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Updates Esophageal and Gastric Cancers

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Metastatic Gastric/GEJ Cancer

- Chemotherapy prolongs survival and improves symptom control (Wagner A, et al. JCO 2006)
  - Supportive care: 4 months
  - 5FU monotherapy: 7 months
  - Platinum + Fluoropyrimidines Combinations: 9 - 11 + months (van Cutsem. J Clin Oncol 2006. Al Batran. J Clin Oncol 2008. Cunningham D. N Engl J Med)
  - HER 2 + Platinum/Fluoropyrimidines/Traztuzumab: 13.8 months. (Bang YJ. Lancet 2010)

Treatment options Metastatic Gastric Adenocarcinoma Before 2020

1st line tx	2nd line tx	3rd line tx	Supportive care
5FU+ platinum (+/- taxane)	Ramucirumab+/- paclitaxell Paclitaxel irinotecan	Pembrolizumab/ Nivolumab PDL1+	
If HER2+, Add trastuzumab			
Pembrolizumab in MSI-high or dMMR			

Immune Checkpoint Inhibitors

Refractory disease

- Keynote 59 pembrolizumab. The trial was positive MSI high and PD-L1 positive disease.

- Attraction 2: Nivolumab versus best supportive care positive trial gastric cancer (Asia)

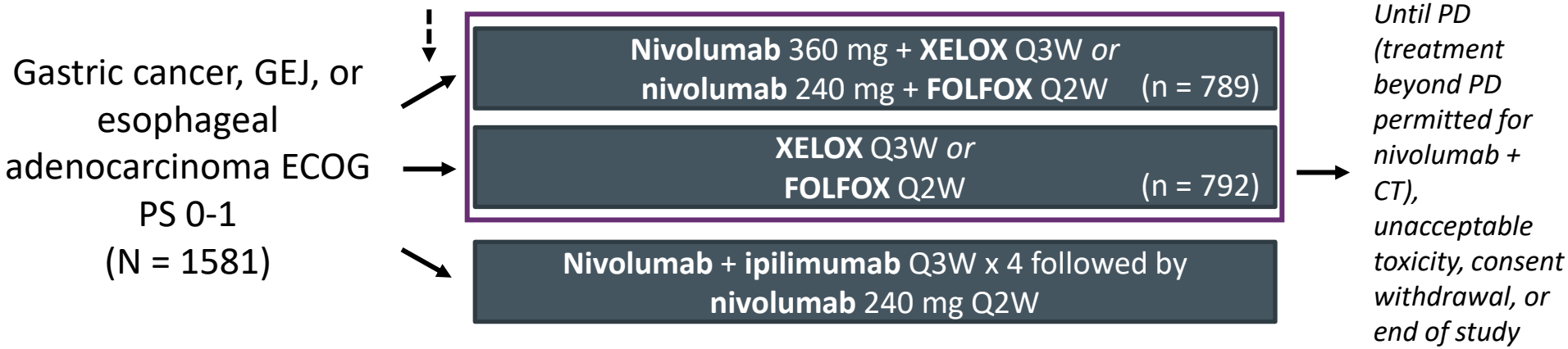
Second-line

- Keynote 61: Pembrolizumab versus paclitaxel and adenocarcinoma. It is a negative trial.
- Keynote 181: Pembrolizumab versus physician's choice of therapy in squamous cell carcinoma of the esophagus.
- Attraction 3: Nivolumab versus physician choice squamous cell carcinoma.

First line with and without chemotherapy.

- Keynote 62: Pembrolizumab +/- chemotherapy in GE junction and gastric. Negative trial
- JAVELIN 100: Avelumab maintenance therapy after systemic chemotherapy with 5-FU and platinum. Negative trial
- **Checkmate 649: Nivolumab plus FOLFOX in gastric GE junction adenocarcinoma. (practice changing?)**
- **Keynote 590 pembrolizumab plus 5-FU and cisplatin esophageal cancer.(practice changing)**

Phase III CheckMate 649: First-line Nivolumab + CT vs CT in Advanced Gastroesophageal Cancers



- Coprimary endpoints: OS and PFS in patients with PD-L1 CPS ≥ 5

Moehler. ESMO 2020. Abstr LBA6_PR. NCT02872116.

CheckMate 649: Response in Patients With PD-L1 CPS ≥ 5

- ORR significantly higher with nivolumab + CT vs CT ($P < .0001$)
  - 60% x 45%

Moehler. ESMO 2020. Abstr LBA6_PR.

