6 ulusal CERRAHİ ONKOLOJİ KONGRESİ

24 - 27 Şubat 2022 | Gloria Golf Resort – ANTALYA

Doç. Dr. Murat KOÇER

S.B.Ü. ANTALYA EĞİTİM VE ARAŞTIRMA HASTANESİ. İÇ HASTALIKLARI AD. TIBBİ ONKOLOJİ KLİNİĞİ

CERRAHİ SONRASI ONKOLOJİK YÖNETİM; ADJUVAN KT, RADYOTERAPİ, İMMÜNOTERAPİ, GENETİK İRDELEME VE HEDEFE YÖNELİK TEDAVİLER...

AJANDA

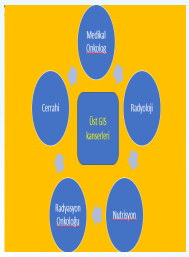
- Giriş
- Adjuvant KT
- Adjuvant RT
- Hedefe yönelik tedaviler
- İmmunoterapi
- Genetik irdeleme
- Kılavuz önerileri
- Özet

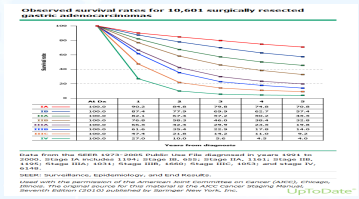
GİRİŞ

- Mortalitede hala üst sıralarda
- Ösefagus:
  - % 90 SCC, Adenokarsinom
  - SCC (% 70), Torasik/Servikal lok. ➡ Adenokarsinom !, Distal torasik Lokalizasyon !
- Mide
  - % 90 Adenokarsinom
  - Distal ➡ Proximale kayma
  - Sınıflama ➡ Moleküler sınıflama !

- Tedavi:
  - KT ➡
    - Adenokarsinom alt tipinde hedef yolaklar !!!
    - İmmun kontrol nokta inhibitörleri:
      - SCC ➡ PD-L1 ekspresyonundan bağımsız etkili gibi !,
      - Adenokarsinom ➡ PD-L1 (-)/↓ Fayda belirsizdir.

- MULTİDİSİPLİNER değerlendirme
- Bimodal/trimodal tedavi !!!!
- Cerrahi (Küratif/Palyatif) ➡ Refere
- Patolojik değerlendirme:
  - Histopatolojik alt tip
  - C Erb B2, MSI, PDL-1
  - Evre





Cerrahi sonrası
EK TEDAVİ GEREKLİLİĞİ !

Ösefagus

ADJUVANT KT

- Preop (RT ile kombine) > Adjuvant
  - Lokal nüks
  - R0
  - Patolojik yanıt !
- Preop tedavi (-)
  - R0
    - SCC → Ø
    - Adenokarsinom → Ø /KT

Ösefagus

ADJUVANT RT

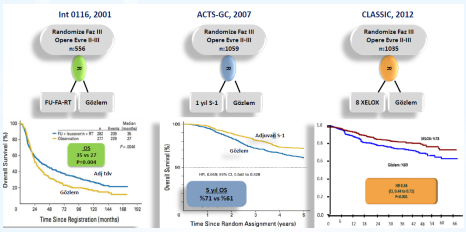
- Cerrahi !
- KT ile kombine uygulamalar
- Preop KRT
  - Neoadjuvan KRT--Cerrahi *vs* Cerrahi
  - Neoadjuvan KRT--Cerrahi *vs* Definitif KemoRT
  - Neoadjuvan KRT--Cerrahi *vs* Neoadjuvan KT--Cerrahi
- Preop tedavi (-)
  - SCC R1-2 de
  - Adenokarsinom R0(T3/4, N+)/R1/R2

Çalışma Adı	Ortanca İzlem (yıl)	Patoloji	Kol	No	pCR %	3y GS %	P (GS)
Urba ve ark.	8.2	SCC+adeno	FVC/45Gy/Cx Cx	50 50	28 -	30 16	0.15
Bosset ve ark. EORTC	4.6	SCC	Sisp/37Gy/Cx Cx	143 138	20 -	33 36	NS
Walsh ve ark. İrlanda	1.5	Adeno	CF/40Gy/Cx Cx	58 55	22 -	32 6	0.01
Burmeister ve ark. Avustralya	5.4	SCC+adeno	CF/35Gy/Cx Cx	128 128	16 -	35 31	NS
Tepper ve ark. CALGB 9871	6	SCC+adeno	CF/50Gy/Cx Cx	30 26	40 -	39 (5y) 16 (5y)	0.008
Shapiro ve ark. CROSS	7	SCC+adeno	Pac-Carbo/41.4Gy/Cx Cx	180 188	29 -	49 ay (ort) 24 ay (ort)	0.001
Mariette ve ark. FFCD	5.7	SCC+adeno	CF/45Gy/Cx Cx	97 98	29 -	32 ay (ort) 44 ay (ort)	NS

Mide

ADJUVANT KT

- Endikasyon (pT2)
- Hangi ajan ? (FU ve/veya kombinasyonları)
- Her hastaya verelim mi ? (MSI-H ?)



Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer

A Meta-analysis

- 2010
- 17 çalışma
- n=3838
- 5 yıllık OS:
- %55.3 vs %49.6, p<0.001

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REVIEWS

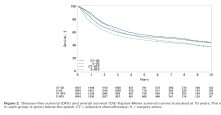
Disease-Free Survival as a Surrogate for Overall Survival in Adjuvant Trials of Gastric Cancer: A Meta-Analysis

Koji Oba, Xavier Paoletti, Steven Alberts, Yung-Jue Bang, Jacqueline Benedetti, Harry Bleiberg, Paul Catalano, Florian Lordick, Stefan Michiels, Satoshi Morita, Yasuo Ohashi, Jean-pierre Pignon, Philippe Rougier, Mitsuru Sasako, Junichi Sakamoto, Daniel Sargent, Kohei Shitara, Eric Van Cutsem, Marc Buyse, Tomasz Burzykowski; on behalf of the GASTRIC group

Manuscript received February 12, 2013; revised July 25, 2013; accepted July 25, 2013.

Correspondence to: Koji Oba, PhD, Translational Research and Clinical Trial Center, Hokkaido University Hospital, Kita 14, Nishi 5, Kita-ku, Sapporo, Hokkaido 0608648, Japan e-mail: k.oba@huhp.hokudai.ac.jp

- 2013
- 14 çalışma
- n=3288
- KT vs Cerrahi
- DFS ve OS avantajı var



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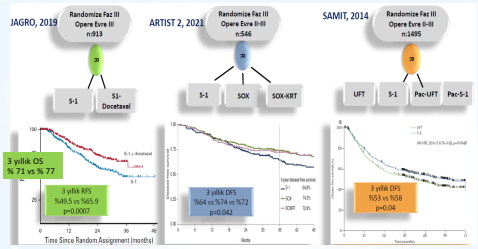

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Neoadjuvant/Perioperatif tedavi

- R0 rezeksiyon oranını artırma
- Evre düşürme
- Mikrometastatik hastalık tedavisi
- Sağkalım avantajı

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		n	Randomizasyon	D2	OS	p
MAGIC	Rezektabl Mide (%74), Distal özofagus (%11), ÖGJ (%15) AdenoCa	503	ECF-Cerrahi-ECF vs Cerrahi	% 42	5 yıl: % 36 vs % 23	0.0009
EORTC	Lokal İleri Mide veya ÖGJ AdenoCa (II/III)	144	ECF-Cerrahi vs Cerrahi	% 92	Medyan: 64 vs 53 ay	0.46
FNCLCC	Rezektabl Alt Özefagus/ GEJ/Mide AdenoCa	202	CF-Cerrahi-CF vs Cerrahi		5 yıl: % 38 vs % 24	0.02

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Cancer Investigation, 32:272–284, 2014
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DOI: 10.3109/07357907.2014.911877

informa healthcare

ORIGINAL ARTICLE

An Updated Meta-Analysis of Randomized Controlled Trial Assessing the Effect of Neoadjuvant Chemotherapy in Advanced Gastric Cancer

Bing-Hong Xiong,[1] Yong Cheng,[1,†] Li Ma,[2] and Cai-Quan Zhang[1]

[1]Department of General Surgery, the First Affiliated Hospital of Chongqing Medical University, Chongqing, P. R. China;
[2]Department of Internal Medicine, Chongqing Huaxi Hospital, Chongqing, P. R. China

- n=1820
- R0 oranını artırıyor
- Sağkalım avantajı sağlıyor

perioperative mortality (OR: 1.14 (0.84, 2.05), $p = 0.65$), and grade 3/4 adverse effects. NAC can significantly down-stage the tumor and improve R0 resection rate of patients with gastric and gastroesophageal cancer. It is safe and feasible, and can be tolerated. NAC can slightly improve the survival rate. It needs further prospective multinational multicenter RCTs to define the clinical benefits of NAC and the most effective strategies for gastric and gastroesophageal cancer.

