6. ulusal CERRAHİ ONKOLOJİ KONGRESİ

24 - 27 Şubat 2022 | Gloria Golf Resort – ANTALYA

DR. BANU ÖZTÜRK
SBÜ ANTALYA EĞİTİM ARAŞTIRMA HASTANESİ
TIBBİ ONKOLOJİ

PANKREAS KANSERİNDE NEOADJUVANT KEMOTERAPİNİN YERİ

SUNUM PLANI

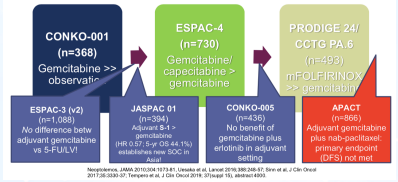
- GİRİŞ
- ADJUVANT TEDAVİ
- NEOADJ TEDAVİ
  - Rasyonel
  - Metaanalizler
  - Lokal ileri hst
  - Borderline rezektabl hst
  - Rezektabıl hst
  - Klavuzlar

Giriş

- En sık 4. kanserden ölüm nedeni
- Çoğunlukla sporadik
- Ancak BRCA2 başta çeşitli genetik yatkınlıklar ..
- %10-20 kadarı küratif rezektabıl
- %50-60 zaten tanıda metastatik
- %30-40 lokal ileri
- Ancak cerrahi sonrası lokal ya da sistemik nüksler sık.
- 5 yıllık sağkalım %5

Adjuvant tedavi: neler biliyoruz?

Evolving standards of care for the adjuvant treatment of resectable pancreatic cancer



PRODIGE 24/CCTG PA.6: Adjuvant mFOLFIRINOX vs Gemcitabine in Resected Pancreatic Cancer

- Multicenter, randomized phase III trial

Patients 18-79 years of age with histologically confirmed R0 or R1 resected pancreatic ductal adenocarcinoma; CA19-9 level < 180 U/mL ≤ 12 wks post surgery; ECOG PS 0/1; no prior chemotherapy or RT (N = 493)

→ **mFOLFIRINOX*** Q2W x 12 cycles (n = 247[1])

→ **Gemcitabine** 1000 mg/m² Day 1, 8, 15 of 28-day cycle x 6 cycles (n = 246[1])

→ *CT scans every 3 mos*

*On Day 1 of each cycle, oxaliplatin 85 mg/m², leucovorin 400 mg/m², and irinotecan 180 mg/m² (reduced to 150 mg/m² due to 20% grade 3/4 diarrhea rate in first 30 patients); continuous fluorouracil IV 2.4 g/m² over 46 hrs. [1]n = 238 treated. [1]n = 243 treated.

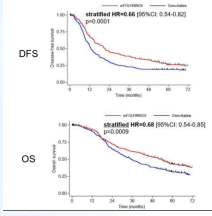
- Primary endpoint: DFS
- Secondary endpoints: toxicity, OS, cancer-specific survival, metastasis-free survival

Conroy. NEJM. 2018;379:2395.

Slide credit: clinicaloptions.com

Adj Folfirinox

Unicancer PRODIGE 24/CCTG PA6 trial: Updated results
(Conroy et al, LBA 57)



	mFOLFIRINOX	Gemcitabine
Median DFS	21.4 months	12.8 months
5-year DFS	26.1%	19.0%
Median OS	53.5 months	35.5 months
5-year OS	43.2%	31.4%

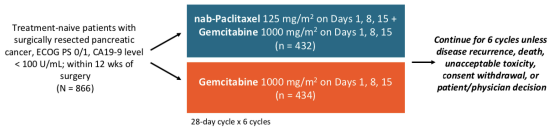
mFOLFIRINOX also confers significant improvements in metastasis-free survival (HR 0.64) and (cancer-)specific survival (HR 0.65)

Adj Folfirinox: sorunlar

- Tüm adj tedaviyi alamayan hastalar
- (tüm siklusları tamamlayanlarda 5 yıllık OS daha iyi (%41 vs 27)
- 5 yıllık OS=kür olabilir mi?
- 2-3 yıldan sonra lokal nüks RT
- Geç nüks=indolen seyir

APACT: Adjuvant nab-Paclitaxel Plus Gemcitabine vs Gemcitabine in Resected Pancreatic Cancer

- Multicenter, randomized, open-label phase III trial

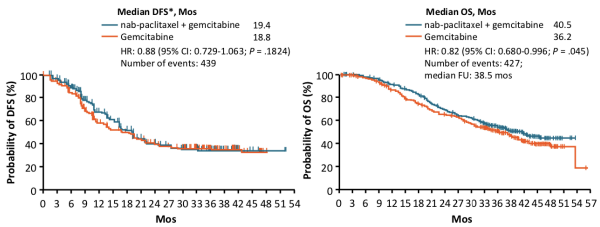


- Primary endpoint: DFS by independent review (first adjuvant trial in pancreatic cancer using independently assessed DFS as the primary endpoint)
- Secondary endpoints: OS, safety

Tempero. ASCO 2019. Abstr 4000.

