Nieuwe ontwikkelingen rond systemische behandelingen alvleesklierkanker

G.A. Cirkel, internist oncoloog

26 September 2025

Alvleeskanker in Nederland: hoeveel beter kan het?

DPCG
Dutch Pancreatic Cancer Group

JAMA Surg. 2024;159(4):429-437

PACAP-1 TRIAL

Impact of nationwide enhanced implementation of best practices in pancreatic cancer care (PACAP-1): a multicenter stepped-wedge cluster-randomized controlled trial

Tara M Mackay, Anouk E Latenstein, Simone Augustinus
www.dpcg.nl – *pacap-1@dpcg.nl*

KWF KANKER BESTRIJDING

Baseline

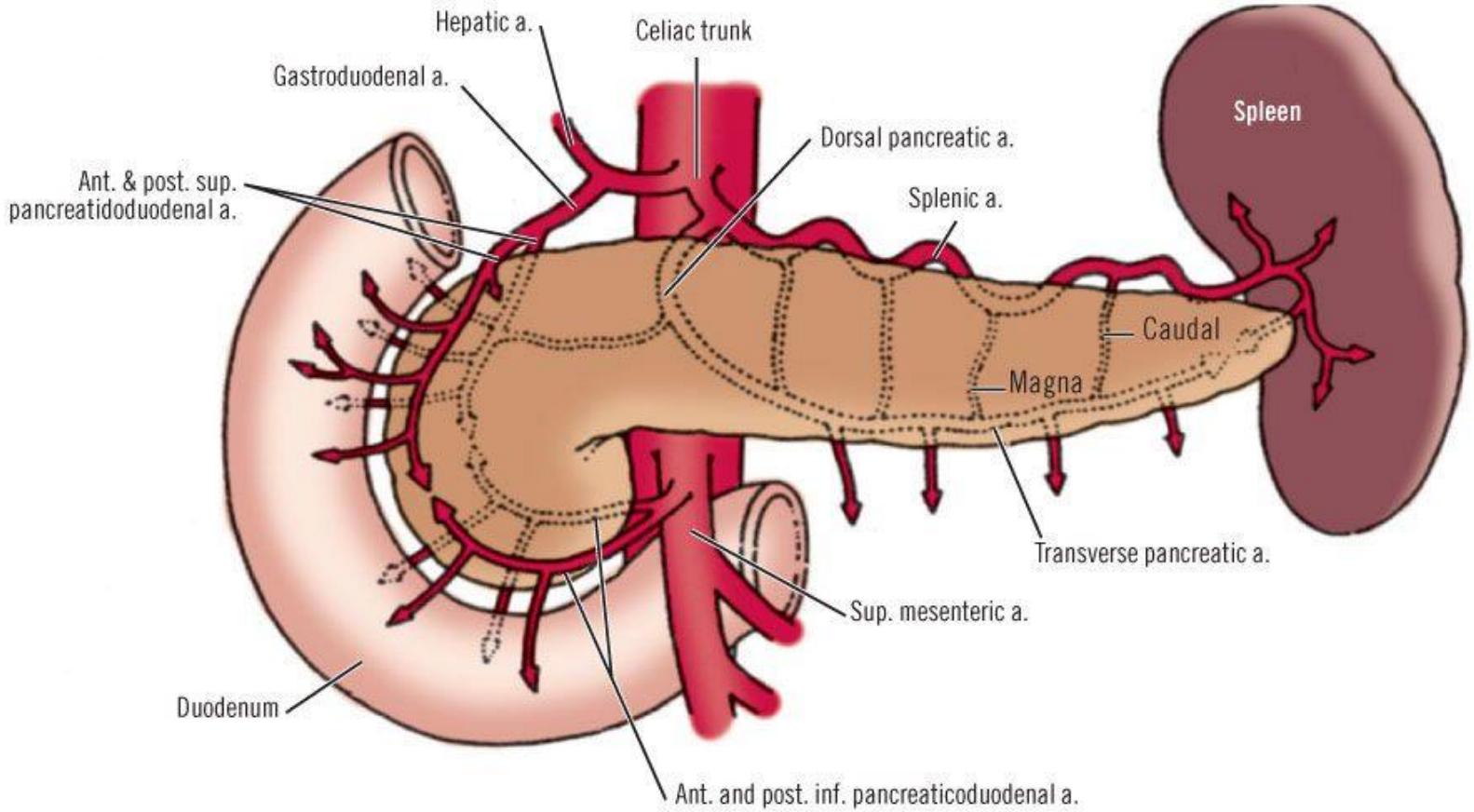
- **6268 patients:**
  - Current practice: 2762
  - Wash in: 307
  - Best practice: 3199

- **Karakteristieken**:

• Leeftijd	72.0 (64.0 – 79.0) - 72.0 (65.0 - 79.0)
• Vrouw	50% - 50%
• Resectabel	21% - 19%
Borderline resectabele	6% - 8%
Lokaal gevorderd	10% - 12%
Gemetastaseerd	62% - 62%

JAMA Surg. 2024;159(4):429-437

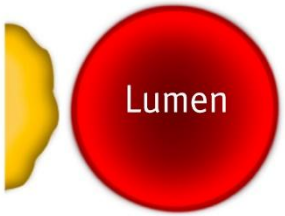
Resectabiliteit



Resectabiliteit

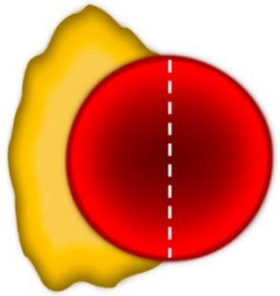
No tumor contact

"Resectable"



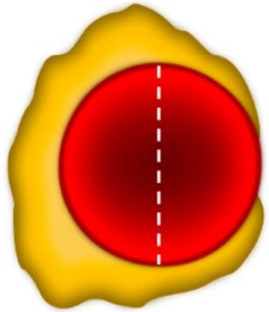
Abutment (≤ 180˚)

"Borderline Resectable"



Encasement (> 180˚)

"Unresectable"



	SMA	Celiac axis	CHA	SMV-PV
Resectable (all four required)	no contact	no contact	no contact	≤ 90° contact
Borderline resectable (minimally one required)	≤ 90° contact	≤ 90° contact	≤ 90° contact	90°-270° contact, and no occlusion
Irresectable (minimally one required)	contact > 90°	contact > 90°	contact > 90°	contact > 270° or occlusion

Best practices

- Perioperative chemotherapy: target was set at 70% of all patients undergoing resection receiving adjuvant chemotherapy
- Palliative chemotherapy: target at 40% of all patients with metastatic disease
- Pancreatic enzyme replacement therapy
- Referral to a dietician
- Endoscopic metal stents instead of plastic for biliary drainage.

JAMA Surg. 2024;159(4):429-437

Best practices

DPCG
Dutch Pancreatic Cancer Group

Table 3. Implementation of Best Practices

Best practice treatments	No.[a]	Adjusted %		Difference in best practice treatments[b]	
		Current practice	Best practice	OR (95% CI)[b]	*P* value
Neoadjuvant chemotherapy in nonmetastasized patients[c]	2433	10.9	11.3	1.31 (0.69-1.45)	.41
Adjuvant chemotherapy in patients after surgical resection[d]	829	48.3	51.2	1.13 (0.71-1.79)	.60
Palliative chemotherapy in patients with metastasized pancreatic cancer	3147	23.9	30.3	1.38 (1.10-1.74)	.01
Pancreatic enzyme replacement therapy	5580	34.2	45.2	1.64 (1.28-2.11)	<.001
Referral to dietician	5580	59.3	62.9	1.16 (0.92-1.45)	.21
Use of metal stents for biliary endoscopic drainage	1725	74.1	83.3	1.78 (1.13-2.80)	.01

Abbreviations: OR, odds ratio; WHO, World Health Organization.

[a] No. of patients in the subgroup the outcome is evaluated in (after imputation of baseline characteristics), in all outcomes with no missing data, or less than 0.1% is present.

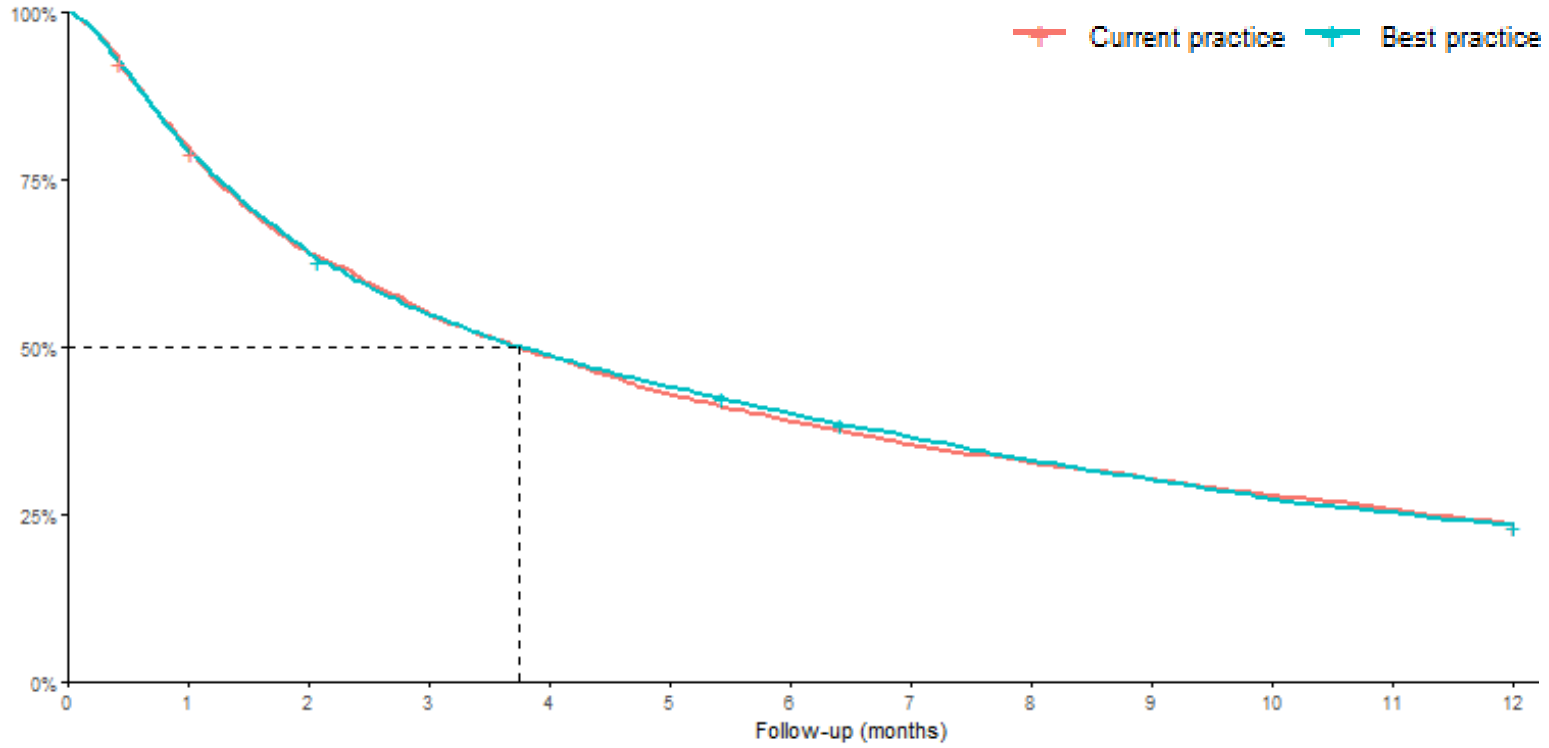
[b] Using a random intercept for hospital and a random slope on intervention effect for hospital and adjusted for (calendar) time.

