cholangiocelulární a pankreatický karcinom

–

pokroky za posledních 5 let

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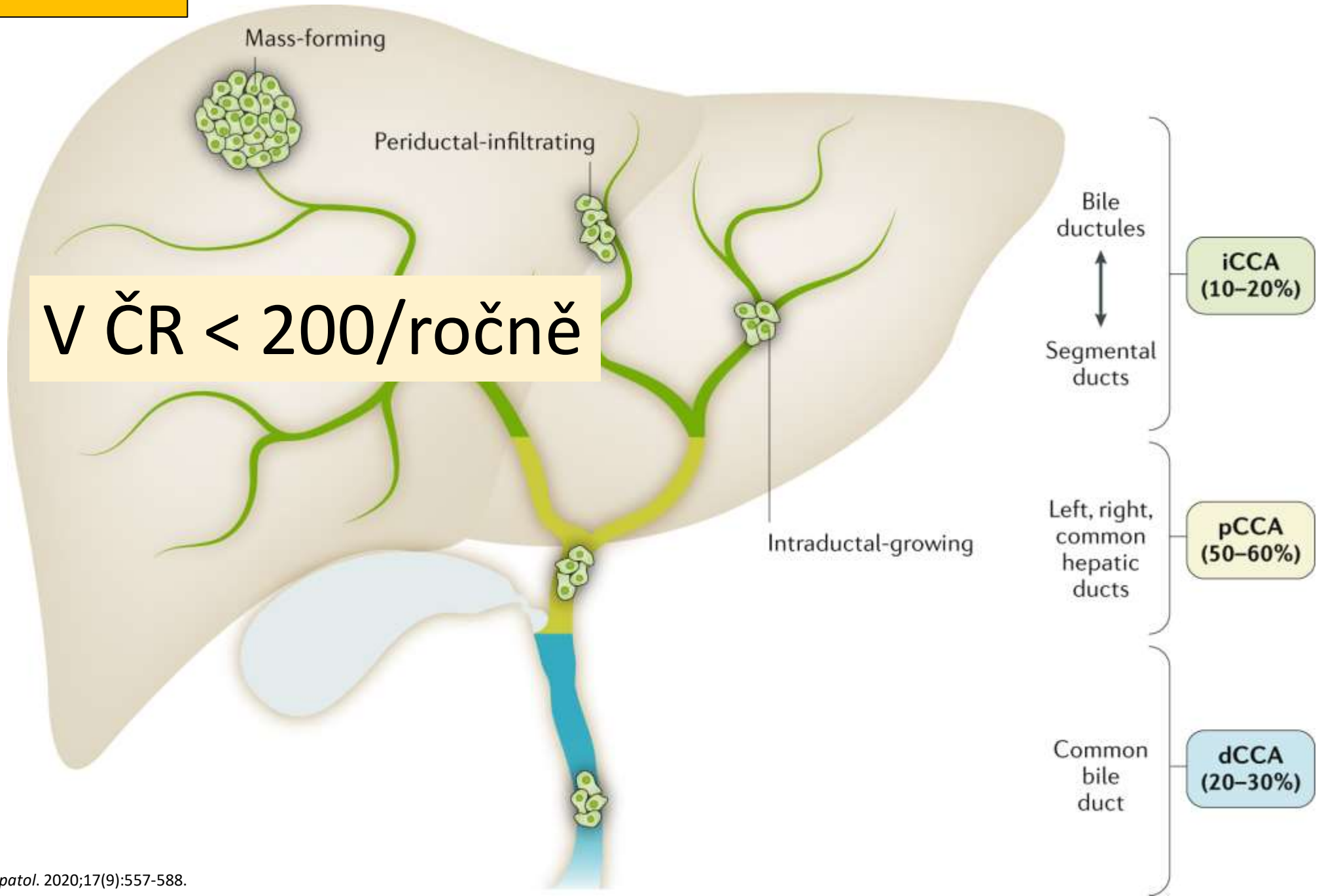
XXV. setkání Klubu mladých onkologů

Medlov

17.6.2023

Podpořeno grantem na specifický výzkum č. MUNI/A/1224/2022

Cholangiocelulární karcinom



V ČR < 200/ročně

Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020;17(9):557-588.

Cholangiocelulární karcinom - adjuvance

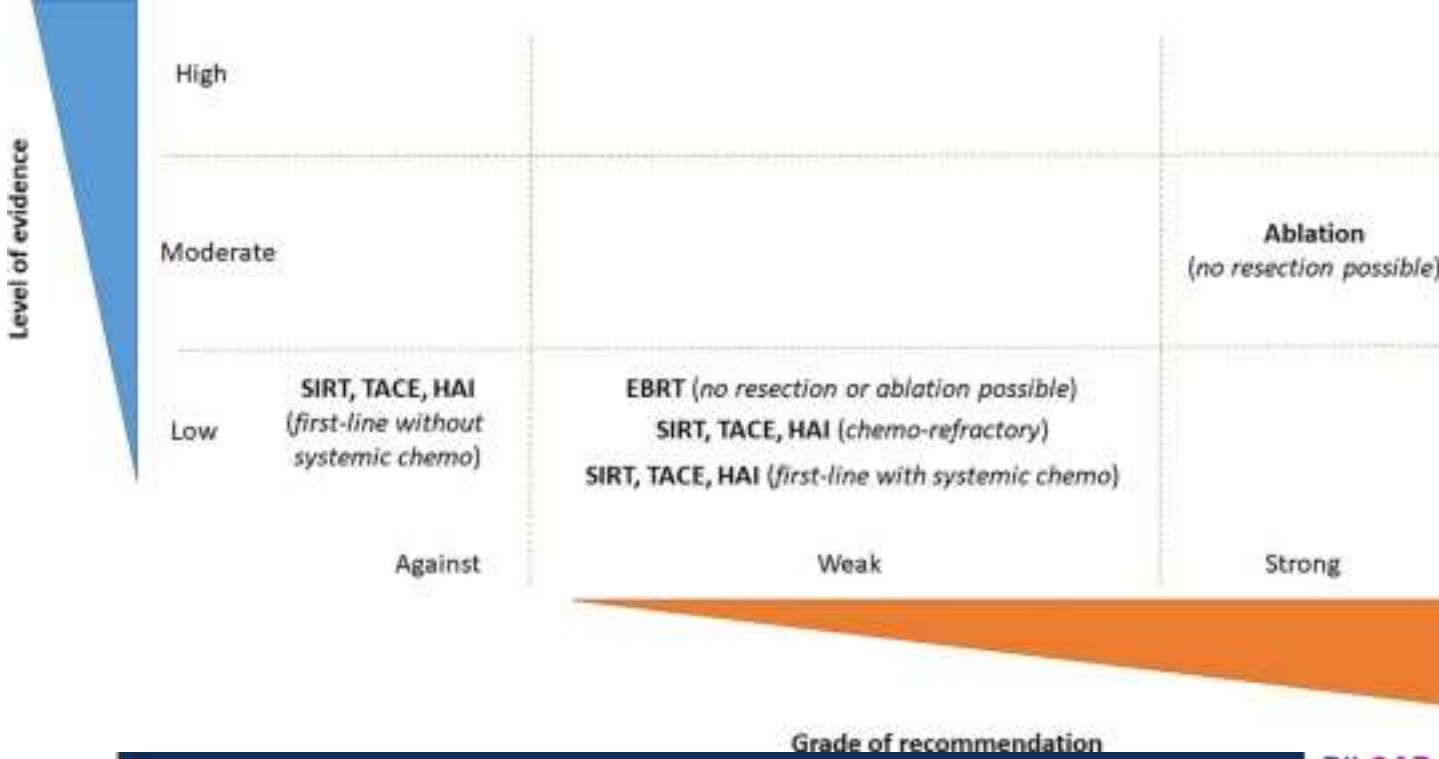
časné stádium

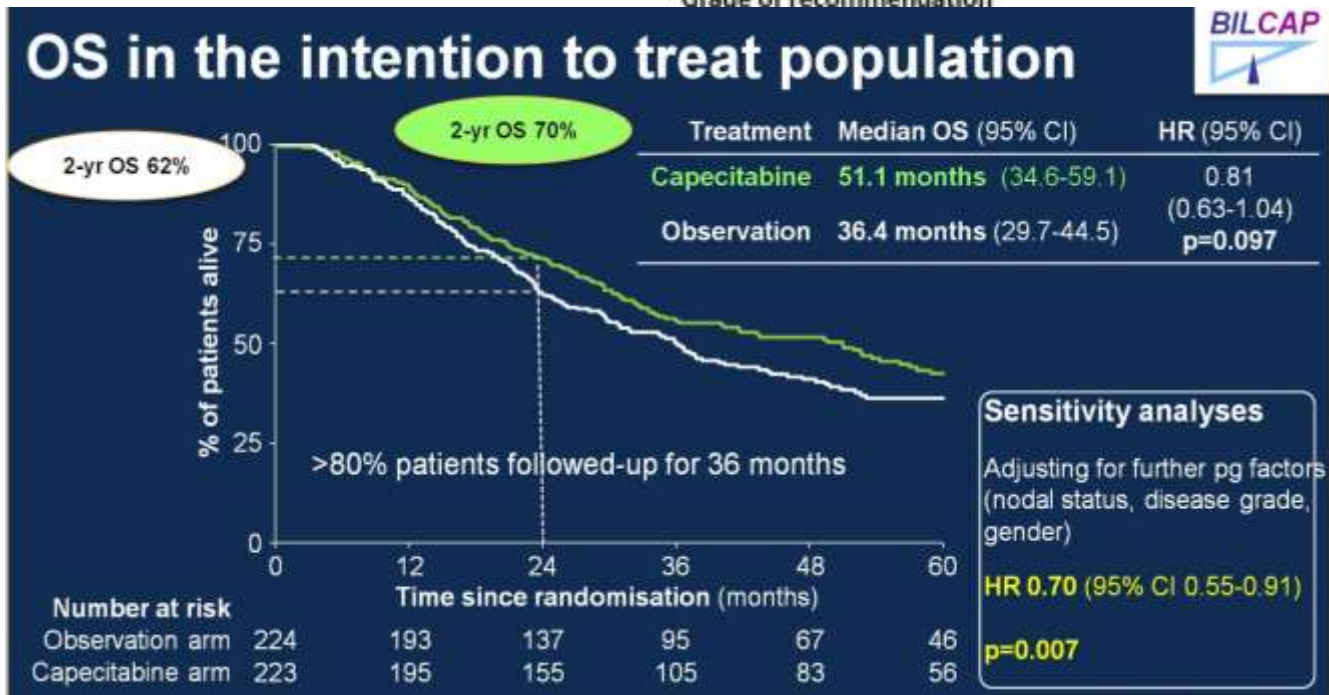
resekce

OS pro RFA: 30,2m

adjuvance

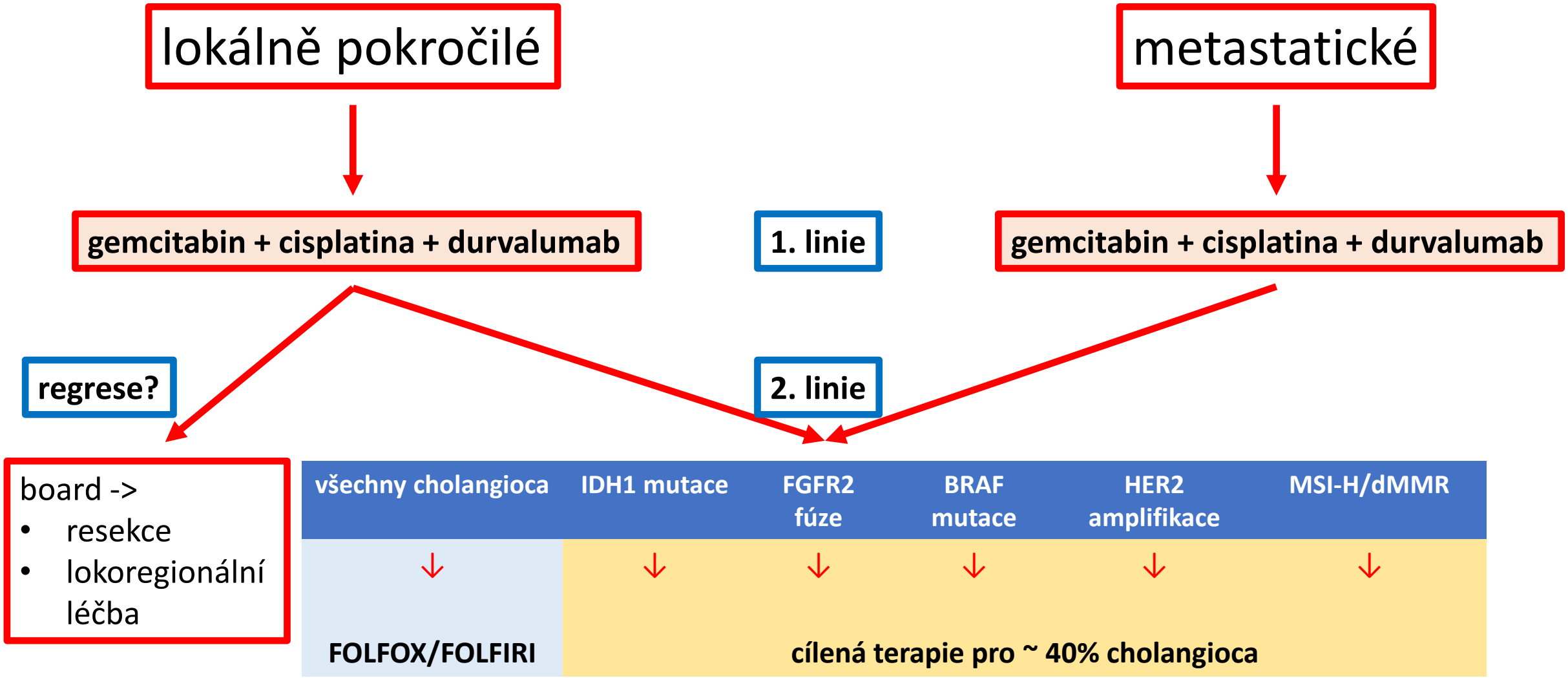
benefit v OS pro CAPE vs observace: 14,7m





Primrose JN, et al. *Lancet Oncol*. 2019;20(5):663-673. Vogel A, et al. *Ann Oncol*. 2023;34(2):127-140.
Edeline J, et al. *Cancer Treat Rev*. 2021;99:102258.