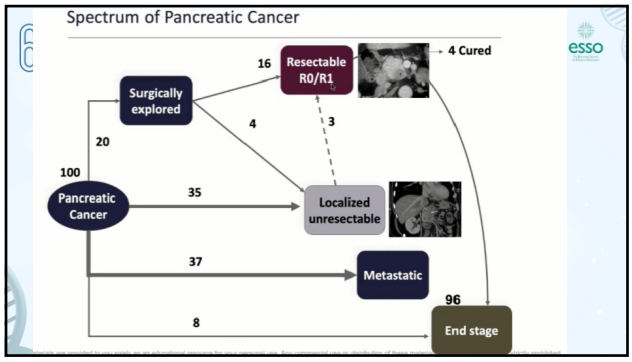
Slide credit: clinicaloptions.com

Apact-sonuç:



Adjuvant KRT-kime?

- Folfirinox alamayacak hasta
- R1 rezeke
- Nod pozitif
- Büyük tm



Rezektabilite: mutlaka multidispiliner takım ile değerlendirilmeli

	Resectable	Borderline Resectable	Locally Advanced Unresectable
Celiac/SMA	None	< 180°	> 180°
CHA	None	Reconstructable	Nonreconstructable
PV	< 180°	> 180° or Reconstructable	Nonreconstructable
SMV	< 180°		
Resectability	Frequent	> 50%	< 5%

Anatomy vs biologic continuum!!

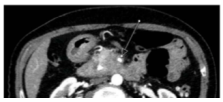


Table 1. Current concept of resectability (definitions vary slightly between major associations).

	Resectable	Borderline Resectable	Unresectable/Locally Advanced
SMA/CA	No contact	<180°	>180° involvement
PV/SMV	No contact	>180°	No reconstruction possible
	Potentially resectable		

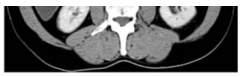
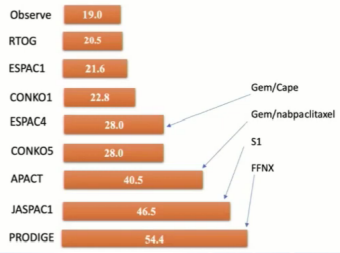


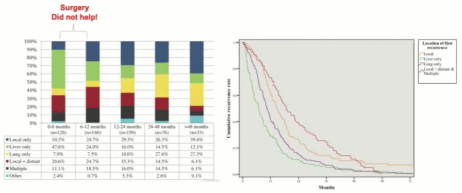
Figure 2. Computed tomography image of a tumor in the uncinate process with tumor contact to the superior mesenteric vein (smv) over a distance of about 2 cm (arrow: "borderline resectable").

The type and extent of systemic therapy does matter in the overall survival of localized pancreatic cancer



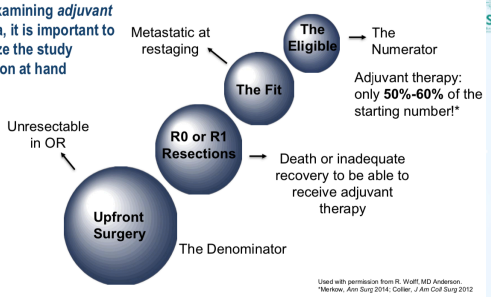
Cerrahi Sonrası erken dönemdeki en sık progresyon şekli sistemik progresyon, lokal rekkürens ise geç dönemin sorunu

Micrometastatic disease progresses early after pancreatectomy requiring earlier application of effective systemic therapy



Groot VP, et al. *Ann Surg.* 2018;267:936-945.

When examining *adjuvant* trial data, it is important to recognize the study population at hand



Used with permission from R. Wolff, MD Anderson.
*Merkow, *Ann Surg* 2014; Coller, *J Am Coll Surg* 2012

Why do Neoadjuvant or Peri-operative Treatment?

- Potential downsizing to maximize margin-negative resections (R0)
- Selecting for surgery patients with stable or responding disease
- Early treatment of micrometastases
- Chemotherapy is better tolerated

Varadhachary GR, et al. *Ann Surg Oncol.* 2006;13:1035-1046; Callery MP, et al. *Ann Surg Oncol.* 2009;16:1727-1733.

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- Metaanalizler ne diyor?

Preoperative/Neoadjuvant Therapy in Pancreatic Cancer: A Systematic Review and Meta-analysis of Response and Resection Percentages

Sonja Gillen[1], Tibor Schuster[2], Christian Meyer zum Büschenfelde[3], Helmut Friess[1], Jörg Kleeff[1,4]

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Abstract

Background: Pancreatic cancer has an extremely poor prognosis and prolonged survival is achieved only by resection with macroscopic tumor clearance. There is a strong rationale for a neoadjuvant approach, since a relevant percentage of pancreatic cancer patients present with non-metastatic but locally advanced disease and microscopic incomplete resections are common. The objective of the present analysis was to systematically review studies concerning the effects of neoadjuvant therapy on tumor response, toxicity, resection, and survival percentages in pancreatic cancer.