[c] Including patients that received induction chemotherapy only, but did not undergo resection.

[d] Random intercept removed to mitigate singularity errors of the random effects.

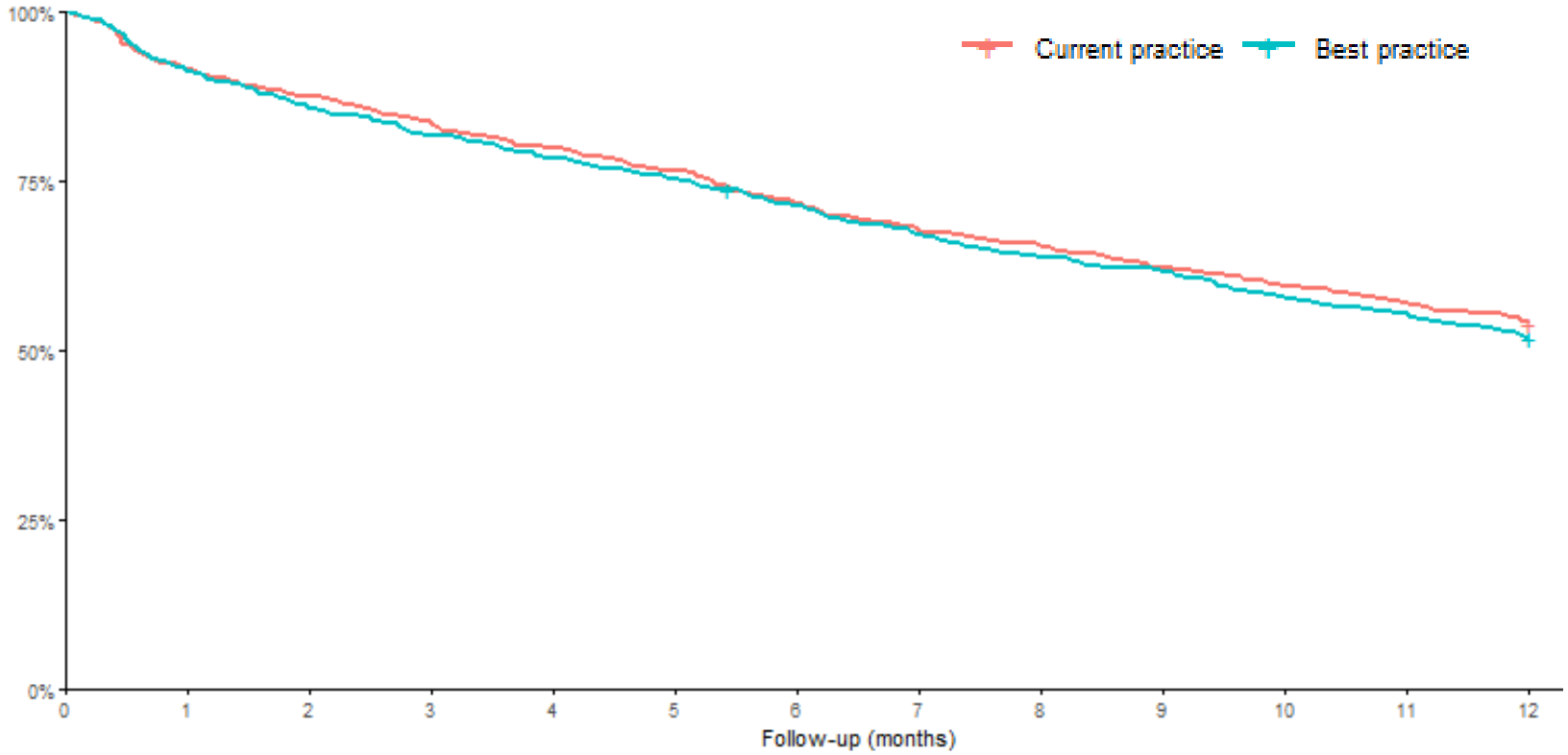
Overleving

- **No significant difference in 1 year survival**
  HR: 0.98, 95% CI 0.89 - 1.08, p = 0.743



