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School of Medicine

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 2021/2022

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			

Gastric Cancer

Immune Checkpoint Inhibitors

Refractory disease

- Keynote 59 pembrolizumab. The trial was positive for MSI high and PD-L1 positive disease.
- Attraction 2: Nivolumab superior to best supportive in metastatic 3L+ GEJ and Gastric adenocarcinoma(Asia) (5.3 x 4.1 mo)
- Attraction 3 Nivolumab superior to docetaxel SCC (OS: 10.9 x 8.4 mo. p=0.019)

Kang et al, Lancet 2017

Kato K et al. Lanceet 2019;.

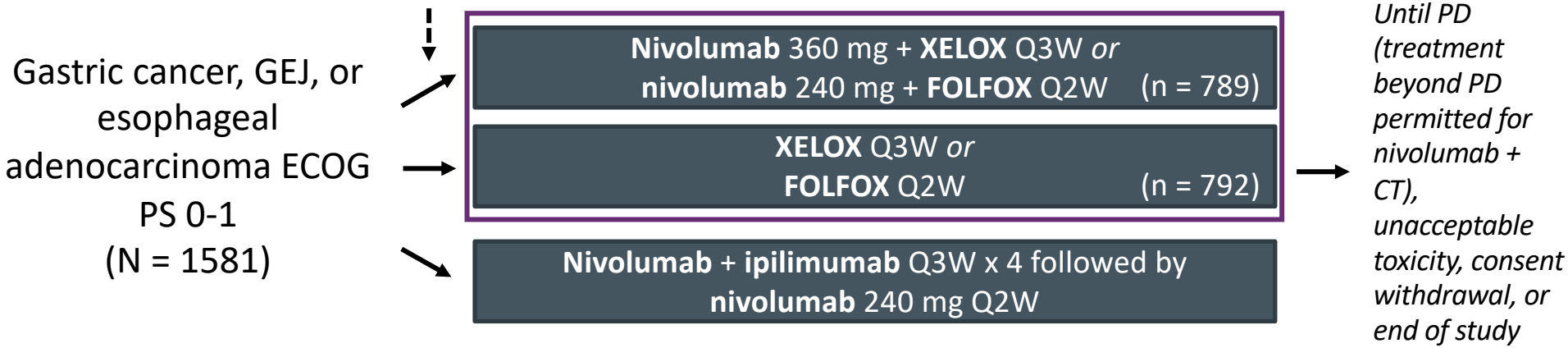
Second-line

- Keynote 61: Pembrolizumab versus paclitaxel and adenocarcinoma. 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: 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)
- ORR significantly higher with nivolumab + CT vs CT (*P* < .0001)
  - 60% x 45%

Janjigian et al, Lancet 2021

NCCN 03/27/22

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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.

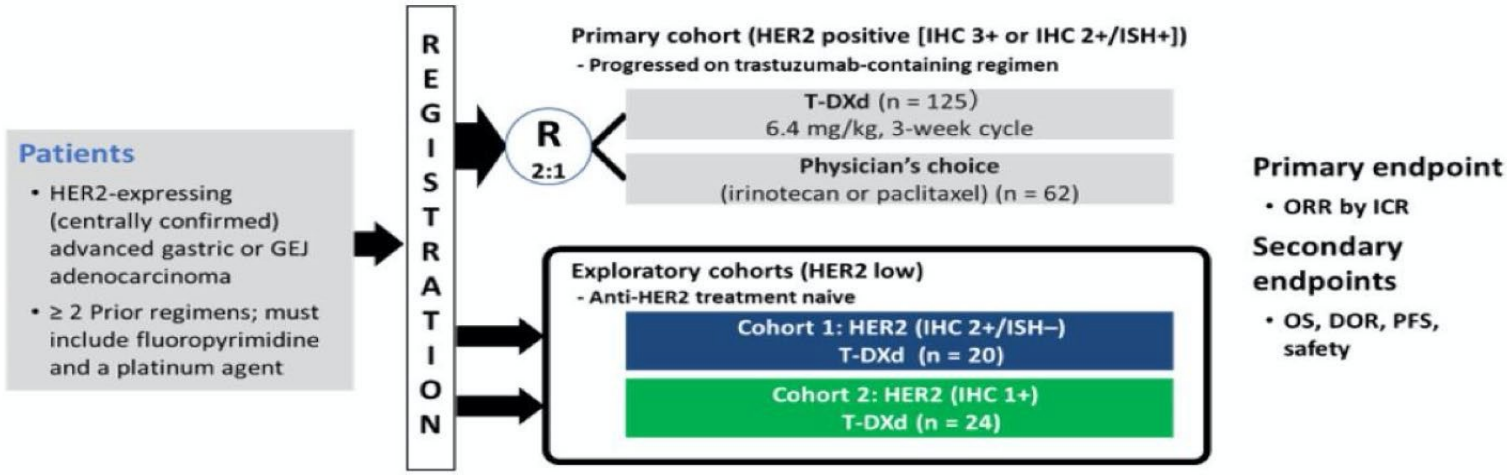
Preferred Regimens
- HER2 overexpression positive adenocarcinoma[f]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,11]
- HER2 overexpression negative[f]
  - Fluoropyrimidine (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]

