritoneal pMMR CRC suitable for cytoreductive surgery

EA2255

Key Eligibility Criteria:
- mCRC pMMR, BRAFwt
- PCI ≥1
- No solid organ metastasis[1]
- Anticipated ability to achieve complete CRS (CCO/1)
- Disease stability following ≥6 cycles of 5-FU based therapy[2]
- ECOG PS 0-1



Stratification:
Grade (well/mod vs. poor/signet)
PCI (< vs. ≥12)
HIPEC (yes/no)

Primary Endpoint:
PFS (median)
H0: 14 months
H1: 23.3 months
HR 0.60
N= 144

[1] Any calcified pulmonary nodules, and/or ≤5 pulmonary nodules measuring ≤6 mm are allowed
[2] Includes doublet or triplet therapy +/- EGFR/VEGF

2025 ASCO ANNUAL MEETING

Perioperative systemic therapy for resectable colorectal peritoneal metastases: a multicenter randomized phase 3 trial (CAIRO6)

Koen P. Rovers; Checca Bakkers; Teun B.M. van den Heuvel; Vincent C.J. van de Vlasakker; Jurriaan B. Tuynman; Arend G.J. Aalbers; Djamila Boerma; Alexandra R.M. Brandt-Kerkhof; Philip R. de Reuver; Patrick H.J. Hemmer; Wilhelmina M.U. van Grevenstein; Kurt van der Speeten; Cornelis J.A. Punt; Marcel G.W. Dijkgraaf; Pieter J. Tanis; Ignace H.J.T. de Hingh on behalf of the Dutch Colorectal Cancer Group (DCCG) & Dutch Peritoneal Oncology Group (DPOG)

Ignace H. De Hingh, MD, PhD

Catharina Hospital Eindhoven, the Netherlands
GROW, Maastricht University, the Netherlands

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Resectable colorectal peritoneal-only metastases

Value of perioperative systemic therapy?

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CAIRO6: A phase 3 multicenter superiority trial

Hypothesis:

Addition of perioperative systemic therapy to CRS & HIPEC results in a 3-year survival of **65%** as compared to **50%** with CRS & HIPEC alone (HR 0.63)

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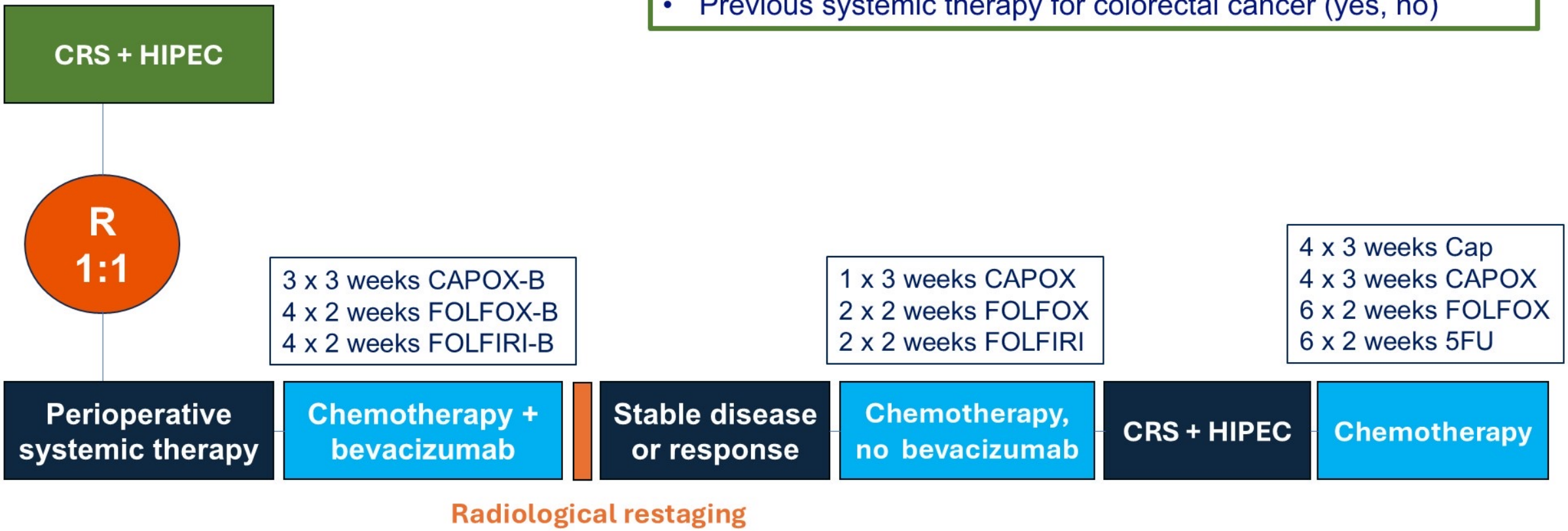
DESIGN