2010 yılı metaanalizi: 1980 sonrası çalışmalar alınmış, faz 3 çalışma yok. Toplam 111 çalışma (78 prospektif) 4394 hasta. KT: %54 5-FU ve %45.6 Gemzar temelli. RT %93 neoadj. (farklı doz ve şemalarda)

Table 3. Estimates of exploration and resection percentages after neoadjuvant treatment and restaging, and estimates of patients with complete response/partial response, stable disease, and progressive disease including the 95% confidence interval from the random effect model and number of assessable studies for each group (*n*).

Group	Complete Response	Partial Response	Stable Disease	Progressive Disease	Explored/ All	Resected/ All	R0/ Resected	Resected/ Explored

Table 6. Estimates of median survival times (m_e) in months and survival probabilities.

Group	Estimated Median Survival (m_e)		Estimated Survival Probability (Resected)	
	Resected (Range)	Not Resected (Range)	1 Year (Range)	2 Year (Range)
All patients	22.4 (9–62) ($n = 70$)	9.5 (6–21) ($n = 51$)	78.9% (0%–100%) $I^2 = 48.1\%$ [28.7%–62.3%] ($n = 54$)	49.2% (0%–82%) $I^2 = 85.2\%$ [80.5%–88.7%] ($n = 37$)
Tumor resectable before treatment (group 1)	23.3 (12–54) ($n = 27$)	8.4 (6–14) ($n = 19$)	77.9% (48%–100%) $I^2 = 70.7\%$ [52.6%–81.8%] ($n = 18$)	47.4% (25%–70%) $I^2 = 69.1\%$ [42.2%–83.4%] ($n = 11$)
Tumor non-resectable before treatment (group 2)	20.5 (9–62) ($n = 29$)	10.2 (6–21) ($n = 25$)	79.8% (0%–100%) $I^2 = 92.1\%$ [89.8%–93.9%] ($n = 29$)	50.1% (0%–82%) $I^2 = 88.6\%$ [84%–91.9%] ($n = 21$)

n, number of assessable studies for each group.
doi:10.1371/journal.pmed.1000267.t006

1/3 rezeke edilemeyen hasta rezeke edilir hale gelmiş rezeke edilmiş ve kt almış hasta baştan rezeke edilip kt alan kadar iyi gitmiş
Sonuç: rezeke edilemeyen neoadj tedavi verelim.

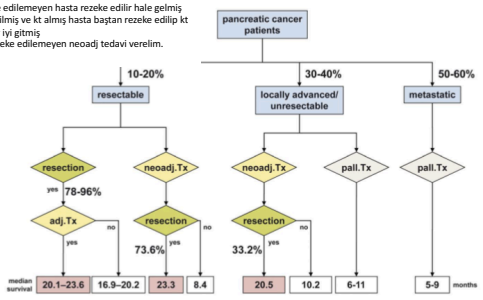
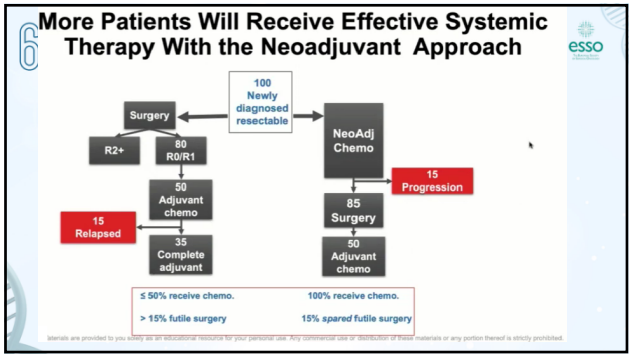


Figure 7. Summary overview of survival and resection percentages of different groups of patients with pancreatic cancer. Note that survival estimates derive from this systematic review and referenced studies.
doi:10.1371/journal.pmed.1000267.g007



Systematic review

Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer

E. Versteijne[1], J. A. Vogel[2], M. G. Besselink[2], O. R. C. Busch[2], J. W. Wilmink[3], J. G. Daams[4], C. H. J. van Eijck[5], B. Groot Koerkamp[3], C. R. N. Rasch[1] and G. van Tienhoven[1], on behalf of the Dutch Pancreatic Cancer Group

Departments of [1]Radiation Oncology, [2]Surgery and [3]Medical Oncology, Cancer Centre Amsterdam, Academic Medical Centre, and [4]Medical Library, Academic Medical Centre, Amsterdam, and [5]Department of Surgery, Erasmus Medical Centre, Erasmus University Rotterdam, Rotterdam, The Netherlands

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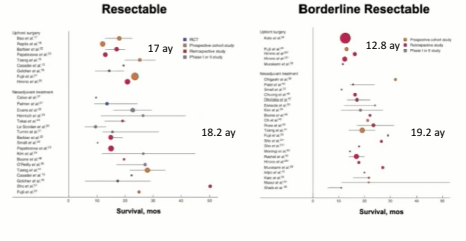
2018 metaanaliz. Rezektabl ve borderline rez hastalar. 18bin kayıttan 122si incelenmiş sonuç olarak 38 çalışma 3484 hasta alınmış. Faz1-2 retro ve pro çalışmalar. Sadece 3 randomize kontrollü çalışma var. genellikle gemcitabin temelli KT. 35 çalışmanın 29'unda RT var. (30-54 Gy). Adj ted oranı neaodj alan grupta %33, upfront cerrahi kolunda %68.