Xiong BH, Cheng Y, Ma L, Zhang CQ. Cancer Invest. 2014 Jul;32(6):272-84. Epub 2014 May 6.

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Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial

AIO/FLOT4 TRIAL

PFS	ECX/ECF	FLOT
2 yıllık	%43	%53
3 yıllık	%37	%46
5 yıllık	%31	%41

OS	ECX/ECF	FLOT
2 yıllık	%59	%68
3 yıllık	%48	%57
5 yıllık	%36	%45

Median OS: 50 vs 35 ay

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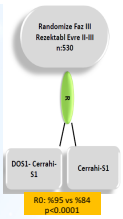
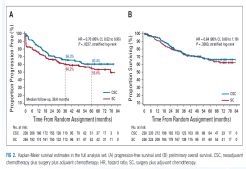
PRODIGY: A Phase III Study of Neoadjuvant Docetaxel, Oxaliplatin, and S-1 Plus Surgery and Adjuvant S-1 Versus Surgery and Adjuvant S-1 for Resectable Advanced Gastric Cancer

Mide (%94), OGJ (%6)
AdenoCa
T2-3N1
T4Nany
n=484





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Mide

ADJUVANT RT

- Adjuvant KRT:
  - 0116
  - ARTIST
  - CRITICS

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VOLUME 30 · NUMBER 3 · JANUARY 20 2012

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase III Trial Comparing Capecitabine Plus Cisplatin Versus Capecitabine Plus Cisplatin With Concurrent Capecitabine Radiotherapy in Completely Resected Gastric Cancer With D2 Lymph Node Dissection: The ARTIST Trial

Jeeyun Lee, Do Hoon Lim, Sung Kim, Se Hoon Park, Joon Oh Park, Young Suk Park, Ho Yeong Lim, Min Gew Choi, Tae Sung Sohn, Jae Hyung Noh, Jae Moon Bae, Yong Chan Ahn, Insuk Sohn, Sin Ho Jung, Cheol Keun Park, Kyoung-Mee Kim, and Won Ki Kang

- ✓ n=458, D2 dis.
- ✓ 6 KT(Kapesitabin/Sisp) vs 2 KT-KRT(45Gy+Kapesitabin)-2 KT
- ✓ DFS

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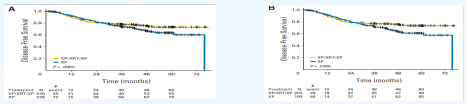

Fig 2. Disease-free survival in (A) all patients and (B) lymph node–positive patients. XP, capecitabine plus cisplatin; XRT, radiotherapy with capecitabine.

Results
Of 458 patients, 228 were randomly assigned to the XP arm and 230 to the XP/XRT/XP arm. Treatment was completed as planned by 75.4% of patients (172 of 228) in the XP arm and 81.7% (188 of 230) in the XP/XRT/XP arm. Overall, the addition of XRT to XP chemotherapy did not significantly prolong disease-free survival (DFS; $P = .0862$). However, in the subgroup of patients with pathologic lymph node metastasis at the time of surgery ($n = 396$), patients randomly assigned to the XP/XRT/XP arm experienced superior DFS when compared with those who received XP alone ($P = .0365$), and the statistical significance was retained at multivariate analysis (estimated hazard ratio, 0.6868; 95% CI, 0.4735 to 0.9952; $P = .0471$).

Conclusion
The addition of XRT to XP chemotherapy did not significantly reduce recurrence after curative resection and D2 lymph node dissection in gastric cancer. A subsequent trial (ARTIST-II) in patients with lymph node–positive gastric cancer is planned.

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ESMO

ANNALS of ONCOLOGY

ORIGINAL ARTICLE

A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial

S. H. Park[1], D. H. Lim[2], T. S. Sohn[3], J. Lee[1], D. Y. Zang[2], S. T. Kim[1], J. H. Kang[3], S. Y. Oh[4], I. G. Hwang[5], J. H. Ji[6], D. B. Shin[7], J. I. Yu[7], K.-M. Kim[8], J. Y. An[9], M. G. Choi[9], J. H. Lee[9], S. Kim[9], J. Y. Hong[9], J. O. Park[9], Y. S. Park[9], H. Y. Lim[9], J. M. Bae[10] & W. K. Kang[1], for the ARTIST 2 Investigators[*]

[1]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Departments of [2]Radiation Oncology, [3]Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [4]Division of Hematology-Oncology, Department of Internal Medicine, Hallym University Medical Center, Hallym University College of Medicine, Anyang si, Gyeonggi-do, [5]Department of Internal Medicine, Gyeongsang

- ✓ n=538, D2 dis.
- ✓ Evre II/III, LN (+)
- ✓ S1, SOX, SOX-RT

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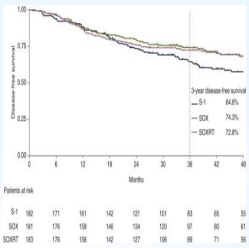
- ✓ Ortanca izlem: 37 ay
- ✓ SOX ve SOXRT S-1'e göre DFS arttırıyor
- ✓ SOX ve SOXRT arasında DFS fark yok (p= 0.667).



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ESMO ANNALS OF ONCOLOGY

ORIGINAL ARTICLE

Adjuvant chemotherapy is superior to chemoradiation after D2 surgery for gastric cancer in the per-protocol analysis of the randomized CRITICS trial

W. O. de Steur[†1], R. M. van Amelsfoort[†1], H. H. Hartgrink[1], H. Putter[2], E. Meershoek-Klein Kranenbarg[1], N. C. T. van Grieken[3], J. W. van Sandick[4], Y. H. M. Claassen[5], J. P. B. M. Braak[6], E. P. M. Jansen[7], K. Sikorska[8], H. van Tinteren[9], I. Walraven[9,2], P. Lind[10], M. Nordsmark[11], M. I. van Berge Henegouwen[12], H. W. M. van Laarhoven[13], A. Cats[14], M. Verheij[†1,15] & C. J. H. van de Velde[†1], on behalf of the CRITICS investigators[†]

Operabl, n=788

– 3ECF-- **Cerrahi** -- 3ECF

– 3ECF-- **Cerrahi** -- RT (45 Gy + Kapesitabin,sisplatin)

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- 5 yıllık OS:
  - KT: % 58, KRT: % 46 (HR, 1.62; P = .0004)

Results: Of the 788 patients, 478 started post-operative treatment according to protocol, 233 (59%) patients in the CT group and 245 (62%) patients in the CRT group. Patient and tumor characteristics between the groups before start of the post-operative treatment were not different. After a median follow-up of 6.7 years since the start of post-operative treatment, the 5-year overall survival was 57.9% (95% confidence interval: 51.4% to 64.3%) in the CT group versus 45.5% (95% confidence interval: 39.2% to 51.8%) in the CRT group (adjusted hazard ratio CRT versus CT: 1.62 (1.24-2.12), $P = 0.0004$). Inverse probability weighted analysis resulted in similar hazard ratios.
Conclusion: After adjustment for all known confounding factors, the PP analysis of patients who started the allocated post-operative treatment in the CRITICS trial showed that the CT group had a significantly better 5-year overall survival than the CRT group (NCT00407186).

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NCCN Guidelines Version 2.2022
Gastric Cancer

NCCN Guidelines Index | Table of Contents | Discussion

FOLLOW-UP/SURVEILLANCE[m]

Tis (successfully treated by ER)[r]	• H&P every 3–6 months for 1–2 years, every 6–12 months for 3–5 y, and annually thereafter • CBC and chemistry profile as clinically indicated • Upper GI endoscopy (EGD) every 6 months for 1 year, then annually for 3 years • Routine imaging (CT chest/abdomen/pelvis with oral and IV contrast) as clinically indicated based on symptoms and concern for recurrence
p stage I (T1a,T1b, N0–1 treated by surgical resection or T1a treated by ER)[r]	• H&P every 3–6 months for 1–2 years, every 6–12 months for 3–5 years, and annually thereafter • CBC and chemistry profile as clinically indicated • For patients treated by ER, EGD every 6 months for 1 year, then annually for up to 5 years • Thereafter, as needed based on symptoms and/or radiographic findings • For patients treated by surgical resection, EGD as clinically indicated[s] • CT chest/abdomen/pelvis with oral and IV contrast as clinically indicated[t] • Monitor for nutritional deficiency (eg, B_{12}, and iron) in surgically resected patients (especially after total gastrectomy) and treat as indicated
p stage IIA/B or yp stage I–III (treated with neoadjuvant ± adjuvant therapy)[r]	• H&P every 3–6 months for 1–2 years, every 6–12 months for 3–5 years, and annually thereafter • CBC and chemistry profile as clinically indicated • For patients who had partial or subtotal gastrectomy, EGD as clinically indicated • CT chest/abdomen/pelvis with oral and IV contrast (preferred) every 6–12 months for first 2 years, then annually up to 5 years[u] and/or can consider FDG-PET/CT as clinically indicated • Monitor for nutritional deficiency (eg, B_{12}, and iron) in surgically resected patients (especially after total gastrectomy) and treat as indicated