Stratification:
- Onset of peritoneal metastases (synchronous, metachronous)
- Peritoneal Cancer Index (1-10, 11-20)
- Previous systemic therapy for colorectal cancer (yes, no)



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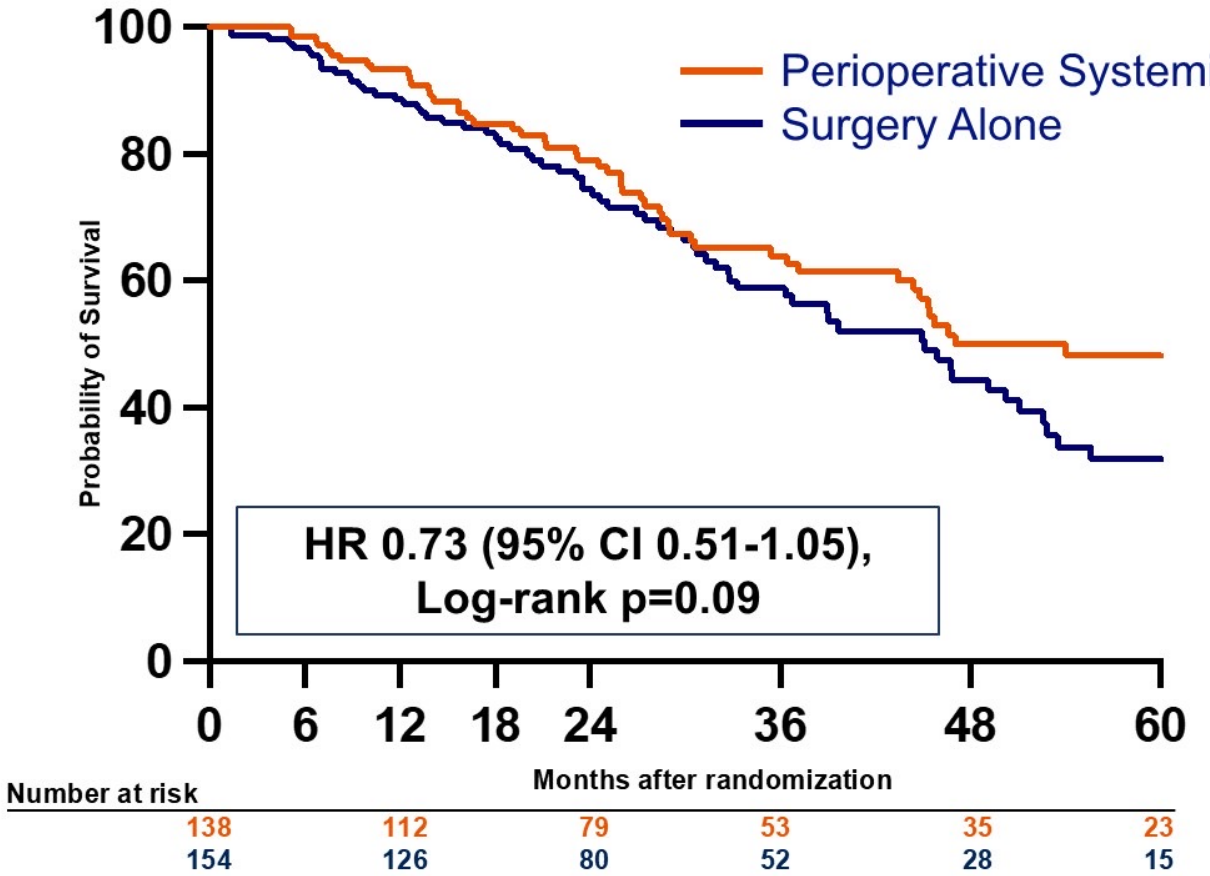
Overall Survival after CRS & HIPEC