Cholangiocelulární karcinom – lokálně pokročilý/metastatický



Vogel A, et al. *Ann Oncol*. 2023;34(2):127-140.

Cholangiocelulární karcinom – 1. linie paliativní terapie

TOPAZ-1 study design

TOPAZ-1 is a double-blind, multicenter, global, Phase 3 study

Key eligibility
- Locally advanced or metastatic BTC (ICC, ECC, GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease >6 months after curative surgery or adjuvant therapy
- ECOG PS 0 or 1

Stratification factors
- Disease status
  - (initially unresectable versus recurrent)
- Primary tumor location
  - (ICC versus ECC versus GBC)

R (1:1) N=685

Durvaluma + GemCis

Plac + GemCis

Primary ob
- Overall

Secondary
- Progres
- Objectiv
- Duratio
- Efficacy
- Safety

GemCis treatment: gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 on Days 1 and 8 Q3W administered for up to 8 cycles.

BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, PD, progressive disease; PD-L1, programmed cell death ligand-1; PS, performance status; QnW, every n weeks; R, randomization.

ASCO Gastrointestinal Cancers Symposium #GI22

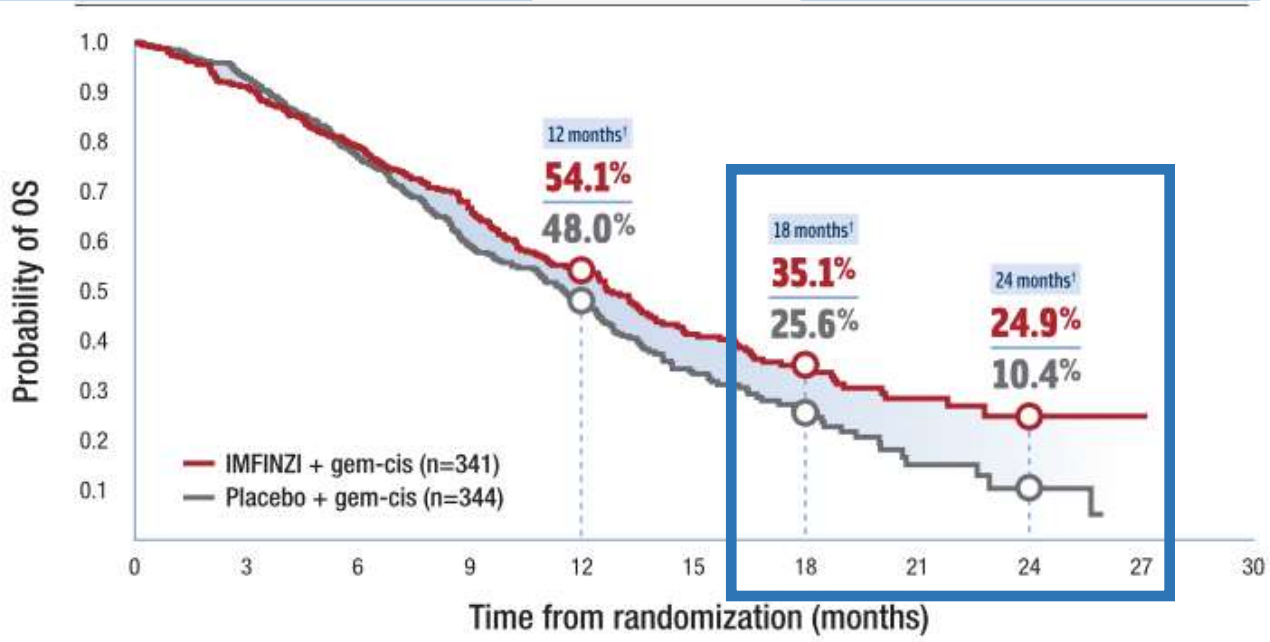
PRESENTED BY: Do-Youn Oh, MD, PhD

HR=0.80 (95% CI, 0.66-0.97); *P*=0.021*

12.8 months median OS with IMFINZI + gem-cis
(95% CI, 11.1-14.0)

vs

11.5 months median OS with gem-cis
(95% CI, 10.1-12.5)



Number of patients at risk

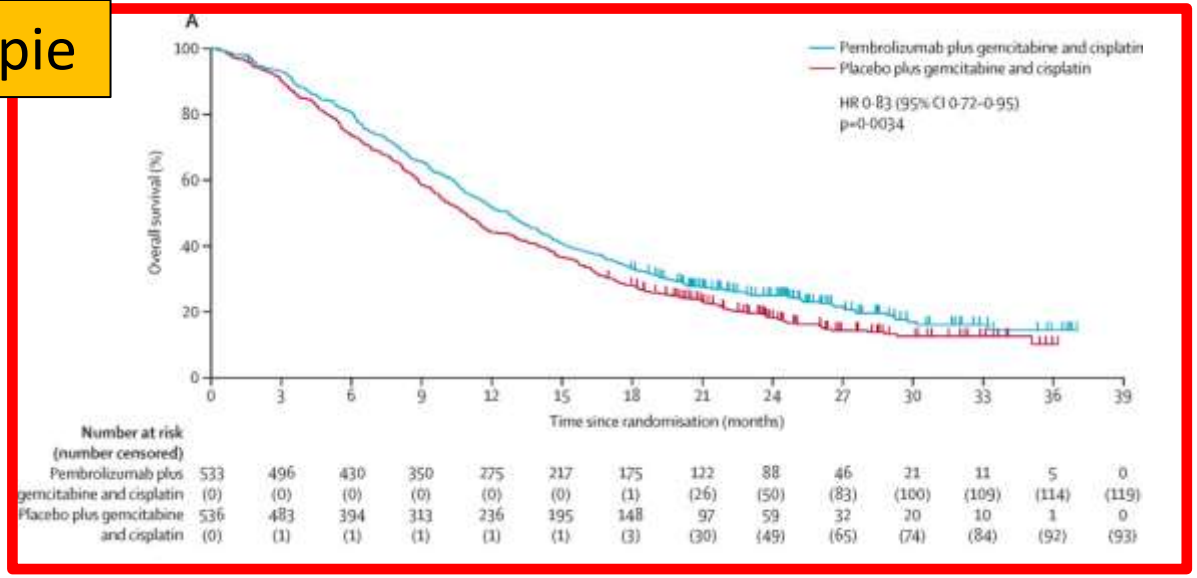
IMFINZI + gem-cis	341	331	324	309	294	278	268	252	238	208	174	151	135	118	93	79	74	57	49	39	29	24	15	12	9	8	4	1	0
Placebo + gem-cis	344	337	329	317	299	283	261	242	220	183	159	143	125	97	78	65	52	40	29	21	15	10	8	4	4	3	0	0	0

Oh DY, et al. *Lancet Gastroenterol Hepatol*. 2022;7(6):522-532.

Cholangiocelulární karcinom – 1. linie paliativní terapie

Clinical Trial > Lancet. 2023 Jun 3;401(10391):1853-1865.
doi: 10.1016/S0140-6736(23)00727-4. Epub 2023 Apr 16.

Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial



Key Eligibility Criteria

- Histologically confirmed extrahepatic or intrahepatic cholangiocarcinoma or gallbladder cancer
- Unresectable locally advanced or metastatic disease measurable per RECIST v1.1 by investigator review
- No prior systemic therapy[a]
- ECOG PS 0 or 1
- Life expectancy >3 months

R 1:1

Pembrolizumab 200 mg IV Q3W (maximum, 35 cycles)
+
Gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W (no maximum)
+
Cisplatin 25 mg/m² IV on days 1 and 8 Q3W (maximum, 8 cycles)

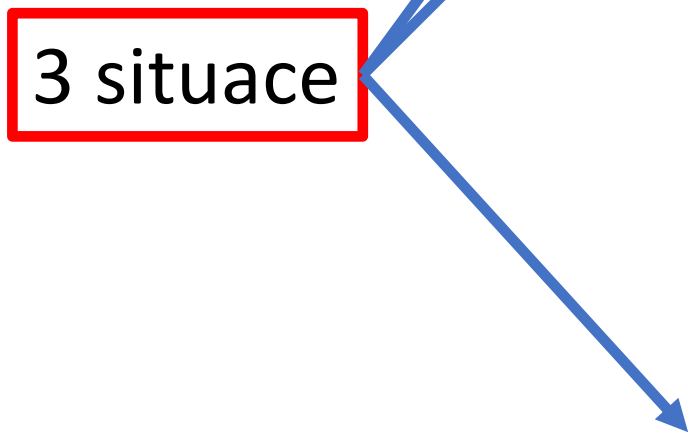
Placebo IV Q3W for (maximum, 35 cycles)
+
Gemcitabine 1000 mg/m² IV on days 1 and 8 Q3W (no maximum)
+
Cisplatin 25 mg/m² IV on days 1 and 8 Q3W (maximum, 8 cycles)

Kelley RK, et al. *Lancet*. 2023;401(10391):1853-1865.

Cholangiocelulární karcinom – 1. linie paliativní terapie

	ABC-02 **GemCis vs Gem, fáze III**	**TOPAZ-1** **GemCis + durva vs GemCis, fáze III**	**KEYNOTE-966** **GemCis + pembro vs GemCis, fáze III**
Rok publikace výsledků	2010	2022	2023
Počet pacientů	206 vs 204	341 vs 344	533 vs 536
Linie	1.	1.	1.
Věk	63 vs 64	64 vs 64	64 vs 63
Design	1:1	1:1	1:1
ORR% ITT	**26,1** vs 15,5	**26,7** vs 18,7	**29** vs 29
PR% ITT	**25,5** vs 14,8	**24,6** vs 18,1	**27** vs 27
CR% ITT	**0,6** vs 0,7	**2,1** vs 0,6	**2** vs 1
mPFS v měsících	**8,0** vs 5,0, HR: 0,63	**7,2** vs 5,7, HR: 0,75	**6,5** vs 5,6, HR: 0,86
mOS v měsících	**11,7** vs **8,1**, HR: 0,64	**12,8** vs **11,5**, HR: 0,80	**12,7** vs **10,9**, HR: 0,83
mDOR v měsících	-	**6,4** vs 6,2	**9,7** vs 6,9
MSI high %	N/A	0,9 vs 7	1 vs 1

Cholangiocelulární karcinom – 2. linie paliativní terapie

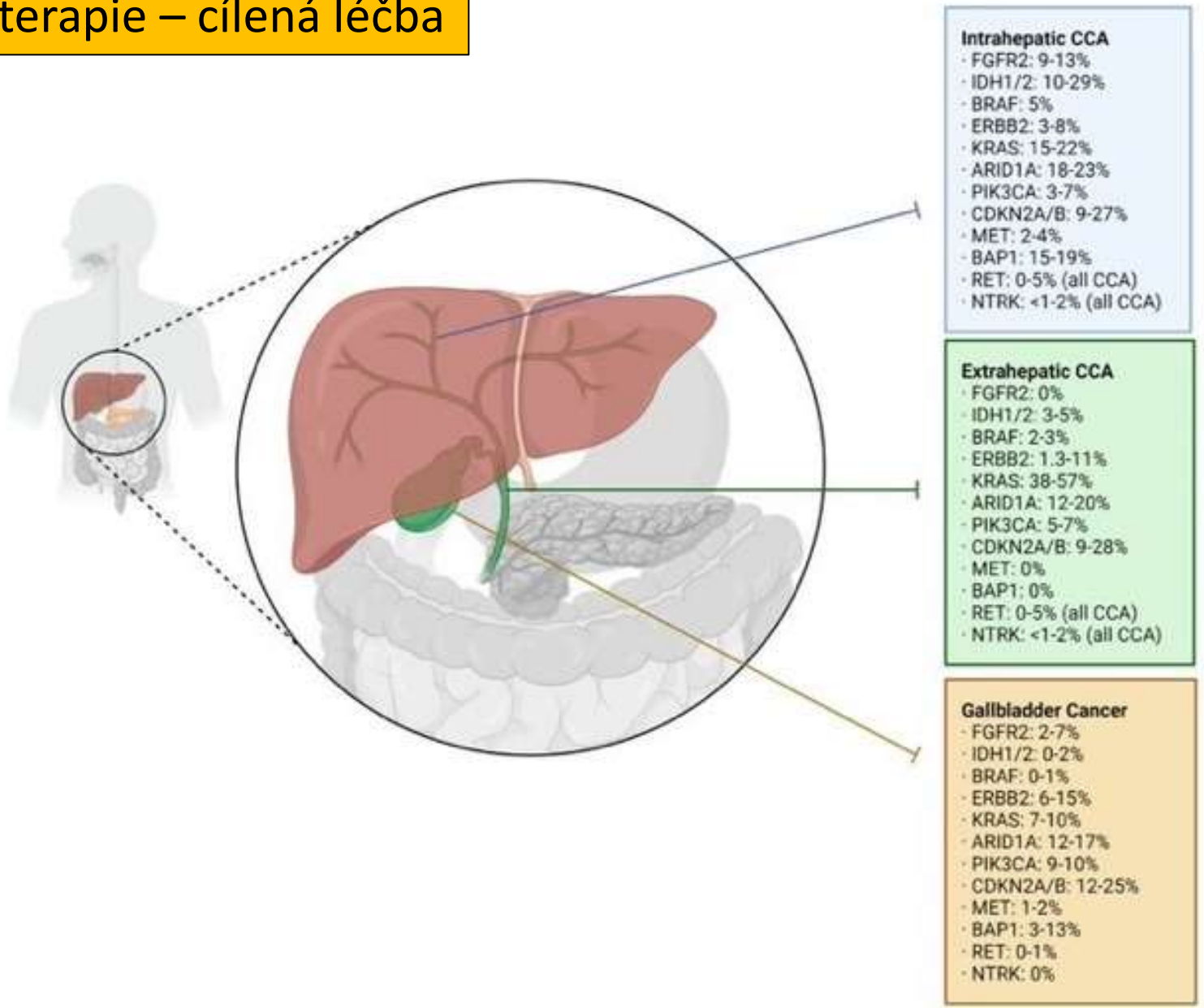


1. BSC
2. STANDARDNÍ CHEMO 2. LINIE
   - FOLFOX/FOLFIRI - efekt omezený
     - ABC-06, fáze III:
       - FOLFOX vs. BSC: mOS **6,2** vs. 5,3 m, p=0,031
     - NALIRICC-AIO-HEP-0116, fáze II:
       - 5-FU + nal-IRI vs. 5-FU: mOS 6,9 vs. 8,2 m
       - ↑ toxicita dubletu
3. MÁM NATESTOVÁNO A MÁM TARGET

Lamarca A, et al. *Lancet Oncol*. 2021;22(5):690-701. Vogel A, et al. *Ann Oncol.* 2022; 33: S19-S26

Cholangiocelulární karcinom

- 2. linie paliativní terapie – cílená léčba



Farha N, et al. *Cancers (Basel)*. 2023;15(7):2105.