→ Recurrence (See GAST-8) or Survivorship[v]

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Mide

HEDEFE YÖNELİK TEDAVİLER

- HER-2 mutasyonu
- Angiogenez- VEGF
- NTRK gen füzyonu

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- Anti HER
  - Trastuzumab (ToGA) (Metastatik 1. basamak tedavide)
  - Trastuzumab Deruxtecan (DESTINY-Gastric01, DESTINY-Gastric02) (Metastatik 2. ve 3. basamak tedavide)
- Anti Angiogenez- Anti VEGF
  - Ramicirumab (RAINFALL, REGARD, RAİNBOW) (Metastatik 2. basamak tedavide)
  - Apatinib (Metastatik 3. basamak tedavide)
- NTRK inhibitörleri
  - Entrectinib
  - Larotrektinib

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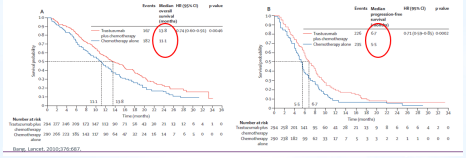
Trastuzumab

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

Yung-Jue Bang, * Eric Van Cutsem, * Andrea Feyereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro, Taroh Satoh, Giuseppe Aprile, Evgeny Kulikov, Julie Hill, Michaela Lehle, Josef Ruschoff, Yoon-Koo Kang, for the ToGA Trial Investigators†



Bang, Lancet, 2010;376:687.

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Trastuzumab Deruxtecan

DESTINY-Gastric01: Study Design

- Multicenter, open-label, randomized phase II study

Stratified by region (Japan vs Korea), ECOG PS (0 vs 1), HER2 status (IHC 3+ vs IHC 2+/ISH+)

Adult patients with HER2+* locally advanced or metastatic gastric or GEJ cancer that progressed on ≥ 2 prior regimens† (N = 188)

Randomized 2:1

T-DXd 6.4 mg/kg, 3-week cycles (n = 126)

Physician's choice:
Irinotecan 150 mg/m² every 2 weeks or
Paclitaxel 80 mg/m² Days 1, 8, 15 every 4 weeks (n = 62)

Until PD, unacceptable AEs, or pt withdrawal

*HER2+ based on IHC 3+ or IHC 2+/ISH+ according to ASCO/CAP guidelines.
†Prior regimens included fluoropyrimidine, a platinum agent, and trastuzumab or approved biosimilar.

- Primary endpoint: ORR by ICR (RECIST v1.1)
- Secondary endpoints: OS (key), DoR, PFS, DCR, confirmed ORR, safety

Shitara, ASCO 2020. Abstr 4513. Shitara. NEJM. 2020;[Epub]

Slide credit: clinicaloptions.com

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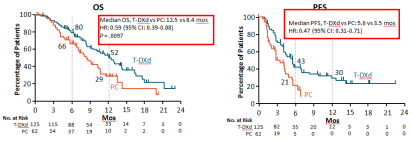
Trastuzumab Deruxtecan

DESTINY-Gastric01: OS and PFS



- Improved ORR and OS with T-DXd vs PC for most subgroups analyzed; ORR and OS higher with T-DXd in pts with HER2 IHC 3+ vs IHC 2+/ISH+; ORR and OS similar with T-DXd vs PC in IHC 2+/ISH+ subgroup

Shitara, ASCO 2020. Abstr 4513. Shitara. NEJM. 2020;[Epub]

Slide credit: clinicaloptions.com

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Trastuzumab Deruxtecan

DESTINY-Gastric02: Trastuzumab Deruxtecan in Western Patients With HER2+ Advanced Gastric or GEJ Cancer With Progression Following First-line Trastuzumab-Containing Therapy

CCO Independent Conference Highlights*
of the *ESMO 2021 Conference*,
September 17-20, 2021, Virtual

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

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Supported by educational grants from AstraZeneca, Daiichi Sankyo, Inc.; Exelixis, Inc.; and Ipsen Biopharmaceuticals, Inc.

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Trastuzumab Deruxtecan

DESTINY-Gastric02: Study Design

- Open-label, multicenter phase II trial

Patients in US, Europe with unresectable or metastatic gastric or GEJ cancer; HER2+* on biopsy after progression on first-line trastuzumab-containing regimen
ECOG PS 0/1
(N = 79)

→ **T-DXd 6.4 mg/kg Q3W**

*Defined as IHC 3+ or IHC 2+/ISH+

- **Primary endpoint:** confirmed ORR (per ICR)
- **Secondary endpoints:** PFS (per ICR), OS, DoR (per ICR), safety, tolerability

Van Cutsem. ESMO 2021. Abstr LBA55.

Slide credit: clinicaloptions.com

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Trastuzumab Deruxtecan

DESTINY-Gastric02: Efficacy

Outcome	T-DXd (N = 79)
Confirmed ORR, n (%) [95% CI]	30 [38] [27.3-49.6]
▪ CR, n (%)	3 (3.8)
▪ PR, n (%)	27 (34.2)
▪ SD, n (%)	34 (43.0)
▪ PD, n (%)	13 (16.5)
▪ NE, n (%)	2 (2.5)
Median DoR,* mo (95% CI)	8.1 (4.1-NE)
Confirmed DCR,† n (%) [95% CI]	64 (81.0) [70.6-89.0]
Median TTR, mo (95% CI)	1.4 (1.4-2.6)
Median PFS,‡ mo (95% CI)	5.5 (4.2-7.3)
Median follow-up, mo (range)	5.7 (0.7-15.2)

*Based on n = 30 responders.
†Exploratory endpoint.
‡Based on 42 events: 36 with progressive disease, and 6 deaths.

Van Cutsem. ESMO 2021. Abstr LBA55.

Slide credit: clinicaloptions.com

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Ramucirumab

First author/trial	Phase	Line	n	Treatment	ORR	Median PFS[95% CI]	HR [95% CI], P value	Median OS [95% CI]	HR [95% CI], P value
Yoso[31]	II	1	84	mFOLFOX6 + RAM	45.2%	6.4 M	0.98 [0.69-1.37] 0.886	11.7 M	1.08 [0.73-1.58] 0.712
			84	mFOLFOX6 + PBO	46.4%	6.7 M		11.5 M	
Muro[32] RAINSTORM	II	1	96	5-1 + Ox + RAM	58%	6.54 M	1.07 [0.86-1.33][a] 0.698	-	
			93	5-1 + Ox + PBO	50%	6.74 M		-	
Yamaguchi[27]	II	2	36	Ramucirumab	0%	6.6 [6.1-7.1] M		8.6 [5.7-10.7] M	
Bando[28]	II	2	45	Nab-PTX + RAM	54.8%	7.6 [5.4-8.1] M	-	NR	-
Fuchs[29] RAINFALL	III	1	326	FP/XP + RAM	41%	5.72 M	0.75 [0.61-0.94] 0.011	11.17 M	0.94 [0.80-1.16] 0.68
			319	FP/XP + PBO	36%	5.59 M		10.74 M	
Fuchs[30] REGARD	III	2	238	RAM	3%	2.1 M	0.48 [0.376-0.620] <0.0001	5.2 M	0.776 [0.603-0.998] 0.042
			117	PBO	3%	1.3 M		3.8 M	
Wilke[33] RAINBOW	III	2	330	PTX + RAM	28%	4.4 [4.2-5.3] M	0.635 [0.536-0.752] <0.0001	9.6 [8.5-10.8] M	0.807 [0.678-0.962] 0.017
			335	PTX + PBO	16%	2.9 [2.8-3.0] M		7.4 [6.3-8.4] M	

Hironaka S, Asia Pac J Clin Oncol 2019

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Apatinib

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Apatinib in Patients With Chemotherapy-Refractory Advanced or Metastatic Adenocarcinoma of the Stomach or Gastroesophageal Junction

Table 2. Analysis of Efficacy in Full Analysis Set

Variable	Apatinib (n = 176)	Placebo (n = 91)	P
Death, No.	146	78	
Median (95% CI), months	6.5 (4.6 to 7.6)	4.7 (3.6 to 5.3)	0.149
HR (95% CI)	0.709 (0.557 to 0.897)		0.166
PFS			
Median (95% CI), months	2.6 (2.0 to 2.8)	1.8 (1.4 to 1.9)	< .001
HR (95% CI)	0.444 (0.337 to 0.585)		< .001
Response			
ORR, %	2.84*	0.00*	.1695*
	1.70†	0.00†	.63321
DCR, %	42.05*	8.79*	< .0011
	31.62†	10.86†	< .0011

Abbreviations: DCR, disease control rate; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
*Assessed by investigators.
†Assessed by an independent response evaluation committee.

Conclusion
These data show that apatinib treatment significantly improved OS and PFS with an acceptable safety profile in patients with advanced gastric cancer refractory to two or more lines of prior chemotherapy.