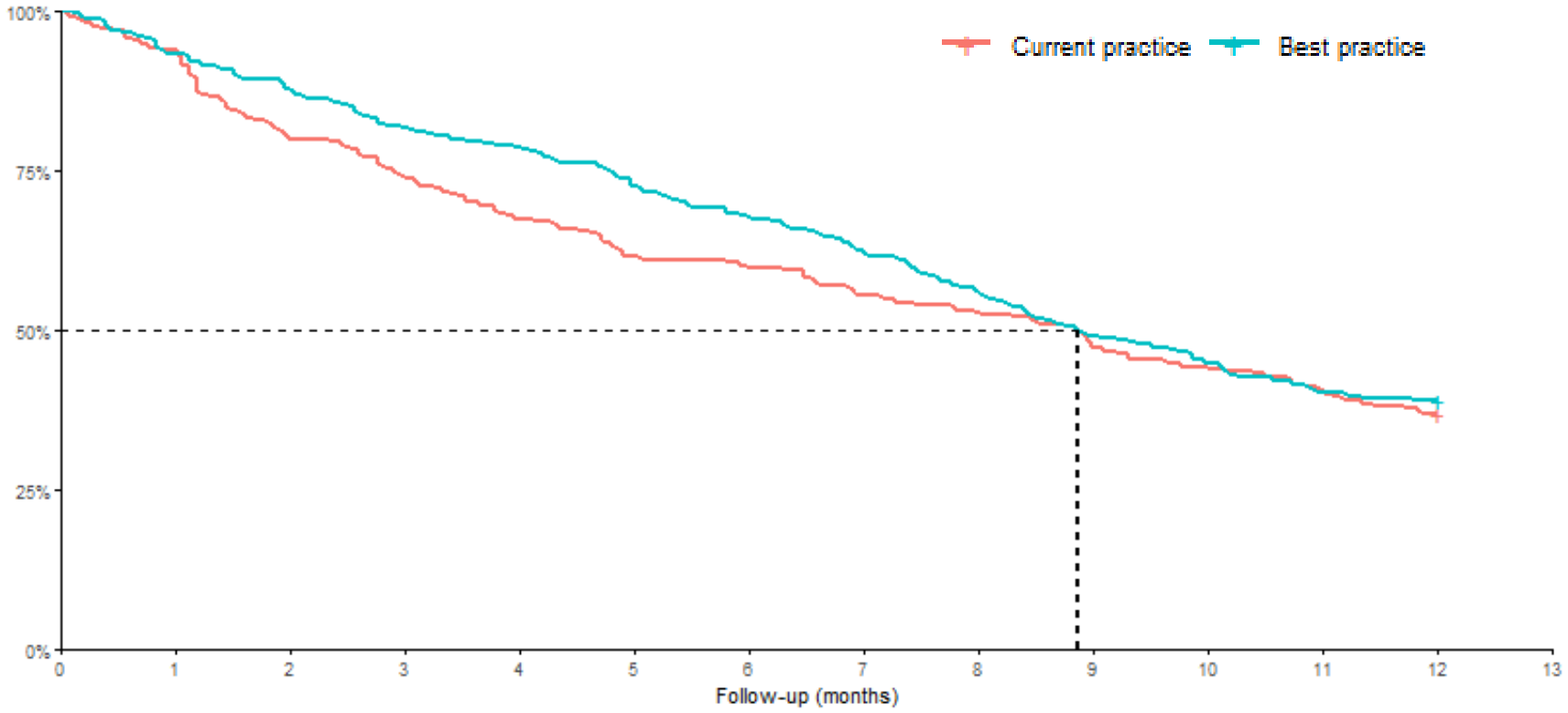
Survival: subgroups

- **(Borderline) resectable patients:**
  HR: 1.16, 95% CI 0.93-1.45, p = 0.174



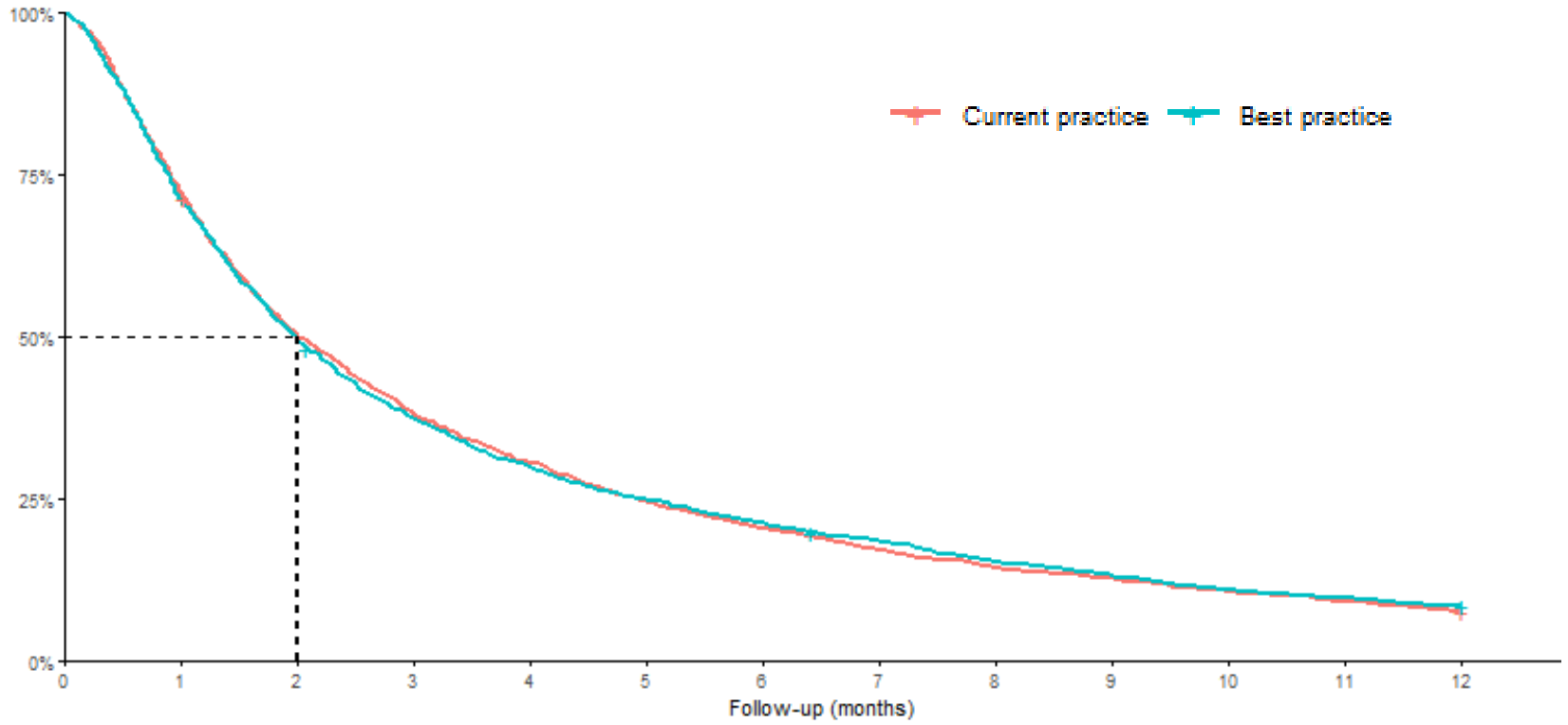
Survival: subgroups

- **LAPC:**
  HR: 0.92, 95% CI 0.71-1.94, p = 0.539



Survival: subgroups

- **Metastatic pancreatic cancer:**
  HR: 0.96, 95% CI 0.86-1.06, p = 0.395



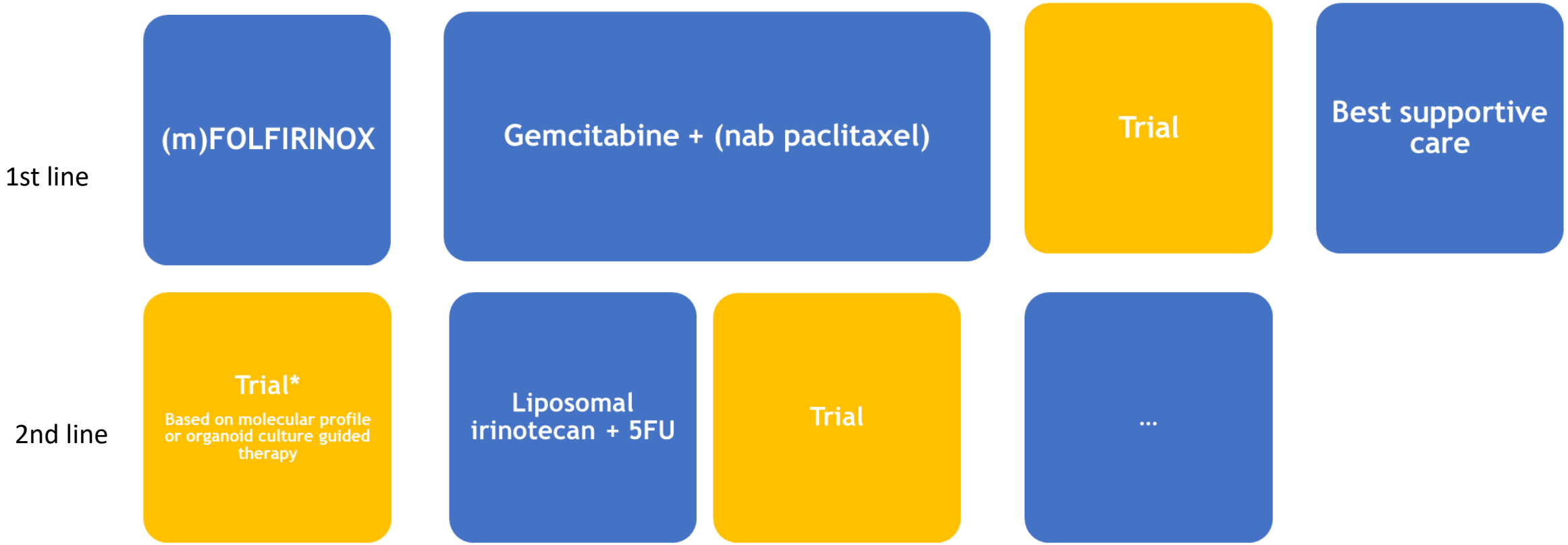
Conclusie

- PACAP-1 studie laat geen toename zien in 1-jaars overleving en kwaliteit van leven
- Wel een verschil in implementatie van de meeste best practices (o.a. palliatieve chemotherapie)

Discussie

- Slechte overleving: veel patiënten geen tumor gerichte therapie
- Chemotherapie: doelen niet bereikt
  - Doel: 70% adjuvant – real world: 52.0%
  - Doel: 40% palliatief – real world: 29.6%

Behandel strategieën M+ ziekte: shared decision



GnP vs. mFOLFIRINOX or S-IROX in metastatic pancreatic cancer: 1-year follow-up updated data from the GENERATE (JCOG1611) .

Satoshi Kobayashi[1], Akihiro Ohba[2], Masato Ozaka[3], Junki Mizusawa[4], Takuji Okusaka[2], Taro Yamashita[5], Masafumi Ikeda[6], Ichiro Yasuda[7], Kazuya Sugimori[8], Naoki Sasahira[3], Kenji Ikezawa[9], Ikuya Miki[10], Naohiro Okano[11], Nobumasa Mizuno[12], Masayuki Furukawa[13], Hirofumi Shirakawa[14], Yusuke Sano[4], Hiroshi Katayama[4], Junji Furuse[1,11], Makoto Ueno[1]. *Hepatobiliary and Pancreatic Oncology Group of Japan Clinical Oncology Group (JCOG), Japan*
Correspondence to: S. Kobayashi. ; E-mail: kobayashis@kcch.jp

JCOG Japan Clinical Oncology Group (www.jcog.jp/en/)

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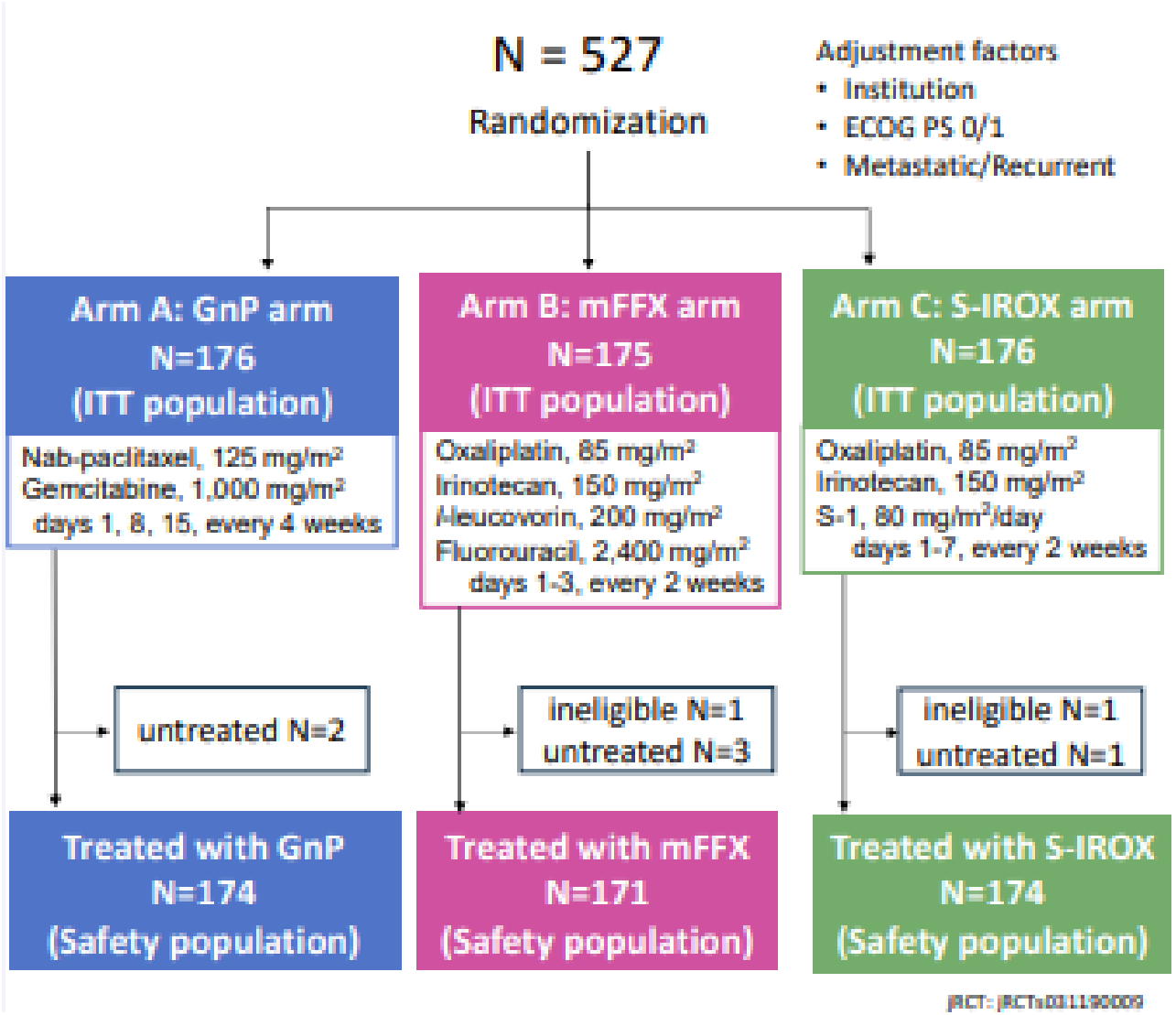


ESMO 2024

CASSANDRA PACT-21: Randomized, Phase III Trial of Preoperative Chemotherapy With mFOLFIRINOX or PAXG for Stage I-III PDAC

CCO Independent Conference Coverage*

of the *ASCO Annual Meeting 2025, May 30 - June 3, 2025*

*CCO is an independent medical education company that provides state-of-the-art medical information to healthcare professionals through conference coverage and other educational programs.