Cholangiocelulární karcinom

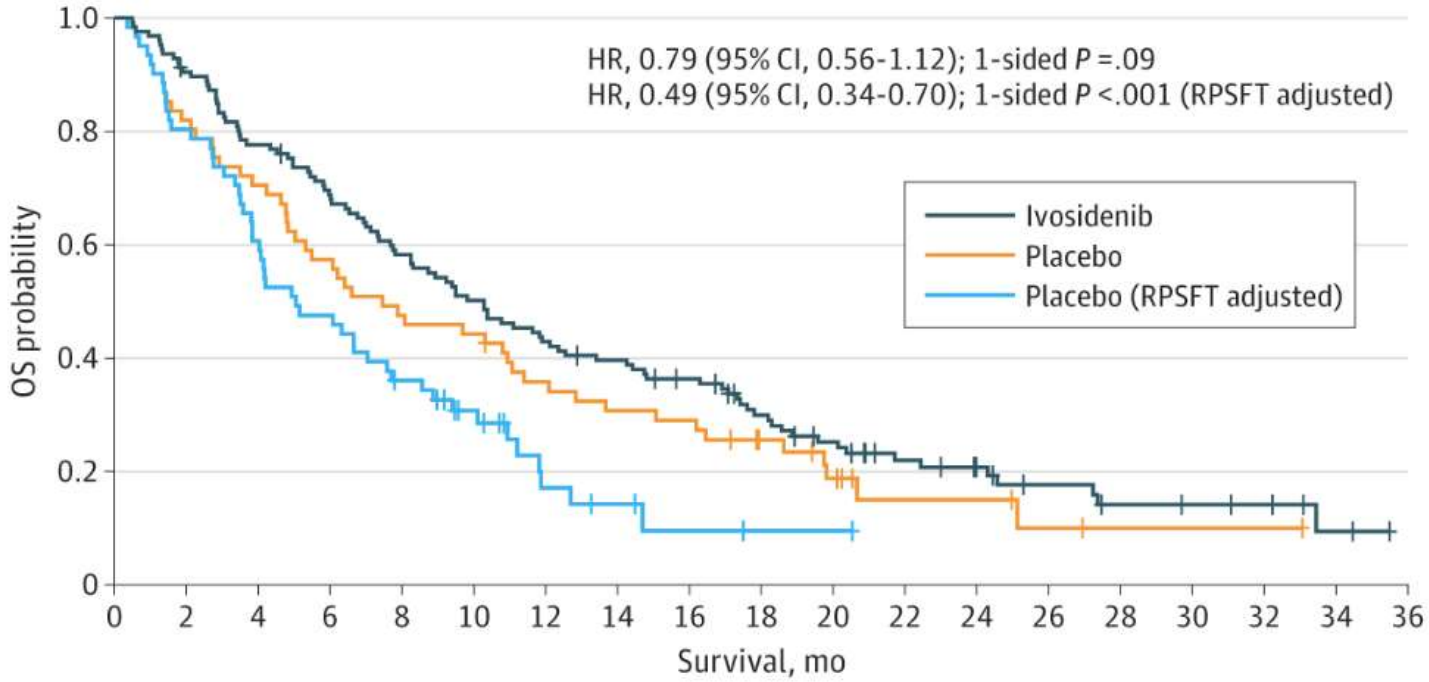
- 2. linie paliativní terapie – cílená léčba
- IDH1 MUTACE = 20%

Clinical Trial > Lancet Oncol. 2020 Jun;21(6):796-807. doi: 10.1016/S1470-2045(20)30157-1.
Epub 2020 May 13.

Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study

mPFS: 2,7 vs. 1,4 m

mOS: 10,3 vs. 5,1 m



No. at risk

Ivosidenib	126	113	97	85	72	62	53	48	42	32	25	18	14	10	7	6	5	2
Placebo	61	50	43	35	29	27	21	18	17	12	8	4	4	2	1	1	1	
Placebo (RPSFT adjusted)	61	49	37	29	21	14	6	4	2	1	1							

Treatment group	Events/patients, No.	OS, median (95% CI), mo
Ivosidenib	100/126	10.3 (7.8-12.4)
Placebo	50/61	7.5 (4.8-11.1)
Placebo adjusted by RPSFT	49/61	5.1 (3.8-7.6)

Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21(6):796-807.

Cholangiocelulární karcinom

- 2. linie paliativní terapie – cílená léčba
- FGFR2 FÚZE = 13%

Clinical Trial > N Engl J Med. 2023 Jan 19;388(3):228-239. doi: 10.1056/NEJMoa2206834.

Futibatinib for *FGFR2*-Rearranged Intrahepatic Cholangiocarcinoma

Clinical Trial > Lancet Oncol. 2020 May;21(5):671-684. doi: 10.1016/S1470-2045(20)30109-1. Epub 2020 Mar 20.

Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study

Clinical Trial > Lancet Gastroenterol Hepatol. 2021 Oct;6(10):803-815. doi: 10.1016/S2468-1253(21)00196-5. Epub 2021 Aug 3.

Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study

ORR: 20-42%
mPFS: 7-9 m
mOS: 12-21,7 m

Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21(5):671-684. Javle M, et al. *Lancet Gastroenterol Hepatol*. 2021;6(10):803-815. Goyal L, et al. *N Engl J Med*. 2023;388(3):228-239.

Cholangiocelulární karcinom

- 2. linie paliativní terapie – cílená léčba
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Clinical Trial > N Engl J Med. 2023 Jan 19;388(3):228-239. doi: 10.1056/NEJMoa2206834.

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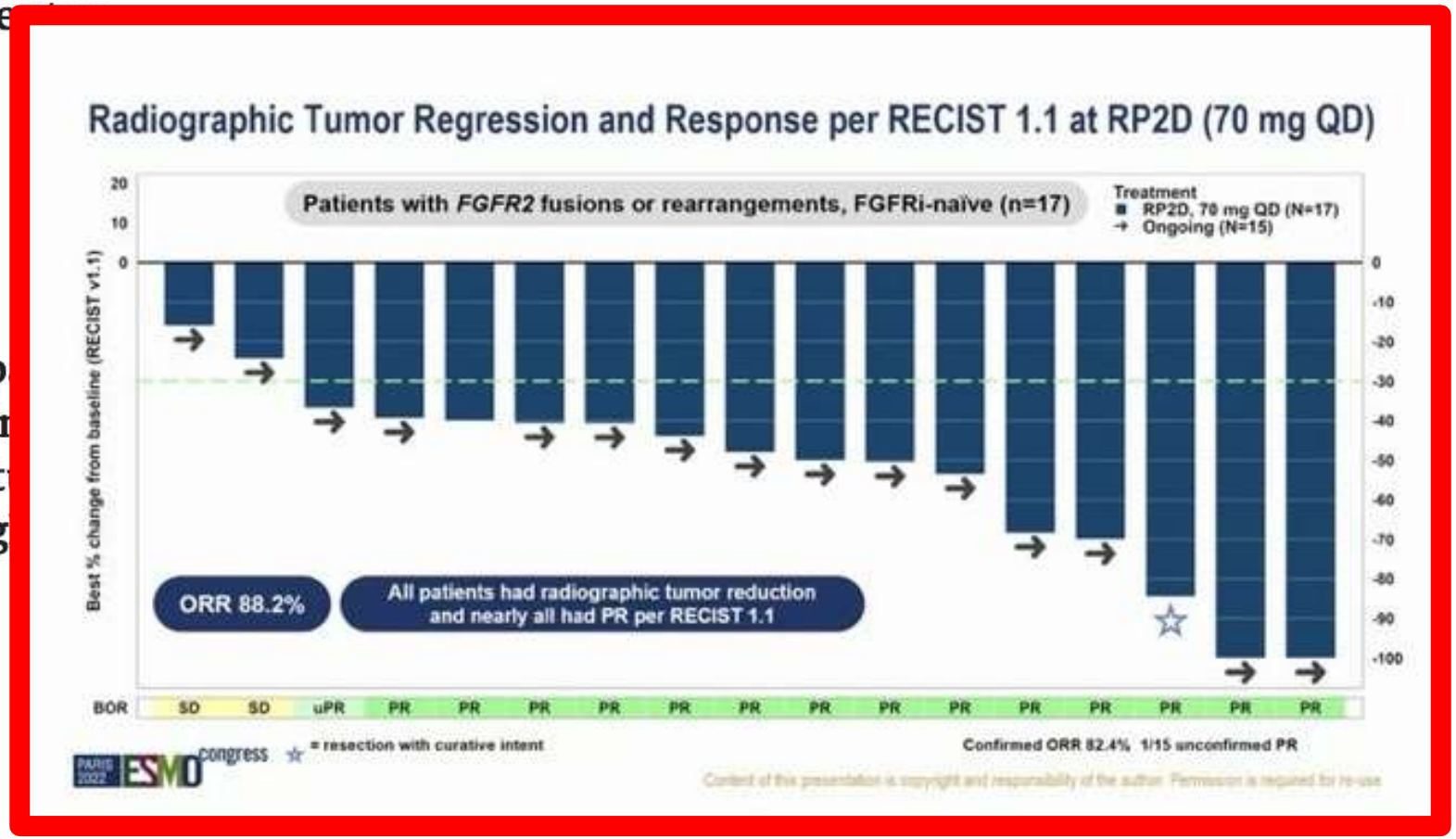
Clinical Trial > Lancet Gastroenterol Hepatol. 2021 Oct;6(10):803-815. doi: 10.1016/S2468-1253(21)00196-5. Epub 2021 Aug 3.

Infigratinib (BGJ398) in previously treated p… with advanced or metastatic cholangiocarci… with FGFR2 fusions or rearrangements: mat… results from a multicentre, open-label, sing… phase 2 study



Subbiah V, et al. *Cancer Discov*. 2023;CD-23-0475.
Abou-Alfa GK, et al. *Lancet Oncol*. 2020;21(5):671-684.
Javle M, et al. *Lancet Gastroenterol Hepatol*. 2021;6(10):803-815.
Goyal L, et al. *N Engl J Med*. 2023;388(3):228-239.

Cholangiocelulární karcinom

- 2. linie paliativní terapie – cílená léčba
- ERBB2 amplifikace = 10 % CHCA, 20% CA ŽLUČNÍKU

Clinical Trial > Lancet Gastroenterol Hepatol. 2023 Jan;8(1):56-65.
doi: 10.1016/S2468-1253(22)00335-1. Epub 2022 Oct 31.

Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19-14)

→

34 pacientů
- **ORR: 29,4%**
- **DCR: 79,4%**
- **mPFS: 5,1 m**
- **mOS: 10,7 m**

Clinical Trial > Lancet Oncol. 2021 Sep;22(9):1290-1300.
doi: 10.1016/S1470-2045(21)00336-3. Epub 2021 Jul 30.

Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study

→

39 pacientů
- **ORR: 23%**

SGNTUC-019: Tucatinib + trastuzumab pro HER2+ CHCA
- basket trial, fáze II, **ASCO23**

→

30 pacientů
- **ORR: 46,7%**
- **DCR: 76,7%**
- **mDoR: 6,0 m**
- **mOS: 15,5 m**

HERIZON-BTC-01: Zanidatanab pro HER2+ CHCA
- Bispecifická protilátka proti 2 HER2 epitopům, fáze IIb
- **ASCO23**

→

87 pacientů
- **ORR: 41,3%**
- **mDoR: 12,9 m**
- **mPFS: 5,5 m**

Lee CK, et al. *Lancet Gastroenterol Hepatol*. 2023;8(1):56-65. Javle M, et al. *Lancet Oncol*. 2021;22(9):1290-1300.
Bekaii-Saab T, et al. ASCO 2023. Harding JJ, et al. ASCO 2023