	Perioperative therapy	Surgery alone
Median OS	54 months	45 months
1-year	93%	89%
3-year	64%	59%
5-year	48%	32%

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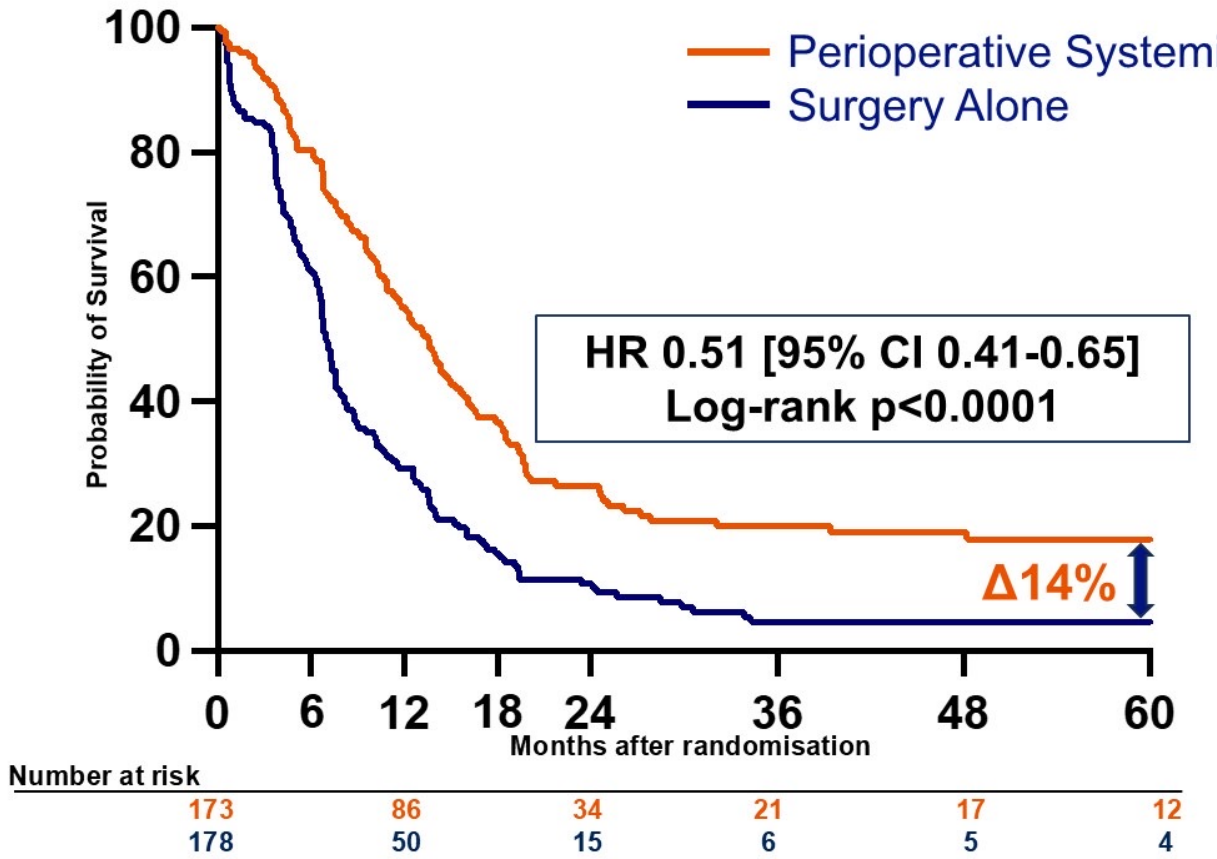
Progression-free Survival



