Gastrointestinal Breakthroughs: Recent Progress in Research and Practice

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I **do not** have any commercial or financial relationship to any topics or products discussed.

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TOPICS COVERED

- Gastric

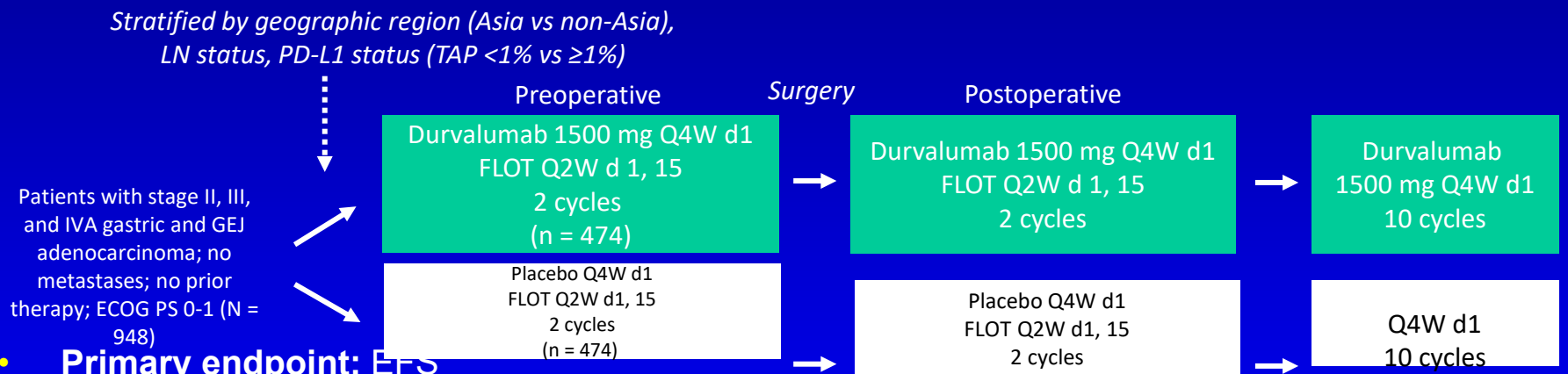
Early Stage	Metastatic
Matterhorn	Keynote 859
	Checkmate 649
	Compassion15/AK104 -302
	Glow/Spotlight

- Hepatobiliary — Herizon-BTC-01
- Pancreatic — NAPOLI trial
- Colorectal — Galaxy，Checkmate8HW, NCT03860272

Gastric Cancer

MATTERHORN: Study Design

- Global randomized, double-blind phase III trial



- **Primary endpoint:** EFS
- **Key secondary endpoints:** central review of pCR by modified Ryan criteria, OS, safety

Al-Batran. ESMO 2023. Abstr LBA73.

MATTERHORN: Baseline Characteristics

		Durvalumab + FLOT (n = 474)	Placebo + FLOT (n = 474)
Median age, yr (range)		62 (26-84)	63 (28-83)
Male, n (%)		326 (69)	356 (75)
Enrollment in Asia, n (%)		90 (19)	90 (19)
ECOG PS 0, n (%)		337 (71)	366 (77)
Primary tumor location, n (%)	▪ Gastric	324 (68)	316 (67)
	▪ GEJ	150 (32)	158 (33)
Primary tumor stage, n (%)	▪ T0-T1a	6 (1)	0
	▪ T1b-T2	44 (9)	36 (8)
	▪ T3	307 (65)	321 (68)
	▪ T4a	101 (21)	103 (22)
	▪ T4b	16 (3)	14 (3)
LN positive, n (%)		329 (69)	330 (70)
PD-L1 expression by TAP, n (%)	▪ <1%	48 (10)	47 (10)
	▪ ≥1%	426 (90)	427 (90)
	▪ <5%	236 (50)	230 (49)
	▪ ≥5%	238 (50)	244 (52)
Histology type, n (%)	▪ Intestinal	174 (37)	168 (35)
	▪ Diffuse	104 (22)	85 (18)
	▪ Unspecified other	196 (41)	221 (47)

Al-Batran. ESMO 2023. Abstr LBA73.

MATTERHORN: Efficacy

Outcome, %	Durvalumab + FLOT (n = 474)	Placebo + FLOT (n = 474)	Absolute Difference Between Arms	OR (95% CI)	*P* Value
pCR rate by central review	19	7	12	3.08 (2.03-4.67)	<.00001
pCR rate by investigator assessment	22	8	13	3.03 (2.05-4.48)	<.00001
Combined pCR and near-pCR* by central review	27	14	12	2.19 (1.58-3.04)	<.00001

*Near-pCR: single or rare small groups of cancer cells at time of resection per modified Ryan criteria.