J Clin Oncol 34:1448-1454. © 2016 by American Society of Clinical Oncology

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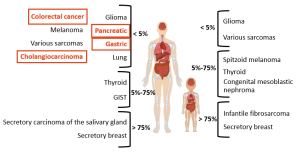
NTRK Gene Fusions in GI Cancers: Rare but Actionable

Tumors Harboring *NTRK* Gene Fusions



Hsiao. J Mol Diagn. 2019;21:553. Lacota. Am J Surg Pathol. 2020;44:162. Lee. Oncotarget. 2015;6:39028. Chou. Mod Pathol. 2020;33:924. Hong. Lancet Oncol. 2020;21:531. Doebele. Lancet Oncol. 2020;21:271.

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İMMUNOTERAPİ

- Nivolumab/Pembrolizumab
  - MSI-H, dMMR, TMB, PDL-1
- Histolojik alt tip:
  - SCC: PD-L1 ekspresyonundan bağımsız etkili gibi ?
  - Adenokarsinom: PDL-1 düşük derecede (+) ise etkinlik ?

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- Ösefagusta:
  - Adjuvant: R0 op sonrası rezidü T/N (+): Nivolumab (Chekmate-577)
  - Metastatik:
    - HER-2 (-), Adeno, CPS ≥5 : 1. basamak: Nivolumab + FOLFOX (Chekmate 649)
    - Her 2 (-) CPS ≥ 10: 1. basamak. Pembrolizumab + KT (Keynote 590)
    - HER-2 (-), PDL 1 den bağımsız-Nivolumab (Attraction-3), Pembrolizumab
- Mide:
  - Adjuvant: Ø
  - Metastatik:
    - HER-2 negatif, CPS ≥5- 1. basamak: Nivolumab + FOLFOX (Chekmate 649)
    - HER-2 pozitif, PDL-1 % 1 üzerinde: 1. basamak: Trastuzumab + Pembrolizumab + KT (Kenote 811)

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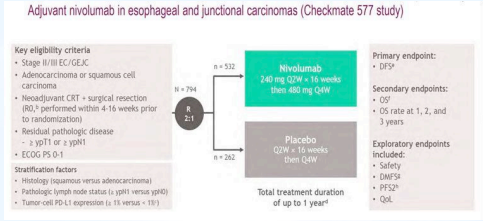
Nivolumab

Ösefagus-Adj

Adjuvant nivolumab in esophageal and junctional carcinomas (Checkmate 577 study)



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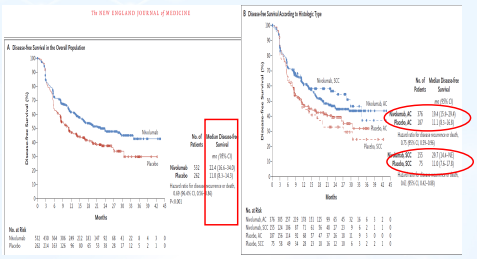

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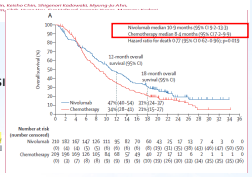
Nivolumab

Ösefagus-Met-2.sıra

Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial

- n=419
- Met Ösafagus SCC
- 1 basamak FU ve platin sonrası
- Nivolumab vs KT
- Fayda PDL-1 den bağımsız

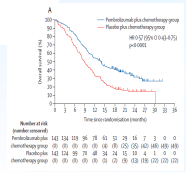


Pembrolizumab

Ösefagus-Met-1.sıra

Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study

- 1. basamak
- Pembrolizumab + KT vs KT
- n= 749 (373 vs 376)
- % 73 SCC, % 27 Adenokarsinom
- PDL-1 CPS > 10: mOS 13,9 vs 8,8



Pembrolizumab

Ösefagus-Met-2.sıra

Efficacy and Safety of Pembrolizumab for Heavily Pretreated Patients With Advanced, Metastatic Adenocarcinoma or Squamous Cell Carcinoma of the Esophagus The Phase 2 KEYNOTE-180 Study

- n=121
- Pembrolizumab monoterapisi
- ORR: % 9.9.
  - SCC (n = 63) %14.3; Adenokarsinom %5,2 (n = 58).
  - PD-L1-(+) (n = 58) %13.8; PD-L1-(-) (n = 63) %6.3.

Pembrolizumab

Ösefagus-Met-2.sıra

Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer

- n=628
- Pembrolizumab vs KT
- OS: PD-L1 CPS ≥10, SCC: 9,3 vs 6,7 ay; (P = 0,007)
- 12 aylık OS oranı: % 43 vs % 20.

CONCLUSION Pembrolizumab prolonged OS versus chemotherapy as second-line therapy for advanced esophageal cancer in patients with PD-L1 CPS ≥ 10, with fewer treatment-related adverse events.

Nivolumab

2021 ESMO congress

Nivolumab plus chemotherapy or ipilimumab vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/ esophageal adenocarcinoma: CheckMate 649 study

Presentation Number LBA7

CheckMate 649 study design

- CheckMate 649 is a randomized, open-label, global phase 3 study (NCT02872116)[1]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%)
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)

R 1:1:1 N = 2031

- n = 789: NIVO 360 mg + XELOX Q3W or NIVO 240 mg + FOLFOX Q2W[1,2]
- n = 833: XELOX Q3W or FOLFOX Q2W[1,2]
- n = 409: NIVO (1 mg/kg) + IPI (3 mg/kg) Q3W × 4 then NIVO 240 mg Q2W[1]

Dual primary endpoints
NIVO + chemo vs chemo
- OS and PFS per BICR (PD-L1 CPS ≥ 5)

Hierarchically tested secondary efficacy endpoints
NIVO + chemo vs chemo
- OS (PD-L1 CPS ≥ 1, all randomized)

NIVO + IPI vs chemo
- OS (PD-L1 CPS ≥ 5, all randomized)

- At data cutoff (May 27, 2021), the minimum follow-up[1] was 24.0 months in the NIVO + chemo arm and 35.7 months in the NIVO + IPI arm

Baseline characteristics

All randomized*	NIVO + chemo (n = 789)†	Chemo (n = 792)†	NIVO + IPI (n = 409)‡	Chemo (n = 404)‡
Median age (range), years	62 (54-69)	61 (53-68)	62 (22-84)	61 (23-90)
Male	68	71	68	69
Non-Asian/Asian	76/24	76/24	70/30	70/30
ECOG PS 1	59	57	53	53
Primary tumor location				
GC	70	70	69	70
GEJC	17	16	20	18
EAC	13	14	11	12
Metastatic disease	96	95	96	96
Liver metastases	38	40	36	40
Signet ring cell carcinoma	18	17	17	21
PD-L1 CPS ≥ 5§	60	61	58	60
Tumor cell PD-L1 ≥ 1%¶	16	16	17	17
MSI status*				
MSS	88	86	87	85
MSI-high	3	3	3	2
FOLFOX/XELOX received on study#	54/46	53/47	NA	47/53

- Baseline characteristics were balanced across the arms and consistent with the PD-L1 CPS ≥ 5 population

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CHECKMATE-649

The impact of PD-L1 expression on CM-649 trial outcomes

A Overall survival

Population*	Median overall survival, months: Nivolumab plus chemotherapy	Median overall survival, months: Chemotherapy alone	Unstratified hazard ratio for death (98% CI)	Interaction test p value
Overall (N=1581)	13·8	11·6	0·79 (0·70–0·89)	
PD-L1 CPS <1 (n=265)	13·1	12·5	0·92 (0·70–1·23)	
PD-L1 CPS ≥1 (n=1296)	14·0	11·3	0·76 (0·67–0·87)	0·2041
PD-L1 CPS ≤5 (n=696)	12·4	12·3	0·84 (0·78–1·13)	
PD-L1 CPS ≥5 (n=955)	14·4	11·1	0·70 (0·60–0·81)	0·0107†

0·5 1 2 4
Nivolumab plus chemotherapy better ↔ Chemotherapy alone better

Janjigian YY et al Lancet 2021 Jul 3;398(10294):27-40

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Summary

- NIVO + chemo continued to demonstrate improvement in OS, PFS, and objective responses vs chemo in previously untreated patients with advanced GC/GEJC/EAC with an additional 12-month follow-up
  - Clinically meaningful long-term OS and PFS benefit with sustained separation of the KM curves
  - Higher ORR and more durable responses
  - Deepening of response with additional complete responses with longer follow-up
- NIVO + IPI did not significantly improve OS vs chemo in patients with PD-L1 CPS ≥ 5
- No new safety signals were identified with NIVO + chemo or NIVO + IPI
- Longer follow-up data for NIVO + chemo further support its use as a new standard 1L treatment in patients with advanced GC/GEJC/EAC

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Pembrolizumab

First line pembrolizumab/placebo plus trastuzumab and chemotherapy for HER2+ positive advanced gastric cancer:

Clinical Trial Protocol Chung, Bang, Fuchs et al.