Neoadjuvant Therapy Appears to Provide Better Survival Than Upfront Surgery

Meta-analysis of 38 studies, 3484 patients

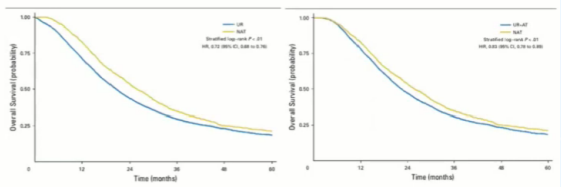


Versteijne E, et al. *Br J Surg.* 2018;105:946-958.

- Rezeksiyon oranı upfront cerrahide %81.3, neoadj kolda %66 (p< 0.001)
- R0 oranı neoadj ted ile %86.8vs 66.9. (p< 0.001)
- neaodj kt ile rezeks oranı %66, rezektabılda %67 borderlineda %65, rezektabıl hst R0 rezeksiyon %85 ve borderline rezektabılda R0 %88
- upfront cerrahide rezeksiyon oranı %81.3 , rezektabıl %76.8 borderline rezektabıl %85.3, R0 oranları rezektabıl %71 borderline rezektabıl %63.9.

Toksisite

- Upfront cerrahi kolunda %15 cerrahi yapılamamış (%42 uzak met, %25 hst progresyonu)
- Neoadj kolda %17.8 cerrahi yapılamamış (%64 hst progresyonu, %18 yan etki, kötü PS)
- Totalde yalnız %3.2 hasta neoadj kt toksisite nedeni ile cerrahi olmadı
- En sık AE: Gıs (bulantı kusma diare), hematolojk (lökopeni, trombsitopeni)
- En az G3 toksisite oranı %64 (en toksik folfirinox)
- Cerrahi morbidite mortalite fark yok
- Neoadj RT sonrası fibrozis rezeksiyon sonrası fistül gelişmini azaltablir



Lokal ileri hastalıkta neoadj tedavi

- %30-40 hasta tanıda lokal ileri (metastaz yok ancak küratif rezeksiyon yapılamıyor)
- NCCN: Biopsi tanısı , Ca19-9 ve PS.
- Cerrahi şansı %4-75.
- yanıt: görüntüleme, Ca 19-9, PS, kilo kaybı.
- Radyolojik progres yoksa mutlaka açılmalı
- Heiadelberg ve ark. 575 hasta. Neaodj Folfirinox vs gem-RT. Rezeks oranı: %61 vs %52. ancak mOS KT rejimler arası fark yok mOS rezeke edilende 15.3 vs 8.5.
- Johns Hopkins data. 415 hasta. Folfirinox ve gem temelli tedavi. Rezeke edilen hasta oranı %20, R0 oranı %89. mOS rezeke edilenlerde daha iyi (35 vs 16 ay)
- Alman RCT. Folfirinox vs gem-nabpakli R0 rezeksiyon oranları benzer (%74 ve %68)

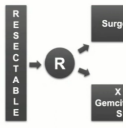
Neoadjuvant therapy improves overall survival in recent randomized trials in resectable and borderline resectable pancreatic cancer

Study	Stage	Treatment	Overall Survival HR	Phase of Study
Prep-02/JSAP-05[a] N = 364	Resectable	Gemcitabine+S1 Rezeks benzer	0.72 36 vs 26 ay	II/III
PREOPANC[b] N = 246	Resectable/ Borderline	Gemcitabine/XRT R0: %71 vs 40	0.78 17.6 vs 13.2 ay	III
ESPAC-5[c] N = 88	Borderline	FOLFIRIONOX, Gem/Cape, C-RT	0.28 Rezeks benzer, 2yıl OS %77 vs 40)	II

[a] Unno et al, JCO 37, 2019, suppl 4, abstr 189; [b] Versteijne et al, JCO, 2020; [c] Ghaneh et al, ASCO, 2020

Prep-02/JSAP-05: Phase 2/3 Neoadjuvant Study in Resectable Pancreatic Cancer

N = 364



Unno M, et al. ASCO® GI 2019. Abstract 189.

Prep-02/JSAP-05: Study Results

R0 rezeksiyon ve morbidite benzer

	Neoadjuvant Then Surgery	Upfront Surgery	
Median OS, months	36.7	26.7	HR 0.72 *P* = .015
Two-year survival, %	63.7	52.5	
Node positive, %	59.6	81.5	< .01
Liver metastases relapse, %	30.0	47.5	.01

Unno M, et al. ASCO® GI 2019. Abstract 189.