Efficacy OS and PFS in Patients With PD-L1 CPS ≥ 5 (Coprimary Endpoints)

- **Median OS**
  - **Nivo + CT (n = 473)** 14.4 (13.1-16.2)
  - **CT (n = 482)1**1.1 (10.0-12.1)
    - HR: 0.71 (98.4% CI: 0.59-0.86; *P* < .0001)
- **Median PFS Mos (95% CI)**
  - **Nivo + CT (n = 473) 7**.7 (7.0-9.2)
  - **CT (n = 482)** 6.0 (5.6-6.9)
    - HR: 0.68 (98% CI: 0.56-0.81; *P* < .0001)

- Additionally, prolonged PFS with nivolumab + CT vs CT in patients with PD-L1 CPS ≥ 1 (HR: 0.74; 95% CI: 0.65-0.85) and in all randomized patients (HR: 0.77; 95% CI: 0.68-0.87)

CheckMate 649: Conclusions

- In the phase III CheckMate 649 trial enrolling patients with advanced gastroesophageal cancers, nivolumab + CT significantly prolonged OS and PFS in patients with PD-L1 CPS ≥ 5 (coprimary endpoints)
  - Median OS, 14.4 vs 11.1 mos (HR: 0.71; *P* < .0001); median PFS, 7.7 vs 6.0 mos (HR: 0.68; *P* < .0001)
  - Significant OS benefit also observed in all randomized patients and those with PD-L1 CPS ≥ 1
- Investigators concluded that First-line treatment with nivolumab + CT may be new potential standard of care for patients with advanced gastroesophageal cancers

Moehler. ESMO 2020. Abstr LBA6_PR.

NCCN 2.2021 (4/24/21)

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Gastric Cancer

NCCN Guidelines Index
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PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

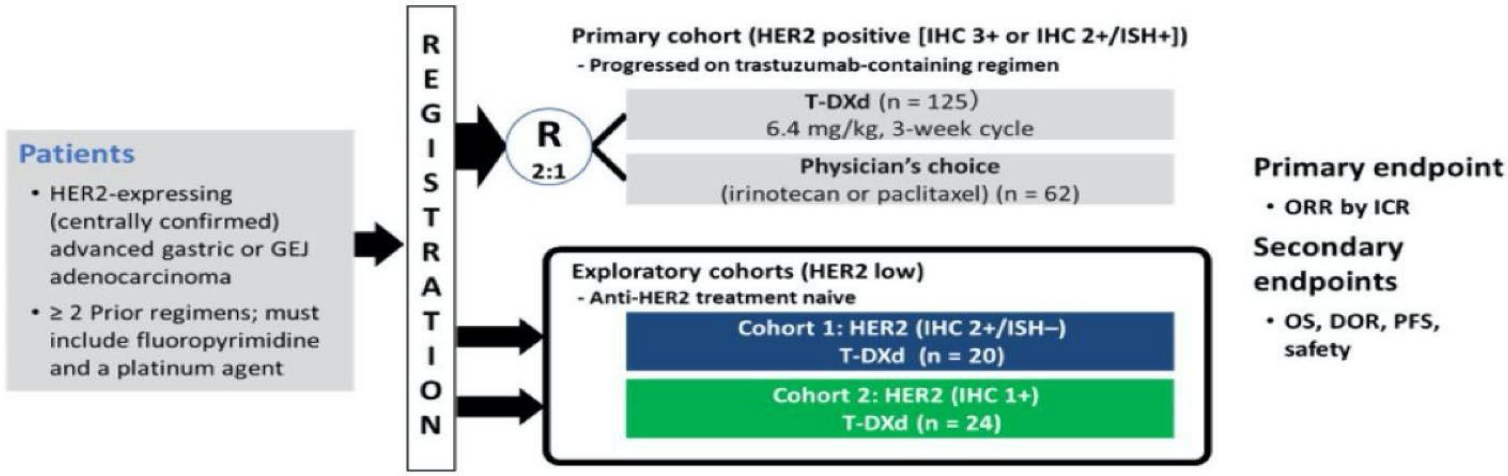
First-Line Therapy
- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,11]
- HER2 overexpression negative[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,12]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[13,15]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[13,16-18]

