Highlights from the 2020 Gastrointestinal Cancers Symposium, San Francisco

Karcinomy slinivky břišní

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Highlights from the 2020 Gastrointestinal Cancers Symposium

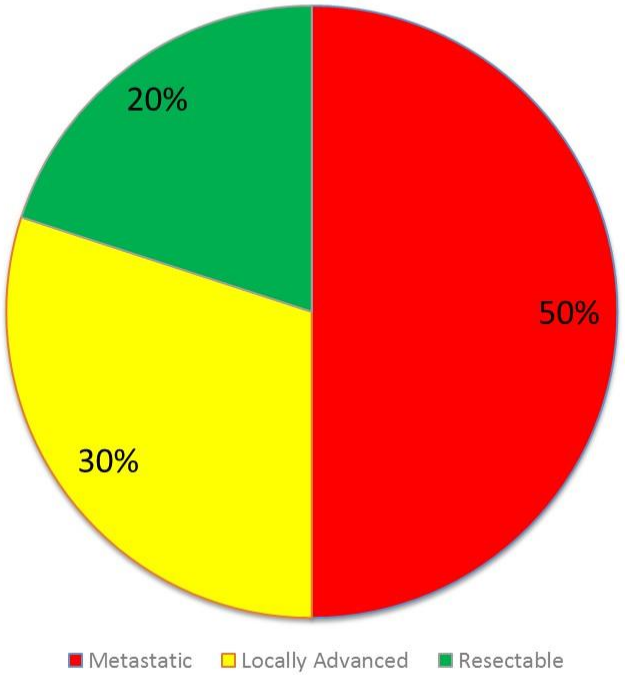
- **Stále platí:**
  - Ve všech klinických stadiích je ve srovnání s ostatními typy zhoubných nádorů **doba přežití nemocných s karcinomem slinivky břišní nejkratší**
  - U většiny nemocných s karcinomem slinivky břišní se jedná v době dg. o **„systémové“ onemocnění !!!!**
  - **Systémová léčba má význam ve všech stadiích onemocnění** *viz dále*
  - Zařazení radioterapie je trvale kontroverzní, ale….
    - U lokálně pokročilého onemocnění vhodná kombinace lokální a systémové léčby *viz dále*
- **Nové možnosti**
  - PARP inhibitory
  - Imunoterapie check point inhibitory (pouze pro MSIh!)

Clinically localized pancreatic cancer is not biologically localized

<u>systemic disease</u>

Northwell Health Cancer Institute

Pancreatic Cancer Treatment Must be **BOTH** Systemic and Local



Median Survival	(months)
Metastatic	6-12
Locally Advanced	10-12
Resectable	24

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Highlights from the 2020 Gastrointestinal Cancers Symposium, San Francisco
Co je nového?

- <u>další negativní klinické studie fáze III</u>
  - Studie HALO -109-301
    - definitivní potvrzení neúčinnosti degradace hyaluronanu
  - Studie SEQUOIA
    - neúčinná modulace chemoterapie druhé linie pegilodecakinem
  - Randomizovaná studie fáze II Cisplatina/gemcitabin +/- PARP inhibitor
    - přidání veliparibu k chemoterapii u BRCA / PALB2 mut nezvyšuje účinnost
  - Není doklad o účinnosti imunoterapie check point inhibitory
    - účinnost pouze u MSIh tumorů

HALO 109-301: A randomized, double-blind, placebo-controlled, global phase 3 study of pegvorhyaluronidase alfa + nab-paclitaxel/gemcitabine in patients with previously untreated hyaluronan-high metastatic pancreatic ductal adenocarcinoma

Margaret A. Tempero,[1] Eric Van Cutsem,[2] Darren Sigal,[3] Do-Youn Oh,[4] Nicola Fazio,[5] Teresa Macarulla,[6] Erika Hitre,[7] Pascal Hammel,[8] Andrew E. Hendifar,[9] Susan E. Bates,[10] Chung-Pin Li,[11] Christelle de la Fouchardiere,[12] Volker Heinemann,[13] Anthony Maraveyas,[14] Nathan Bahary,[15] Laura Layos,[16] Vaibhav Sahai,[17] Lei Zheng,[18] Jill Lacy,[19] Andrea J. Bullock,[20] on behalf of the HALO 109-301 Investigators

[1]UCSF Medical Center, San Francisco, CA, USA; [2]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium; [3]Scripps Clinic, La Jolla, CA, USA; [4]Seoul National University College of Medicine, Seoul, South Korea; [5]European Institute of Oncology, IEO, IRCCS, Milan, Italy; [6]Vall d´Hebrón Institute of Oncology (VHIO), Barcelona, Spain; [7]National Institute of Oncology, Budapest, Hungary; [8]Hôpital Beaujon (AP-HP), Clichy, and Université Paris VII-Denis Diderot, France; [9]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [10]Columbia University Medical Center, New York, NY, USA; [11]Taipei Veterans General Hospital, Taipei, Taiwan; [12]Centre Léon Bérard, Lyon, France; [13]Klinikum Grosshadern, Ludwig-Maximilians-University of Munich, Munich, Germany; [14]Hull York Medical School, Castle Hill Hospital, Cottingham, UK; [15]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [16]Hospital Germans Trias i Pujol, Badalona, Barcelona, Catalonia, Spain; [17]University of Michigan, Ann Arbor, MI, USA; [18]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [19]Yale School of Medicine, New Haven, CT, USA; [20]Beth Israel Deaconess Medical Center, Boston, MA, USA