- Pathologic response rate was similar in all subgroups, with exception of German vs non-German patients (30% vs 13%)

Al-Batran. ESMO 2023. Abstr LBA73.

MATTERHORN: Investigators' Conclusions

- In this preplanned interim analysis of randomized, double-blind phase III MATTERHORN trial, addition of durvalumab to perioperative FLOT in patients with gastric/GEJ cancer was associated with efficacy benefits vs placebo + FLOT, including:
  - Clinically relevant improvement in pCR (absolute difference, 12%; *P* <.00001)
  - Improvement in downstaging (T0: 23% vs 11%; N0: 52% vs 37%)
- Rates of AEs were similar between arms and as expected, with no new safety issues identified
- Trial is ongoing to assess for primary endpoint of EFS

Al-Batran. ESMO 2023. Abstr LBA73.

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 preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive[c]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin and trastuzumab[f]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, trastuzumab[f] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[g,h,17-18]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin and trastuzumab (category 1)[f,19]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, trastuzumab[f] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[g,h,17-18]
- HER2 overexpression negative[c]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,20]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥1[g,h,21] (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin[22-24]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥1[g,h,21] (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin[22,25-27]
- MSI-H/dMMR tumors (independent of PD-L1 status)[c]
  - Pembrolizumab[g,h,28-30]
  - Dostarlimab-gxly[g,h,31]
  - Nivolumab and ipilimumab[g,h,20]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab[g,h,20]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab[g,h,29,30]

Other Recommended Regimens
- Fluorouracil[a,i] and irinotecan[j,32]
- Paclitaxel with or without carboplatin or cisplatin[j,33-37]
- Docetaxel with or without cisplatin[j,38-41]
- Fluoropyrimidine[j,26,42,43] (fluorouracil[a] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[a,j,44,45]

Useful in Certain Circumstances
- HER2 overexpression negative[c]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS <5) (category 2B)[g,h,20]

[a] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[c] Principles of Pathologic Review and Biomarker Testing (GAST-B).
[f] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[g] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[h] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i] Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.
[j] Trastuzumab should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued
References

Keynote-859 NCT 03675737

- KEYNOTE-859 (NCT03675737), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1579 treatment naive patients with HER2-negative advanced gastric or GEJ adenocarcinoma with no previous treatment
- 207 centers across 33 countries. Inclusion criteria > 18 years with untreated locally advanced or metastatic HER2 - gastric or GEJ adenocarcinoma and ECOG of 0 or 1
- Randomized (1:1) to receive pembrolizumab 200 mg or placebo with investigator's choice of combination chemotherapy consisting either of cisplatin 80 mg/m2 plus 5-FU 800 mg/m2/day for 5 days (FP) or oxaliplatin 130 mg/m2 on Day 1 plus capecitabine 1000 mg/m2 twice a day for 14 days (CAPOX) of each 21-day cycle

Lancet Oncol. 2023 Nov;24(11):1181-1195

Keynote-859 NCT 03675737

- Nov 2018 to June 2021, 1579 (66%) of 2409 screened participants were randomly assigned to receive pembrolizumab plus chemo (pembrolizumab group; n=790) or placebo plus chemotherapy (placebo group; n=789).

- M (527 [67%] of 790 participants in the pembrolizumab plus chemotherapy group; 544 [69%] of 789 participants in the placebo plus chemotherapy group) and White (426 [54%]; 435 [55%]). Median follow-up at the data cutoff was 31·0 months (IQR 23·0–38·3).

- Median overall survival was longer in the pembrolizumab group than in the placebo group in the ITT population (12·9 months [95% CI 11·9–14·0] *vs* 11·5 months [10·6–12·1]; hazard ratio [HR] 0·78 [95% CI 0·70–0·87]; p<0·0001), in participants with a PD-L1 CPS of 1 or higher (13·0 months [11·6–14·2] *vs* 11·4 months [10·5–12·0]; 0·74 [0·65–0·84]; p<0·0001), and in participants with a PD-L1 CPS of 10 or higher (15·7 months [13·8–19·3] *vs* 11·8 months [10·3–12·7]; 0·65 [0·53–0·79]; p<0·0001).