Cholangiocelulární karcinom

- 2. lin
- ERBE

Clinical Trial
doi: 10.1016/S246

**Trastuzun
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Clinical Trial
doi: 10.1016/S1470-

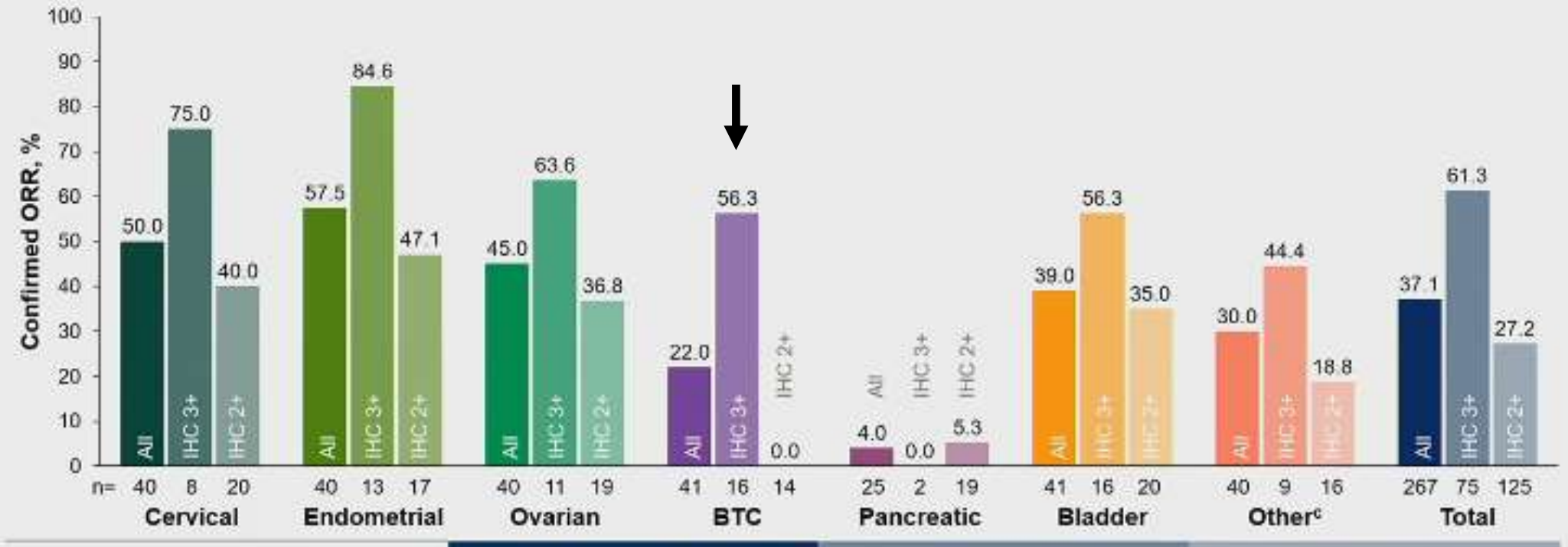
**Pertuzuma
metastatic
multicentr
study**

SGNTUC
- basket

HERIZON
- Bispe
- **ASCO23**

DESTINY-PanTumor02

Objective Response Rate by HER2 status



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of CRR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267, including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [c]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

2023 ASCO ANNUAL MEETING #ASCO23

PRESENTED BY: Funda Meric-Bernstam, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

- **mDoR: 12,9 m**
- **mPFS: 5,5 m**

Lee CK, et al. *Lancet Gastroenterol Hepatol*. 2023;8(1):56-65. Javle M, et al. *Lancet Oncol*. 2021;22(9):1290-1300.
Bekaii-Saab T, et al. ASCO 2023. Harding JJ, et al. ASCO 2023

Cholangiocelulární karcinom

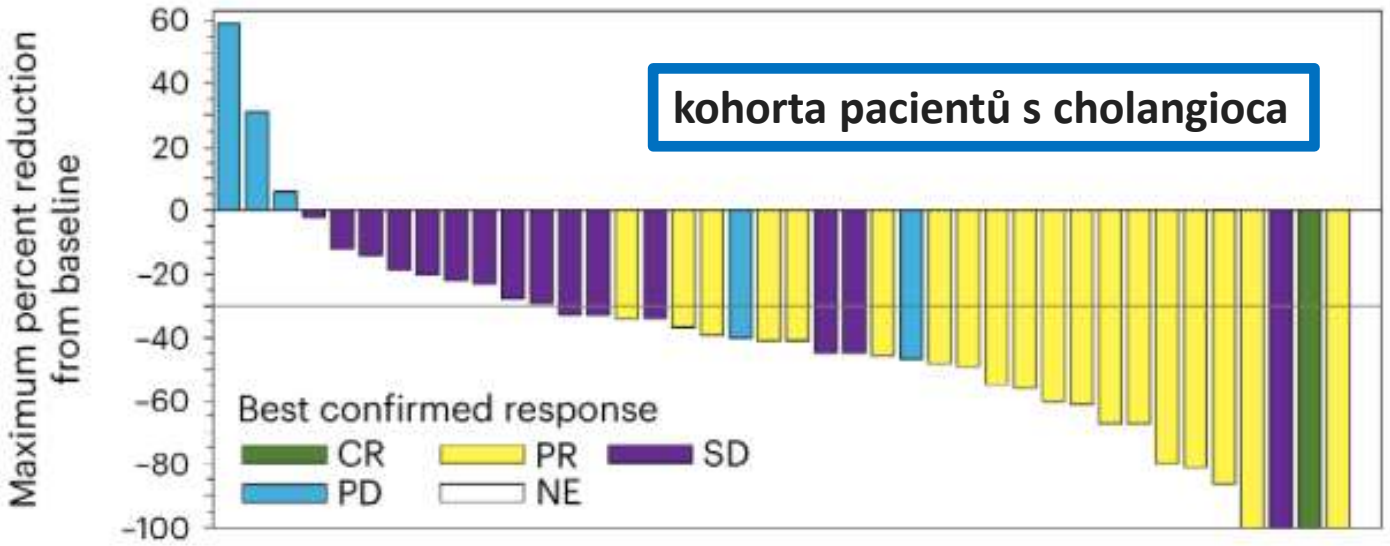
- 2. linie paliativní terapie – cílená léčba
- BRAF V600E mutace = 5 %

Clinical Trial > Nat Med. 2023 May;29(5):1103-1112. doi: 10.1038/s41591-023-02321-8.
Epub 2023 Apr 14.

Dabrafenib plus trametinib in BRAFV600E–mutated rare cancers: the phase 2 ROAR trial

43 pacientů s cholangioca

- **ORR: 58,1%**
- **mPFS: 9 m**
- **mOS: 13,5 m**



Subbiah V, et al. *Nat Med*. 2023;29(5):1103-1112.

Cholangiocelulární karcinom

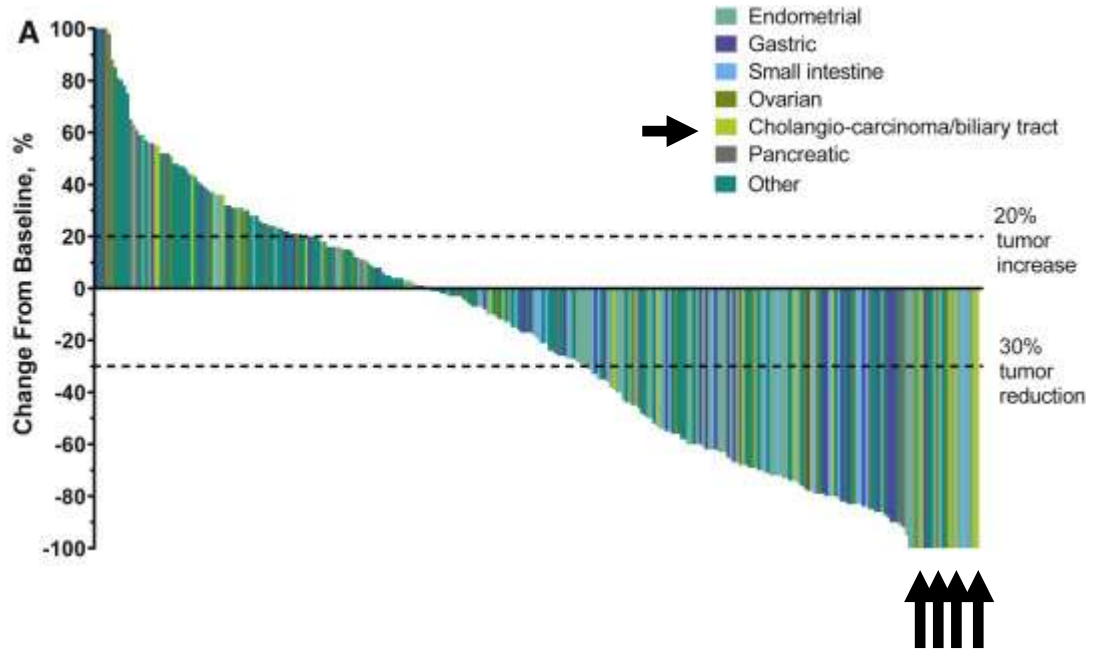
- 2. linie paliativní terapie – cílená léčba
- MSI-high/MMRd = 1 %

Clinical Trial > J Clin Oncol. 2020 Jan 1;38(1):1-10. doi: 10.1200/JCO.19.02105. Epub 2019 Nov 4.

Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

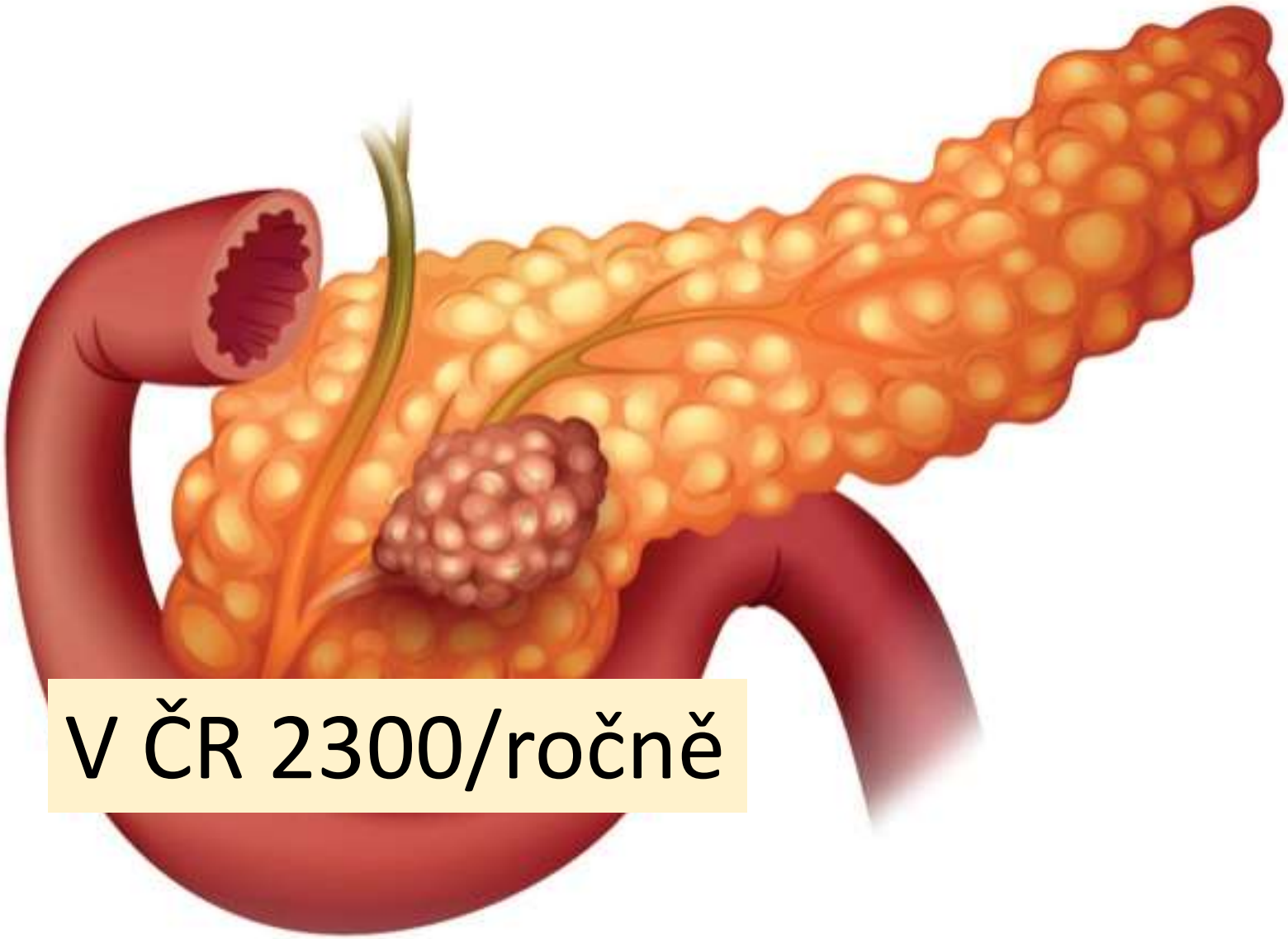
22 pacientů

- **ORR: 40,9%**
- **mPFS: 4,2 m**
- **mOS: 24,3 m**



Marabelle A, et al. *J Clin Oncol*. 2020;38(1):1-10.

Karcinom pankreatu



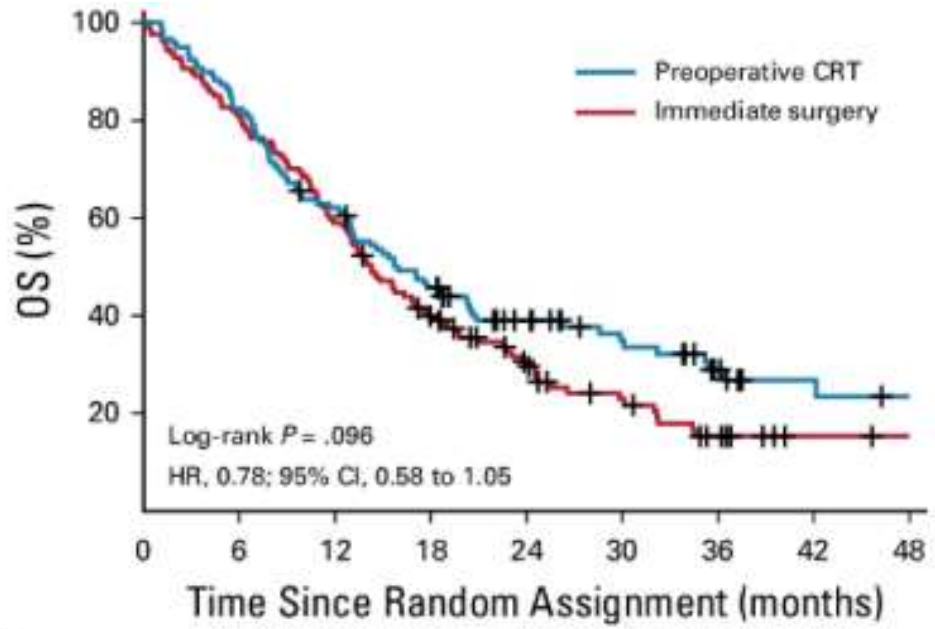
V ČR 2300/ročně

Karcinom pankreatu – neoadjuvance

Randomized Controlled Trial > J Clin Oncol. 2022 Apr 10;40(11):1220-1230.
doi: 10.1200/JCO.21.02233. Epub 2022 Jan 27.