Key eligibility criteria
- Histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma
- Measurable disease per RECIST v1.1
- ECOG performance status of 0 or 1
- Adequate tissue sample

Stratification
- Geographic region
- PD-L1 status
- Chemotherapy regimen

R (1:1)

Pembrolizumab 200 mg Q3W + trastuzumab 8 mg/kg loading dose, and 6 mg/kg thereafter Q3W + investigator's choice of FP or CAPOX

Placebo (normal saline) Q3W + trastuzumab 8 mg/kg loading dose, and 6 mg/kg thereafter Q3W + investigator's choice of FP or CAPOX

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Pembrolizumab

TRASTUZUMAB + PEMBROLIZUMAB IN ADVANCED GASTRIC CANCER

KEYNOTE-811 phase 3 study

Pembrolizumab/trastuzumab/chemotherapy FDA approved May 2021 in HER2+ disease

Adapted from Janjigian 2021.

Adapted from Janjigian 2021.

Grade 3-5 AE rates did not differ between treatment arms (57%)

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GENETİK İRDELEME

Ösefagus

- ❑Risk değerlendirmesi için spesifik öneri yok
- ❑Bilinen yüksek riskli sendromu olan bireyler için bir kanser genetiği uzmanına sevk edilmesi önerilir.
  - ✓ Tylosis
  - ✓ Familial Barrett Esafagus
  - ✓ Bloom Sendromu
  - ✓ Fanconi Anemisi

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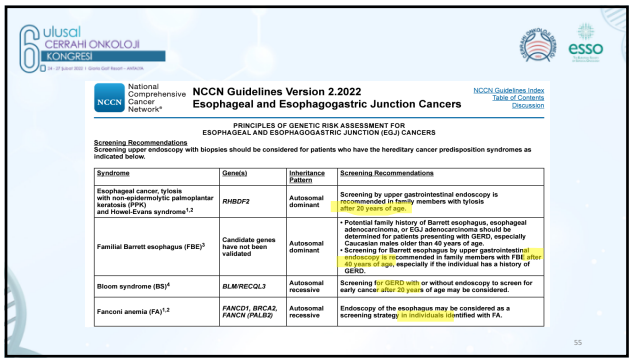

NCCN Guidelines Version 2.2022
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
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Discussion

PRINCIPLES OF GENETIC RISK ASSESSMENT FOR ESOPHAGEAL AND ESOPHAGOGASTRIC JUNCTION (EGJ) CANCERS

Screening Recommendations
Screening upper endoscopy with biopsies should be considered for patients who have the hereditary cancer predisposition syndromes as indicated below.

Syndrome	Gene(s)	Inheritance Pattern	Screening Recommendations
Esophageal cancer, tylosis with non-epidermolytic palmoplantar keratosis (PPK) and Howel-Evans syndrome[1,2]	*RHBDF2*	Autosomal dominant	Screening by upper gastrointestinal endoscopy is recommended in family members with tylosis after 20 years of age.
Familial Barrett esophagus (FBE)[3]	Candidate genes have not been validated	Autosomal dominant	• Potential family history of Barrett esophagus, esophageal adenocarcinoma, or EGJ adenocarcinoma should be determined for patients presenting with GERD, especially Caucasian males older than 40 years of age. • Screening for Barrett esophagus by upper gastrointestinal endoscopy is recommended in family members with FBE after 40 years of age, especially if the individual has a history of GERD.
Bloom syndrome (BS)[4]	*BLM/RECQL3*	Autosomal recessive	Screening for GERD with or without endoscopy to screen for early cancer after 20 years of age may be considered.
Fanconi anemia (FA)[1,2]	*FANCD1, BRCA2, FANCN (PALB2)*	Autosomal recessive	Endoscopy of the esophagus may be considered as a screening strategy in individuals identified with FA.

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Mide

GENETİK İRDELEME

% 5-10 familyal (+), % 3-5 kalıtsal genetik sendromu ile ilişkili

Hasta:

❑< 40 y

❑< 50 y + 1 veya 2. derece bir akrabası Mide Ca (+)

❑Herhangi bir yaşta Mide Ca + 1. ve 2. derece akraba ≥2 Mide Ca (+)

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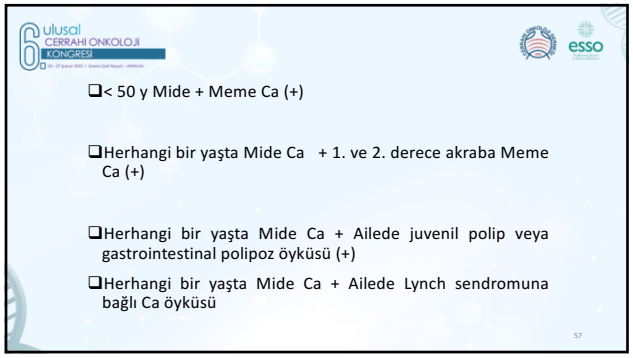

❑< 50 y Mide + Meme Ca (+)

❑Herhangi bir yaşta Mide Ca + 1. ve 2. derece akraba Meme Ca (+)

❑Herhangi bir yaşta Mide Ca + Ailede juvenil polip veya gastrointestinal polipoz öyküsü (+)

❑Herhangi bir yaşta Mide Ca + Ailede Lynch sendromuna bağlı Ca öyküsü

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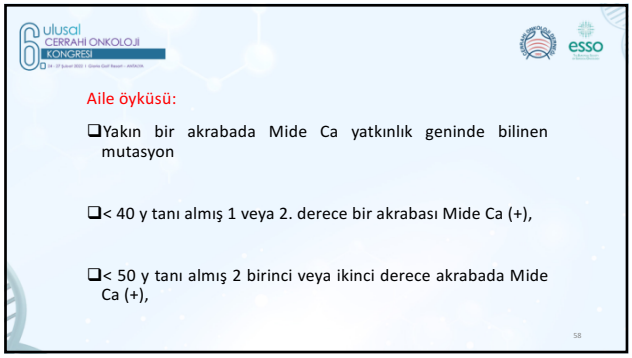

Aile öyküsü:

❑Yakın bir akrabada Mide Ca yatkınlık geninde bilinen mutasyon

❑< 40 y tanı almış 1 veya 2. derece bir akrabası Mide Ca (+),

❑< 50 y tanı almış 2 birinci veya ikinci derece akrabada Mide Ca (+),

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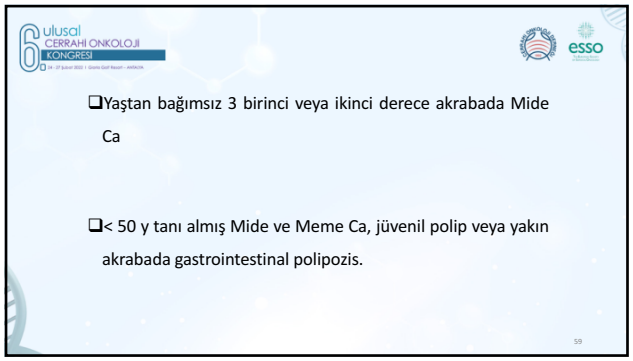

❑Yaştan bağımsız 3 birinci veya ikinci derece akrabada Mide Ca

❑< 50 y tanı almış Mide ve Meme Ca, jüvenil polip veya yakın akrabada gastrointestinal polipozis.

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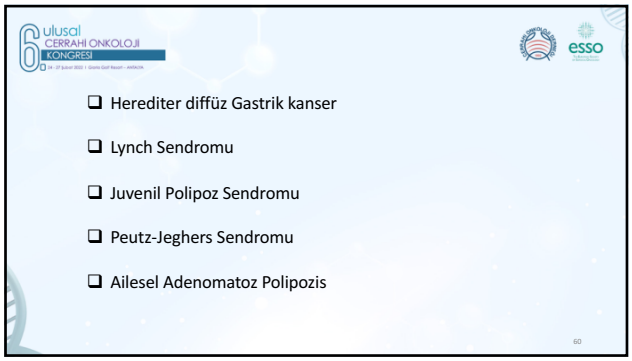

- ❑ Herediter diffüz Gastrik kanser
- ❑ Lynch Sendromu
- ❑ Juvenil Polipoz Sendromu
- ❑ Peutz-Jeghers Sendromu
- ❑ Ailesel Adenomatoz Polipozis

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❑Herediter diffüz Gastrik kanser

✓Genç yaş, otozomal dominant.

✓**CDH1'de mutasyon %30-50 (+)**

✓Yaşam boyu risk: Erkekler için % 67 ve kadınlar için % 83

✓CDH1 mutasyonu olan kadınlarda meme lobüler karsinomu gelişme riski !!!