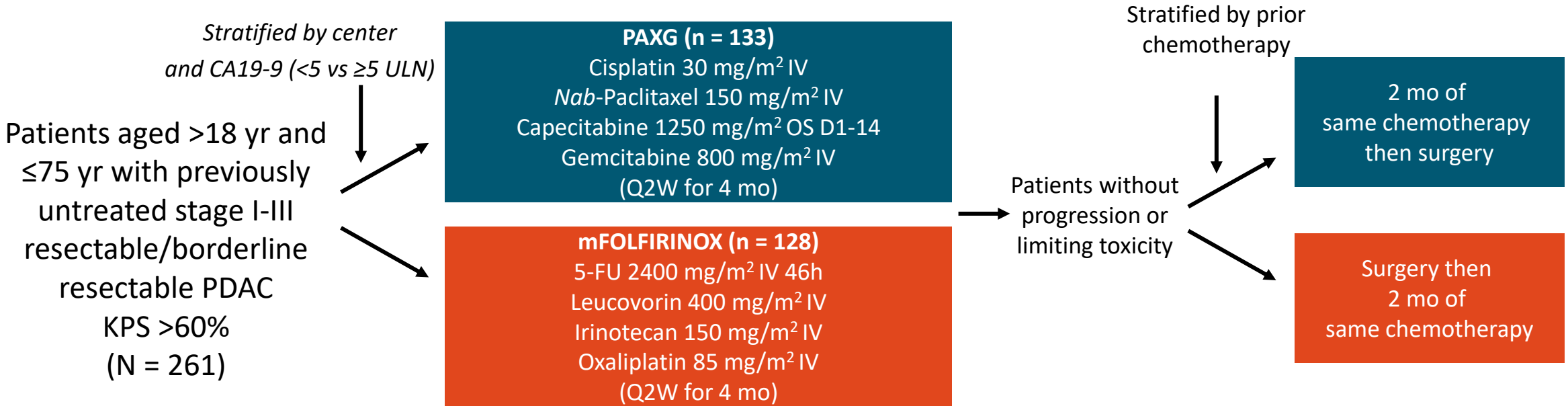
Provided by Clinical Care Options, LLC

This program is supported by educational grants from
Daiichi Sankyo, Inc. and Genentech, a member of the Roche Group

powered by cea

CASSANDRA PACT-21: Study Design

- Randomized, phase III trial conducted at 17 Italian centers



- **Primary endpoint:** EFS event per RECIST 1.1 (progression, recurrence, unresectability), intraoperative M+, CA-19-9 failure (eg, 2 consecutive increases ≥20%, separated by ≥4 wk, or death)
- **Secondary endpoints:** ORR, CA19-9 response rate, resectability rate, pathologic response rate, toxicity, QoL, OS

Reni. ASCO 2025. LBA4004.

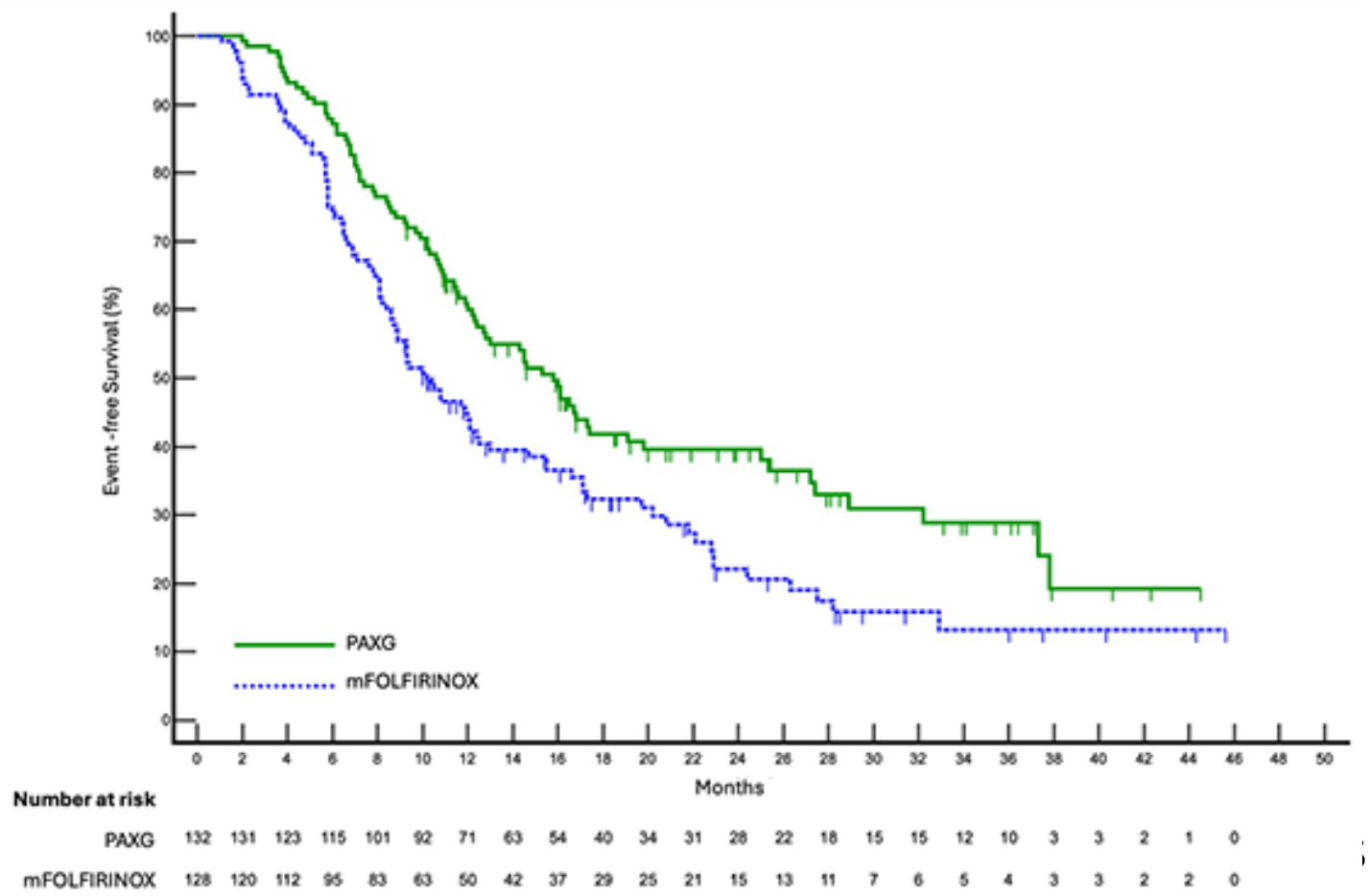
Slide credit: clinicaloptions.com

CASSANDRA PACT-21: Baseline Characteristics

Patient Characteristic	PAXG (n = 132)	mFOLFIRINOX (n = 128)
Median age, yr (range)	65 (42-76)	63 (41-76)
Male, n (%)	64 (48)	66 (52)
KPS ≤80, n (%)	9 (7)	11 (9)
Borderline resectable, n (%)	69 (52)	65 (51)
CA19-9 > ULN, n (%)	100 (76)	85 (66)
AJCC stage III, n (%)	11 (8)	13 (10)
Tumor located in pancreatic head, n (%)	104 (79)	105 (82)

Reni. ASCO 2025. LBA4004.

CASSANDRA PACT-21: EFS Outcomes



- E

  – Improvement in 3-yr EFS with PAXG vs mFOLFOXIRI was seen in resectable (41% vs 22%) and borderline resectable (19% vs 9%) subgroups

Reni. ASCO 2025. LBA4004.

Slide credit: clinicaloptions.com

CASSANDRA PACT-21: OS and Subsequent Therapies

Parameter	PAXG (n = 132)	mFOLFIRINOX (n = 128)
Median OS,* mo	37.3	26.0
HR (95% CI); *P*	0.70 (0.47-1.04); .07	
2-yr OS, %	68	58
3-yr OS, %	51	40

**OS data not mature.*

Subsequent therapy, n (%)	PAXG (n = 132)	mFOLFIRINOX (n = 128)
Any	71 (87)	79 (81)
Single agent	10 (12)	8 (8)
Nab-gemcitabine–based	32 (39)	57 (59)
(nal)IRI-FU	20 (24)	5 (5)
Other	9 (11)	9 (10)
None	11 (13)	18 (19)

Reni. ASCO 2025. LBA4004.

CASSANDRA PACT-21: Safety

Selected AEs, %	PAXG (n = 132)		mFOLFIRINOX (n = 128)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Neutropenia	93 (70)	56 (42)	71 (56)	37 (29)
Thrombocytopenia	31 (24)	1 (1)	29 (23)	1 (1)
Anemia	45 (34)	3 (2)	30 (23)	0
Diarrhea	52 (39)	3 (2)	83 (65)	7 (6)
AST/ALT increased	11 (8)	4 (3)	31 (24)	10 (8)
Infusion-related reaction	8 (6)	1 (1)	9 (7)	5 (4)
Hand-foot syndrome	52 (36)	5 (4)	2 (2)	0
Vomiting	33 (25)	3 (2)	43 (34)	5 (4)
Fatigue	97 (73)	11 (8)	91 (71)	10 (8)
Nausea	82 (62)	6 (5)	98 (77)	8 (6)
Peripheral neuropathy	61 (46)	7 (5)	86 (68)	4 (3)
Paresthesia	33 (25)	3 (2)	48 (38)	1 (1)
Infection/sepsis	22 (15)	9 (7)	17 (13)	10 (8)

Reni. ASCO 2025. LBA4004.