PRESENTED AT: Gastrointestinal Cancers Symposium

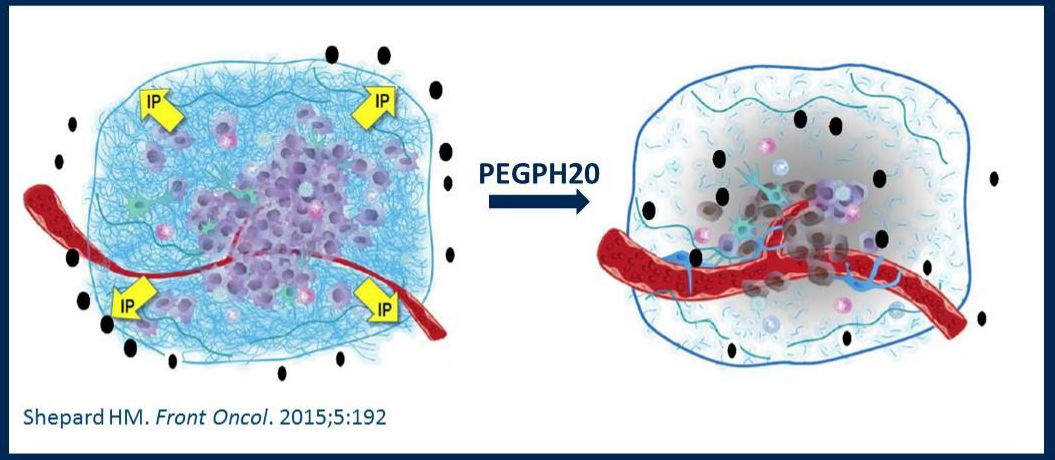
PRESENTED BY: Margaret A. Tempero, MD

#GI20

Presented By Margaret Tempero at 2020 Gastrointestinal Cancer Symposium

Background

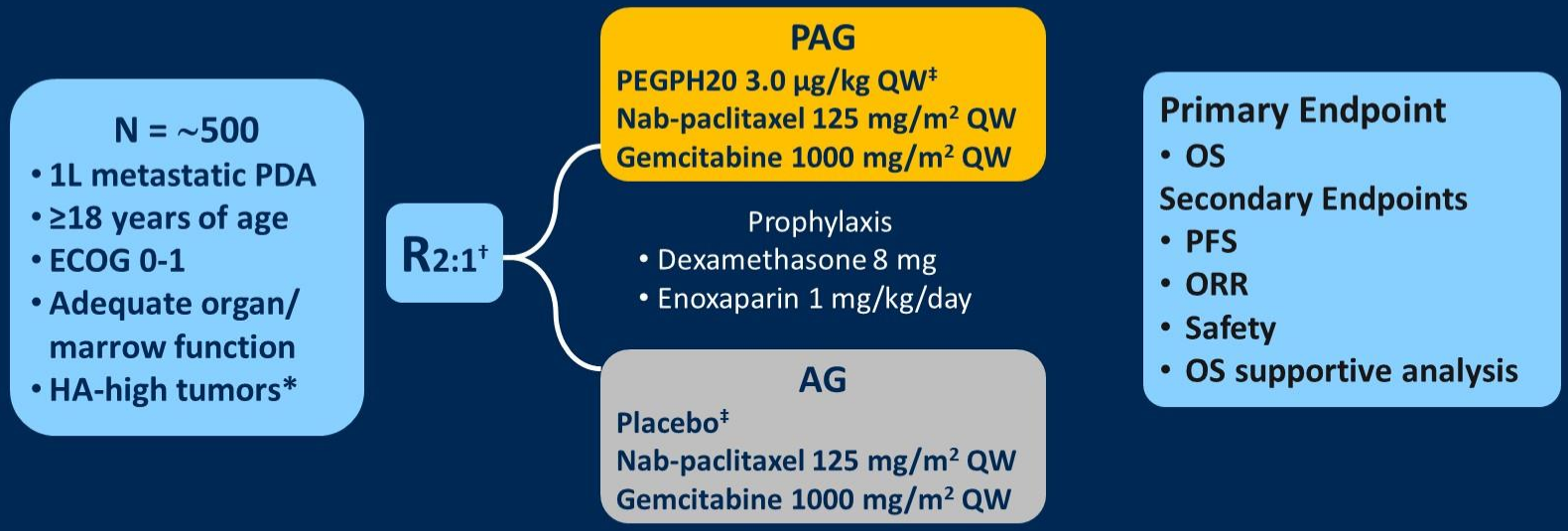
- Hyaluronan (HA) is a major component of the TME in PDA[1-2]
  - Accumulation is associated with tumor stroma desmoplasia and poor prognosis
  - Stromal desmoplasia increases TME interstitial pressure, compressing tumor vasculature and impeding perfusion and delivery of systemic agents
- PEGPH20 degrades tumor HA, remodeling the TME[1-4]
  - Antitumor activity in PDA models
  - Increases delivery of anticancer agents to improve efficacy



Shepard HM. *Front Oncol*. 2015;5:192

IP=interstitial pressure; PDA=pancreatic ductal adenocarcinoma; PEGPH20=pegvorhyaluronidase alfa; TME=tumor microenvironment. **1.** Weniger M, et al. *Cancers.* 2018;10:E316. **2.** Wong KM, et al. *Curr Oncol Rep.* 2017;19:47. **3.** Provenzano PP, et al. *Cancer Cell*. 2012;21:418-29. **4.** Cao J, et al. *Clin Cancer Res.* 2019;25:2314-22.

HALO 109-301 Study Design

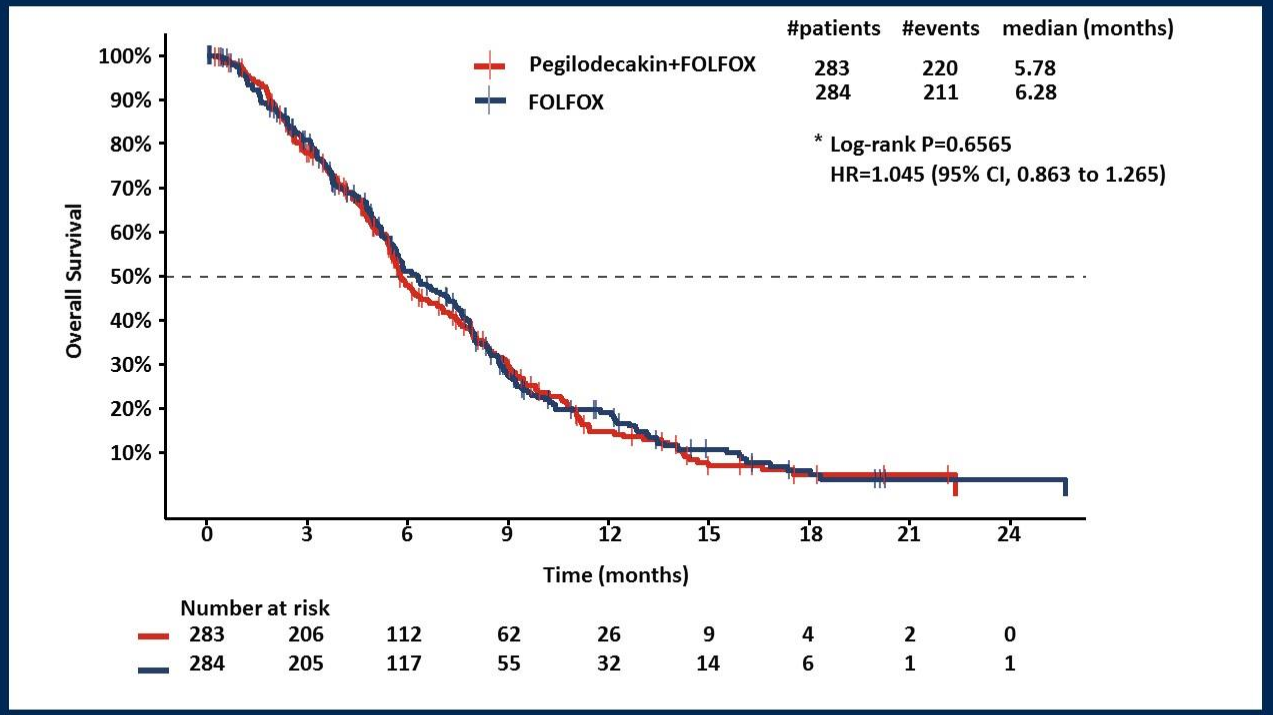


Statistical assumptions

- Median OS of ~8.5 months for AG arm
- 330 deaths will have 93% power to detect HR 0.67 with 2-sided alpha of 0.05
- 50% increase in median OS to 12.7 months