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❑CDH1 mutasyonları bakılması düşünülen durumlar:

✓Yaştan bağımsız: Ailede 2 mide Ca vakası (biri diffüz mide Ca)

✓ Aile öyküsü olmaksızın: 50 y önce diffüz mide kanseri

✓Kişisel veya ailede: Diffüz mide Ca ve lobüler meme Ca öyküsü, biri 70 y önce tanı almış

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✓ 50 y önce aile bireylerinde 2 lobüler meme Ca (+)

✓ Māori etnik kökenine sahip bireylerde herhangi bir yaşta Diffüz mide kanseri, veya kişisel veya ailede yarık dudak/yarık damak öyküsü olan bireylerde

✓ 70 y önce bilateral lobüler meme Ca

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Syndrome	Gene(s)	Inheritance Pattern	Gastric Screening Recommendations
Hereditary diffuse gastric cancer[1-3]	*CDH1*	Autosomal dominant	• Prophylactic total gastrectomy is recommended between ages 18 and 40 for CDH1 mutation carriers. A baseline endoscopy is indicated prior to prophylactic total gastrectomy. Intraoperative frozen sections should be performed to verify that the proximal margin contains esophageal squamous mucosa and the distal margin contains duodenal mucosa, to ensure complete removal of gastric tissue. A D2 lymph node dissection is not necessary for prophylactic total gastrectomy. • Prophylactic gastrectomy prior to 18 years of age is not recommended, but may be considered for certain patients, especially those with family members diagnosed with gastric cancer before 25 years of age. • *CDH1* mutation carriers, who elect not to undergo prophylactic gastrectomy, should be offered screening every 6–12 months by upper endoscopy with multiple random biopsies. Women with *CDH1* mutations are at increased risk for breast cancer and should be followed using high-risk guidelines as outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. • For those patients without a strong family history of DGC, genetics counseling with multidisciplinary review is indicated.
Lynch syndrome (LS)	*EPCAM, MLH1, MSH2, MSH6, PMS2*	Autosomal dominant	Selected individuals or families or those of Asian descent may consider EGD with extended duodenoscopy (to distal duodenum or into the jejunum). See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for additional screening recommendations.
Juvenile polyposis syndrome (JPS)	*SMAD4, BMPR1A*	Autosomal dominant	Consider EGD starting at around age 12 years and repeat annually if polyps are found (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal) for additional screening recommendations.
Peutz–Jeghers syndrome (PJS)	*STK11*	Autosomal dominant	Consider EGD starting in late teens and repeating every 2–3 years. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for additional screening recommendations.
Familial adenomatous polyposis (FAP)/ Attenuated FAP (AFAP)	*APC*	Autosomal dominant	• There is no clear evidence to support screening for gastric cancer in FAP/AFAP. However, given the increased risk for duodenal cancer in FAP/AFAP, the stomach should be carefully viewed at the time of duodenoscopy. • Non-fundic gland polyps in the stomach should be managed endoscopically if possible. Patients with polyps that cannot be removed endoscopically, but with high-grade dysplasia or invasive cancer detected on biopsy, should be referred for gastrectomy. • Baseline EGD with side-viewing endoscope is recommended at age 25–30 years and repeated based on duodenal polyp status (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for duodenoscopic findings and interval of duodenoscopy). See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for additional screening recommendations.

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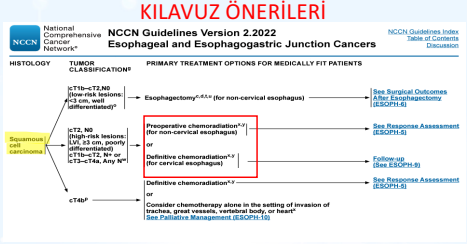
KILAVUZ ÖNERİLERİ



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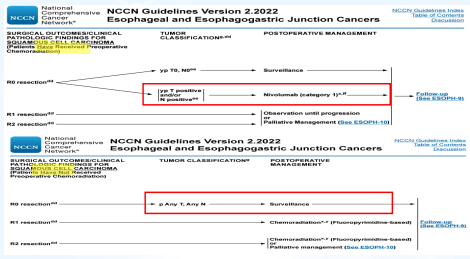