TRASTUZUMAB DERUXTECAN - ≥3RD LINE

DESTINY-Gastric01

An open-label, multicenter, randomized, phase 2 study



- All patients received T-DXd 6.4 mg/kg q3w
  - Cohort 1 IHC 2+/ISH– (n = 20); cohort 2 IHC 1+ (n = 24)
- Patients had not previously received anti-HER2 treatment
- Median of 2 prior lines of therapy for advanced/metastatic disease
  - 18% had irinotecan, 84% had ramucirumab, 32% had anti–PD-1/PD-L1
- At data cutoff (8 November 2019), no patients in cohort 1 and 2 in cohort 2 (8.3%) remained on treatment

Shitara K et al. N Engl J Med. 2020

TRASTUZUMAB DERUXTECAN - ≥3RD LINE

DESTINY-Gastric01

- The percentage of patients with an ORR (primary endpoint) higher in the trastuzumab deruxtecan (51% vs. 14%). (IHC 3+ or IHC2+/ISH+)
  - Exploratory analysis (IHC2+/ISH-), 36.8% (7 out of 19 pts)
- Overall survival was longer in the trastuzumab deruxtecan group than in the physician's choice group (median, 12.5 months vs. 8.4 months).
- Notable adverse events were myelosuppression and interstitial lung disease (10%, 1/4 G3-4).

Shitara K et al. N Engl J Med. 2020

NCCN 02.2021 (04/24/21)

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Ramucirumab and paclitaxel (category 1)[34]
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[35]
- Docetaxel (category 1)[23,24,36]
- Paclitaxel (category 1)[23,24,36]
- Irinotecan (category 1)[36-39]
- Fluorouracil[b,i] and irinotecan[37,40,41]
- Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[42]
- Pembrolizumab[g,h] for third-line or subsequent therapy for gastric cancer with PD-L1 expression levels by CPS of ≥1[j,43]

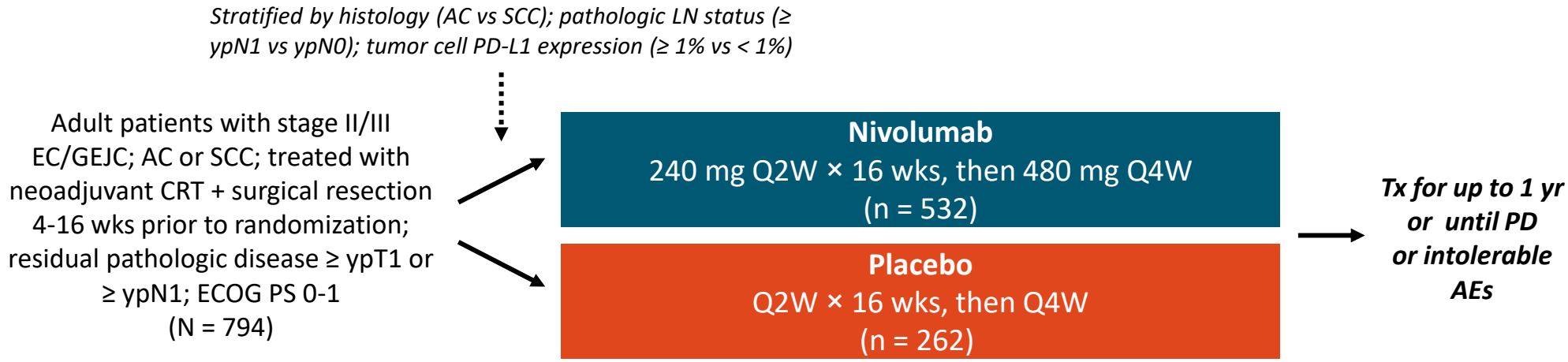
Other Recommended Regimens
- Ramucirumab (category 1)[44]
- Irinotecan and cisplatin[14,44]
- Fluorouracil and irinotecan + ramucirumab[b,i,46]
- Irinotecan and ramucirumab[47]
- Docetaxel and irinotecan (category 2B)[48]

Useful in Certain Circumstances
- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[49,50]
- Pembrolizumab[g,h] for MSI-H or dMMR tumors[51-53]
- Pembrolizumab[g,h] for TMB high (≥ 10 mutations/megabase) tumors[54]

Esophageal/GEJ Adenocarcinoma Adjuvant

CheckMate 577: Adjuvant Nivolumab vs Observation Following Neoadjuvant CRT and Resection in EC/GEJC