	Perioperative therapy	Surgery alone
Median PFS	14 months	7 months
1-year	55%	29%
3-year	20%	4%
5-year	18%	4%

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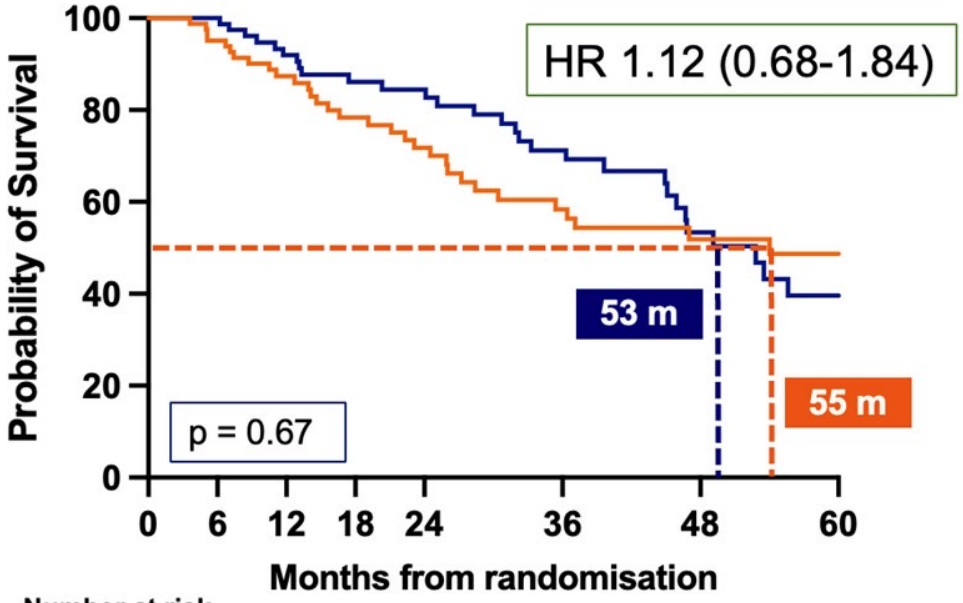
Primary Tumor Location

Perioperative Systemic Therapy
Surgery Alone

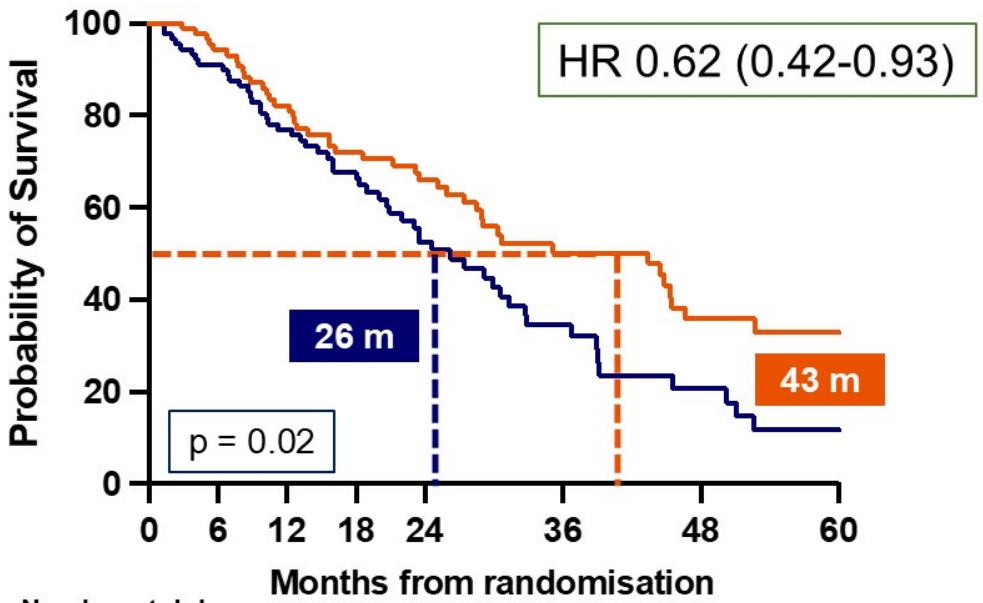
Left-sided colon cancer (n=162)