CASSANDRA PACT-21: QoL Outcomes

Outcome	PAGX Only	mFOLFOXIRI Only	*P* value
Completed questionnaires	100 (83)	82 (64)	.0004
Reason for not completing			
▪ Progression/toxicity	7 (5)	20 (16)	.006
▪ Refusal/administrative	15 (11)	26 (20)	

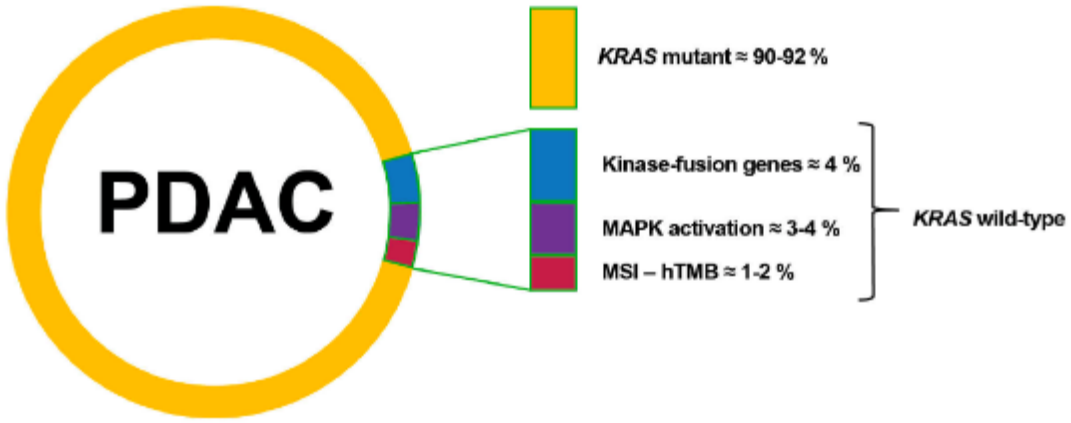
Reasons for Clinically Meaningful Deterioration at Mo 4 vs Baseline		
Both Regimens	**PAGX Only**	**mFOLFOXIRI Only**
▪ Fatigue ▪ Taste ▪ Weight loss concern ▪ Hepatic symptoms	▪ Weakness in limbs ▪ Body image	▪ Role functioning ▪ Social functioning ▪ Nausea/vomiting ▪ Dry mouth ▪ Activity planning

- No meaningful dissimilarities in deterioration among groups at baseline and Mo 4 (nausea/vomiting numerically worse in mFOLFIRINOX group, *P* =.057)

Reni. ASCO 2025. LBA4004.

Slide credit: clinicaloptions.com

Moleculaire diagnostiek



Adapted from Luchini C et al. 2020[1]

- 90% Kras mutatie; beperkt aantal targets geidentificeerd (eg, G12C)
- Bij de 10% Kras WT patienten meer mogelijkheden:
  - Fusie genen (NRG, FGFR)
  - MAPK activatie (BRAF mutatie)
  - MSI-hTMB[1] 1-2 %
- +/-25% patienten actionable mutaties, inclusief including homologe recombinatie deficiency [3]

Veel nieuwe therapeutische targets worden momenteel onderzocht, uiteindelijk resulterend in “precision medicine”[1]

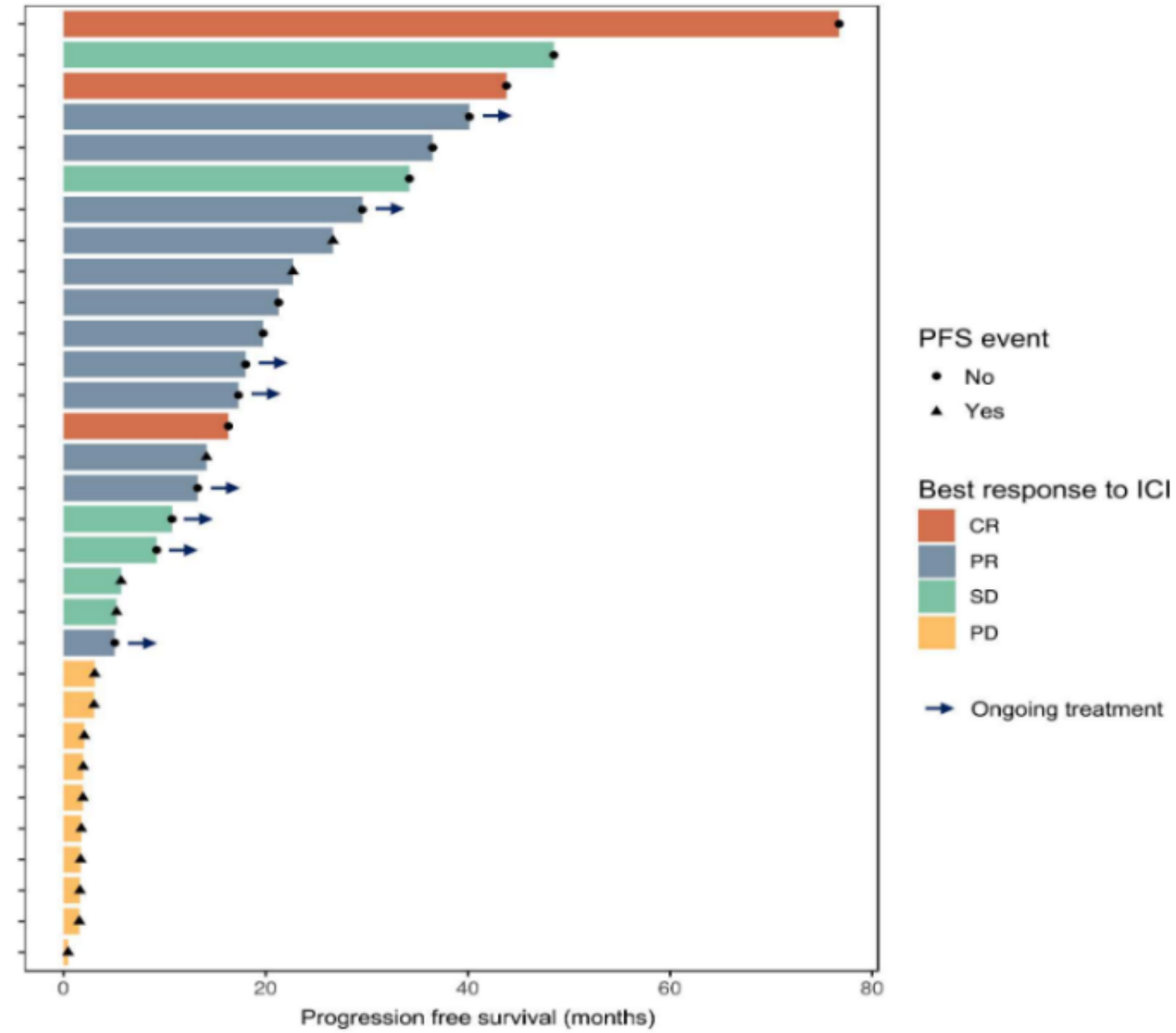
1. Chakrabarti S, Kamgar M, Mahipal A. *Cancers (Basel)*. 2022;14(11):2588; 2. Luchini C, Paolino G, Mattiolo P, et al. *J. Exp. Clin. Cancer Res.* 2020; 39: 1-10; 3. Pishvaian MJ, Blais EM, Brody JR, et al. *Lancet Oncol*. 2020;21(4):508-518. 4. Strickler JH, Satake H, Hollebecque A, et al. JCO. 2022;40(36_suppl):360490-360490.

Efficacy of immune checkpoint inhibitors in microsatellite unstable/mismatch repair-deficient advanced pancreatic adenocarcinoma: an AGEO European Cohort

Julien Taïeb (MD-PhD) [a,b,*,1], Lina Sayah (MD) [a,1], Kathrin Heinrich (MD) [c,d], Volker Kunzmann (MD) [e], Alice Boileve (MD) [f,g], Geert Cirkel (MD) [h,i], Sara Lonardi (MD) [j], Benoist Chibaudel [k], Anthony Turpin (MD) [l], Tamar Beller (MD) [m], Vincent Hautefeuille (MD) [n], Caterina Vivaldi (MD) [°o], Thibault Mazard (MD-PhD) [p], Lucile Bauguion (MD) [q], Monica Niger (MD) [r], Gerald W. Prager (MD) [s], Clelia Coutzac [t,u], C. Benedikt Westphalen (MD) [c,d], Edouard Auclin (MD) [v], Lorenzo Pilla (MD) [a,1]

European Journal of Cancer, 2023-07-01, Volume 188, Pages 90-97

Characteristics (n or %)	N = 31
Gender (M / F)	17/ 14
Median age (IQ range)	62.1 (37–82)
ECOG PS (0 /1 /2/NA)	17 / 9 / 4/1
Metastatic sites n (%)	
Liver	16 (51.6%)
Nodes	16 (51.6%)
Peritoneal	11 (35.5%)
Lung	9 (29.0%)
Other	6 (19.3%)
Number of metastatic sites (%)	
≤1	13 (41.9%)
>1	18 (58.1%)
Number of prior regimens	
0	5
1	12
>1	14
Techniques for MSI/dMMR diagnosis	
Immunohistochemistry/PCR/Both	27/24/20



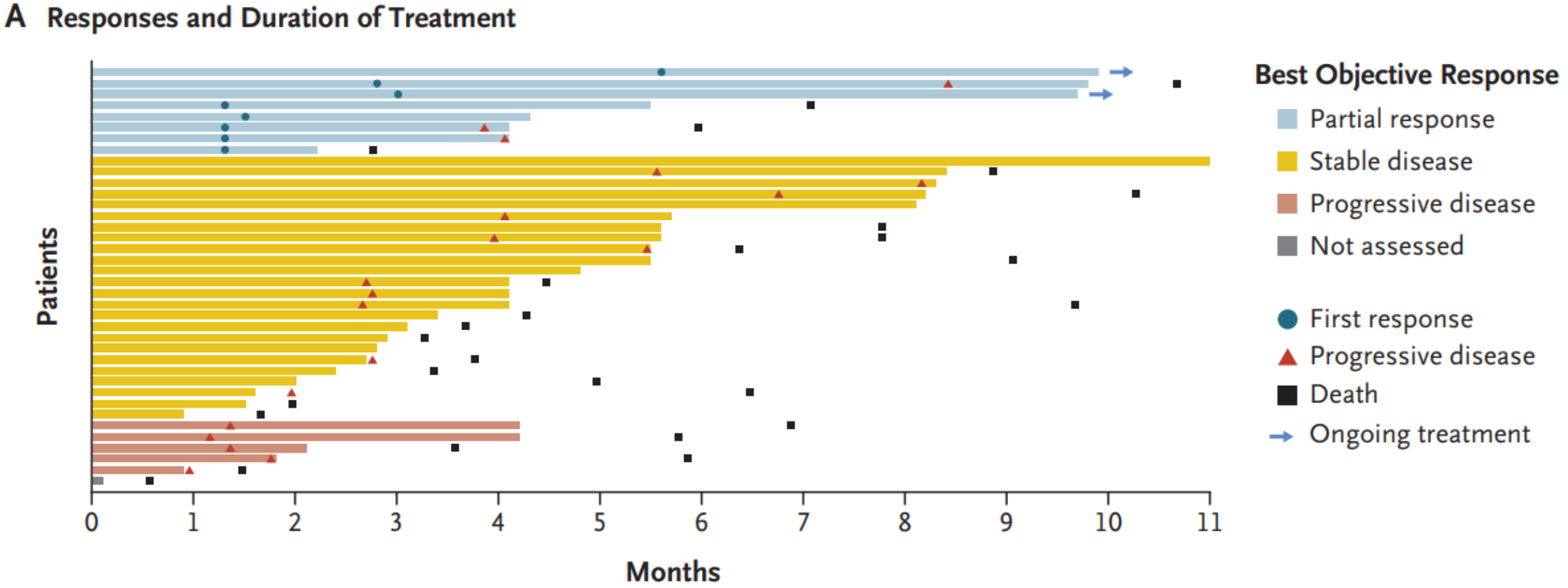
European Journal of Cancer, 2023-07-01, Volume 188, Pages 90-97