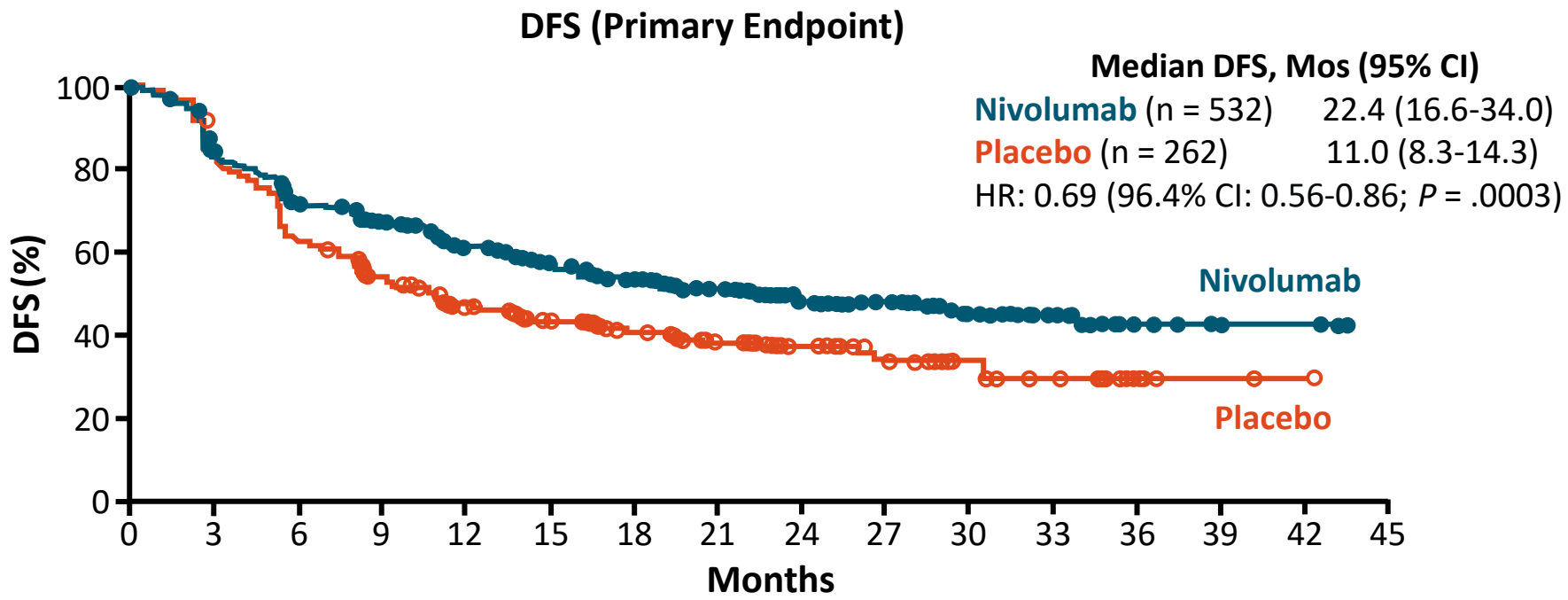
- Global, randomized, double-blind, phase III, placebo-controlled



- Median follow-up: 24.4 mos (range, 6.2-44.9)
- Primary endpoint: DFS assessed by investigator
- Secondary endpoints: OS, OS rate at 1, 2, and 3 yrs

Kelly. ESMO 2020. Abstr LBA9_PR. NCT02743494.

CheckMate 577: DFS



- 6-mo DFS rate was 72% in nivolumab group vs 63% in placebo group
- DFS favored nivolumab vs placebo across prespecified subgroups

Kelly. ESMO 2020. Abstr LBA9_PR. Reproduced with permission.