Lancet Oncol. 2023 Nov;24(11):1181-1195

Keynote-859 NCT 03675737

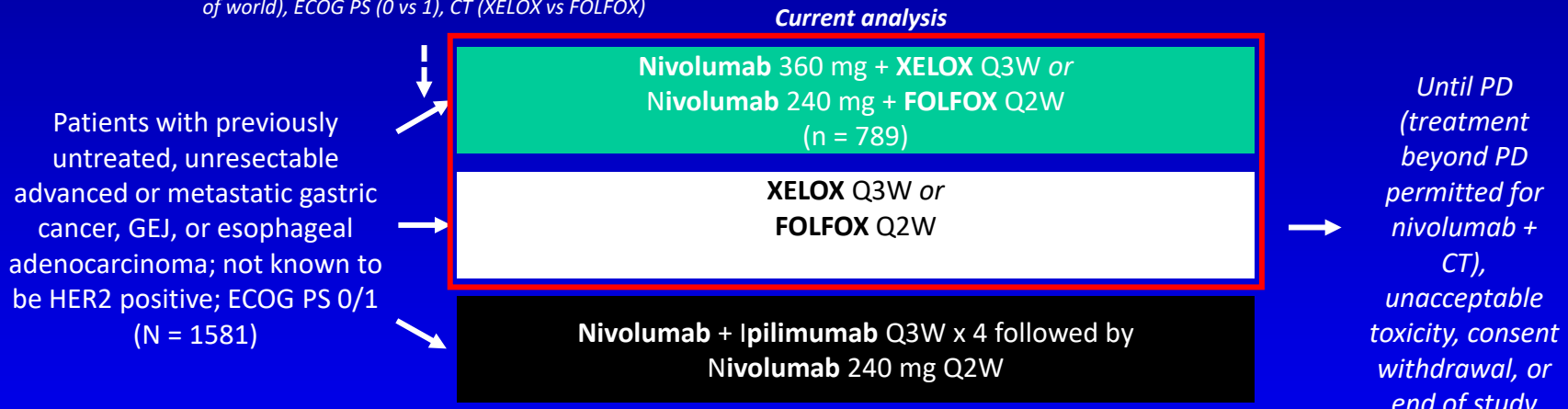
- The most common grade 3–5 adverse events of any cause were anemia (95 [12%] of 785 participants in the pembrolizumab group *vs* 76 [10%] of 787 participants in the placebo group) and decreased neutrophil count (77 [10%] *vs* 64 [8%]).
- Serious treatment-related adverse events occurred in 184 (23%) participants in the pembrolizumab group and 146 (19%) participants in the placebo group. Treatment-related deaths occurred in eight (1%) participants in the pembrolizumab group and 16 (2%) participants in the placebo group.
- No new safety signals were identified.

Lancet Oncol. 2023 Nov;24(11):1181-1195

CheckMate 649

- International, randomized, open-label phase III trial

Stratified by PD-L1 (≥1% vs <1%), region (Asia vs US/Canada vs rest of world), ECOG PS (0 vs 1), CT (XELOX vs FOLFOX)



- Coprimary endpoints: OS and PFS in patients with PD-L1 CPS ≥5
- Secondary endpoints: OS and PFS in all randomized patients and patients with PD-L1 CPS ≥10 and ≥ 1, BICR-assessed ORR

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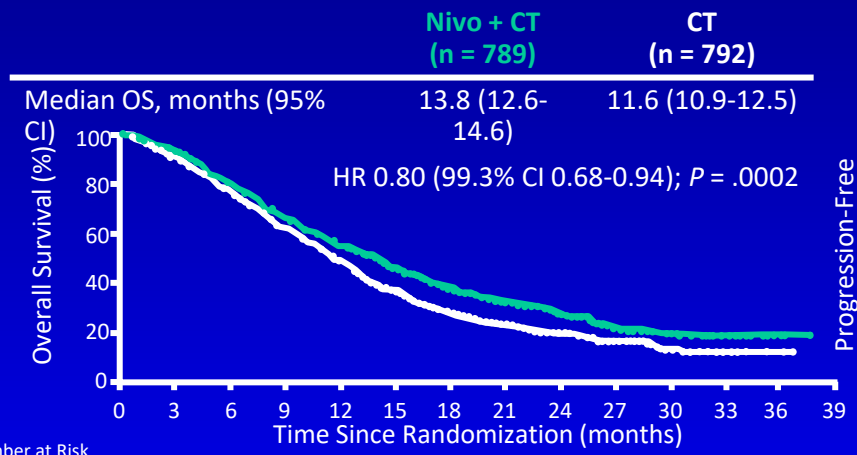
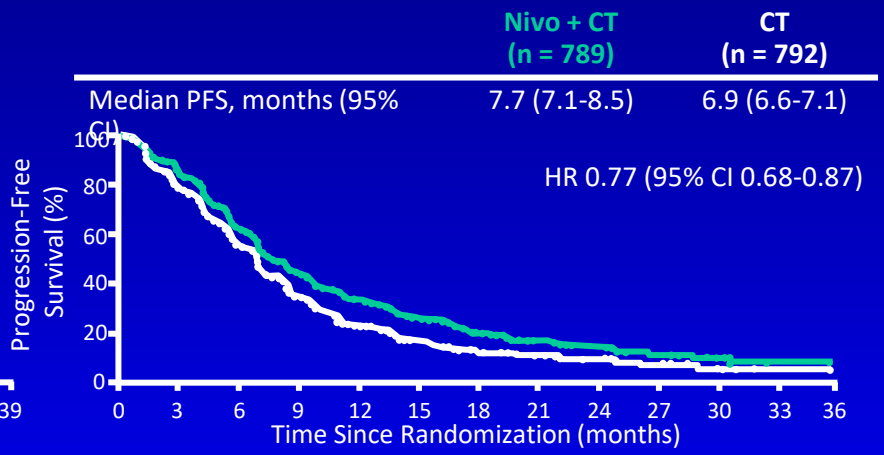
https://doi.org/10.1200/JCO.23.01601