HER-2 Positive Esophageal, GEJ, and Gastric Adenocarcinoma

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 03/27/2022

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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)[24,25]
- Paclitaxel (category 1)[24,25,37]
- Irinotecan (category 1)[37-40]
- Fluorouracil[b,i] and irinotecan[38,41,42]
- Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[43]

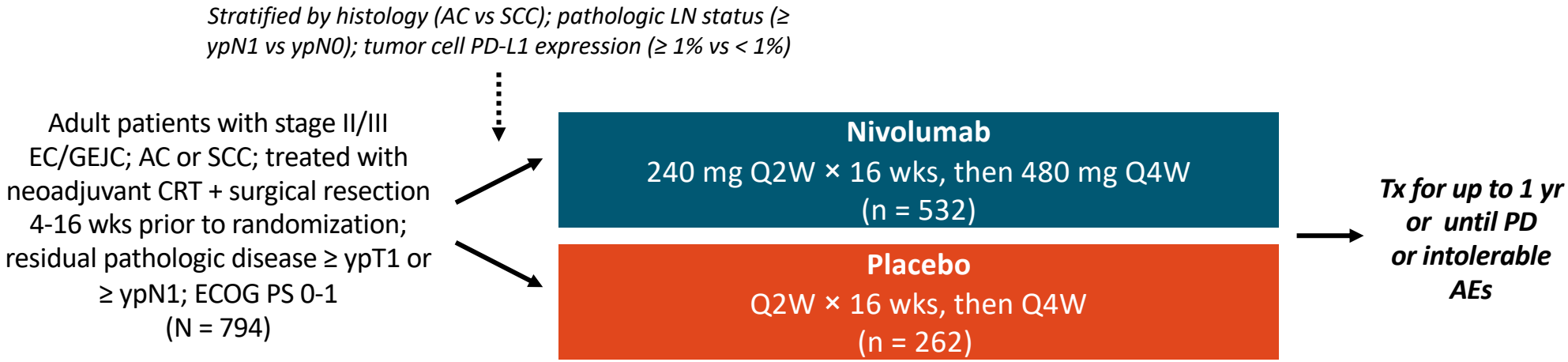
Other Recommended Regimens
- Ramucirumab (category 1)[44]
- Irinotecan and cisplatin[14,45]
- Fluorouracil and irinotecan + ramucirumab[b,i,46]
- Irinotecan and ramucirumab[47]
- Docetaxel and irinotecan (category 2B)[48]

Useful in Certain Circumstances
- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[49,50]
- Pembrolizumab[g,h] for MSI-H or dMMR tumors[51-53]
- Pembrolizumab[g,h] for TMB high (≥10 mutations/megabase) tumors[54]
- Dostarlimab-gxly[g,h,k] for MSI-H or dMMR tumors[55]

Esophageal/GEJ Adenocarcinoma Adjuvant

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

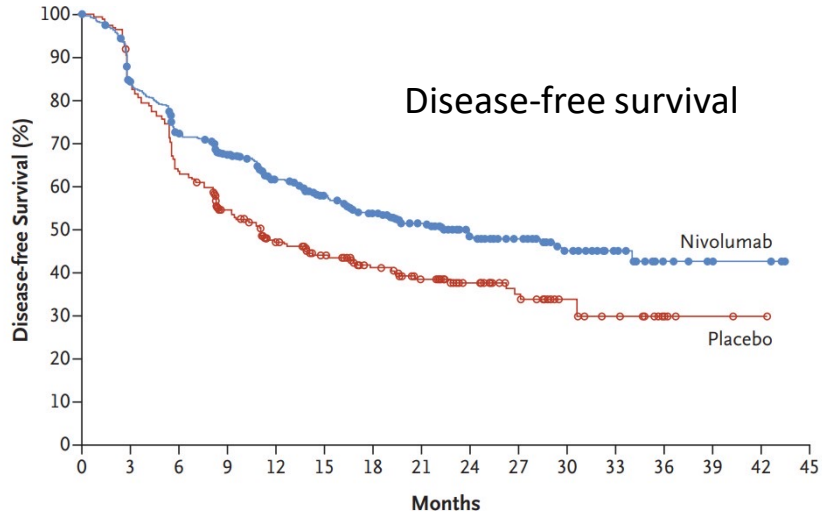
- Global, randomized, double-blind, phase III, placebo-controlled