Number at risk

	82	60	42	29	21	12
	80	66	47	36	19	11

Right-sided colon cancer (n=175)



Number at risk

	86	66	41	25	15	10
	89	65	33	15	7	4

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

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PIPAC

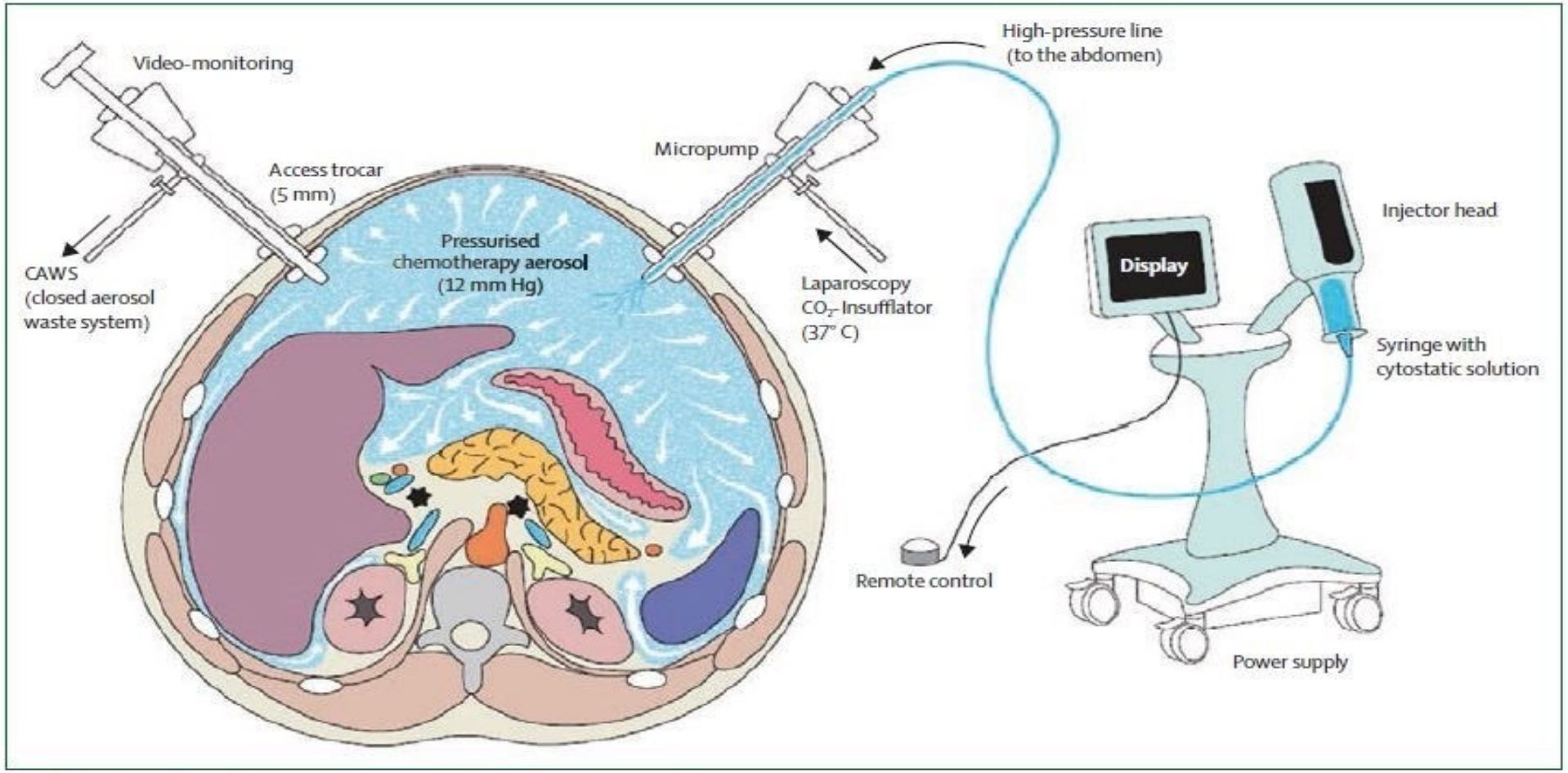


Figure 2: **Schematic of PIPAC set-up**
A hermetically sealed 10–12-mm trocar and a 5-mm balloon trocar are inserted. The liquid chemotherapy regimen is