*≥50% hyaluronan staining in tumor samples (fresh or archival after metastatic diagnosis) by HA affinity histochemistry assay (Ventana HA RxDx Assay); †stratified by geographic region (North America, Europe, other territories); ‡twice weekly for Cycle 1 (4-week cycles: 3 weeks on/1 week off)
1L=first line; ECOG=Eastern Cooperative Oncology Group; ORR=objective response rate; OS=overall survival; QW=once weekly; R=randomization

Primary Endpoint: OS (ITT)



The patients receiving post-discontinuation therapy were balanced between two treatment arms.
*Log-rank test was 2-sided

Presented By J. Hecht at 2020 Gastrointestinal Cancer Symposium

Summary and Conclusions

- HALO 109-301 was a well conducted, blinded, randomized phase 3 study
- Baseline characteristics, administration of therapy, and use of post-progression therapies were similar between treatment arms
- There was no statistical difference in OS or PFS between PAG vs AG
  - Median OS was 11.2 vs 11.5 months (HR 1.00; 95% CI 0.80, 1.27; P=0.97)
  - Median PFS was 7.1 vs 7.1 months (HR 0.97; 95% CI 0.75, 1.26)
  - Lack of treatment effect observed in all analyzed subgroups
- ORR was 47% for PAG vs 36% for AG
  - DOR was 6.1 vs 7.4 months
- The side effect profile was consistent with the established safety profile of both regimens
  - Sepsis and severe, fatal gastrointestinal bleeds were reported more frequently in the PAG arm than in the AG arm but did not impact the survival endpoint of the study

Randomized Phase III Study of FOLFOX Alone and with Pegilodecakin as Second-line Therapy in Patients with Metastatic Pancreatic Cancer (SEQUOIA)

J. Randolph Hecht, MD, Sara Lonardi, MD, Johanna Bendell, MD, Hao-Wen Sim, MBBS FRACP, Teresa Macarulla, MD, Charles D. Lopez, MD, PhD, Eric Van Cutsem, MD, PhD, Andres J. Muñoz Martin, MD, PhD, Joon Oh Park, MD, Richard Greil, MD, Yong Lin, PhD, Sujata Rao, MD, and Baek-Yeol Ryoo, MD.

PRESENTED AT: Gastrointestinal Cancers Symposium

PRESENTED BY: Johanna Bendell, MD

#GI20

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IL-10 and Pegilodecakin

- Pegilodecakin is a pegylated recombinant interleukin-10[1]
- N-terminal pegylation provides increased half-life and sustained systemic exposure of pegilodecakin[1]
- Pegilodecakin is an IL-10 receptor agonist[2] and induces STAT1 and STAT3 phosphorylation in CD8+ T cells, increasing antigen-activated intra-tumoral CD8+ T cells[3]
- In animal models IL-10 induced tumor rejection via tumor-specific CD8+ T cell activation and established anti-tumor immune memory[4]
- Pegilodecakin expands and invigorates a subset of exhausted CD8+ T-cell[5]

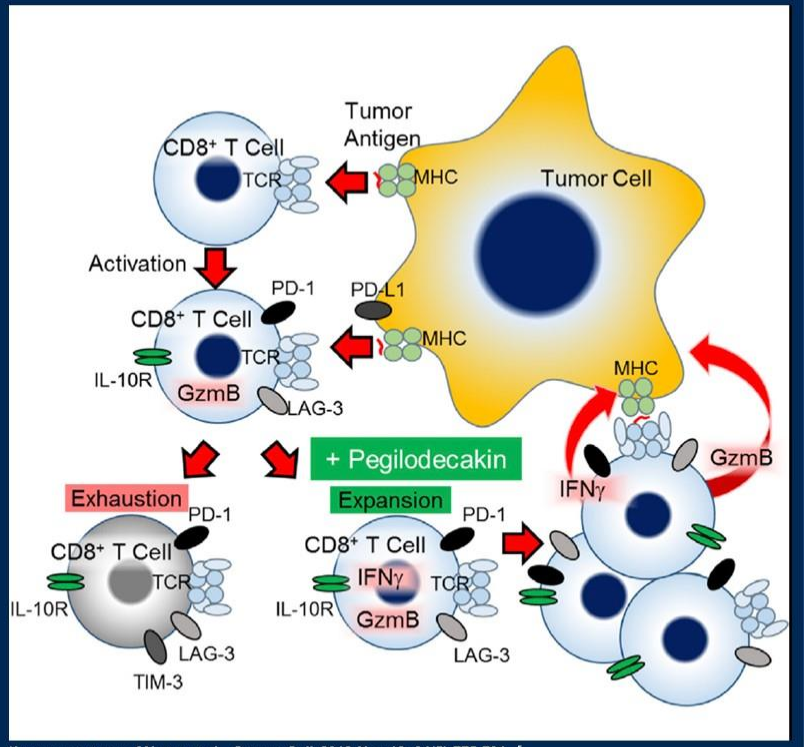
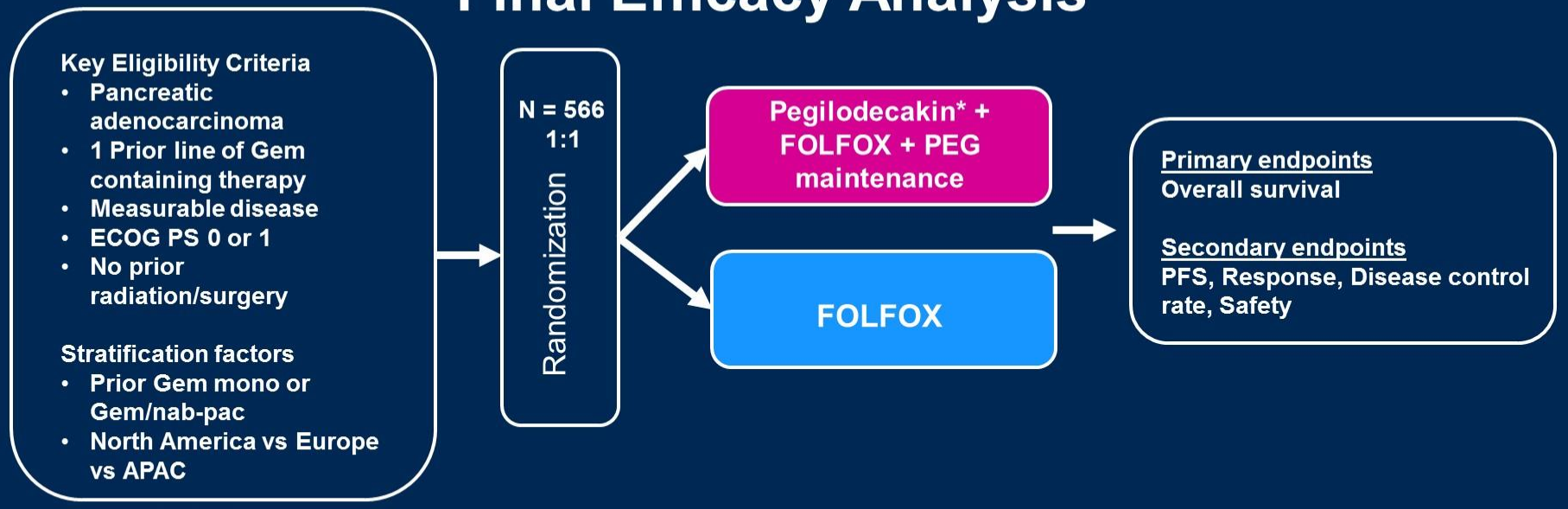