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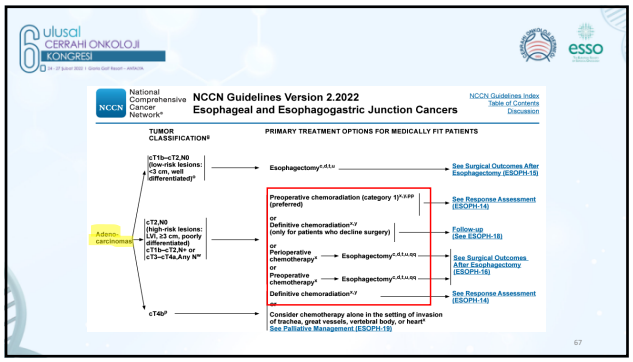
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TUMOR CLASSIFICATION[a]
PRIMARY TREATMENT OPTIONS FOR MEDICALLY FIT PATIENTS
Adeno-carcinomas
cT1b–cT2,N0 (low-risk lesions: <3 cm, well differentiated)[d]
cT2,N0 (high-risk lesions: LVI, ≥3 cm, poorly differentiated)
cT1b–cT2,N+ or cT3–cT4a,Any N[e]
cT4b[f]
Esophagectomy[c,d,l,u]
See Surgical Outcomes After Esophagectomy (ESOPH-15)
Preoperative chemoradiation (category 1)[c,k,ff,gg] (preferred)
or
Definitive chemoradiation[c,y] (only for patients who decline surgery)
or
Perioperative chemotherapy[x]
Esophagectomy[c,d,l,u,qq]
See Surgical Outcomes After Esophagectomy (ESOPH-16)
or
Preoperative chemotherapy[x]
Esophagectomy[c,d,l,u,qq]
Definitive chemoradiation[c,y]
See Response Assessment (ESOPH-14)
Follow-up (See ESOPH-18)
Consider chemotherapy alone in the setting of invasion of trachea, great vessels, vertebral body, or heart[x]
See Palliative Management (ESOPH-19)
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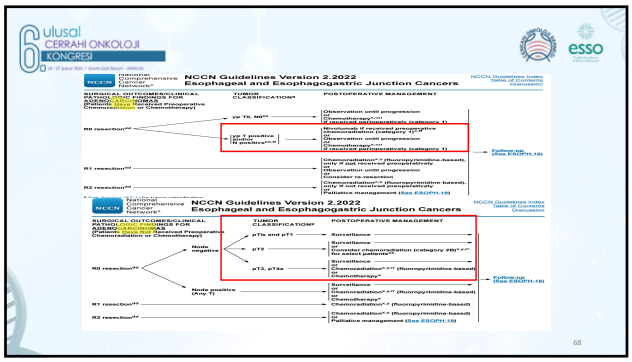
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SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR PATIENTS RECEIVING Preoperative Chemoradiation or Chemotherapy
TUMOR CLASSIFICATION[a]
POSTOPERATIVE MANAGEMENT
ypT0, N0[ee]
ypT+ positive lymph node (N+)[ee]
R0 resection[ee]
R1 resection[ee]
R2 resection[ee]
Observation until progression
or
Nivolumab if received preoperative chemoradiation (category 1)[ff]
or
Observation until progression
or
Pembrolizumab if received preoperative chemoradiation (category 1)
Follow-up (See ESOPH-18)
Chemoradiation[c,y] (fluoropyrimidine-based), only if not received preoperatively
or
Observation until progression
or
Chemoradiation[c,y] (fluoropyrimidine-based), consider re-resection if received preoperatively
or
Palliative management (See ESOPH-19)
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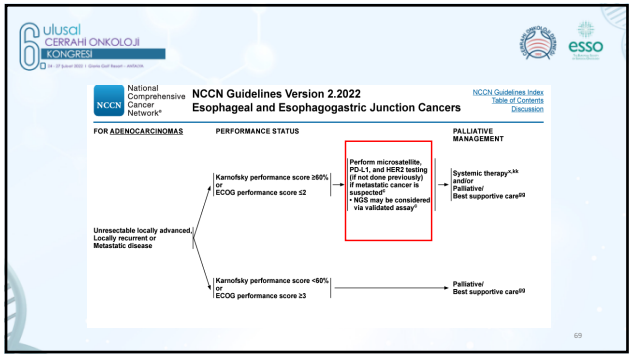
TUMOR CLASSIFICATION[a]
POSTOPERATIVE MANAGEMENT
pTis and pT1
pT2
pT3, pT4a
Node negative
Node positive (Any T)
Surveillance
or
Consider chemoradiation (category 2B)[c,y,ff] for select patients[hh]
Surveillance
or
Chemoradiation[c,y,ff] (fluoropyrimidine-based)
or
Chemotherapy[x]
R0 resection[ee]
R1 resection[ee]
R2 resection[ee]
Surveillance
or
Chemoradiation[c,y,ff] (fluoropyrimidine-based)
or
Chemotherapy[x]
Chemoradiation[c,y,ff] (fluoropyrimidine-based)
Palliative management (See ESOPH-19)
Follow-up (See ESOPH-18)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FOR ADENOCARCINOMAS
PERFORMANCE STATUS
PALLIATIVE MANAGEMENT
Unresectable locally advanced, Locally recurrent or Metastatic disease
Karnofsky performance score ≥60% or ECOG performance score ≤2
Karnofsky performance score <60% or ECOG performance score ≥3
Perform microsatellite, PD-L1, and HER2 testing (if not done previously) if metastatic cancer is suspected[ii]
• NGS may be considered via validated assay[ii]
Systemic therapy[x,kk] and/or Palliative/ Best supportive care[ll]
Palliative/ Best supportive care[ll]
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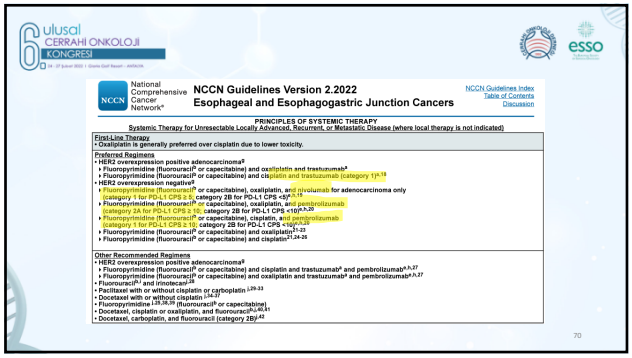
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First-Line Therapy
• Oxaliplatin is generally preferred over cisplatin due to lower toxicity.
Preferred Regimens
• HER2 overexpression positive adenocarcinoma[jj]
▸ Fluoropyrimidine (fluorouracil[l] or capecitabine) and oxaliplatin and trastuzumab[kk]
▸ Fluoropyrimidine (fluorouracil[l] or capecitabine) and cisplatin and trastuzumab (category 1)[kk,18]
• HER2 overexpression negative[jj]
▸ Fluoropyrimidine (fluorouracil[l] or capecitabine), oxaliplatin, and nivolumab for adenocarcinoma only (category 1 for PD-L1 CPS ≥ 5, category 2B for PD-L1 CPS <5)[kk,9,19]
▸ Fluoropyrimidine (fluorouracil[l] or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[kk,20]
▸ Fluoropyrimidine (fluorouracil[l] or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[kk,9,19]
▸ Fluoropyrimidine (fluorouracil[l] or capecitabine) and oxaliplatin[21-23]
▸ Fluoropyrimidine (fluorouracil[l] or capecitabine) and cisplatin[21,24-26]
Other Recommended Regimens
• HER2 overexpression positive adenocarcinoma[jj]
▸ Fluoropyrimidine (fluorouracil[l] or capecitabine) and cisplatin and trastuzumab[kk] and pembrolizumab[kk,h,27]
▸ Fluoropyrimidine (fluorouracil[l] or capecitabine) and oxaliplatin and trastuzumab[kk] and pembrolizumab[kk,h,27]
• Fluorouracil[ll] and irinotecan[28]
• Paclitaxel with or without cisplatin or carboplatin[1,29-33]
• Docetaxel with or without cisplatin[1,34-37]
• Fluoropyrimidine[1,29,36,38] (fluorouracil[l] or capecitabine)
• Docetaxel, cisplatin or oxaliplatin, and fluorouracil[ll][1,40,41]
• Docetaxel, carboplatin, and fluorouracil (category 2B)[1,42]
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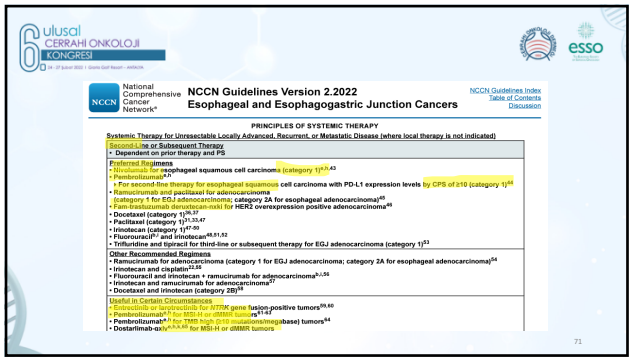
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Second-Line or Subsequent Therapy
• Dependent on prior therapy and PS
Preferred Regimens
• Nivolumab for esophageal squamous cell carcinoma (category 1)[h,43]
• Pembrolizumab[44]
▸ For second-line therapy for esophageal squamous cell carcinoma with PD-L1 expression levels by CPS of ≥10 (category 1)[44]
• Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[45]
• Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[46]
• Docetaxel (category 1)[36,37]
• Paclitaxel (category 1)[31,33,47]
• Irinotecan (category 1)[47-50]
• Fluorouracil[ll] and irinotecan[48,51,52]
• Trifluridine and tipiracil for third-line or subsequent therapy for EGJ adenocarcinoma (category 1)[53]
Other Recommended Regimens
• Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[54]
• Irinotecan and cisplatin[22,55]
• Fluorouracil and irinotecan + ramucirumab for adenocarcinoma[b,l,56]
• Irinotecan and ramucirumab for adenocarcinoma[57]
• Docetaxel and irinotecan (category 2B)[58]
Useful In Certain Circumstances
• Entrectinib or larotrectinib for NTRK gene fusion-positive tumors[59,60]
• Pembrolizumab[h,i] for MSI-H or dMMR tumors[61,62]
• Pembrolizumab[h,i] for TMB High (≥10 mutations/megabase) tumors[44]
• Dostarlimab-gxly[h,i,k,63] for MSI-H or dMMR tumors
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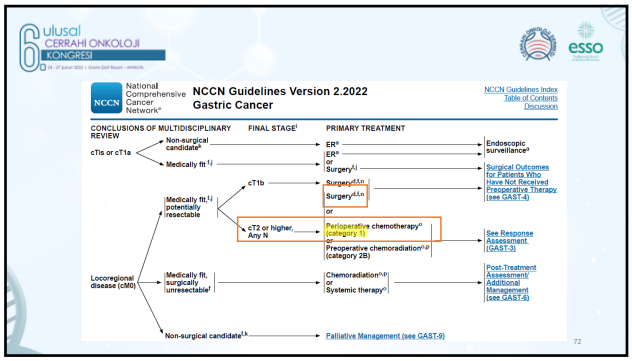
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CONCLUSIONS OF MULTIDISCIPLINARY REVIEW
FINAL STAGE[t]
PRIMARY TREATMENT
cTis or cT1a
Non-surgical candidate[k]
Medically fit[t,j]
ER[s]
Endoscopic surveillance[s]
Surgery[t,j]
Surgical Outcomes for Patients Who Have Not Received Preoperative Therapy (see GAST-4)
Locoregional disease (cM0)