PREOPANC-1: Neoadjuvant Chemoradiotherapy vs

TABLE 1. Baseline Patient and Tumor Characteristics by Treatment Regimen

Characteristic	Preoperative CRT, No. (%)	Immediate Surgery, No. (%)
No. of patients	119	127
Female sex	55 (46)	53 (42)
Median age at random assignment, years (IQR)	66 (59-71)	67 (60-73)
Median BMI, kg/m^2 (IQR)	25 (22-28)	25 (23-28)
Initial WHO performance status[a]		
0	69 (58)	49 (39)
1	49 (41)	78 (61)
2	1 (1)	0 (0)
Pancreatic head tumors	97 (82)	117 (92)
Resectable pancreatic cancer[b]	65 (55)	68 (53)
Borderline resectable pancreatic cancer	54 (45)	59 (47)
Median initial maximum tumor diameter, mm (IQR)	30 (25-38)	30 (23-35)
Regional suspicious lymph nodes	27 (23)	44 (35)
Median CA 19-9,[c] kU/L (IQR)	111 (26-603)	257 (83-727)

locoregional recurrence-free interval, perioperative complications

Versteijne. JCO. 2020;38:1763.

Slide credit: clinicaloptions.com

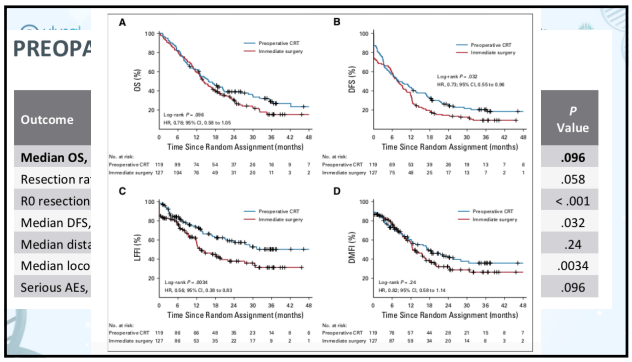
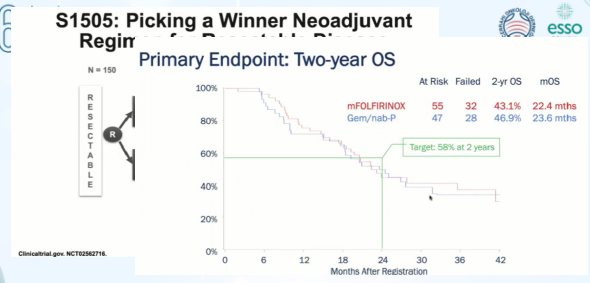


TABLE 3. Intention-to-Treat Analyses of Primary and Secondary End Points for Both Subgroups of Patients With Resectable and Borderline Resectable Pancreatic Cancer

Outcome	Resectable Pancreatic Cancer (n = 133)				Borderline Resectable Pancreatic Cancer (n = 113)			
	Preoperative CRT (n = 65)	Immediate Surgery (n = 68)	HR (95% CI)	P	Preoperative CRT (n = 54)	Immediate Surgery (n = 59)	HR (95% CI)	P
Primary								
Median OS, months	14.6	15.6	0.96 (0.64 to 1.44)	.830	17.6	13.2	0.62 (0.40 to 0.95)	.029
Secondary								
Median DFS, months	9.2	9.3	0.88 (0.60 to 1.28)	.520	6.3	6.2	0.59 (0.39 to 0.89)	.013
Median LFFI, months	NR	20.0	0.59 (0.33 to 1.04)	.067	27.7	11.8	0.54 (0.32 to 0.91)	.022
Median DMFI, months	17.0	13.5	0.93 (0.59 to 1.47)	.770	21.5	12.2	0.69 (0.42 to 1.15)	.150
	No. (%)	No. (%)	OR (95% CI)		No. (%)	No. (%)	OR (95% CI)	
Resection rate	44 of 65 (68)	54 of 68 (79)	0.54 (0.25 to 1.19)	.170	28 of 54 (52)	38 of 59 (64)	0.60 (0.28 to 1.27)	.190
R0 rate	29 of 44 (66)	32 of 54 (59)	1.33 (0.58 to 3.04)	.540	22 of 28 (79)	5 of 38 (13)	24.20 (6.57 to 89.12)	< .001
Safety								
Patients with SAEs (all grades)	35 of 65 (54)	31 of 68 (46)	1.39 (0.70 to 2.76)	.390	27 of 54 (50)	21 of 59 (36)	1.81 (0.85 to 3.85)	.130

Abbreviations: CRT, chemoradiotherapy; DFS, disease-free survival; DMFI, distant metastasis–free interval; HR, hazard ratio; LFFI, locoregional failure-free interval; NR, not reached; OR, odds ratio; OS, overall survival; SAE, serious adverse event.

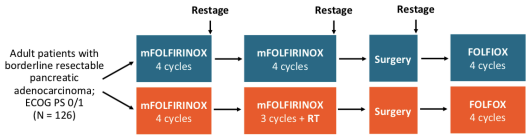
S1505: Picking a Winner Neoadjuvant Regim



Rezeks oranı %73 ve 70 benzer, sağkalımlar benzer 2 yıllık hedef OS ulaşımalamış
Merkezi radyoloji değerlendirme sonrası uygun olmayan hastalar var

Alliance A021501: Neoadjuvant mFOLFIRINOX With or Without RT in Borderline Resectable Pancreatic Cancer

- Multicenter, randomized phase II trial



- Primary endpoint: binary 18-month OS rate
- Key secondary endpoints: EFS, safety, R0 resection rate, pCR rate

Katz. ASCO GI 2021. Abstr 377.