vaporised using a standard injector connected to a nebuliser. Reprinted from Hübner and colleagues[36] with permission from Médicine et Hygiène. PIPAC=pressurised intraperitoneal aerosol chemotherapy.

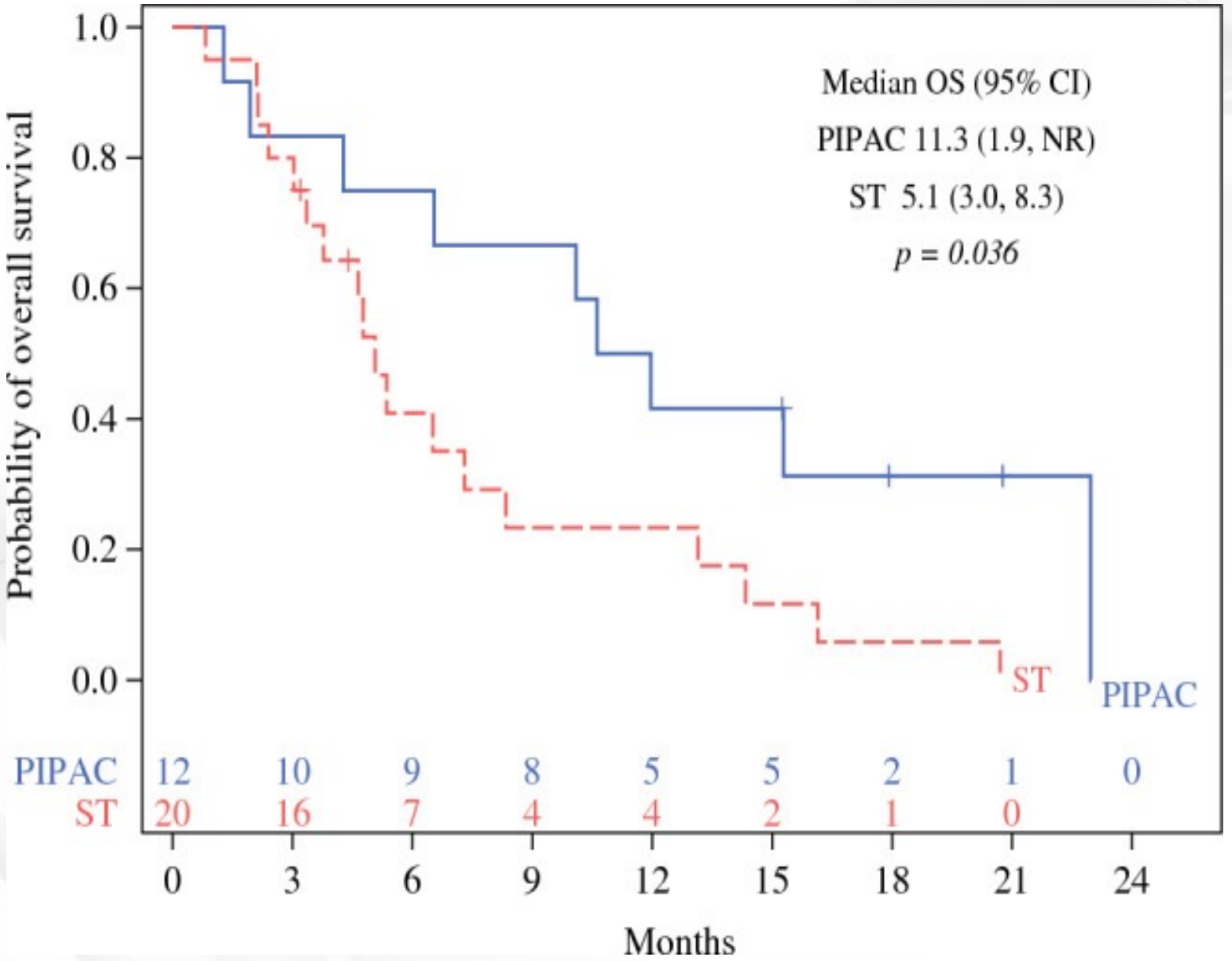
IMPACT OF PIPAC-OXALIPLATIN ON FUNCTIONAL RECOVERY, GOOD DAYS, AND SURVIVAL IN A REFRACTORY COLORECTAL AND APPENDICEAL CARCINOMATOSIS: SECONDARY ANALYSIS OF THE US PIPAC COLLABORATIVE PHASE 1 TRIAL
CITY OF HOPE