- 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 RJ, et al. *N Engl J Med* 2021;384:1191-1203. *ASCO* 2021 Presentation No. LBA4003

LOCALIZED ESOPHAGEAL CANCER – CHECKMATE-577



	No. of Patients	Median Disease-free Survival
		mo (95% CI)
Nivolumab	532	22.4 (16.6–34.0)
Placebo	262	11.0 (8.3–14.3)

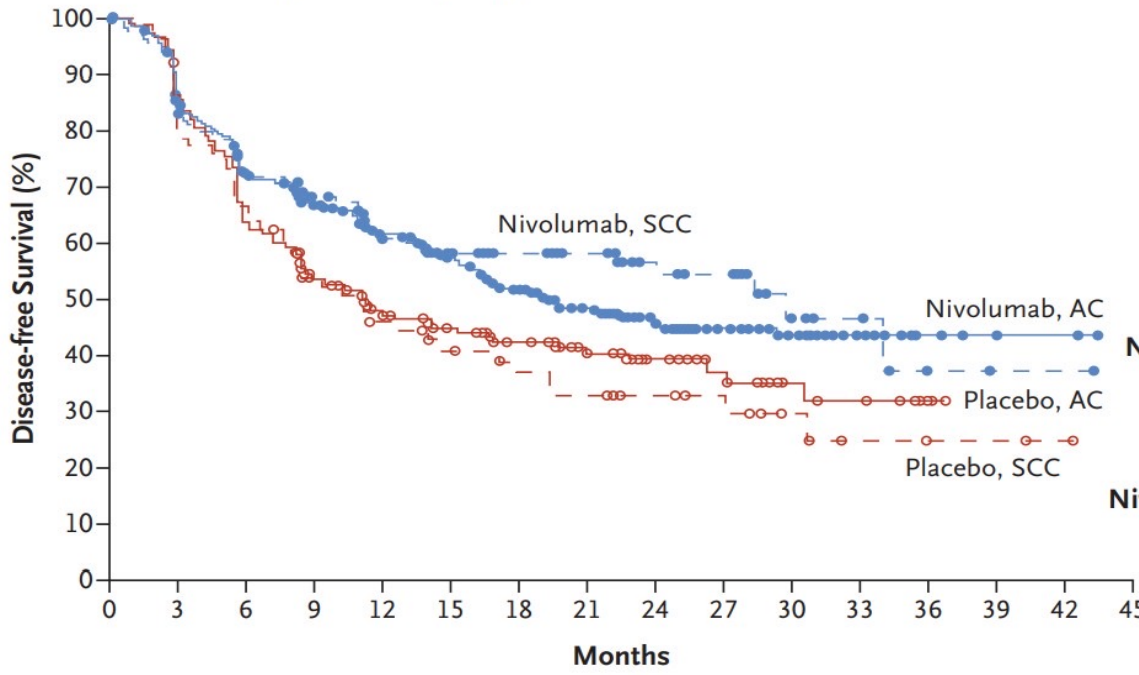
Hazard ratio for disease recurrence or death, 0.69 (96.4% CI, 0.56–0.86)
P<0.001

- Nivolumab showed a 26% reduction in the risk of distant recurrence or death versus placebo
- Distant (29% vs 39%) and locoregional (12% vs 17%) recurrences were less frequent with Nivolumab
- Adverse events in the Nivolumab group occurred early (median, 6–13 wks) and resolved for most pts

Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203. *ASCO* 2021 Presentation No. LBA4003

LOCALIZED ESOPHAGEAL CANCER – CHECKMATE-577

B **Disease-free Survival According to Histologic Type**



	No. of Patients	Median Disease-free Survival *mo (95% CI)*
Nivolumab, AC	376	19.4 (15.9–29.4)
Placebo, AC	187	11.1 (8.3–16.8)
Hazard ratio for disease recurrence or death, 0.75 (95% CI, 0.59–0.96)		
Nivolumab, SCC	155	29.7 (14.4–NE)
Placebo, SCC	75	11.0 (7.6–17.8)
Hazard ratio for disease recurrence or death, 0.61 (95% CI, 0.42–0.88)		