*Image courtesy of Naing et al., *Cancer Cell*. 2018 Nov 12; 34(5):775-791. [5]

1. Naing A et al., *JCO*. 2016 Oct 10;34(29):3562-3569.
2. Naing A et al., *Lancet Oncol*. 2019 Nov; 20(11):1544-1555.
3. Oft M. *Cancer Immunol Res*. 2014 Mar; 2(3):194-9.
4. Emmerich J et al., *Cancer Res*. 2012 72:3570-3581.
5. Naing et al., *Cancer Cell*. 2018 Nov 12; 34(5):775-791.*

SEQUOIA (NCT02923921): Study Design and Final Efficacy Analysis



*PEG + FOLFOX arm received PEG (0.4 mg/d if ≤80kg and 0.8mg/d if >80 kg) on Days 1-5 then Days 8-12 + FOLFOX, administered on Day 1 of each 14 day cycle. Patients could continue PEG monotherapy (0.8mg/d if ≤80 kg and 1.6 mg/d if >80 kg) after FOLFOX discontinuation.

Statistics: 393 death events for 85% power at a total two sided α = 0.05 assuming a true HR of 0.74.

As of 9 Sep 2019: 567 Subjects randomized with 431 OS events.

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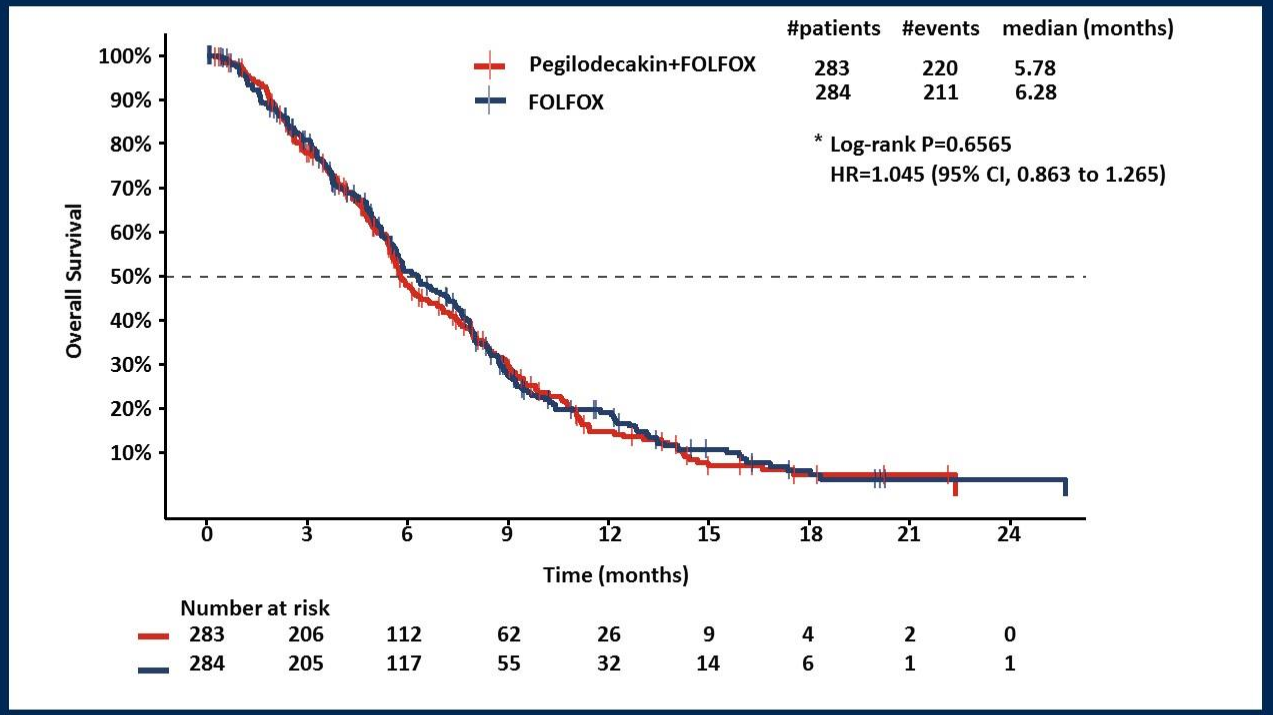
Primary Endpoint: OS (ITT)



The patients receiving post-discontinuation therapy were balanced between two treatment arms.
*Log-rank test was 2-sided

Presented By J. Hecht at 2020 Gastrointestinal Cancer Symposium

Conclusions

- Pegilodecakin with FOLFOX was well tolerated, with manageable toxicity similar to that observed in prior studies with pegilodecakin
- Combination therapy, however, did not improve overall survival, PFS, or objective response rate in second line pancreatic adenocarcinoma
- Exploratory biomarker analyses are ongoing (cytokine levels and TCR clonality)
- Studies of pegilodecakin in combination with PD-1 inhibitors in other tumor types are ongoing