The NEW ENGLAND JOURNAL of MEDICINE

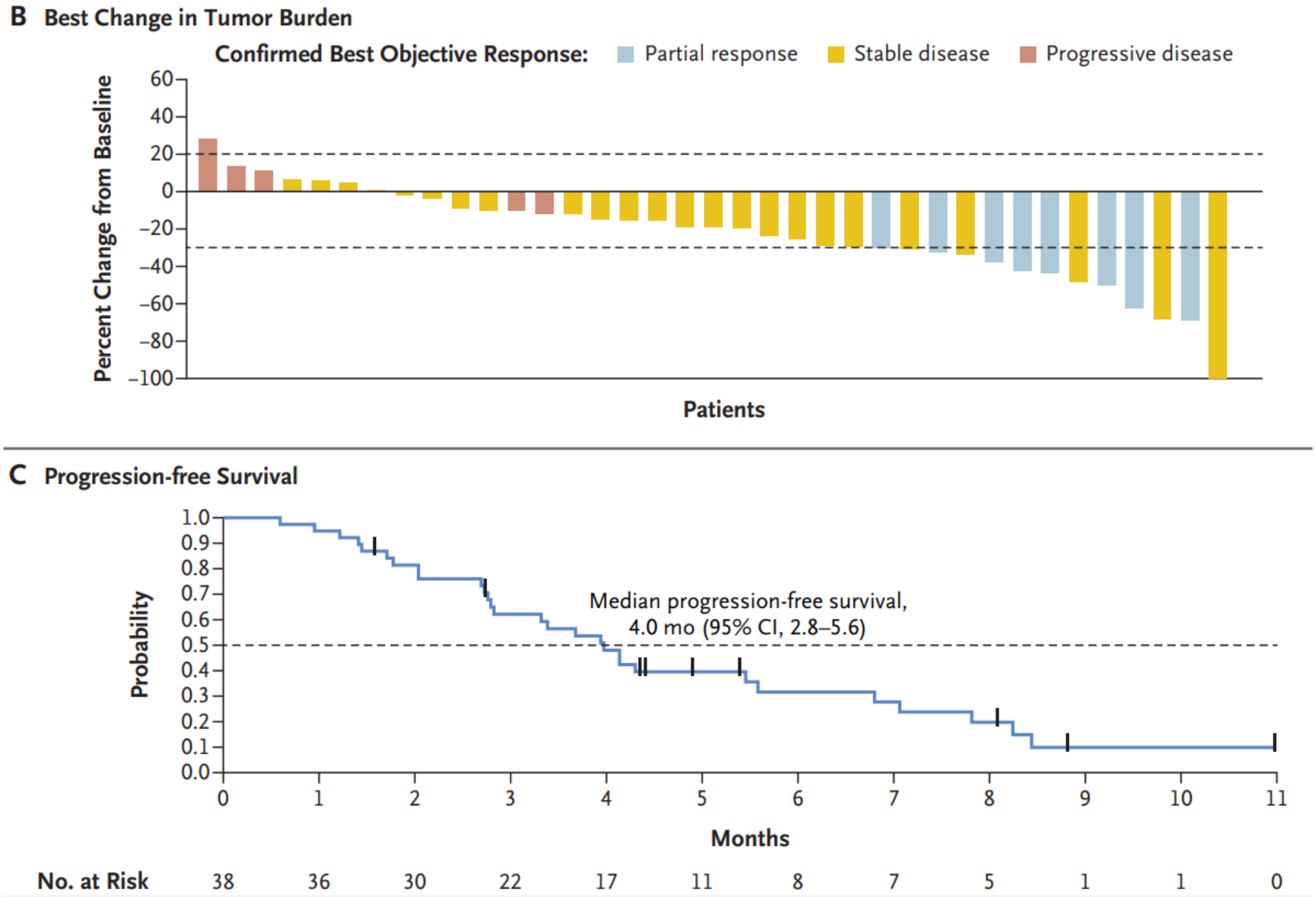
ORIGINAL ARTICLE

Sotorasib in *KRAS* p.G12C–Mutated Advanced Pancreatic Cancer

J.H. Strickler, H. Satake, T.J. George, R. Yaeger, A. Hollebecque, I. Garrido-Laguna, M. Schuler, T.F. Burns, A.L. Coveler, G.S. Falchook, M. Vincent, Y. Sunakawa, L. Dahan, D. Bajor, S.-Y. Rha, C. Lemech, D. Juric, M. Rehn, G. Ngarmchamnanrith, P. Jafarinasabian, Q. Tran, and D.S. Hong



N Engl J Med 2023;388:33-43



N Engl J Med 2023;388:33-43

Precisiegeneeskunde heeft nieuwe mogelijkheden geboden voor de ontwikkeling van nieuwe therapieën.

Klinisch onderzoek blijft nodig voordat deze behandelingen met succes kunnen worden toegepast

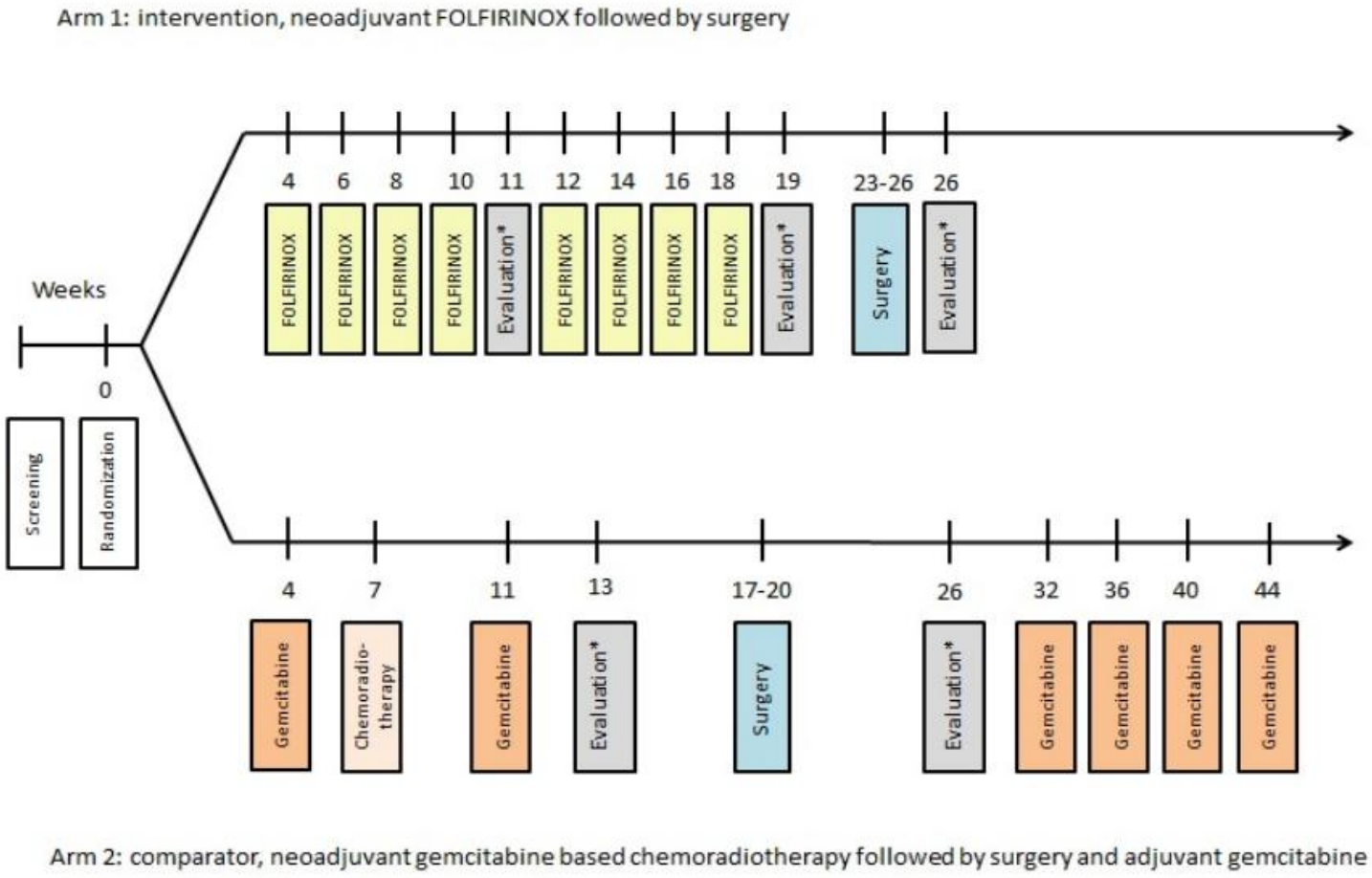
Chemotherapie blijft de standaard behandeling maar er zijn wel manieren om het gebruik te optimaliseren

Neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy in resectable and borderline resectable pancreatic cancer (PREOPANC-2): a multicentre, open-label, phase 3 randomised trial

Quisette P Janssen, Jacob L van Dam*, Marlies L van Bekkum, Bert A Bonsing, Hendrik Bos, Koop P Bosscha, Stefan A W Bouwense, Lieke Brouwer-Hol, Anna M E Bruynzeel, Olivier R Busch, Peter-Paul L O Coene, Casper H J van Eijck, Jan Willem B de Groot, Brigitte C M Haberkorn, Ignace H J T de Hingh, Tom M Karsten, Geert Kazemier, Marion B van der Kolk, Mike S L Liem, Olaf J L Loosveld, Saskia A C Luelmo, Misha D P Luyer, Leonie J M Mekenkamp, J Sven D Mieog, Vincent B Nieuwenhuijs, Joost J M E Nuyttens, Gijs A Patijn, Hjalmar C van Santvoort, Martijn W J Stommel, Eva Versteijne, Judith de Vos-Geelen, Roeland F de Wilde, Babs M Zonderhuis, Bronno van der Holt, Marjolein Y V Homs†, Geertjan van Tienhoven†, Marc G Besselink†, Johanna W Wilmink†, Bas Groot Koerkamp†, for the Dutch Pancreatic Cancer Group‡*