Slide credit: clinicaloptions.com

Alliance A021501: OS and EFS

Outcome	mFOLFIRINOX (n = 65)	mFOLFIRINOX + RT (n = 55)
OS		
▪ Events	35	40
▪ Median OS, mos	29.8	17.1
▪ 18-mo OS rate, %	66.4	47.3
EFS		
▪ Events	45	44
▪ Median EFS, mos	15.0	10.2

Rezektabıl hst ,

- Un rezektabıl ve borderline rezektabl hastalarda alınan cesaret verici sonuçlar,
- upfront cerrahide R1 riski,
- op sonrası kötü cerrahi morbidite, kötü PS ve genel durum nedeniyle alınamayan ya da tamamlanamayan adj KT siklusları
- Neoadj tedavi verelim isteği doğuruyor

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- KT neoadj daha etkili henüz tm hücrelerine kan sunumu intakt. (postop tm vaskülarizayon bozuluyor)
- Rezektabıl da olsa mikrometastatik hst uzun dönem SK engelliyor erkenden eradike edelim.
- Ancak çalışma yapmak zor
- Hasta sayısı yetersiz kalıyor
- Çeşitli modaliteler denenmiş:

What about the R0 resection and nodal down-staging rates with neoadjuvant therapy?

Study	Stage	Treatment	R0 %	Node neg %
Prep-02/JSAP-05[a] N = 364	Resectable	Gemcitabine+S1	-	60 vs 82
PREOPANC[b] N = 133	Resectable	Gemcitabine/XRT	66 vs 59[d]	-
		R0 rezeksiyon ve sağkalım farkı anlamlı degil		
SWOG 1505[c] N =102	Resectable	FOLFIRINOX vs. gem/nabpaclitaxel	85 & 85	40 & 45

PACT-15 (italyan çalışması) rezektabıl adj (gem/PEXG) vs neoadj KT (PEXG) 1yılık EFS %23-50-66. median OS 20-26-38 ay

[a] Unno et al, JCO 37, 2019, suppl 4., abstr 189; b Versteijne et al, JCO, 2020; c Sohal et al, ASCO, 2020; d radiotherapy was in the treatment

Rezektabl hst-Klavuzlar:

- ASCO ve ESMO önermiyor
- NCCN yüksek riskli rezektabıl hst öneriyor (aşırı kilo kaybı, şiddetli ağrı, yüksek Ca19-9, görüntüleme)

Desigr

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- ECOG 0-1
- Bilirubin ≤ 2.

N = 127 (arr

22 sites in G

Translationa

ESMO20

EONAX trial

Baseline characteristic	ITT-Population (n=118) Arm A: perioperative % (n=59)	Arm B: adjuvant % (n=59)
Male	57.6 (34)	62.7 (37)
Female	42.4 (25)	37.3 (22)
Caucasian	98.3 (58)	100 (59)
Age, median, years (range)	65 (48-82)	68 (41-88)
BMI, median (kg/m², range)	25.1 (18-35)	24.9 (18-39)
ECOG 0	78.0 (46)	78.0 (46)
ECOG 1	22.0 (13)	22.0 (13)
Pancreatic head tumor	69.5 (41)	78.0 (46)
Pancreatic body tumor	18.6 (11)	15.3 (9)
Pancreatic tail tumor	11.9 (7)	6.8 (4)
cT1/2	57.6 (34)	46.2 (29)
cT3	40.7 (24)	45.8 (27)
n.e.	1.7 (1)	5.1 (3)
cN0	54.2 (32)	47.5 (28)
cN1	33.9 (20)	37.3 (22)
n.e.	11.9 (7)	15.3 (9)

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juvant

s required for re-use.

AIO NEONAX trial

Tumor response in arm A (RECIST 1.1)

Tumor response (RECIST 1.1)	Arm A: neoadjuvant % (n=45)
DCR	93.3 (42)

Arm A

- ORR 28.9%
- PD 6.7%
- lower than expected (1

AIO NEONAX trial

Surgical outcome

- Resection rate was lower in arm A
- More intraoperative irresectability in arm B
- More R0 resections in arm A

Resection status	Arm A: perioperative % (n=59)	Arm B: adjuvant % (n=59)
Resection rate	69.5 (41)	78.0 (46)
Drop outs	30.5 (18)	22.0 (13)
Progression	6.7 (4)	1.7 (1)
Irresectability	5.1 (3)	17.0 (10)
Pat. Choice	11.9 (7)	3.4 (2)
Toxicity/Clinical Deterioration	6.7 (4)	0.0 (0)

Resections	Arm A: perioperative % (n=41)	Arm B: adjuvant % (n=46)
R0	87.8 (36)	67.4 (31)
R1	7.3 (3)	28.3 (13)
R2	4.9 (2)	4.3 (2)

DFS in the ITT population

	Arm A (n=59)	Arm B (n=59)
DFS @18 mo	28.7%	19.3%
mDFS	11.4 mo	

Treatment arm
Arm A: perioperative arm
Arm B: adjuvant arm

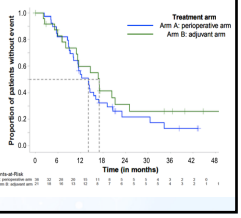
AIO NEONAX trial

Primary endpoint:
DFS in the mITT population

Perioperative gemcitabine/nab exhibited a long mDFS and a l rate @ 18 months in the ITT p

	Arm A: % (n=39)	Arm B (n=25)
DFS @ 18 mo	32.2%	41.4%
mDFS	14.1 mo.	17.0 mo.