CheckMate 577 Conclusions

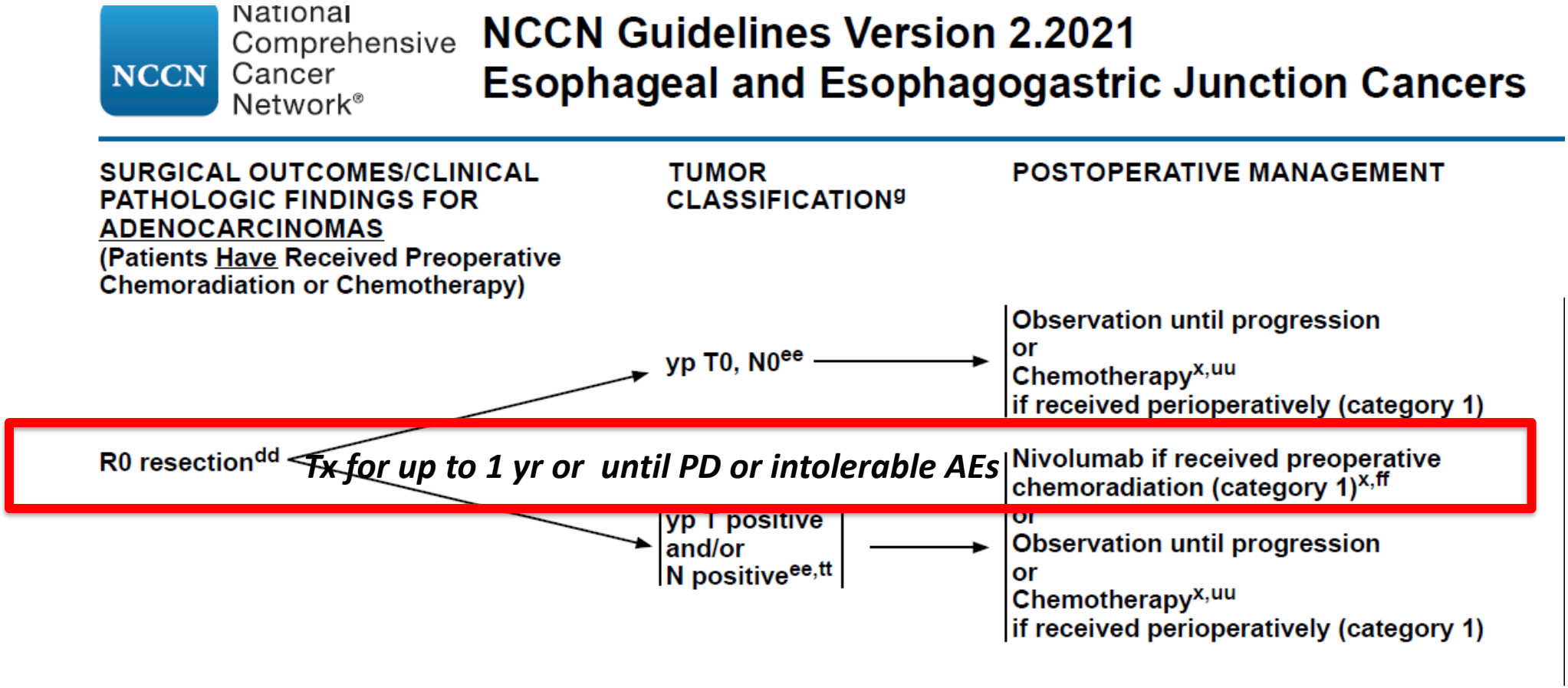
- Nivolumab adjuvant therapy provided a statistically significant and clinically meaningful DFS improvement vs placebo in patients with resected esophageal and gastroesophageal junction cancers following neoadjuvant CRT
  - 31% reduction in the risk of recurrence or death
  - Median DFS doubled in the nivolumab arm (22.4 mos) vs placebo arm (11.0 mos)
  - DFS benefit across multiple prespecified subgroups
  - Nivolumab well tolerated, with an acceptable safety profile
- Incidence of serious TRAEs and TRAEs leading to discontinuation ≤ 9% with nivolumab vs 3% with placebo
- Investigators suggest that adjuvant nivolumab could become a new standard of care in patients with resected esophageal and gastroesophageal junction cancers

Kelly. ESMO 2020. Abstr LBA9_PR.

NCCN Updates

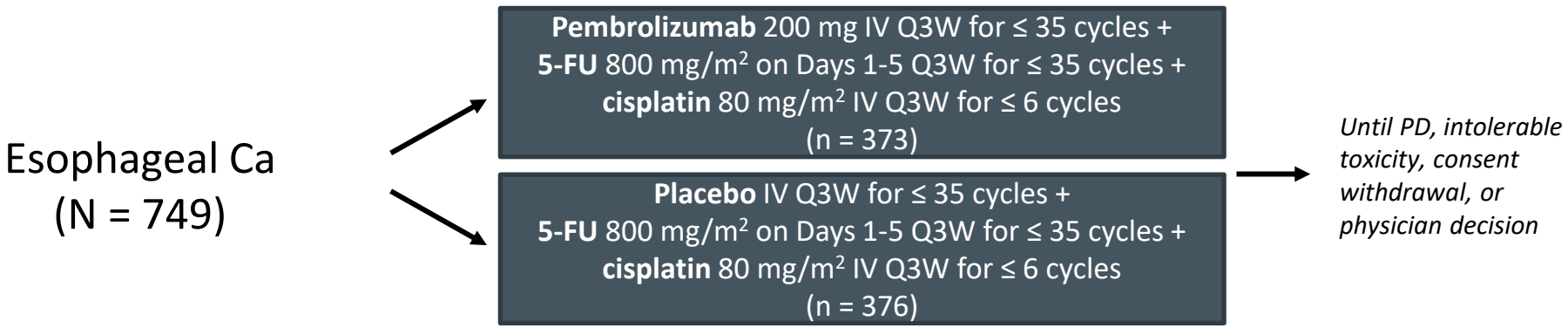
National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Esophageal and Esophagogastric Junction Cancers