Medically fit, potentially resectable
cT1b
cT2 or higher, Any N
Surgery[t,l,n]
or
Perioperative chemotherapy[o] (category 1)
or
Preoperative chemoradiation[o,p] (category 2B)
See Response Assessment (GAST-3)
Medically fit, surgically unresectable[t]
Chemoradiation[o,p] or Systemic therapy[o]
Post-Treatment Assessment/ Additional Management (see GAST-6)
Non-surgical candidate[t,k]
Palliative Management (see GAST-9)
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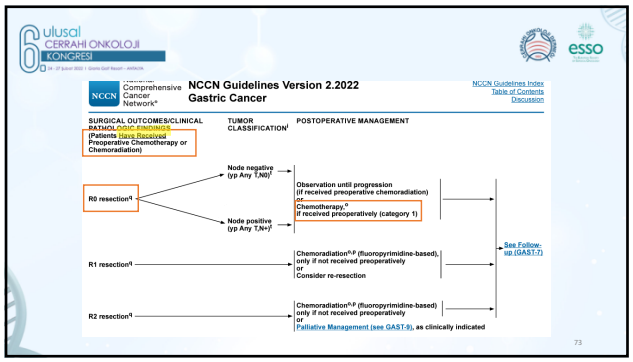
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TUMOR CLASSIFICATION[1]
POSTOPERATIVE MANAGEMENT
(Patients Have Received Preoperative Chemotherapy or Chemoradiation)
R0 resection[q]
Node negative (yp Any T,N0)[r]
Node positive (yp Any T,N+)[r]
Observation until progression (if received preoperative chemoradiation) or Chemotherapy[o] If received preoperatively (category 1)
R1 resection[q]
Chemoradiation[n,p] (fluoropyrimidine-based), only if not received preoperatively or Consider re-resection
R2 resection[q]
Chemoradiation[n,p] (fluoropyrimidine-based) only if not received preoperatively or Palliative Management (see GAST-9), as clinically indicated
See Follow-up (GAST-7)
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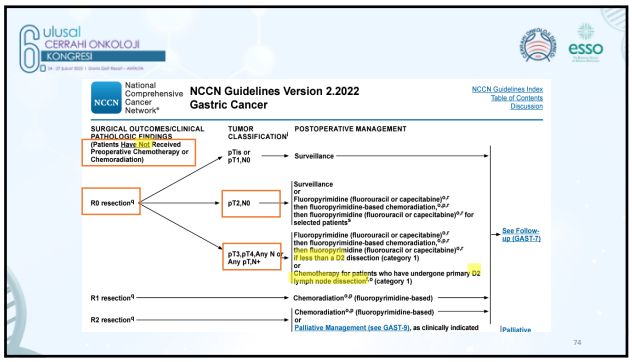
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SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS
TUMOR CLASSIFICATION[1]
POSTOPERATIVE MANAGEMENT
(Patients Have Not Received Preoperative Chemotherapy or Chemoradiation)
R0 resection[q]
pTis or pT1,N0
pT2,N0
pT3,pT4,Any N or Any pT,N+
Surveillance
Surveillance or Fluoropyrimidine (fluorouracil or capecitabine)[n,r] then fluoropyrimidine-based chemoradiation,[n,p,r] then fluoropyrimidine (fluorouracil or capecitabine)[n,r] for selected patients[s]
Fluoropyrimidine (fluorouracil or capecitabine)[n,r] then fluoropyrimidine-based chemoradiation,[n,p,r] then fluoropyrimidine (fluorouracil or capecitabine)[n,r] If less than a D2 dissection (category 1) or Chemotherapy for patients who have undergone primary D2 lymph node dissection[1,2] (category 1)
R1 resection[q]
Chemoradiation[n,p] (fluoropyrimidine-based)
R2 resection[q]
Chemoradiation[n,p] (fluoropyrimidine-based) or Palliative Management (see GAST-9), as clinically indicated
See Follow-up (GAST-7)
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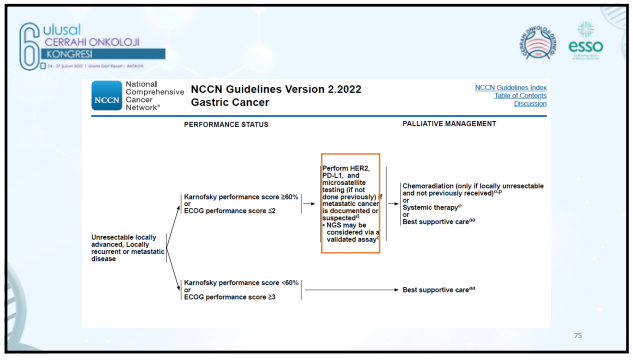
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PALLIATIVE MANAGEMENT
Unresectable locally advanced, Locally recurrent or metastatic disease
Karnofsky performance score ≥60% or ECOG performance score ≤2
Karnofsky performance score <60% or ECOG performance score ≥3
Perform HER2, PD-L1, and microsatellite testing (if not done previously) if metastatic cancer is documented or suspected[f]
• NGS may be considered via a validated assay[t]
Chemoradiation (only if locally unresectable and not previously received)[o,p]
Systemic therapy[v]
Best supportive care[aa]
Best supportive care[aa]
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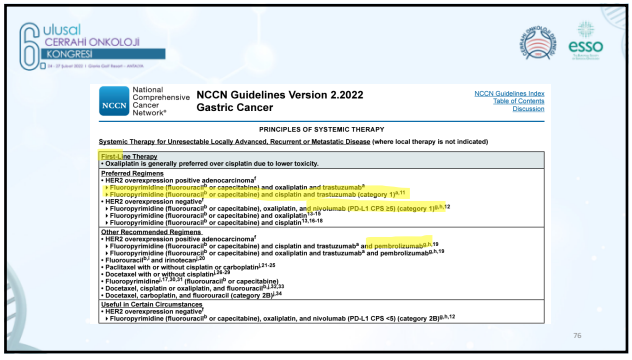
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First-Line Therapy
• Oxaliplatin is generally preferred over cisplatin due to lower toxicity.
Preferred Regimens
• HER2 overexpression positive adenocarcinoma[f]
• Fluoropyrimidine (fluorouracil[ff] or capecitabine) and oxaliplatin and trastuzumab[b]
• Fluoropyrimidine (fluorouracil[ff] or capecitabine) and cisplatin and trastuzumab (category 1)[b,11]
• HER2 overexpression negative[f]
• Fluoropyrimidine (fluorouracil[ff] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[b,12]
• Fluoropyrimidine (fluorouracil[ff] or capecitabine) and oxaliplatin[13-16]
• Fluoropyrimidine (fluorouracil[ff] or capecitabine) and cisplatin[13,16-18]
Other Recommended Regimens
• HER2 overexpression positive adenocarcinoma[f]
• Fluoropyrimidine (fluorouracil[ff] or capecitabine) and cisplatin and trastuzumab[b] and pembrolizumab[b,h,19]
• Fluoropyrimidine (fluorouracil[ff] or capecitabine) and oxaliplatin and trastuzumab[b] and pembrolizumab[b,h,19]
• Fluorouracil[ff] and irinotecan[20]
• Paclitaxel with or without cisplatin or carboplatin[i,21-25]
• Docetaxel with or without cisplatin[26-28]
• Fluoropyrimidine[ff,17,29,31] (fluorouracil[ff] or capecitabine)
• Docetaxel, cisplatin or oxaliplatin, and fluorouracil[ff,i,22,23]
• Docetaxel, carboplatin, and fluorouracil (category 2B)[i,24]
Useful in Certain Circumstances
• HER2 overexpression negative[f]
• Fluoropyrimidine (fluorouracil[ff] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS <5) (category 2B)[b,h,12]
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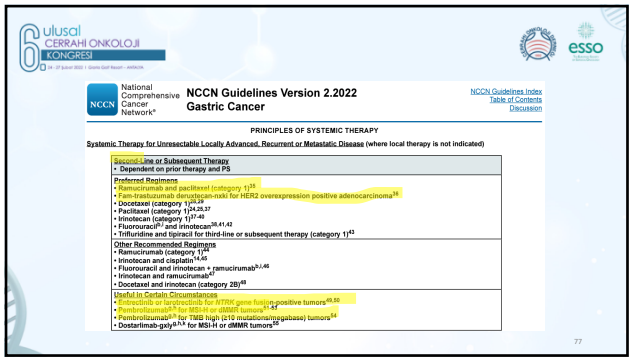
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Second-Line or Subsequent Therapy
• Dependent on prior therapy and PS
Preferred Regimens
• Ramucirumab and paclitaxel (category 1)[35]
• Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[36]
• Docetaxel (category 1)[25,29]
• Paclitaxel (category 1)[24,25,37]
• Irinotecan (category 1)[37-40]
• Fluorouracil[ff] and irinotecan[35,41,42]
• Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[43]
Other Recommended Regimens
• Ramucirumab (category 1)[44]
• Irinotecan and cisplatin[14,45]
• Fluorouracil and irinotecan + ramucirumab[b,i,46]
• Irinotecan and ramucirumab[47]
• Docetaxel and irinotecan (category 2B)[48]
Useful in Certain Circumstances
• Entrectinib or larotrectinib for NTRK gene fusion positive tumors[49,50]
• Pembrolizumab[b,h] for MSI-H or dMMR tumors[51-53]
• Pembrolizumab[b,h] for TMB high (≥10 mutations/megabase) tumors[54]
• Dostarlimab-gxly[b,h,k] for MSI-H or dMMR tumors[55]
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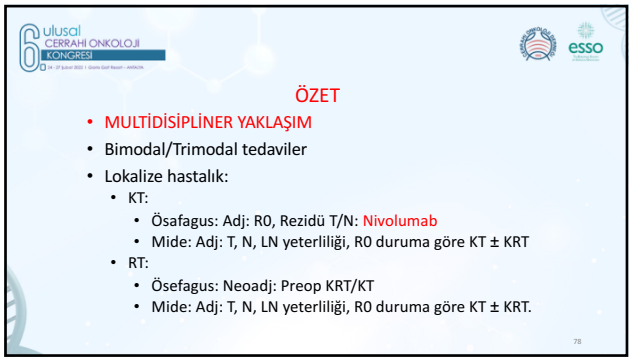
ÖZET
• MULTİDİSİPLİNER YAKLAŞIM
• Bimodal/Trimodal tedaviler
• Lokalize hastalık:
• KT:
• Ösafagus: Adj: R0, Rezidü T/N: Nivolumab
• Mide: Adj: T, N, LN yeterliliği, R0 duruma göre KT ± KRT
• RT:
• Ösefagus: Neoadj: Preop KRT/KT
• Mide: Adj: T, N, LN yeterliliği, R0 duruma göre KT ± KRT.
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- Metastatik hastalık:
  - Hedef tedaviler:
    - 1. ve 2. basamak: Adenokarsinom, Her 2 (+) ise KT + Anti Her ajanlar
    - 2. basamakta Ramicirumab ± KT
  - İmmunoterapi: PDL 1 +, MSI-H/dMMR, TMB
    - Ösefagus (CPS !): 1. ve 2. basamakta KT ile kombine
    - Mide (CPS !): 1. ve 2. basamakta KT ile kombine
  - Sitotoksik tedavi:
    - 1. basamak: Her-2 (-), PDL-1 (-) ise Kombine KT (2/3)
- Çıkış yaşı ve aile öyküsü gözetilerek Genetik danışmanlık

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Sabrınız için teşekkür ederim

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