Phase 1 trial PIPAC vs standard therapy
32 patients
Primary outcome # of good days, secondary outcome OS, PFS and quality of life

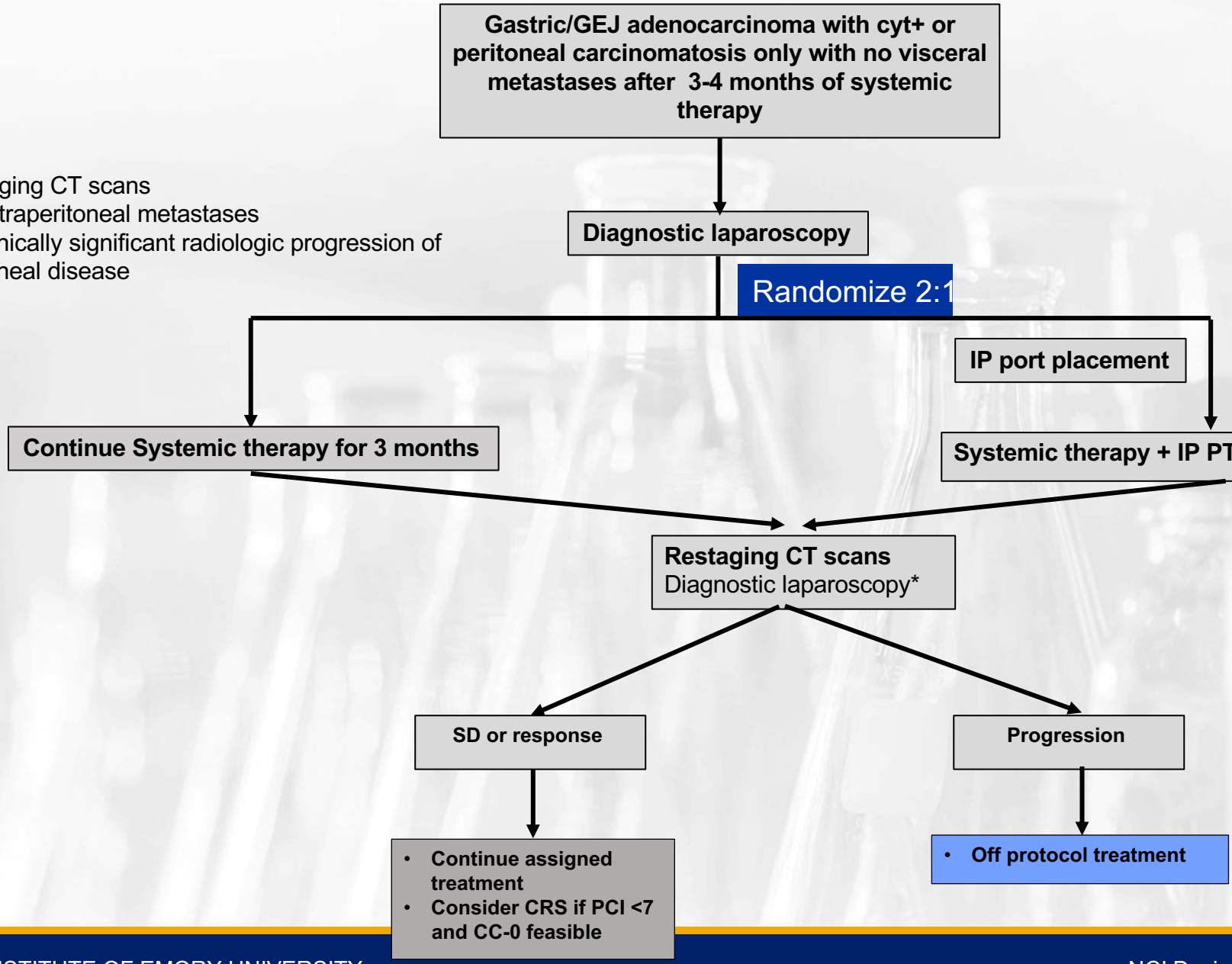
Comparison of hospital stays and good days between the ST and PIPAC cohorts