Lancet oncol 2025 Sep 10:S1470-2045(25)00363-8

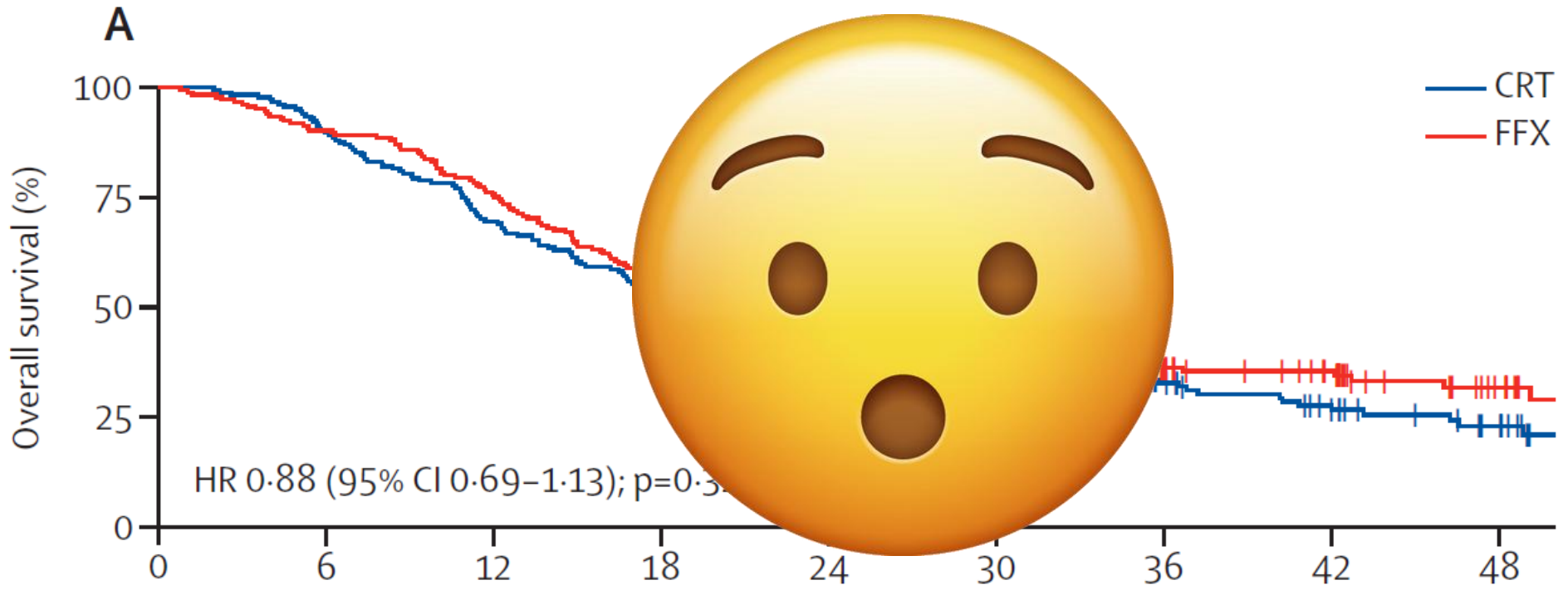
- **Investigator-initiated, open-label, nationwide, phase 3 randomised trial**
- **Resectable or borderline resectable PDAC**



Lancet oncol 2025 Sep 10:S1470-2045(25)00363-8

	FFX group (n=185)	CRT group (n=184)
Age, years	66 (59–72)	68 (61–73)
<65	88 (48%)	68 (37%)
65–74	70 (38%)	84 (46%)
≥75	27 (15%)	32 (17%)
Sex		
Male	115 (62%)	93 (51%)
Female	70 (38%)	91 (49%)
Resectability status		
Resectable	120 (65%)	121 (66%)
Borderline resectable	65 (35%)	63 (34%)
WHO status		
0	112 (61%)	110 (60%)
1	73 (39%)	74 (40%)
CA 19–9, U/mL	164 (52–471)	193 (51–622)
<500	135/175 (77%)	122/175 (70%)
≥500	40/175 (23%)	53/175 (30%)

Lancet oncol 2025 Sep 10:S1470-2045(25)00363-8



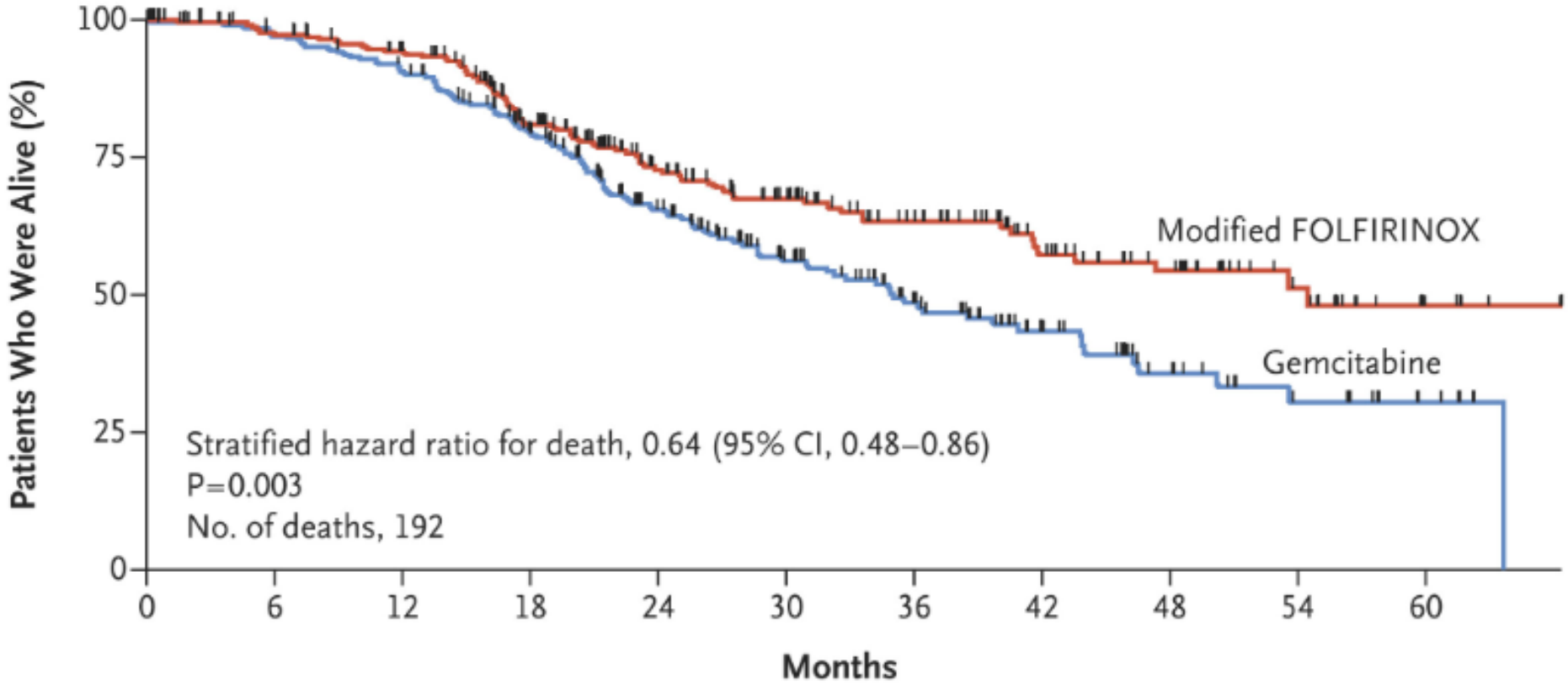
Number at risk (censored)

CRT	184 (0)	165 (0)	128 (0)	100 (0)	83 (1)	67 (2)	43 (19)	27 (28)	16 (36)
FFX	185 (0)	167 (0)	140 (0)	103 (0)	90 (0)	71 (3)	49 (19)	37 (30)	16 (48)

Lancet oncol 2025 Sep 10:S1470-2045(25)00363-8

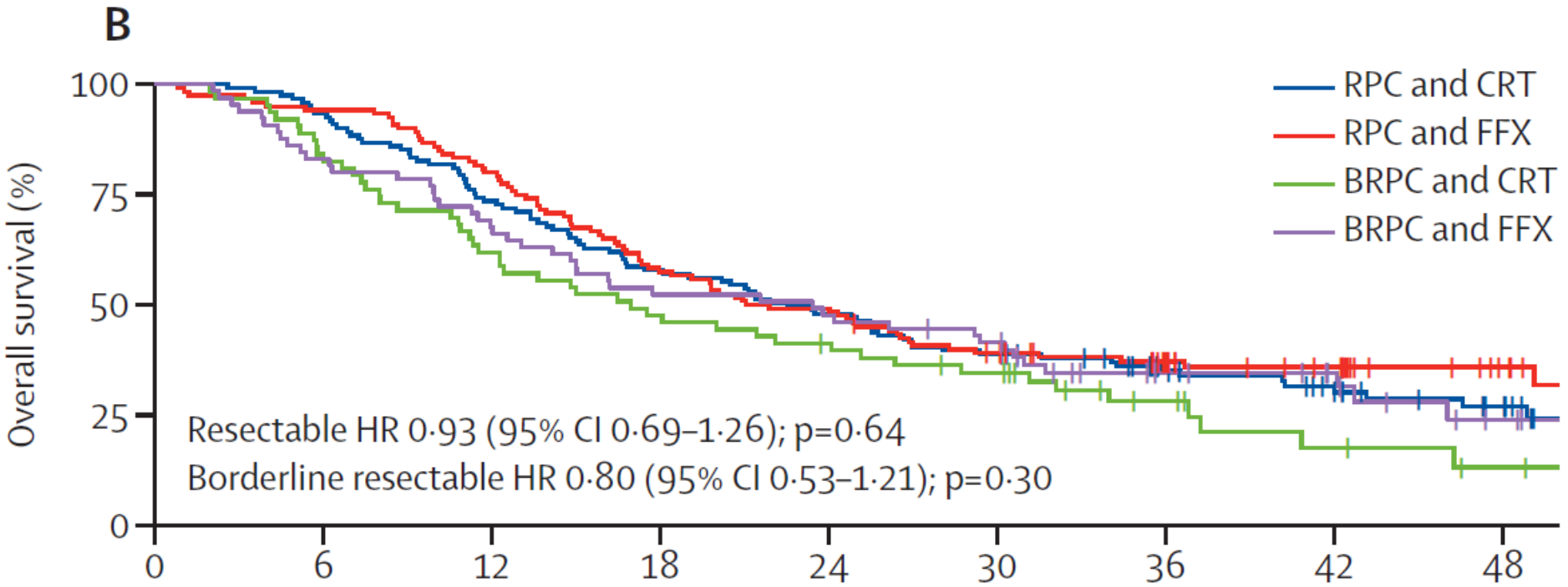
FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