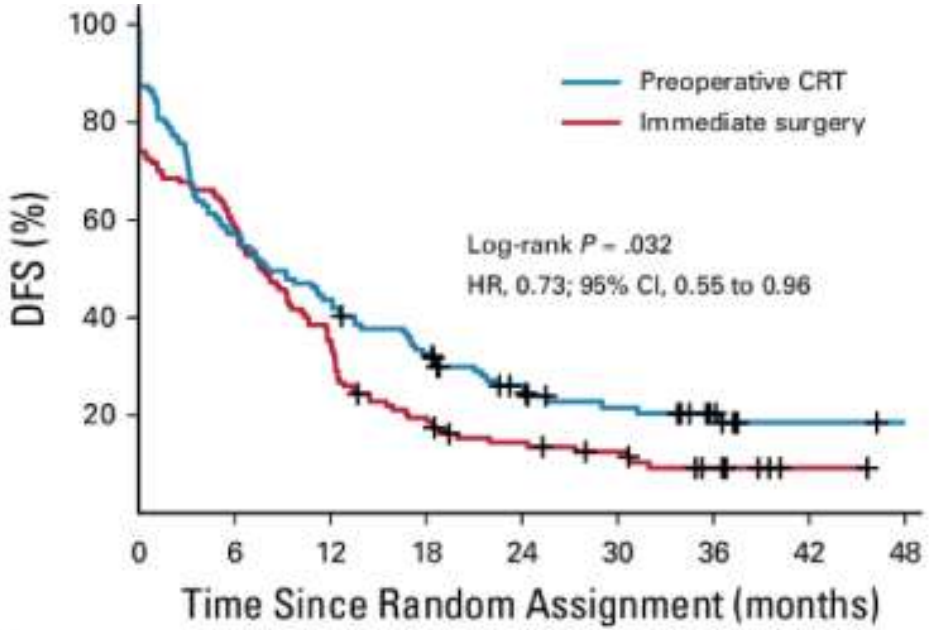
Neoadjuvant Chemoradiotherapy Versus Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Long-Term Results of the Dutch Randomized PREOPANC Trial

- **Resection rate: 61% vs. 72%**
- **R0 resection rate: 71 % vs. 40%**
- **5y OS: 20,5% vs. 6,5%**



No. at risk:

Preoperative CRT	119	99	74	54	37	26	16	9	7
Immediate surgery	127	104	76	49	31	20	11	3	2



No. at risk:

Preoperative CRT	119	69	53	39	26	19	13	7	6
Immediate surgery	127	75	48	25	17	13	7	2	1

Versteijne E, et al. *J Clin Oncol*. 2022;40(11):1220-1230.

Karcinom par

Randomized Controlled Tria

doi: 10.1200/JCO.21.02233. E

Neoadjuvant Ch
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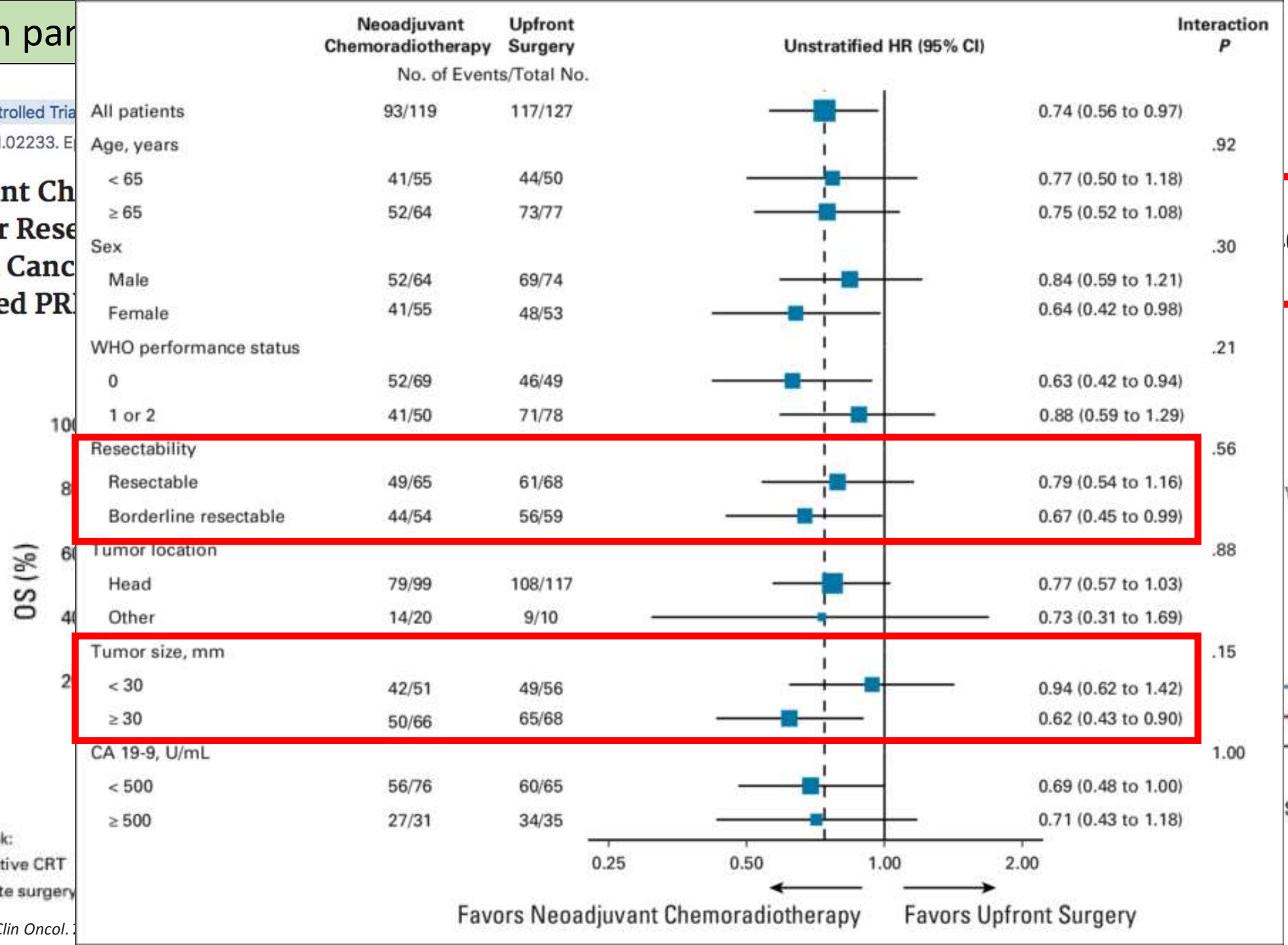
Randomized PR



Versteijne E, et al. *J Clin Oncol*.

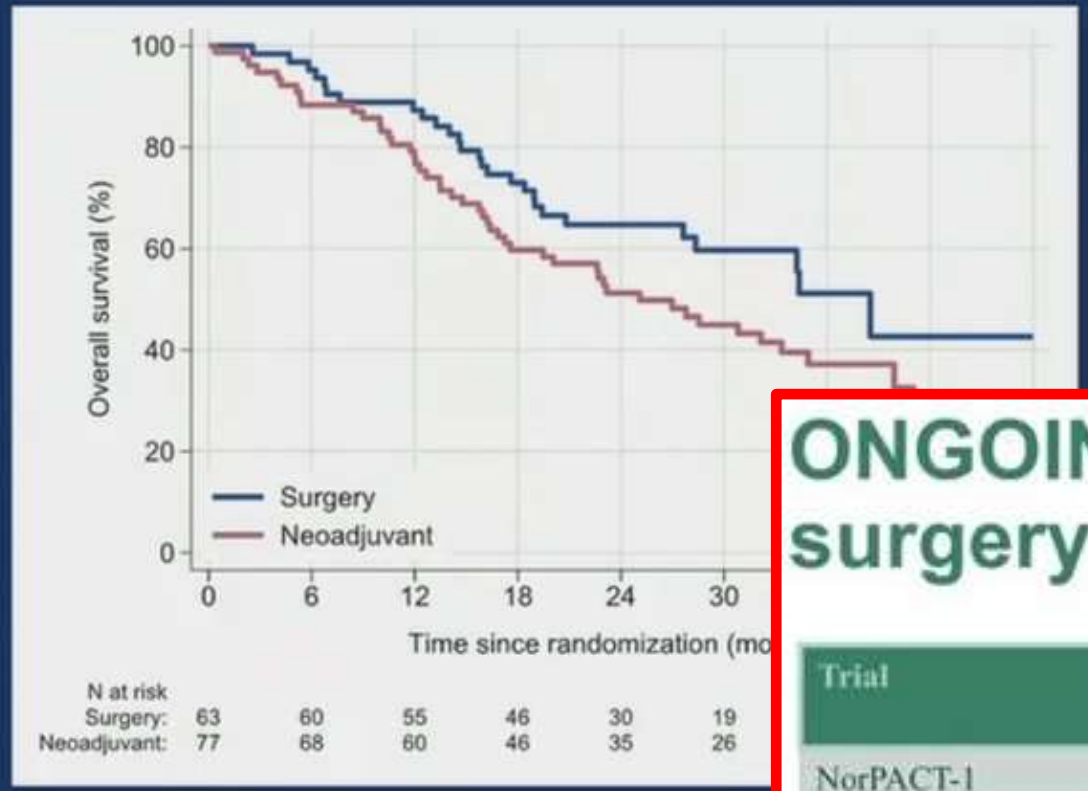
Karcinom pankreatu – neoadjuvance

Randomize
doi: 10.1200/

Neoadj
Surgery
Pancre
Rando

11

Overall survival - Intention-to-treat



Median overall survival
25.1 months (neoadjuvant)
38.5 months (upfront surgery)
HR 1.52 (95% CI, 0.94-2.46), p=0.096

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Knut Jørgen Labor
Presentation is property of the author and ASCO.

ONGOING RCTs – neoadj vs upfront surgery

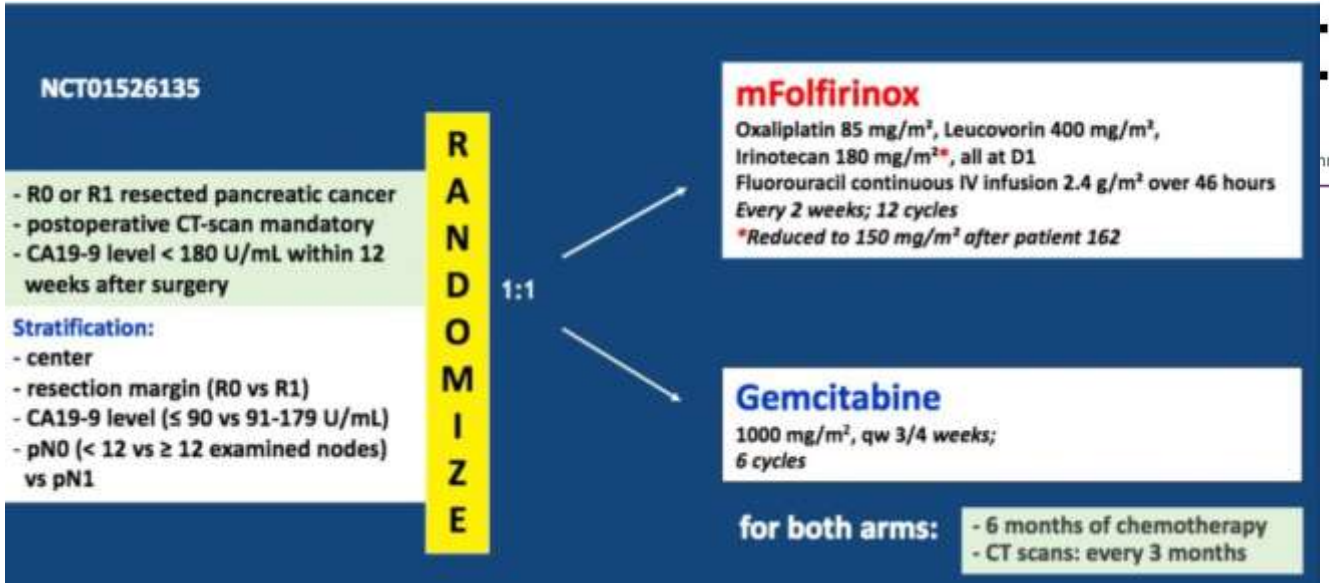
Trial	Sample size	Neoadjuvant FOLFIRINOX	Adjuvant FOLFIRINOX	*Status*
NorPACT-1	140	4-8	12	ASCO 2023
ALLIANCE A021806	352	8-4	12	180 accrued
PREOPANC-3	378	8-4	12	145 accrued

Versteijne E, et al. *J Clin Oncol*. 2022;40(11):1220-1230.

Karcinom pankreatu – adjuvance

Clinical Trial > N Engl J Med. 2018 Dec 20;379(25):2395-2406. doi: 10.1056/NEJMoa1809775.