No. at Risk

Nivolumab, AC	376	305	257	219	178	151	125	99	65	45	32	16	6	3	2	0
Nivolumab, SCC	155	124	106	87	71	61	56	48	27	23	9	6	2	1	1	0
Placebo, AC	187	156	114	92	68	57	47	37	26	18	11	9	3	0	0	0
Placebo, SCC	75	58	49	34	28	23	18	16	12	10	6	3	2	2	1	0

Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203. *ASCO* 2021 Presentation No. LBA4003

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

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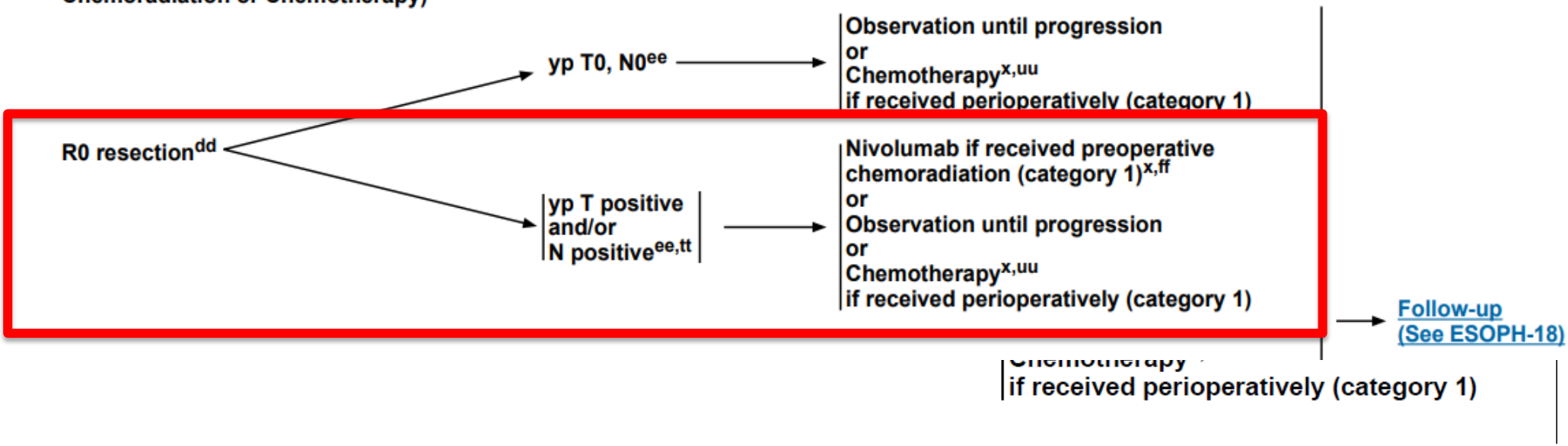
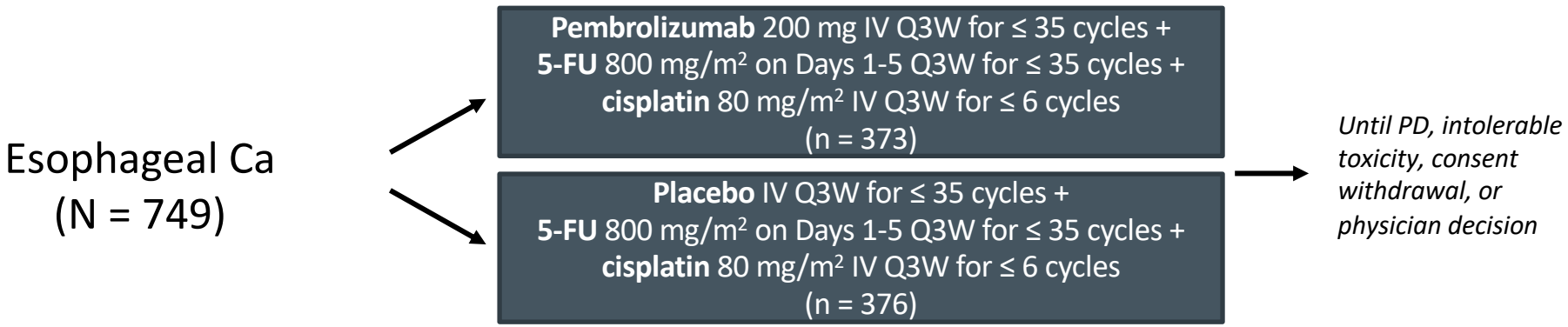


Advanced/Metastatic Esophageal

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%)