B Overall Survival



No. at Risk											
Modified FOLFIRINOX	247	223	210	165	119	91	68	46	32	16	4
Gemcitabine	246	233	215	171	120	81	55	33	18	9	4

N Engl J Med 2018;379:2395-2406



Number at risk (censored)									
RPC and CRT	121 (0)	113 (0)	89 (0)	70 (0)	58 (0)	47 (0)	32 (11)	22 (17)	14 (23)
RPC and FFX	120 (0)	113 (0)	96 (0)	69 (0)	59 (0)	45 (2)	34 (11)	26 (18)	12 (32)
BRPC and CRT	63 (0)	52 (0)	39 (0)	30 (0)	25 (1)	20 (2)	11 (8)	5 (11)	2 (13)
BRPC and FFX	65 (0)	54 (0)	44 (0)	34 (0)	31 (0)	26 (1)	15 (8)	11 (12)	4 (16)

	FFX group (n=175)			CRT group (n=176)		
	Grade 3	Grade 4	Grade 5 (deaths)	Grade 3	Grade 4	Grade 5 (deaths)
Alanine aminotransferase increased	4 (2%)	0	0	11 (6%)	0	0
Aspartate aminotransferase increased	4 (2%)	0	0	10 (6%)	0	0
Biliary tract infection	11 (6%)	0	0	7 (4%)	0	0
Dehydration	15 (9%)	0	0	3 (2%)	0	0
Diarrhoea	41 (23%)	0	0	2 (1%)	0	0
Fatigue	9 (5%)	0	0	7 (4%)	0	0
Febrile neutropenia	10 (6%)	0	0	2 (1%)	0	0
GGT increased	11 (6%)	1 (1%)	0	19 (11%)	4 (2%)	0
Hyperglycaemia	9 (5%)	1 (1%)	0	4 (2%)	1 (1%)	0
Hypertension	9 (5%)	0	0	4 (2%)	0	0
Hypokalaemia	21 (12%)	2 (1%)	0	4 (2%)	1 (1%)	0
Multi-organ failure	0	0	1 (1%)	0	0	0
Nausea	14 (8%)	0	0	11 (6%)	0	0
Neutropenia	24 (14%)	19 (11%)	0	26 (15%)	12 (7%)	0
Small intestinal mucositis	4 (2%)	2 (1%)	1 (1%)	1 (1%)	0	0
Upper gastrointestinal haemorrhage	0	0	0	0	0	1 (1%)
Vomiting	13 (7%)	0	0	5 (3%)	0	0
Leukopenia	9 (5%)	5 (3%)	0	24 (14%)	2 (1%)	0

Overview of the number of patients with grade 3–5 adverse events with an incidence of 5% or more in either treatment group. CRT=gemcitabine-based chemoradiotherapy. FFX=FOLFIRINOX. GGT=gamma-glutamyltransferase.

Table 3: **Common grade 3–4 adverse events and all grade 5 adverse events in the safety population**

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Conclusie Preopanc 2

- Gelijke overleving chemoradiatie versus FOLFIRINOX
- Geen verschil in adverse event gr 3 or serious adverse event (wel beduidend minder diarree in chemoradiatiegroep)
- FOLFIRINOX patienten hadden wel vaker 2 of meer gr 3 toxiciteiten
- Geen verschil in resectiepercentage
- Beide behandelmethoden kunnen overwogen worden

Rol immuuntherapie bij niet MSI pancreaskanker?

Rol immuuntherapie pancreaskanker?

Effectiviteit immuuntherapie in pancreaskanker beperkt

- Immuunsuppressieve microenvironment
- Niet-immunogene tumor met lage neo-antigeen load

Rol immuuntherapie pancreaskanker

- MSI high of dMMR: 1-2% (Lynch)
- Huidige evidence voor gebruik PD-1 and PDL-1 inhibitie is teleurstellend
- Combinatie chemotherapie/ RT / lokaal ablatieve therapie/ targeted therapie en checkpoint remmers?

Chemotherapie

- Vrijkomen van tumor antigenen uit kanker cellen

- Reactivatie van anti-kanker immuun respons
  → remming tumorgroei

- Toevoeging immuuntherapie aan chemotherapie

  → versterkt/ synergistisch antitumor effecten van therapie afzonderlijk

- Chemotherapie “herstelt” de immuuncel gemedieerde antitumor respons

  → toevoeging checkpoint inhibitie?

(Stereotactische) Radiotherapie

- Niet alleen lokaal → werkt als een *in-situ* vaccine
- Tumor antigeen presentatie
- Anti-tumor cytotoxische T cell respons
- Wel intact host's immuun respons noodzakelijk

→ Toevoeging checkpoint inhibitie?

PREOPANC 5 studie

Neoadjuvant Triple Treatment with FOLFIRINOX, SBRT and Pembrolizumab in patients with borderline resectable pancreatic cancer

Studie team:

Marc Besselink, Geertjan van Tienhoven, Anna Bruynzeel, Bas Groot Koerkamp, Casper van Eijck, Marjolein Homs, Geert Cirkel, Judith de Vos en Hanneke Wilmink

Hypothese

- Gecombineerde neoadjuvante therapie uitkomst BRPC verbetert

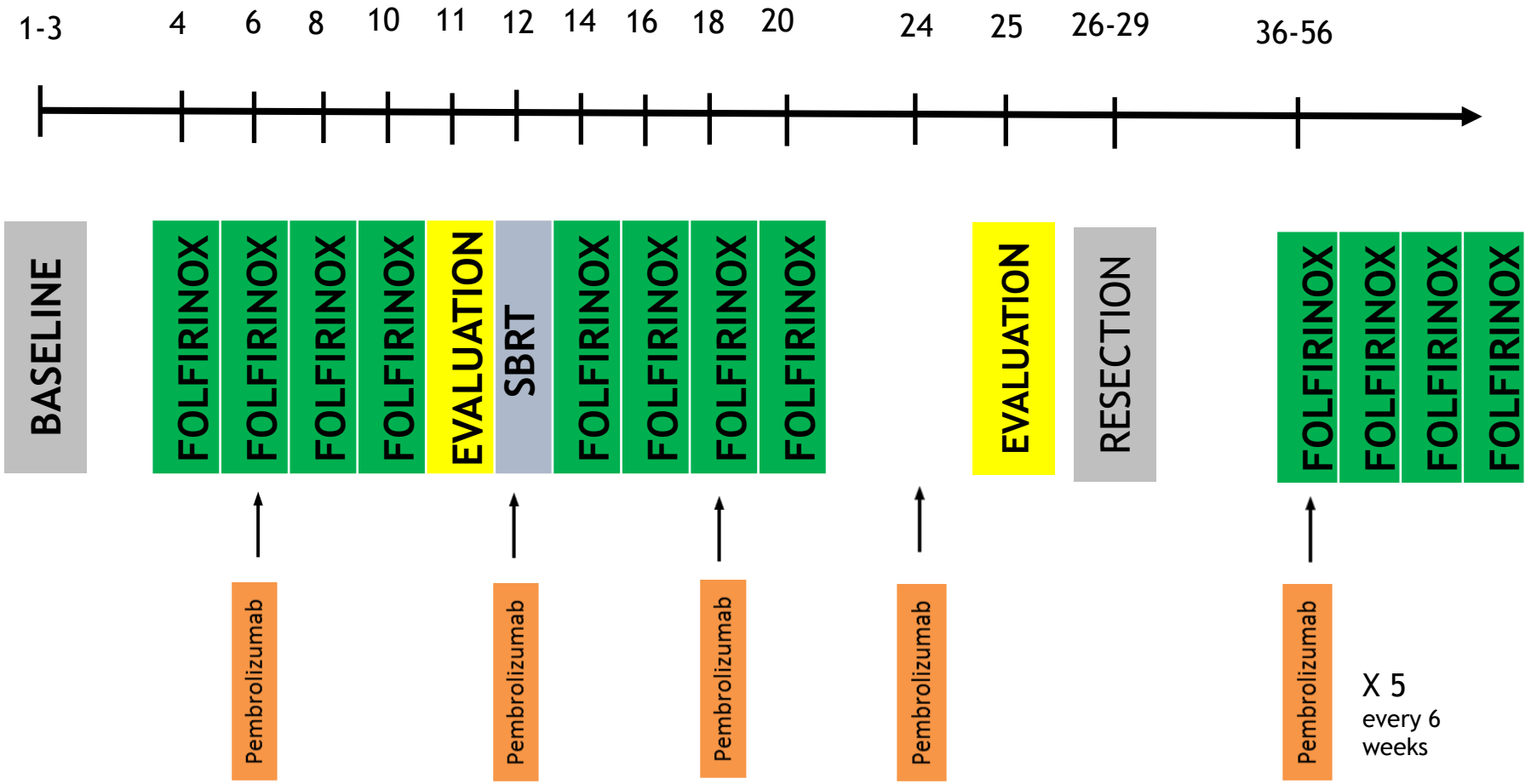
- FOLFIRINOX, maar ook SBRT, maakt tumor gevoelig voor CI

→ Logische vervolg stap:

“neoadjuvant triple treatment” winst in overleving?

Studie design

- Fase I/II
- Multicenter, singel arm studie
- BRCP (DPCG criteria) en WHO 0-1


1-3
4
6
8
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14
16
18
20
24
25
26-29
36-56
BASELINE
FOLFIRINOX
FOLFIRINOX
FOLFIRINOX
FOLFIRINOX
EVALUATION
SBRT
FOLFIRINOX
FOLFIRINOX
FOLFIRINOX
FOLFIRINOX
EVALUATION
RESECTION
FOLFIRINOX
FOLFIRINOX
FOLFIRINOX
FOLFIRINOX
Pembrolizumab
Pembrolizumab
Pembrolizumab
Pembrolizumab
Pembrolizumab
X 5
every 6
weeks

Objectives

Primary objective: progressie vrije overleving

Secondary objectives

- Overall survival.
- Resectie rate.
- Toxiciteit
- Quality of life (QoL)
- Response rate.
- Serum CA 19-9/ CEA en pathologische respons

Statistiek

- Totaal 66 patiënten

- Safety analyse na 10 patiënten (na chirurgie):
  - Haalbaarheid gedefinieerd > 65% ptn behandeling afgemaakt

Vragen?