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer



PRODIGE 24/CCTG PA.6: Survival Outcomes

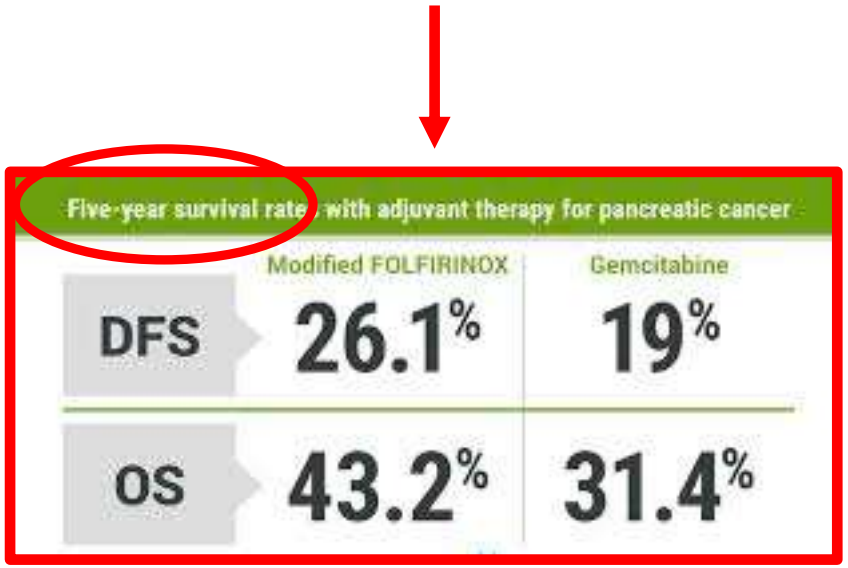
Survival Outcome	mFOLFIRINOX (n = 247)	Gemcitabine (n = 246)	HR (95% CI)	*P* Value
DFS*				
▪ Median, mos (95% CI)	21.6 (17.7-27.6)	12.8 (11.7-15.2)	0.58 (0.46-0.73)	< .0001
▪ 3-yr, % (95% CI)	39.7 (32.8-46.6)	21.4 (15.8-27.5)		
Median MFS,† mos (95% CI)	30.4 (21.7-NR)	17.7 (14.2-21.5)	0.59 (0.46-0.75)	< .0001
OS				
▪ Median, mos (95% CI)	54.4 (41.8-NR)	35.0 (28.7-43.9)	0.64 (0.48-0.86)	.003
▪ 3 yr,‡ %	63.4	48.6		
3-yr disease-specific survival,§ %	66.2	51.2	0.63 (0.47-0.85)	.003

*314 events. †273 events. ‡192 events. §180 events.

- DFS benefit favored mFOLFIRINOX across all predefined subgroups
- Per multivariable analysis, prognostic factors for DFS included mFOLFIRINOX tx (HR: 0.59; *P* < .001), moderately to poorly differentiated tumor (HR: 1.42; *P* < .001), portal vein resection (HR: 1.43; *P* < .001)

nroy T, et al. ASCO 2018. Abstract LBA4001.

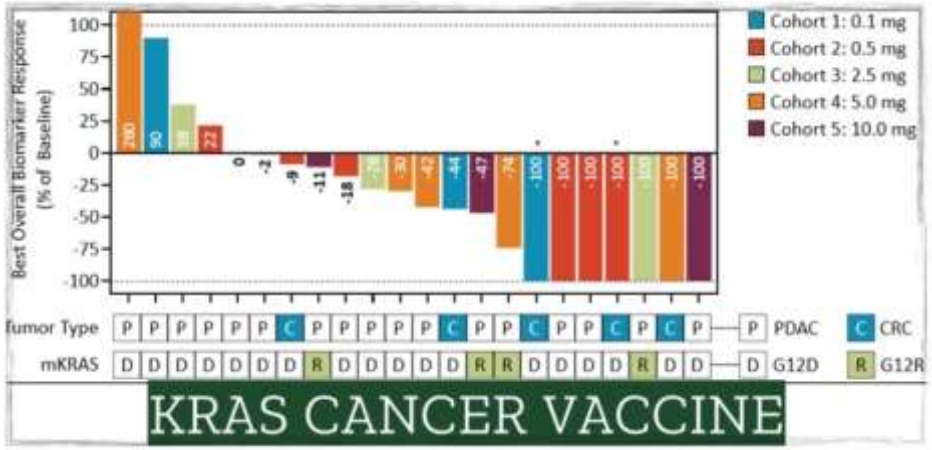
Slide credit: clinicaloptions.com



Conroy T, et al. *N Engl J Med*. 2018;379(25):2395-2406. Conroy T, et al. *JAMA Oncol*. 2022;8(11):1571-1578.

Karcinom pankreatu – adjuvance + vakcinace

AMPLIFY-201:
a first-in-human safety and efficacy trial of adjuvant ELI-002 2P immunotherapy for patients with high-relapse risk with **KRAS G12D**- or **G12R**-mutated pancreatic and colorectal cancer

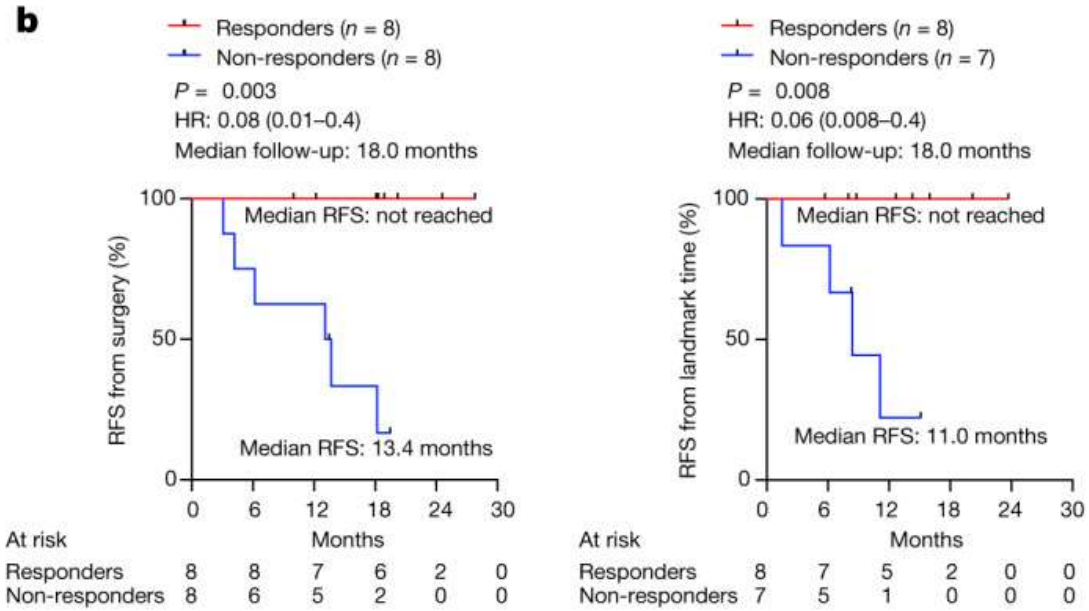


ELI-002 Amph-CpG Dose Level	0.1 mg	0.5 mg	2.5 mg	5.0 mg	10.0 mg
Number of pts/mKRAS G12D or G12R	3/DDD	6/DDDDDD	5/DRDDD	5/DDRDD	3/RRD
Safety (DLT)	0/3 (0%)	0/6 (0%)	0/5 (0%)	0/5 (0%)	0/3 (0%)
Biomarker reduction/clearance	2/3 (67%)	5/6 (83%)	3/5 (60%)	3/3* (100%)	2/2* (100%)
T cell response	2/3 (67%)	5/6 (83%)	2/3 (67%)*	3/3 (100%)*	*

*Subset of pts evaluable at data cut.

Nature. 2023; 618(7963): 144–150.
Published online 2023 May 10. doi: 10.1038/s41586-023-06063-y
PMCID: PMC10171177
PMID: 37165196

Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer



O'Reilly EM, et al. *J Clin Oncol* 41, 2023 (suppl 16; abstr 2528). Rojas LA, et al. *Nature*. 2023;618(7963):144-150.

NAPOLI 3: mOS (ITT population)

15

NALIRIFOX vs FOLFIRINOX

	NALIRIFOX	FOLFIRINOX*
Median OS	11.1 months	11.1 months
Median PFS	7.4 months	6.4 months
Objective RR	41.8%	31.6%
Grade 3/4 Diarrhea	20.3%	12.7%
Grade 3/4 Vomiting	7.0%	14.5%
Grade 3/4 Sensory Neuropathy	3.5%	9.0%

- **1 cyklus NALIRIFOX (BSA 1,7m2): 5398 $**
- **1 cyklus mFOLFIRINOX (BSA 1,7m2): 37,77 $**

*Conroy, et al, NEJM 2011

Stratified by ECOG PS (0 vs 1), region (North America vs ROW), live metastases (yes vs no) per IRT. P boundary for efficacy claim p value < 0.048.
CI, confidence interval; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; mOS, median overall survival; NabP, nab-paclitaxel.

Karcinom pankreatu

- 1. linie paliativní terapie - maintenance

Clinical Trial > N Engl J Med. 2019 Jul 25;381(4):317-327. doi: 10.1056/NEJMoa1903387.
Epub 2019 Jun 2.

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

154 pacientů s PDAC se zárodečnou BRCA1/2 mutací:

- Předchozí platina-based CHT: FOLFIRINOX > 80%, gem + cis < 5%, další režimy < 13%
- CR/PR či SD (medián délky 1. linie terapie 5m)

Randomizace 3:2:

- 92 do ramene s olaparibem
- 62 do ramene s placebem

Výsledky:

- mOS: 19,0 vs. 19,2m, p=0,3487
- mPFS: 7,4 vs. 3,8m, HR: 0,53, P=0,004
- Olaparib ↑ čas do zahájení CHT další linie

Kindler HL, et al. *J Clin Oncol,* 2022. Golan T, et al. *N Engl J Med*, 2019

Karcinom pankreatu – 2. linie paliativní terapie

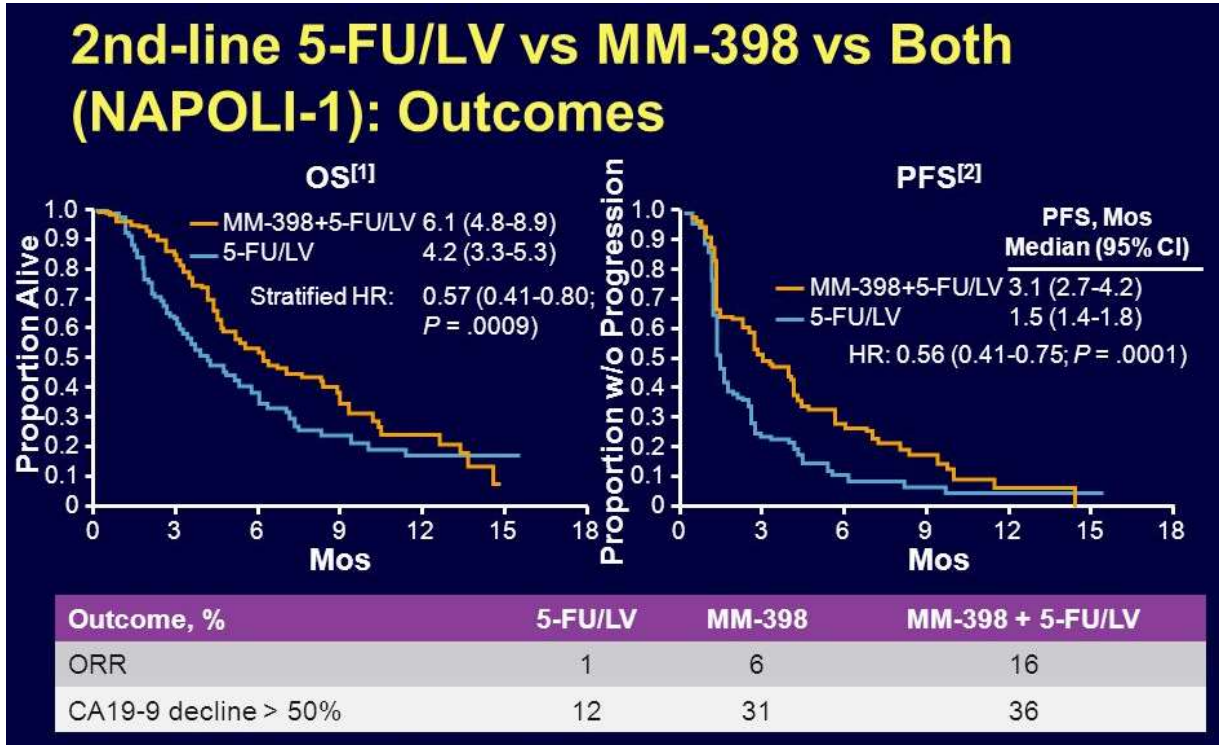
Týká se do 50% pacientů

Gemcitabin based → nal-IRI + 5-FU/LV nebo FOLFIRINOX/FOLFOX/OFF/FOLFIRI/CAPOX/kapecitabin/5-FU

5-FU based → gemcitabin + nab-paklitaxel nebo gemcitabin/gemcitabin+cisplatina u BRCA1/2 nebo PALB2 mutovaných

Clinical Trial > Lancet. 2016 Feb 6;387(10018):545-557.
doi: 10.1016/S0140-6736(15)00986-1. Epub 2015 Nov 29.

Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial



Outcome, %	5-FU/LV	MM-398	MM-398 + 5-FU/LV
ORR	1	6	16
CA19-9 decline > 50%	12	31	36

Wang-Gillam A,, et al. *Eur J Cancer*. 2019;108:78-87. Maire F et al. *Eur J Gastoenteral Hepatol*, 2017. Lambert A et al. *Ther Adv Med Oncol,* 2019

Karcinom pankreatu – 2. a další linie paliativní terapie

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Pancreatic Adenocarcinoma

NCCN Guidelines Index
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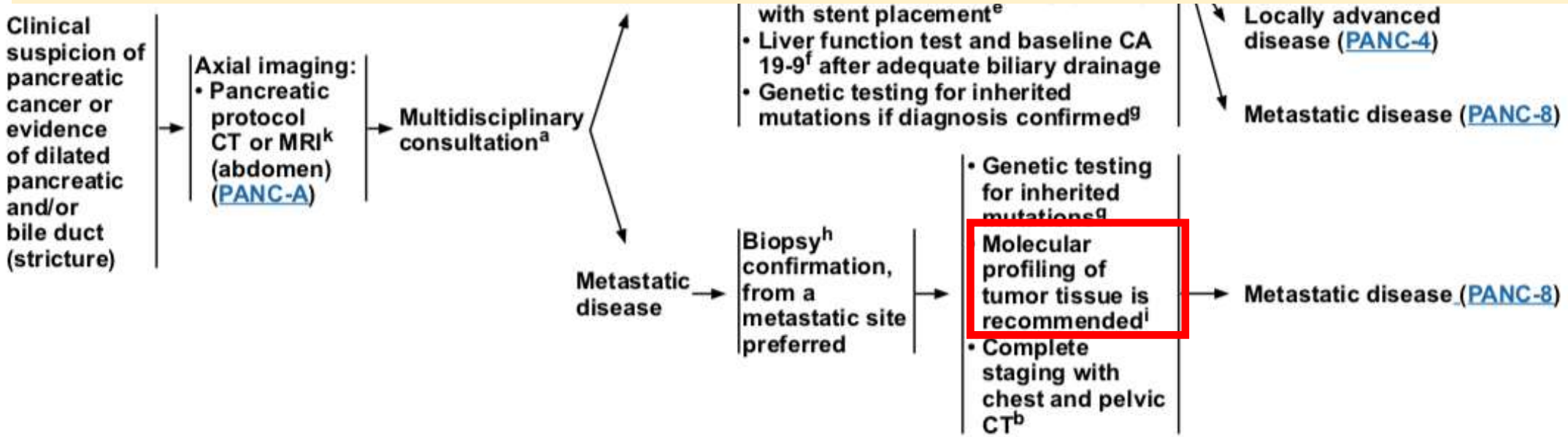
Discussion

Tumor/somatic molecular profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to: **fusions (*ALK, NRG1, NTRK, ROS1, FGFR2,* and *RET*), mutations (*BRAF, BRCA1/2, KRAS,* and *PALB2*), amplifications (*HER2*), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB)** via an FDA-approved and/or validated next-generation sequencing (NGS)-based assay. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible.