CheckMate 649: Overall OS and PFS





Number at Risk (Number Censored)

Nivolumab plus chemotherapy	789 (0)	731 (4)	621 (13)	506 (16)	420 (20)	308 (63)	226 (90)	147 (167)	100 (167)	49 (201)	34 (212)	14 (231)	2 (243)	0 (245)
Chemotherapy alone	792 (0)	607 (17)	586 (22)	469 (29)	359 (34)	239 (68)	160 (94)	94 (136)	59 (157)	35 (172)	15 (187)	7 (194)	2 (199)	0 (201)

Nivolumab plus chemotherapy	789 (0)	639 (38)	429 (84)	287 (105)	197 (125)	136 (149)	83 (173)	51 (193)	31 (207)	15 (217)	11 (220)	1 (229)	0 (230)	
Chemotherapy alone	792 (0)	544 (92)	351 (133)	202 (155)	120 (173)	65 (199)	38 (211)	28 (216)	18 (222)	12 (225)	6 (229)	1 (234)	0 (235)	

- Minimum follow-up: 12.1 mo
- Nivolumab + CT increased OS vs CT in most prespecified subgroups

Janjigian. Lancet. 2021;[Epub].

Slide credit: clinicaloptions.com

https://doi.org/10.1200/JCO.23.01601

CheckMate 649

- 48.1 months, the median OS in the overall population was 13.7 months (95% CI, 12.4-14.5) with the combination (n = 789) vs 11.6 months (95% CI, 10.9-12.5) with chemotherapy (n = 792; HR, 0.79; 95% CI, 0.71-0.88)

- Patients with a PD-L1 CPS of 5 or greater experienced a median OS of 14.4 months (95% CI, 13.1-16.2) vs 11.1 months (95% CI, 10.1-12.1) with the combination (n = 473) and chemotherapy (n = 482), respectively (HR, 0.70; 95% CI, 0.61-0.81).

- In those with a PD-L1 CPS of 1 or higher, the median OS was 13.8 months (95% CI, 12.4-14.8) and 11.4 months (95% CI, 10.7-12.3), respectively (HR, 0.75; 95% CI, 0.67-0.85).

https://doi.org/10.1200/JCO.2024.42.3_suppl.306

Gastric Cancer

- Phase III COMPASSION-15/AK104-302 trial (NCT05008783) showed that human bispecific antibody cadonlimib (AK104) PD-1/CTLA bispecific antibody plus oxaliplatin and capecitabine regardless of PD-L1 expression
- Double blind trial randomly assigned patients (18 to 75 years) to cadonilimab plus oxaliplatin (n=305) and capecitabine versus oxaliplatin and capecitabine + placebo (n=304) in previously untreated patients
- Patients were stratified by ECOG (0 vs 1), CPS >5% or < 5%) and liver metastasis (yes vs no)

Ji J, Shen L, Li Z et. al. Cadonilimub plus chemotherapy versus chemotherapy
Presented at:2024 AACR Annual Meeting, April 5-10, 2024, Sand Diego CA

Efficacy COMPASSION-15/AK104-302

- Median OS of 15 (95%CI,12-3-19.3) compared to 10.8 months (95%CI, 9.8-12.0)
- 18 months OS rates were 45.8% versus 25.5%
- In PD-L1 CPS >5 (n=116) median OS was not reached versus 10.6 months OS (95%CI, 8.8-12.8)
- In PD-L1 CPS <5 (n=157) median OS 14.8 months compared to 11.1 months OS (95%CI, 11.8-18.8)