Characteristic	ST cohort(n = 20)	PIPAC cohort(n = 12)	p value
6-Month hospital stays: n (%)			
No	5 (27.8)	7 (58.3)	0.098
Yes	13 (72.2)	5 (41.7)	
1-Year hospital stays: n (%)			
No	2 (11.1)	4 (33.8)	0.2
Yes	16 (88.9)	8 (66.7)	
6-Month hospital stays: median (IQR)	1 (0–2)	0 (0–1)	0.015
1-Year hospital stays: median (IQR)	2 (1–2.25)	1 (0–1.75)	0.052
Good days in 6 months: median (IQR)	131 (90–180)	181 (151–184)	0.042
Good days in 1-year: median (IQR)	131 (90–227)	323 (160–365)	0.032
Good days in 6 months: mean ± SD	127 ± 53	154 ± 54	0.042
Good days in 1 year: mean ± SD	170 ± 115	262 ± 128	0.032

No decrease in Quality of life with PIPAC


Probability of overall survival
1.0
0.8
0.6
0.4
0.2
0.0
Median OS (95% CI)
PIPAC 11.3 (1.9, NR)
ST 5.1 (3.0, 8.3)
p = 0.036
ST
PIPAC
PIPAC 12 10 9 8 5 5 2 1 0
ST 20 16 7 4 4 2 1 0
0 3 6 9 12 15 18 21 24
Months

EA2234 –STOPGAP Phase II/III Study Schema



Restaging CT scans
No extraperitoneal metastases
No clinically significant radiologic progression of peritoneal disease

MSI-H excluded
Stratification:
PCI = 0, 1-6, 7-14, 15 or greater
Chemo + targeted agent / IO vs. Chemo alone

Primary endpoint:
- PFS – Phase II
- OS- Phase III

Secondary Endpoints:
- Adverse events
- QOL

* If clinically indicated to assess surgical candidacy

SUMMARY

Oxaliplatin based HIPEC not beneficial

CRS alone shows surprising improved survival of almost 4 years

Prophylactic and adjuvant HIPEC(oxali) not beneficial

Mitomycin HIPEC still being investigated- Spanish trial pending

Routine use of perioperative chemotherapy in HIPEC patients in some doubt

Role of 2nd gen immunotherapy for PM most interesting

Role of PIPAC in palliation stay tuned