Karcinom pankreatu – 2. a další linie paliativní terapie

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Pancreatic Adenocarcinoma

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease

Preferred Regimens	Other Recommended Regimens		Useful in Certain Circumstances
• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Pembrolizumab[i] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb])	• Dabrafenib + trametinib (if *BRAF* V600E mutation positive)[18,19] • Dostarlimab-gxly[i] (if MSI-H or dMMR) • Selpercatinib (if *RET* gene fusion-positive)[23] • Nivolumab + ipilimumab[i] (if TMB-H [≥10 mut/Mb]) (category 2B)	If prior fluoropyrimidine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[24] (if no prior irinotecan) • Gemcitabine • Gemcitabine + albumin-bound paclitaxel • Gemcitabine + cisplatin (only for known *BRCA1/2* or *PALB2* mutations) • Gemcitabine + erlotinib[f,29] • Gemcitabine + albumin-bound paclitaxel + cisplatin[14,15] (category 2B)	• Adagrasib (if *KRAS G12C* mutation positive) • Sotorasib (if *KRAS G12C* mutation positive) • Chemoradiation,[b] if not previously given, only an option for: ▸ Locally advanced disease if primary site is the sole site of progression ▸ Select patients with recurrent disease in combination with systemic therapy
	If prior gemcitabine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[24] (category 1 for metastatic disease) • Capecitabine • CapeOx • Continuous infusion 5-FU • FOLFIRI[25-27] • FOLFIRINOX or modified FOLFIRINOX[e,28] • FOLFOX • OFF		

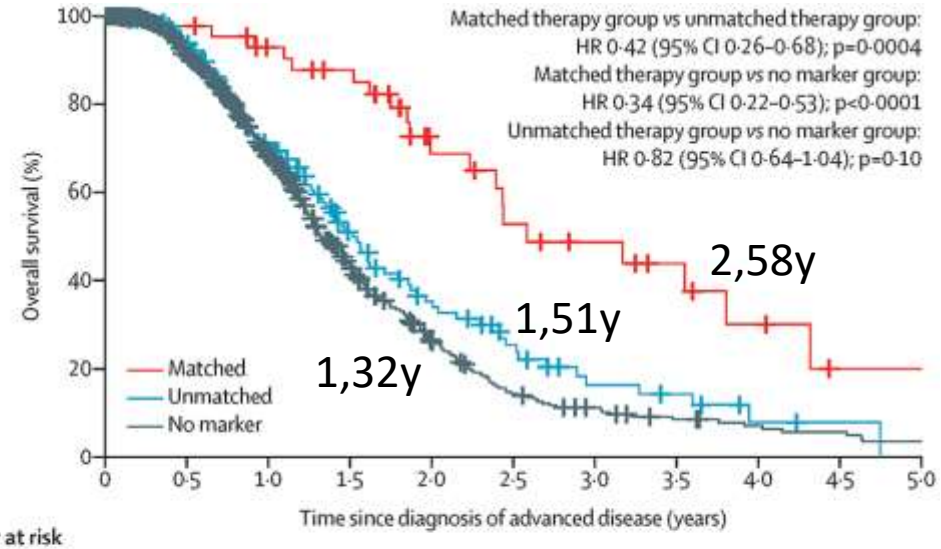
6 prediktivních markerů

Karcinom pankreatu – 2. a další linie paliativní terapie

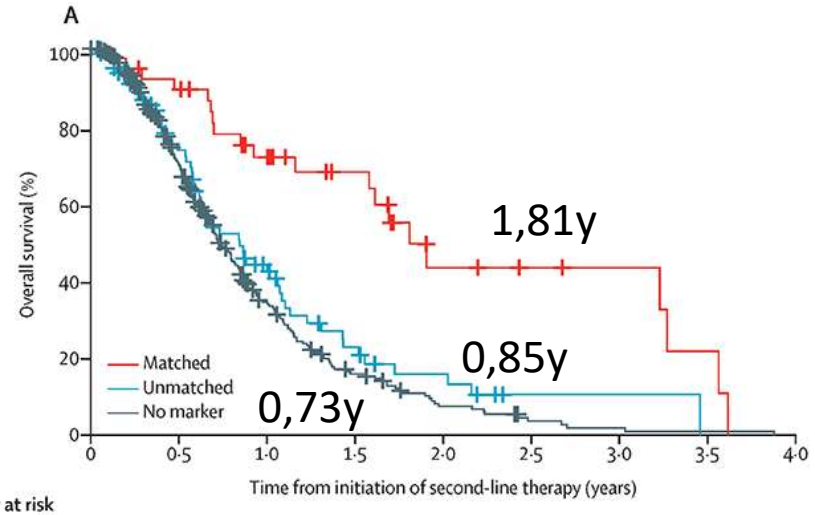
> Lancet Oncol. 2020 Apr;21(4):508-518. doi: 10.1016/S1470-2045(20)30074-7. Epub 2020 Mar 2.

Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial

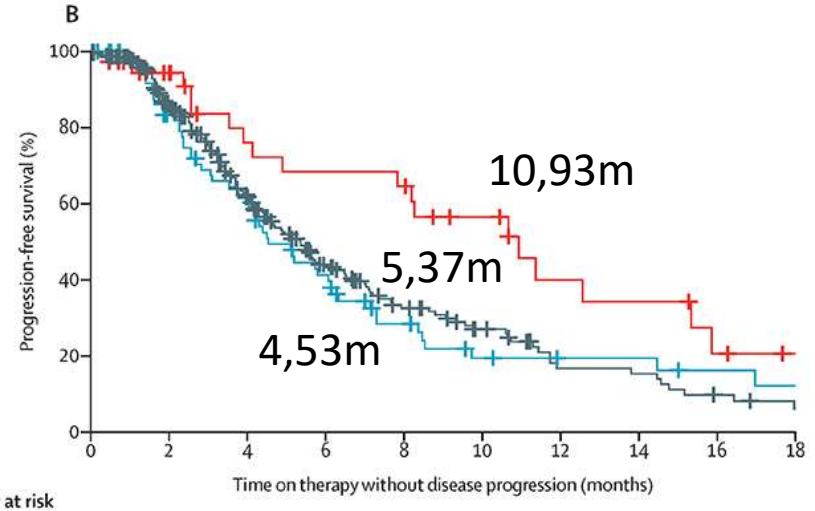
26% (282) pacientů s targetabilním nálezem



Number at risk (number censored)											
Matched therapy	46	42	36	32	18	13	10	7	4	1	1
	(0)	(3)	(4)	(2)	(8)	(1)	(2)	(2)	(1)	(2)	(0)
Unmatched therapy	143	116	78	44	27	16	8	6	2	1	0
	(0)	(19)	(11)	(15)	(4)	(4)	(3)	(1)	(2)	(1)	(0)
No marker	488	384	241	124	63	33	22	14	10	8	5
	(0)	(66)	(55)	(39)	(15)	(4)	(4)	(3)	(2)	(0)	(0)



Number at risk (number censored)									
Matched therapy	39	33	23	16	7	5	4	2	0
	(0)	(2)	(4)	(6)	(4)	(2)	(1)	(0)	(0)
Unmatched therapy	83	49	24	11	6	1	1	0	0
	(0)	(15)	(6)	(3)	(2)	(3)	(0)	(0)	(0)
No marker	288	167	65	27	11	4	2	1	0
	(0)	(45)	(25)	(4)	(3)	(2)	(0)	(0)	(0)



Number at risk (number censored)										
Matched therapy	38*	29	20	18	17	12	7	6	3	1
	(0)	(8)	(3)	(0)	(0)	(3)	(2)	(0)	(1)	(2)
Best unmatched therapy	84	58	41	25	14	8	6	6	4	3
	(0)	(14)	(2)	(3)	(4)	(2)	(2)	(0)	(1)	(0)
Best therapy, no marker	288	195	120	65	40	26	12	11	6	3
	(0)	(61)	(26)	(21)	(10)	(8)	(6)	(0)	(1)	(1)

Pishvaian MJ et al., *Lancet Oncol,* 2020

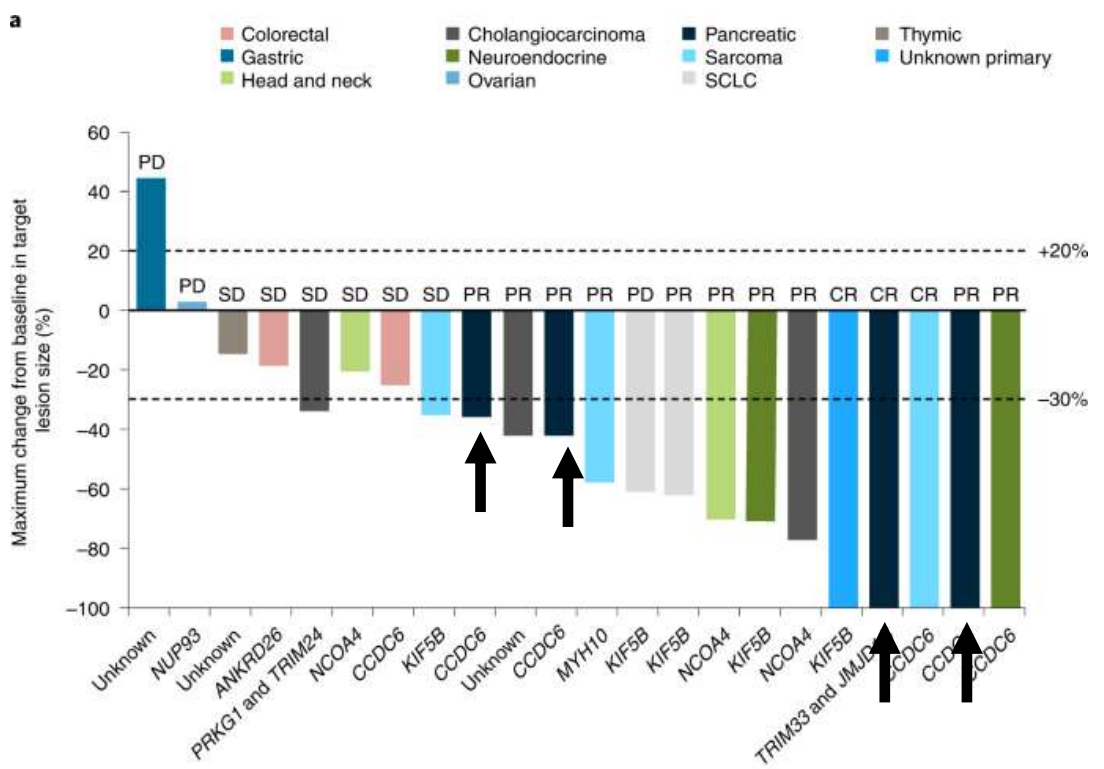
Karcinom pankreatu

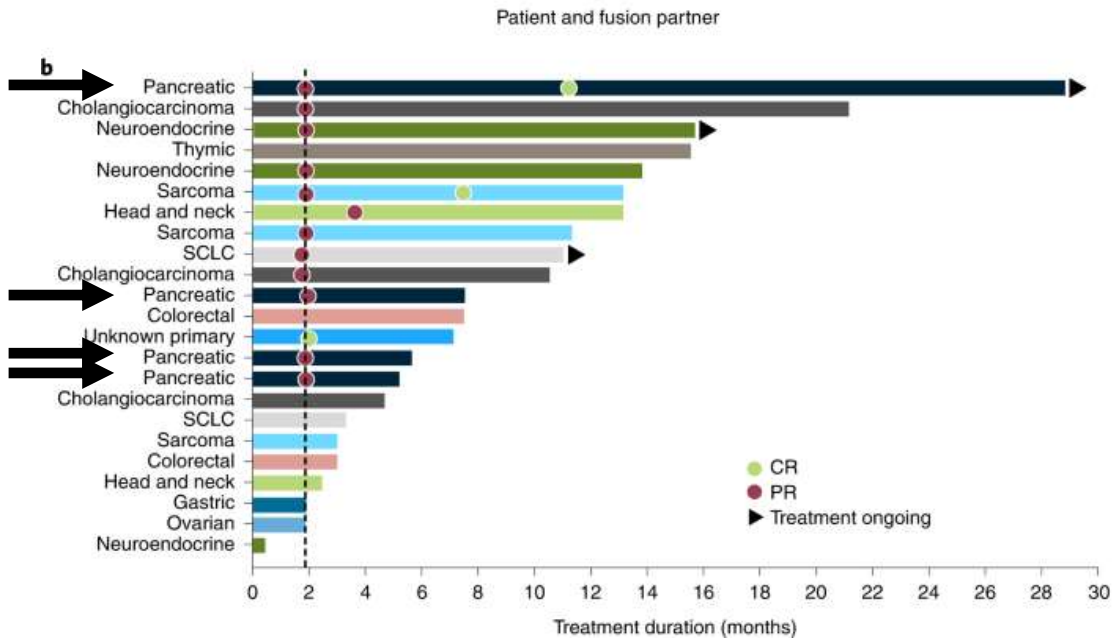
- 2. a další linie paliativní terapie – cílená léčba
- RET fúze < 1 %

Clinical Trial > Nat Med. 2022 Aug;28(8):1640-1645. doi: 10.1038/s41591-022-01931-y.
Epub 2022 Aug 12.

Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial

- **ORR: 57%**
- **mDoRS: 12 m**
- **mPFS: 7 m**
- **mOS: 14 m**





Subbiah V, et al. *Nat Med*. 2022;28(8):1640-1645.

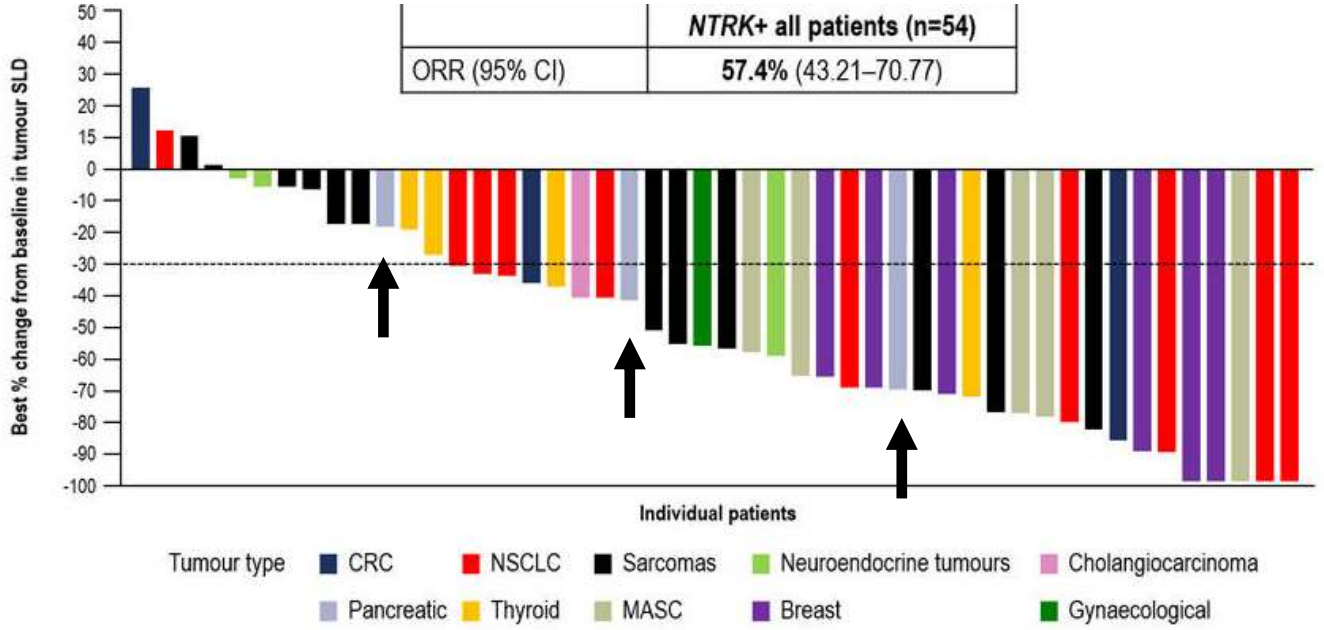
Karcinom pankreatu

- 2. a další linie paliativní terapie – cílená léčba
- NTRK fúze < 1 %

> Lancet Oncol. 2020 Feb;21(2):271-282. doi: 10.1016/S1470-2045(19)30691-6. Epub 2019 Dec 11.

Entrectinib in patients with advanced or metastatic NTRK fusion–positive solid tumours: integrated analysis of three phase 1–2 trials

Efficacy outcomes	*NTRK*+ patients (n=54)
ORR*, % (95% CI)	57.4 (43.2–70.8)
CR* n (%)	4 (7.4)
Median DoR,* months (95% CI)	10.4 (7.1–NR)
Median PFS,* months (95% CI)	11.2 (8.0–14.9)
Median OS, months (95% CI)	20.9 (14.9–NR)



Doebele RC, et al. *Lancet Oncol*. 2020;21(2):271-282.

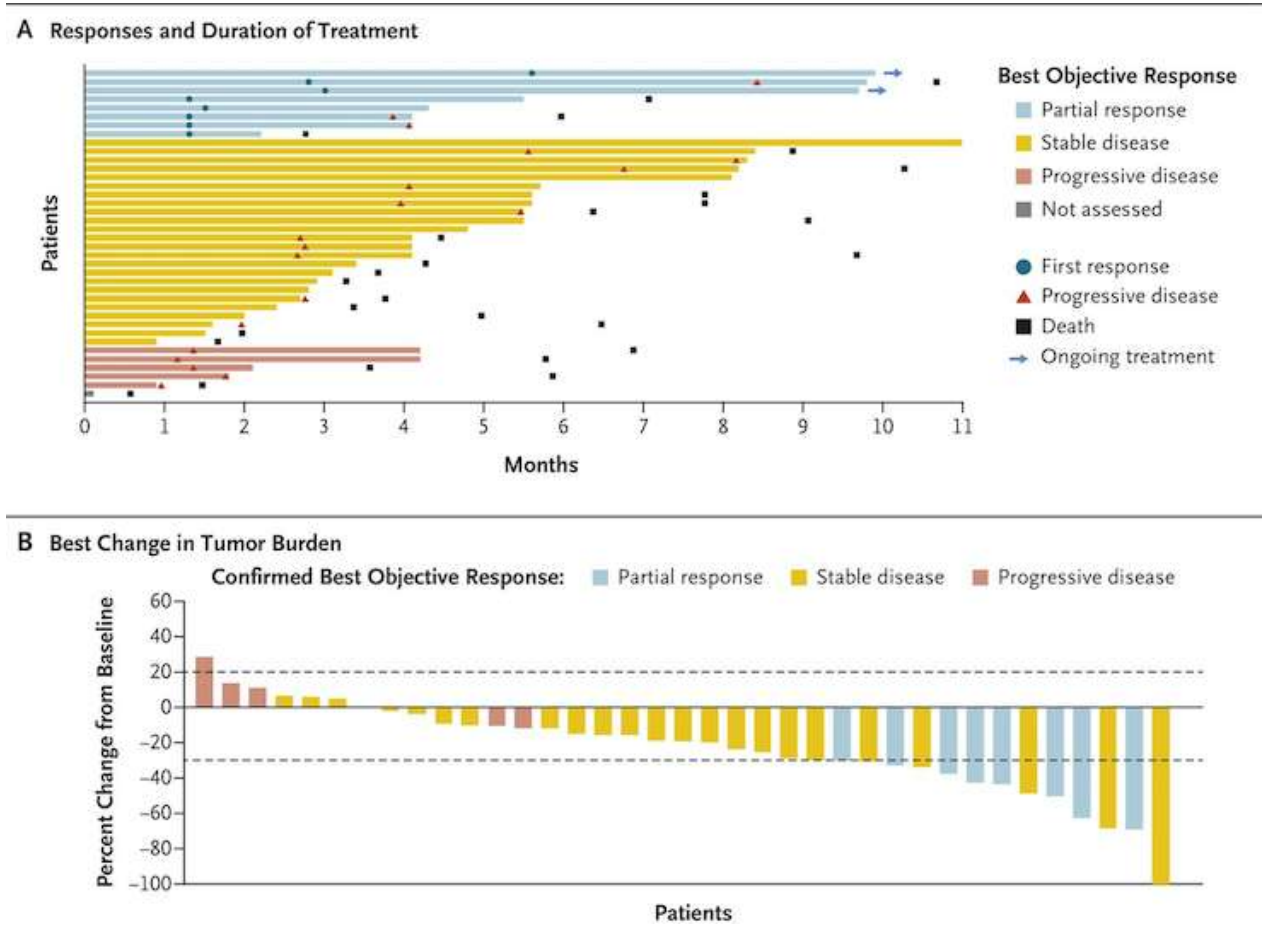
Karcinom pankreatu

- 2. a další linie paliativní terapie – cílená léčba
- KRAS G12C mutace = 2 %

Clinical Trial > N Engl J Med. 2023 Jan 5;388(1):33-43. doi: 10.1056/NEJMoa2208470.
Epub 2022 Dec 21.

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

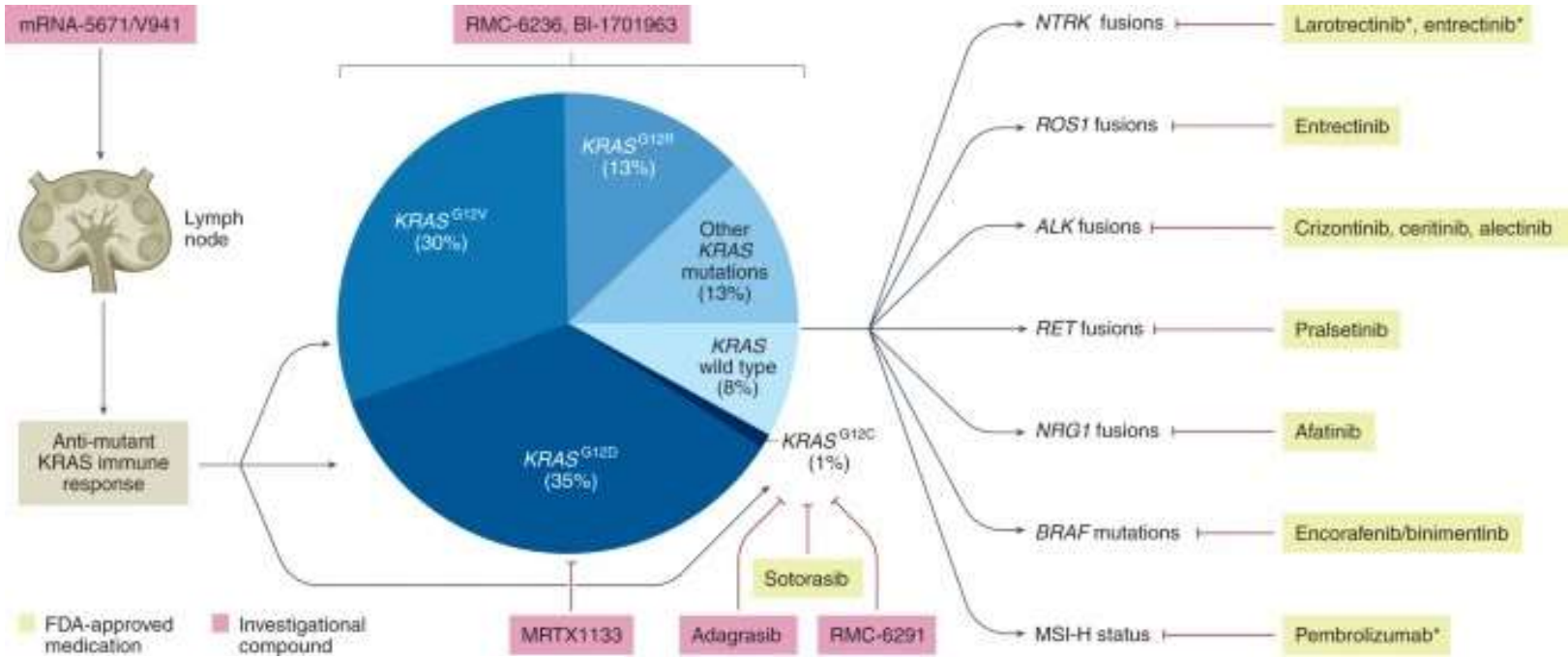
- **Medián předchozích linií CHT = 2**
- **ORR: 21%**
- **SD: 63%**
- **mPFS: 4 m**
- **mOS: 6,9 m**

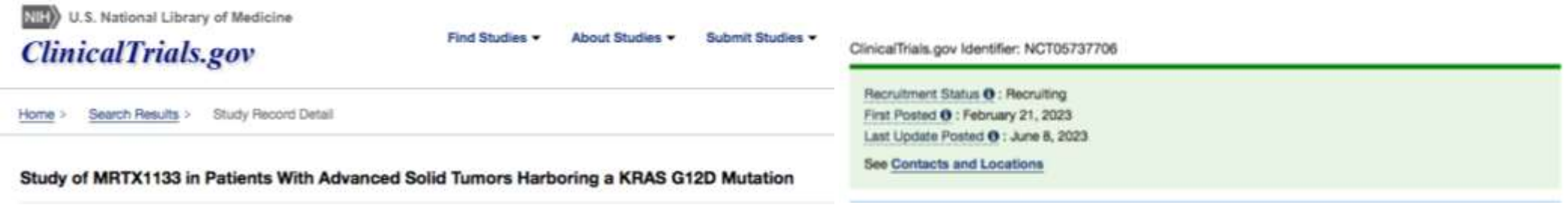


Strickler JH, et al. *N Engl J Med*. 2023

Karcinom pankreatu

- 2. a další linie paliativní terapie – cílená léčba
- KRAS mutace = 90 %





Hosein AN, et al. *Nat Cancer*. 2022;3(3):272-286.

“Take-home message“

- CHCA
  - adjuvance (51,1m)
  - paliace (chemo v 1.L: 11-12m, 2.L: 6,2m)
    - chemoimuno do 1. linie paliace -> + 1,8m v OS
    - prediktory pro cílenou terapii u 40% CHCA -> + 4-18 m v OS u předléčených

- PDAC
  - neoadjuvance (R?, **BR, LA**) -> ↑R0 RR, ↑5y OS u R a BR
  - adjuvance (28-54,4m), vakcinace -> ↑RFS?
  - paliace (chemo v 1.L: 11,1m, 2.L: 6,1m)
    - prediktory pro cílenou terapii u 26% pacientů -> + 12 m v OS u předléčených

DĚKUJI ZA POZORNOST