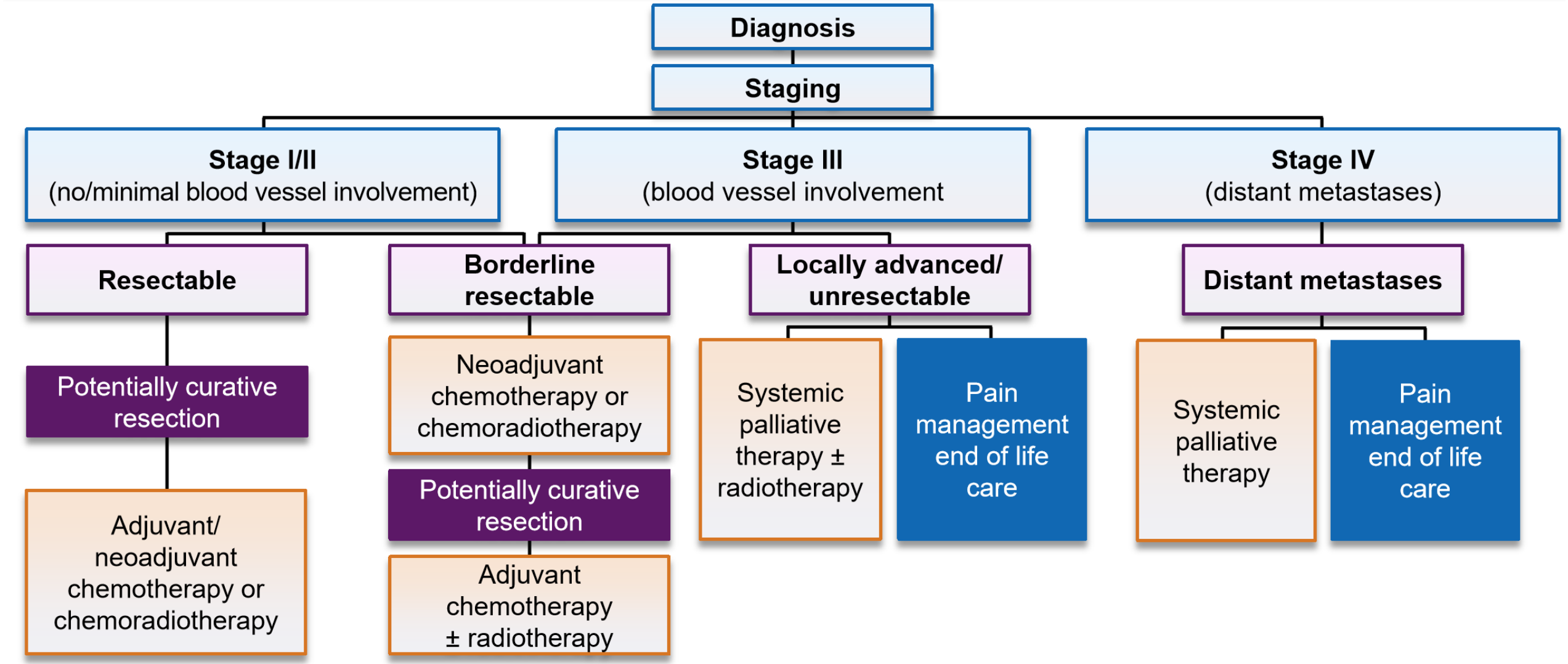
Shrnutí současného stavu léčby

- Lokalizované onemocnění

ONLY 3 POSSIBLE SCENARIOS

1. Occult metastases not controlled with chemotherapy
   - Surgery will have no significant survival benefit
   - Can't control mets prior to resection, zero probability can control after
2. Occult metastases controlled with chemotherapy
   - Derive a finite benefit for surgical resection
   - Completely dependent on magnitude of chemotherapeutic response
3. Cancer is truly non-metastatic
   - Potentially cured with an operation, Neoadjuvant allows selection
   - Subset of patients, "locally dominant phenotype"

NCCN Recommendations for Early-Stage PDAC[1]



1. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. v1.2020. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 6, 2020.

Guideline Recommendations for Neoadjuvant Therapy in Pancreatic Cancer[1]

Resectable/ borderline resectable disease

Preferred neoadjuvant regimens

- Gemcitabine + nab-paclitaxel ± subsequent chemoradiation
- FOLFIRINOX/mFOLFIRINOX ± subsequent chemoradiation

Only for known BRCA1/2 or PALB2 mutations:

- FOLFIRINOX/mFOLFIRINOX ± subsequent chemoradiation
- Gemcitabine + cisplatin ± subsequent chemoradiation

1. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. v1.2020. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 6, 2020.

Guideline Recommendations for Adjuvant Therapy in Pancreatic Cancer[1]

Post-resection, no evidence of metastatic disease/recurrence

Adjuvant options

Preferred regimens

- Gemcitabine + capecitabine (category 1)
- Modified FOLFIRINOX (category 1)

Other recommended regimens

- Gemcitabine (category 1)
- 5-FU/leucovorin (category 1)
- Continuous-infusion 5-FU
- Capecitabine (category 2B)
- Induction chemotherapy

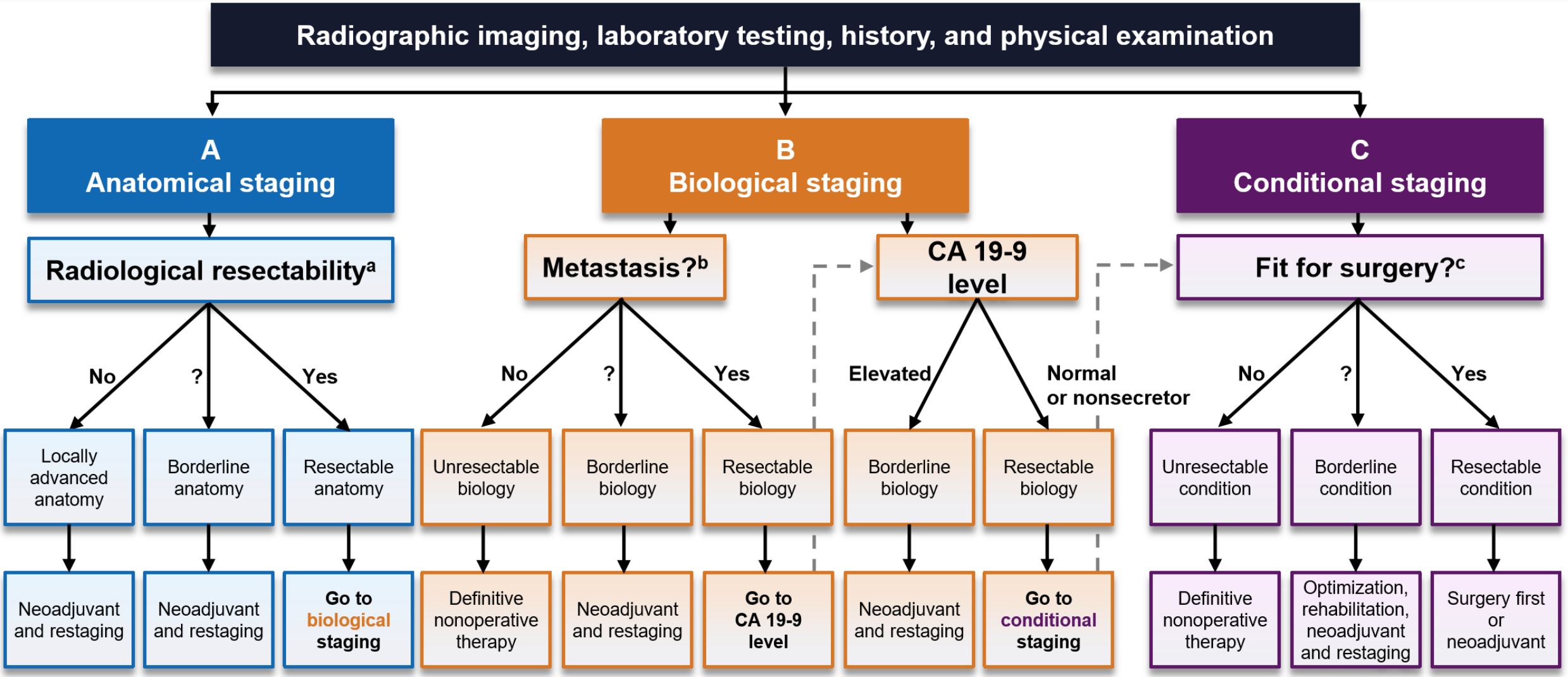
1. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. v1.2020. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 6, 2020.