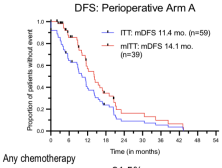
A 55% DFS rate @ 18 months in the mITT population was not achieved in both arms.



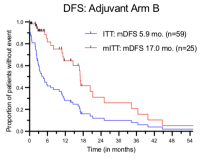
DFS ITT vs mITT population

AIO NEONAX trial

DFS: Perioperative Arm A



DFS: Adjuvant Arm B



Any chemotherapy exposure: 91.5% 42.4%

There is a major difference in the ITT/mITT DFS curves in the adjuvant arm B due to many patients not starting adjuvant treatment for various reasons

ESMO congress Thomas Seufferlein

Neonax: sonuç

- NEONAX 18 aylık %55 DFS oranına ulaşamadı (Arm A: 32.2%, Arm B: 41.4%).
- Neoadjuvant Iki siklus Gem-Nabpakli tedavi ile :
- Tm yanıtı iyi (ORR 28.9%)
  Tm progres oranı düşük (6.7%)
  R0 oranı yüksek (87.8%; upfront surgery: 67.4%)
- Periop KT tamamlama: 90%
  Adjuvant arm B: sadece %42 başladı %27 tamamladı
- mDFS periop KT 11 .4 ay adj KT 5.9 ay (cerrahi öncesi daha faydalı)
- Neoadj KT standart olmalı
- Demişlerdi.

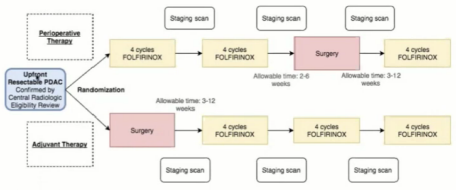
Neonax:sorunlar

- Pre-specifying the patient population of interest (mITT vs ITT) makes a **big difference** in interpreting study outcomes!
- Confirmatory: a lot of patients (>50%) in whom up-front surgery is planned never make it to adjuvant chemotherapy (or even to successful R0/R1 resection, for that matter)
- • Meanwhile, in the neoadjuvant arm, the dropout rate (~30%) prior to surgery, due to a variety of factors, represents... a mixed blessing
- • There may be some putative advantages to neoadjuvant therapy, including higher R0 resection rates (87.8% vs 67.4%); but any actual survival benefit of neoadjuvant rx a/w contemporary regimens requires much further validation

Neonax:sorunlar

- Higher than expected rates of unresectability in this “resectable” patient population (17% in up-front surgery arm) – highlights need for central radiology review in such studies!
- Unresolved questions:
  - Duration of neoadjuvant rx (impact of 2 cycles of preop chemotherapy? Would more be better?)
  - Selection of gemcitabine/nab-paclitaxel in this trial given negative APACT adjuv trial results (Tempero et al, *J Clin Oncol* 2019 [abstr]) vs SWOG 1505 periop data (Sohal et al, *JAMA Oncol* 2021)
  - Role of radiation in periop/adjuvant setting (awaiting results of RTOG 0848)
  - Can we use circulating tumor (ct)DNA to risk-stratify in future trial design?

New Intergroup Phase III Trial: Perioperative vs Adjuvant Therapy for Resectable Pancreatic Cancer



Stratification by:
Location of tumor: pancreatic head vs nonhead tumors
ECOG PS: 0 vs 1

Sonuç Olarak…

- Neoadj tedavi Lokal ileri hst (borderline rezektabl ve unrezektabl) için standart olmalı. Neoadj KRT KT'e göre üstün çünkü lokal güçlü lokal etkisi var.
- Rezektabl hst: neoadj tedavi cerrahi komplikasyonu artırmadan R0 rezeksiyon artırıyor. Mikrometastazı erkenden azaltıp OS katkısı yapıyor.
- Literatür daha çok 5FU ve gemzar temelli KT içeriyor.
- RCT az.
- Ancak hangi modalite. (%20 hasta yanıt vermeyeblir)
- Neoadj Folfirinox içeren RCT sonuçları bekleniyor

- Mutlaka multidisipliner takım
- Mutlaka deneyimli merkez
- Sadece görüntüleme değil, Ca 19-9 düzey ve PS önemli
- Neoadj tedavi sonrası progresyon bulgusu yoksa mutlaka rezeksiyon kararı cerrahi explorasyonla verilmeli.