Sun et al, Lancet 2021

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)	12.6	9.8 (HR=0.72)	13.9	8.8 (HR 0.57)	12.6	9.8
mPFS (mos)	6.3	5.8 (HR 0.65)	7.5	5.5 (HR 0.51)	6.3	5.8
ORR, %	45.0	29.3	--	--	--	--
▪ Difference	15.8 (P < .0001)		--		--	

- All results above were statistically significant

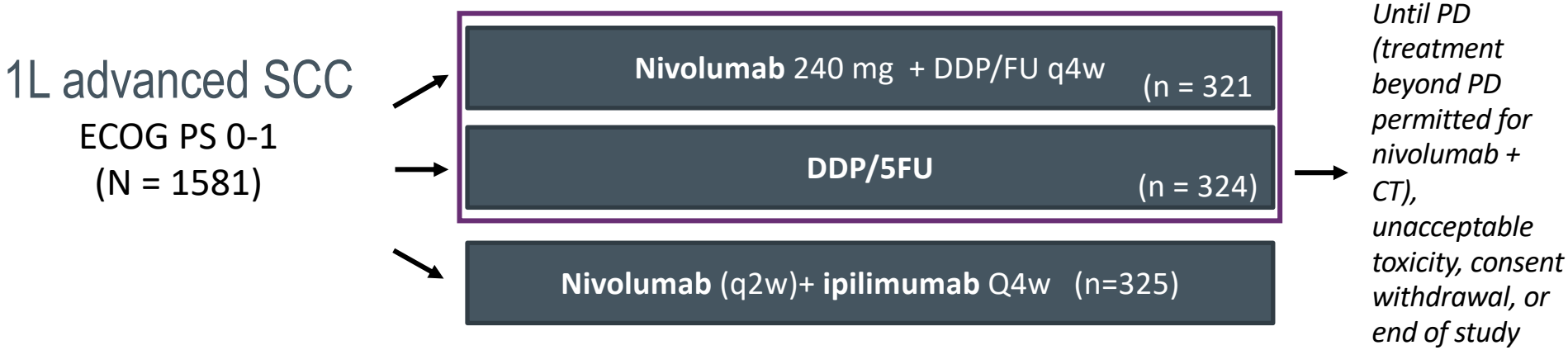
Sun et al, Lancet 2021

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
  - Magnitude of benefit higher in SCC over adenoca
  - No significant benefit in OS for patients with PDL-1 CPS <10

Kato. ESMO 2020. Abstr LBA8_PR.

CHECKMATE 648



Doki et al, NEJM 2022

CHECKMATE 648

Nivolumab + DDP/FU vs DDP/FU		
	SCC	PDL 1 TPS > 1%
OS	13.2 vs 10.7 HR 0.74 (0.58-0.96)	15.4 vs 9.1 HR 0·57 (0·37–0·80)
PFS	5.8 vs 5.6 HR 0.81 (0.64-1.04)	6.9 vs 4.4 HR 0·65 (0.46-0.92)

Benefit most pronounced in SCC with PD-L1 TPS ≥1%

Doki et al, NEJM 2022

CHECKMATE 648

Nivolumab + Ipilumumab vs DDP/FU		
	SCC	PDL 1 TPS > 1%
OS	12.7 vs 10.7 HR 0.78 (0.62 – 0.98)	13.7 vs 9.1 HR 0·64 (0·46–0·90)
PFS	2.9 vs 5.6 HR 1.26 (1.04-1.52)	4.0 vs 4.4 HR 1.02 (0.73-1.43)

Doki et al, NEJM 2022

CHECKMATE 648 Conclusion

- Nivolumab plus platinum-fluoropyrimidine id a standard as first line advanced SCC of the esophagus
  - Patients with PD-L1 TPS ≥1% tumors appear to derive higher benefit
  - No clear benefit in PD-L1 TPS or CPS negative patients

Doki et al, NEJM 2022

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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 for adenocarcinoma only (category 1 for PD-L1 CPS ≥ 5; category 2B for PD-L1 CPS <5)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[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
  - Both PFS (9.5 x 7.4 mo) and OS (not reached x 12.9 months) favored **Bemarituzumab arm**.
- FAST trial: EOX +/- Zolbetuximab (Targeting Claudin18.2)
  - PFS: 9 vs 5.7 months and ORR: 39% vs 25%
- CART CELL targeting CLDN18.2 expression
  - At a dose of 2.5×10^8 CAR T cells achieved ORR of 61.1%, DCR of 83.3%, mPFS of 5.6 months, mOS of 9.5 months

Wainberg ZA, et al. ASCO GI 2021
Sahin U, et al. Ann Oncol. 2021
Qi C, et al. ESMO 2021

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!!!