Adjuvant Therapy Considerations[1,2]

- Prior to beginning adjuvant therapy, all patients should undergo formal restaging with CT scans and a serum level of tumor marker CA 19-9
- The optimal timing and duration of adjuvant therapy are not established
  - ASCO recommends adjuvant systemic chemotherapy for 6 months starting within 8 weeks of surgery, assuming adequate recovery from surgery

1. NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. v1.2020. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 6, 2020. 2. Khorana AA et al. *J Clin Oncol.* 2016;34:2541.

Treatment Sequencing Algorithm for Patients With Localized Pancreatic Adenocarcinoma[1]



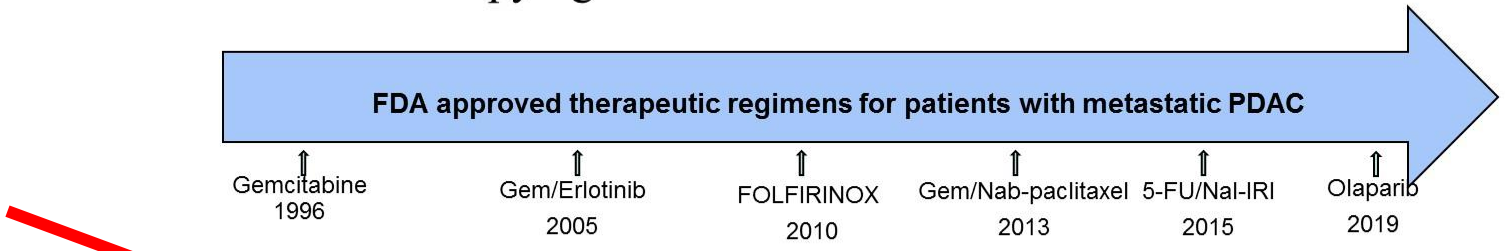
[a] Based on Alliance criteria (or other classification system). [b] Indeterminate radiologic lesions or regional nodal metastases.
[c] Age, comorbidities, PS, nutrition/weight loss, and cancer symptoms. 1. Provided courtesy of Dr. Mark Truty.

Algoritmus léčby metastazujícího onemocnění

- Chemoterapie zůstává základní modalitou systémové léčby, ale…

Pancreatic Ductal Adenocarcinoma (PDAC)

- Patients with mPDAC have very poor prognosis.
- Chemotherapy agents remain to be the cornerstone treatments.