REHBERLER NE DİYOR?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Pancreatic Adenocarcinoma

NCCN Guidelines Index
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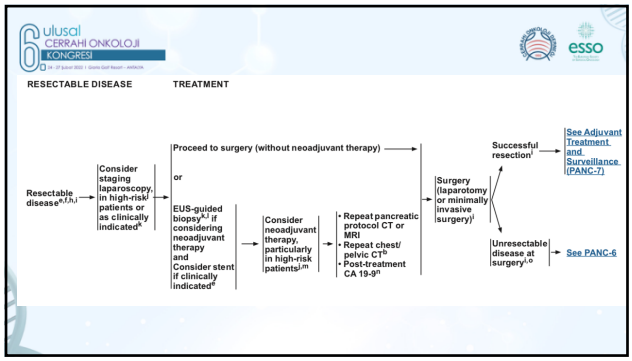
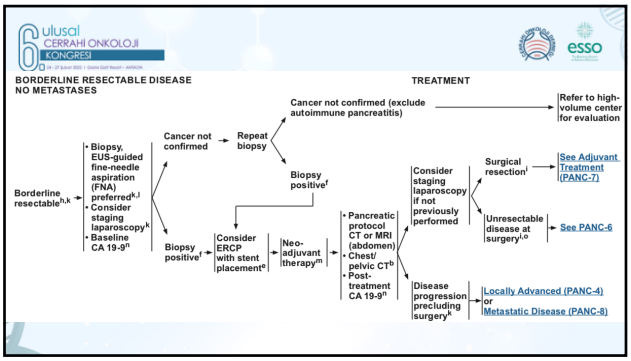
Discussion

INTRODUCTION

Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with use of appropriate imaging studies.





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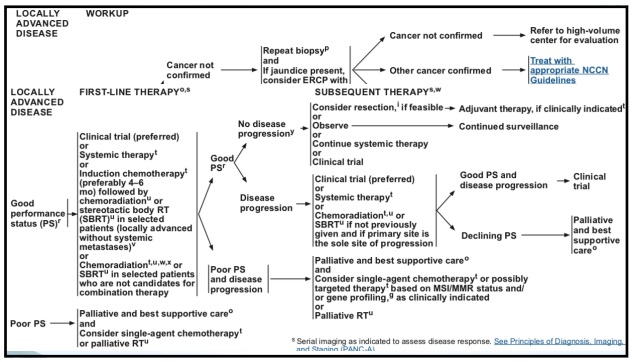
Neoadjuvant Therapy (Resectable/Borderline Resectable Disease)

- There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and radiation. Subsequent chemoradiation is sometimes included. When considering neoadjuvant therapy, consultation at a high-volume center is preferred. If neoadjuvant therapy is recommended, treatment at or coordinated through a high-volume center is preferred, when feasible. Participation in a clinical trial is encouraged.

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• FOLFIRINOX or modified FOLFIRINOX[a] ± subsequent chemoradiation[b] • Gemcitabine + albumin-bound paclitaxel ± subsequent chemoradiation[b] Only for known BRCA1/2 or PALB2 mutations: • FOLFIRINOX or modified FOLFIRINOX[a] ± subsequent chemoradiation[b] • Gemcitabine + cisplatin (≥2–6 cycles) ± subsequent chemoradiation[b]	• None	• None



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Locally Advanced Disease (First-Line Therapy)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS	• FOLFIRINOX or modified FOLFIRINOX[d,e,f,6] • Gemcitabine + albumin-bound paclitaxel[d,f,7] Only for known BRCA1/2 or PALB2 mutations: • FOLFIRINOX or modified FOLFIRINOX[d,e,f,6] • Gemcitabine + cisplatin[10]	• Gemcitabine + erlotinib[b,8] • Gemcitabine + capecitabine[9] • Gemcitabine • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Fixed-dose-rate gemcitabine, docetaxel, capecitabine (GTX regimen)[11] (category 2B) • Fluoropyrimidine + oxaliplatin (5-FU + leucovorin + oxaliplatin [OFF][12] or CapeOx[13]) (category 2B)	• Induction chemotherapy with any of the preferred/other regimens (≥4–6 cycles) followed by chemoradiation[b,h] or SBRT[14] (in selected patients, locally advanced disease without systemic metastases)[15] • Chemoradiation[h,i] or SBRT[i] (in select patients who are not candidates for combination therapy)
Poor PS	• Gemcitabine ▸ 1000 mg/m2 over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m2/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B) • Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B)	• None	• None

See Subsequent Therapy on PANC-F (6 of 8)

Ongoing Trials of Interest in the Neoadjuvant and Adjuvant Settings

Trial	Phase	Treatment	Notes
NCT03941093	III	Gem + nab-paclitaxel ± pamrevlumab (anti-CTGF Ab)	▪ Unresectable, locally advanced disease
Alliance A021806 (NCT04340141)	III	Perioperative vs adjuvant FOLFIRINOX	▪ Resectable disease
PANDAS-PRODIGE 44 (NCT02676349)	II	Neoadjuvant mFOLFIRINOX ± CRT	▪ Borderline resectable disease

Teşekkür ederim…