Advanced/Metastatic Esophageal

KEYNOTE-590: First-line Pembrolizumab + CT vs Placebo + CT in Patients With Advanced Esophageal Cancer



- PD-L1 CPS ≥ 10 in half (49.9% to 52.4%)

Kato. ESMO 2020. Abstr LBA8_PR. NCT03189719.

KEYNOTE-590: Efficacy Outcomes

Outcome	All Patients		Patients With PD-L1 CPS ≥ 10		ESCC	
	Pembro + CT (n = 373)	CT (n = 376)	Pembro + CT (n = 186)	CT (n = 197)	Pembro + CT (n = 274)	CT (n = 274)
mOS, (mos)	12.4	9.8	13.5	9.4	12.6	9.8
mPFS (mos)	6.3	5.8	7.5	5.5	6.3	5.8
ORR, %	45.0	29.3	--	--	--	--
▪ Difference	15.8 (P < .0001)		--		--	

- All results above were statistically significant

Kato. ESMO 2020. Abstr LBA8_PR.

KEYNOTE-590: Conclusions

- In this randomized phase III trial, First-line pembrolizumab + CT significantly improved OS, PFS, and ORR vs CT alone in patients with advanced esophageal cancer
  - Significantly prolonged OS in all patients and subgroups, including PD-L1 CPS ≥ 10, ESCC, and ESCC with PD-L1 CPS ≥ 10 (all $P \leq .0006$)
  - Significantly prolonged PFS in all patients and subgroups, including PD-L1 CPS ≥ 10, ESCC (all $P < .0001$)
  - Significantly higher ORR in all patients (45.0% vs 29.3%; $P < .0001$)
- Investigators concluded that First-line pembrolizumab + CT represents new standard of care for patients with locally advanced/metastatic esophageal cancer

Kato. ESMO 2020. Abstr LBA8_PR.

NCCN Guidelines

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  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,18]
- HER2 overexpression negative[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PDL1 CPS ≥ 5) for adenocarcinoma only (category 1)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (PDL1 CPS ≥ 10)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (PDL1 CPS ≥ 10) (category 1)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[21-23]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[21,24-26]

Gastric/Gastroesophageal Cancer Other Recent Studies

- FIGHT: First-line treatment with bemarituzumab, a first-in-class humanized IgG1 monoclonal antibody targeting *FGFR2b*, combined with mFOLFOX showed statistically significant PFS, ORR, and OS in patients with gastric/GEJ cancers with FGFR2b overexpression or *FGFR2* gene amplification vs mFOLFOX plus placebo
- LEAP-005 Gastric Cohort: Treatment with pembrolizumab + lenvatinib in patients with previously treated advanced gastric cancer who progressed on 2 prior lines of therapy showed promising response
- TAGS: Analyses from the phase III trial of trifluridine/tipiracil vs placebo in previously treated metastatic gastric/GEJ adenocarcinoma showed:
  - Improved survival in patients with ≥ 3 prior therapies regardless of previous treatment
  - Superior survival after 3 lines of therapy vs later lines
  - Early body weight loss was associated with unfavorable survival outcomes regardless of trial treatment

Conclusions

- Nivolumab adjuvant therapy provided a statistically significant and clinically meaningful DFS improvement vs placebo in patients with resected esophageal and gastroesophageal junction cancers following neoadjuvant CRT

- Platinum based chemotherapy is an acceptable first-line treatment for metastatic disease in HER negative cancers and PDL1 negative Cancers
- Trastuzumab improves survival in HER2 positive cancers (+++) first line and TRASTUZUMAB DERUXTECAN have impressive activity ≥3RD LINE
  - Should we move it to second line chemotherapy prolongs survival in good PS patients
- Immunotherapy with checkpoint inhibitors is active are options in first and later line of therapies pending on CPS PDL-1 score, TMB, and MSI status.

Thank you!!!