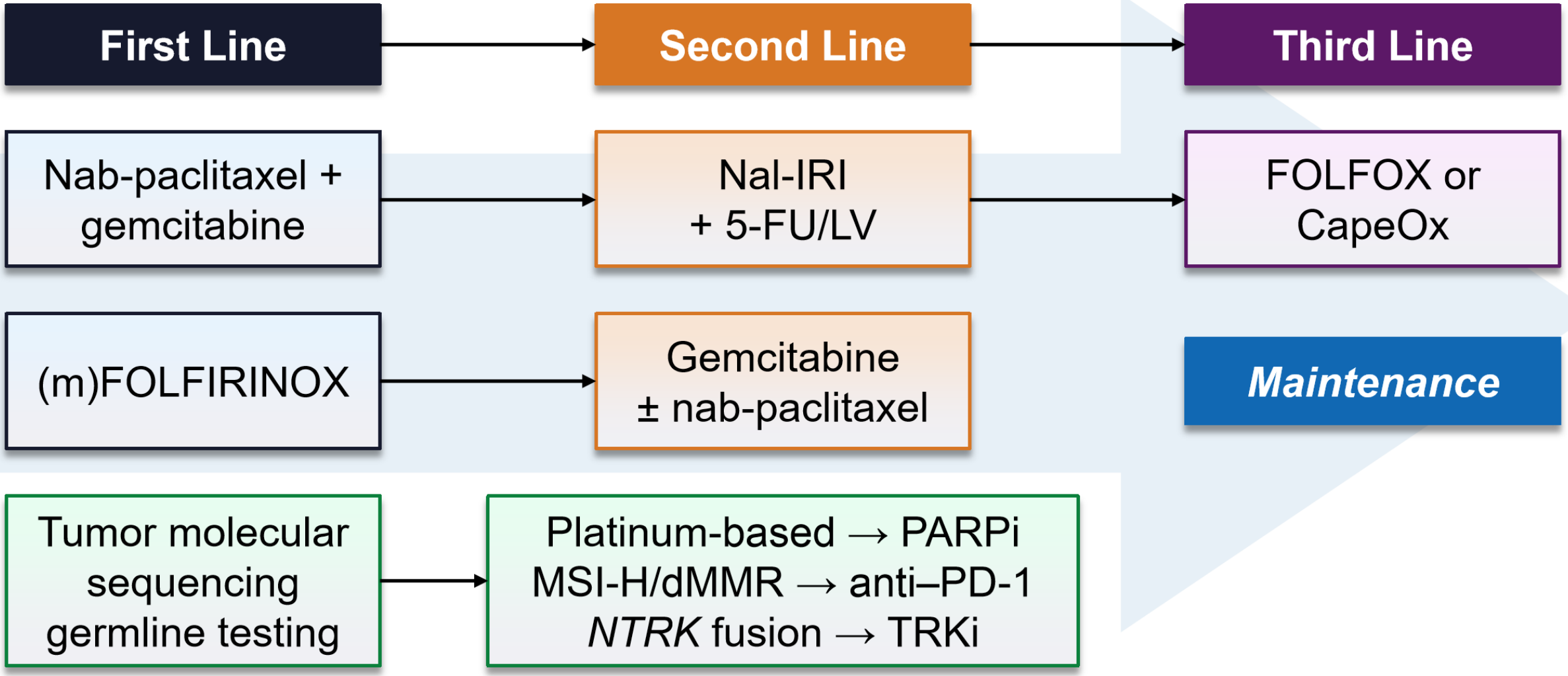


FDA APPROVED

Tumor Agnostic Drugs
-MSI high
Checkpoint inhibitor
-NTRK fusion
NTRK inhibitors

Burris et al. *J Clin Oncol* 1997;15:2403-23
Moore et al. *J Clin Oncol*. 2007; 20:1960-6
Conroy et al. *N Eng J Med* 2011; 364: 1817-25
Von Hoff et al. *N Eng J Med* 2013; 369: 1691-1703
Wang-Gillam et al. *Lancet* 2016; 387: 545-57
Golan et al. *N Eng J Med* 2019;38:317-327

Sequencing Therapy in Advanced PDAC (2020)[1]



1. Provided courtesy of Dr. Eileen O'Reilly.

Guideline Recommendations: Metastatic Disease (Maintenance Therapy)[1]

Good Performance Status[a]

Preferred

- If previous first-line FOLFIRINOX
  - FOLFIRI

Other recommended regimens

- If previous first-line FOLFIRINOX
  - FOLFOX[b]
- Clinical trial

Useful in certain circumstances

- If previous first-line FOLFIRINOX
  - Capecitabine
- If previous first-line nab-paclitaxel + gemcitabine
  - Nab-paclitaxel + gemcitabine (modified schedule)[b]
  - Gemcitabine (single agent)[b]
- If previous platinum-based chemotherapy
  - Olaparib (only for germline *BRCA1/2* mutations)

[a] Patients who have response or stable disease after 4-6 mo of chemotherapy may undergo maintenance therapy. [b] NCCN category 2B recommendation.

1. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. v1.2020. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 6, 2020.

Precizní medicína v léčbě karcinomů slinivky břišní

- NGS pro všechny „fit“ pacienty

GI Cancers DO Harbor Actionable Mutations[1-5]

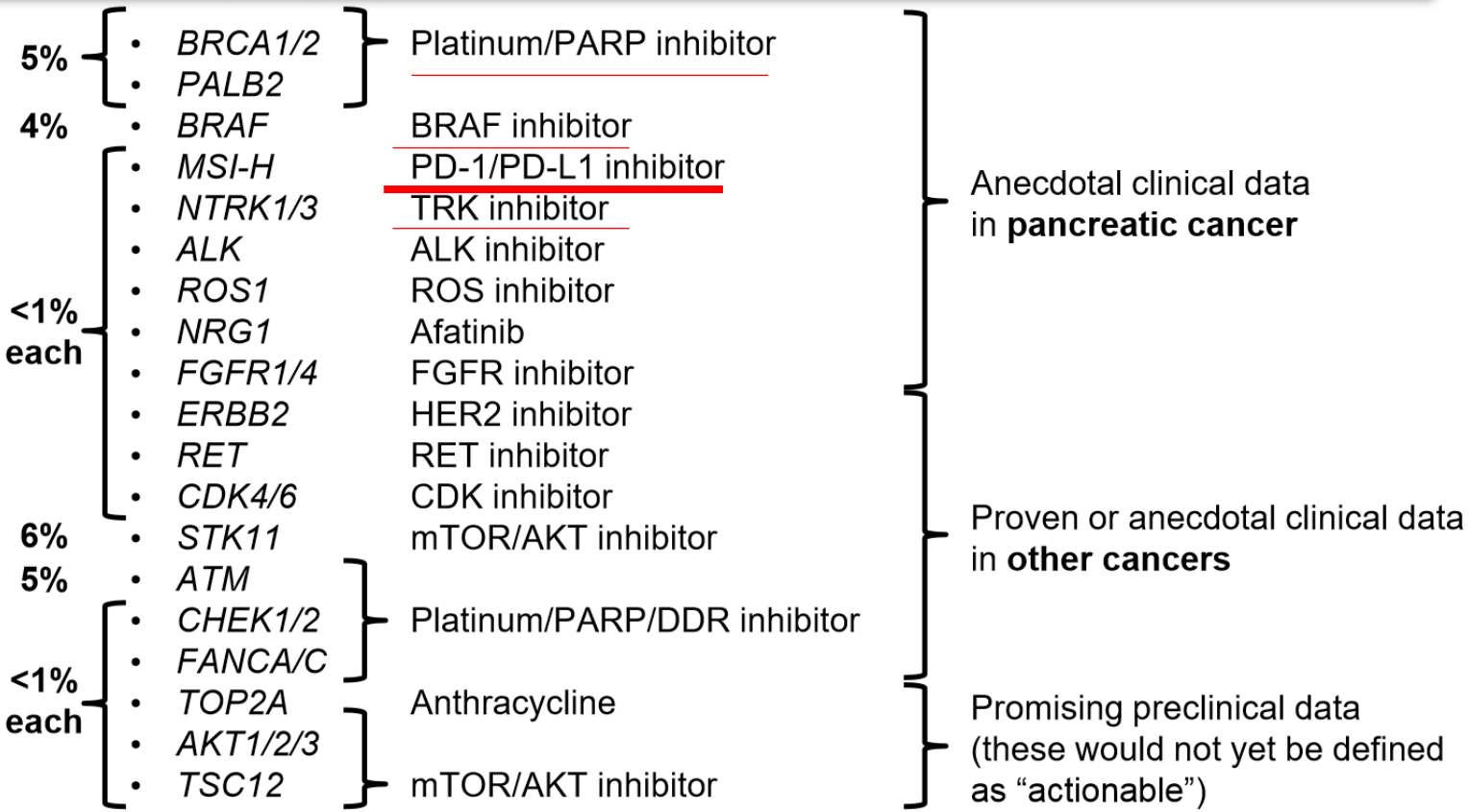
- Actionable mutations have been identified in every GI malignancy
  - Pancreatic cancer: ~25%
  - Biliary cancer: ~20%
  - Upper GI cancers: ~30% (includes *HER2/ERBB2*)
  - CRC: ~10% (70% if you count *RAS/RAF*)

1. Pishvaian MJ et al. *Clin Cancer Res*. 2018;24:5018-5027. 2. Aguirre AJ et al. *Cancer Discov*. 2018;8:1096-1111. 3. Nakamura H et al. *Nat Genet*. 2015;47:1003-1010. 4. Jain A, Javle M. *J Gastrointest Oncol*. 2016;7:797-803. 5. Cristescu R et al. *Nat Med*. 2015;21:449-456.

Actionable Findings in Pancreatic Cancer[1-11]

NGS efforts have consistently revealed that ≥25% of pancreatic cancers have potentially highly actionable molecular biomarkers

Absolute frequencies



1. Singhi AD et al. *Gastroenterology*. 2019;156:2242-2253.e4. 2. Pishvaian MJ et al. *Clin Cancer Res*. 2018;24:5018-5027. 3. Heeke AL et al. *JCO Precis Oncol*. 2018;2018. 4. Aguirre AJ et al. *Cancer Discov*. 2018;8:1096-1111. 5. Witkiewicz AK et al. *Nat Commun*. 2015;6:6744. 6. Lowery MA et al. *Clin Cancer Res*. 2017;23:6094-6100. 7. Waddell N et al. *Nature*. 2015;518:495-501. 8. Bailey P et al. *Nature*. 2016;531:47-52. 9. Biankin AV et al. *Nature*. 2012;491:399-405. 10. Collisson EA et al. *Nat Med*. 2011;17:500-503. 11. Pishvaian MJ, Brody JR. *Oncology (Williston Park)*. 2017;31:159-166.

Cesta k prodloužení přežití

- Selektivní léčba specifických podskupin podle NGS biomarkerů

Summary: We Should Be Testing

- Actionable mutations are not “rare”
  - EU definition of rare: <1/2,000 people = 0.05%
- Testing is **much less expensive** than standard (and targeted) therapies
- Testing **does reveal** legitimately actionable mutations
- Actionable mutations lead to a ***disproportionate benefit***
  - With survival benefit

2020 NCCN Guidelines on PDAC[1]

"Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes"

All patients should undergo germline testing

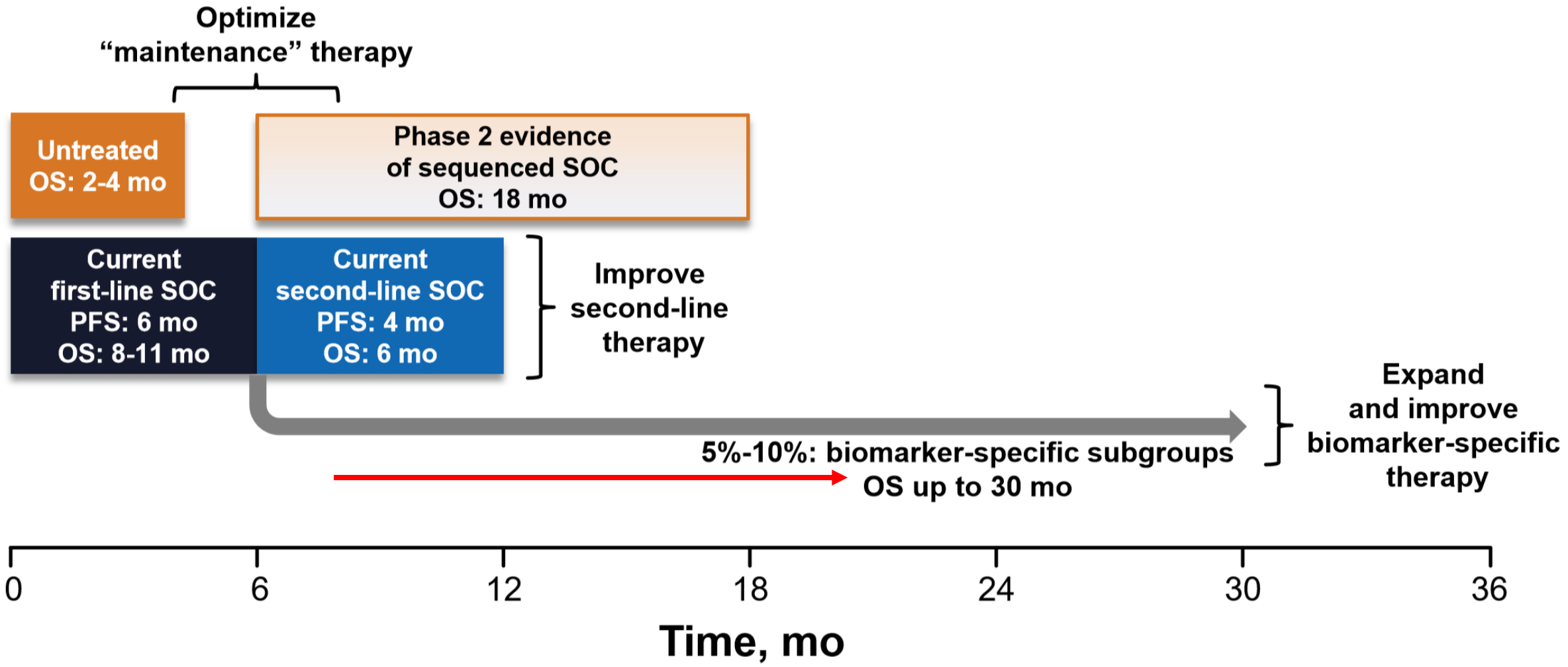
1. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. v1.2020. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 6, 2020.

2020 NCCN Guidelines on PDAC[1]

"Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease (80% of patients) who are candidates for anticancer therapy to identify uncommon but actionable mutations"

1. NCCN Clinical Practice Guidelines in Oncology. Pancreatic Adenocarcinoma. v1.2020. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 6, 2020.

Metastatic Pancreatic Cancer Survival



Proč má léčba karcinomů slinivky břišní nejhorší výsledky
Existují cesty k okamžitému zlepšení

Bez rozdílů mezi Evropou a USA

- Pozdní diagnostika
  - Zavedení specializované péče o jedince ve zvýšeného rizika
- Rychlé lokální šíření a časné metastazování
  - Diagnoza karcinomu slinivky břišní jako klinická urgence
    - Rychlá diagnostika, staging a chirurgický výkon
- Vysoké % recidiv po chirurgickém výkonu
  - Centralizace chirurgické péče
  - Zařazení radioterapie do předoperačního schématu léčby
  - Optimální pooperační adjuvantní chemoterapie pro všechny nemocné
- Rezistence na konvenční terapii
  - Urychlené zavedení principů precizní onkologie
    - NGS reflexnní testování u většiny nemocných
      - Genetické minimum: BRCA ½ , MSI, NTRK
  - Urychlení úhrady imunoterapie u MSIh
  - Urychlení úhrady PARP inhibitorů při BRCA mutaci

- V současnosti 4. nejčastější příčina úmrtí na nádorové onemocnění
- V roce 2020 2. nejčastější příčina úmrtí na nádorové onemocnění

Děkuji za pozornost