Ji J, Shen L, Li Z et. al. Cadonilimub plus chemotherapy versus chemotherapy
Presented at:2024 AACR Annual Meeting, April 5-10, 2024, Sand Diego CA

Safety -COMPASSION-15/AK104-302

- -No new safety signals
- -Grade 3 or higher treatment-related adverse effect occurred in 65.9% versus 53.6% of patients receiving placebo
- TRAEs led to discontinuation in 23.9% versus 6.6% of patients
- Comparable to Checkmate 649 and Keynote 859 trials

Ji J, Shen L, Li Z et. al. Cadonilimub plus chemotherapy versus chemotherapy
Presented at:2024 AACR Annual Meeting, April 5-10, 2024, Sand Diego CA

CLDN18.2

- CLDN18. 2, a targetable biomarker, is a tight junction protein confined to gastric mucosa of healthy tissue and often retained in GE/GEJ
- Zolbetuximab, a chimeric IgG1 monoclonal antibody, binds to CLDN18
- Phase 3: SPOTLIGHT (NCT03504397) and GLOW (NCT03653507)
- Spotlight – placebo controlled, double blind trial CLDN18.2+ (>75% tumor cells expression), HER2-, treatment naïve, locally unresectable or metastatic gastric or GEJ adenocarcinoma. Randomized 1:1 zolbetuximab 800mg/m2 loading dose followed by 600 mg/m2 every 3 weeks in combination with FOLFOX6 (n=279) versus placebo plus FOLFOX6 (n=278)

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CLDN18.2

- SPOTLIGHT – median OS 18.32 months (95%CI, 16.43-22.90) and 15.54 months (95%,CI,13.47-16.53) HR =0.75
- Glow – global, double blind CLDN18.2+ (>75% tumor cells expression), HER2-, treatment naïve, locally unresectable or metastatic gastric or GEJ adenocarcinoma. Randomized 1:1 zolbetuzimab 800 mg/m2 on day 1 of cycle 1 followed by 600 mg/m2 on day 1 plus CAPOX (n=254) or placebo plus CAPOX (n=253)
- GLOW – median OS 14.39 months versus 12.16 months (HR, 0.771;95%CI,0.615-0.965;P=.0118)
- Most common any grade AE nausea (82%), vomiting (67%), diarrhea (44%) and peripheral sensory neuropathy (42%)

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Nature Medicine **volume 29**, pages2133–2141 (2023)

Hepatobiliary

NCCN Guidelines Version 1.2024
Biliary Tract Cancers

PRINCIPLES OF MOLECULAR TESTING

Table 1: Recommendations for Molecular Testing in Unresectable or Metastatic Biliary Tract Cancers[a-d]

Recommended Molecular Testing	Anatomic Subsite		
	Gallbladder	Intrahepatic CCA	Extrahepatic CCA
NTRK gene fusion	X	X	X
MSI-H/dMMR	X	X	X
TMB-H	X	X	X
BRAF V600E mutation	X	X	X
FGFR2 fusion or rearrangement	–	X	X
IDH1 mutation	–	X	X
HER2 *(ERBB2)* overexpression and/or amplification	X	X	X
RET gene fusion	X	X	X
KRAS G12C	X	X	X

MSI-H: microsatellite instability-high
dMMR: mismatch repair deficient
TMB-H: tumor mutational burden-high

[a] Consider repeat biopsy or performing cfDNA analysis if initial biopsy sample yields insufficient tumor content, depending on clinical context.
[b] If unsure about the primary anatomic site within the biliary tree, comprehensive testing is recommended, including consideration of *FGFR2* fusion or rearrangement testing and *IDH1* mutation testing in gallbladder cancer or in large tumors of uncertain anatomic origin within the biliary tree.
[c] Testing for *FGFR2* fusions or rearrangements and *IDH1* mutations should be considered in patients with unresectable or metastatic gallbladder cancer.
[d] Genetic counseling referral and germline testing should be considered in patients with any of the following characteristics: young age at diagnosis; a strong personal or family history of cancer; no known risk factors for liver disease; or presence of mutations identified during tumor testing that are suspected to be possible germline alterations.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF MOLECULAR TESTING

Table 2: Incidence of Therapeutic Targets in Advanced Biliary Tract Cancers

Aberration	Approximate Incidence[e]
NTRK fusion	<1%
MSI-H/dMMR	1%–3%
TMB-H	<5%
BRAF V600E mutation	1%–5%
FGFR2 fusion or rearrangement	9%–15% of intrahepatic CCAs and rare in other subsites
IDH1 mutation	10%–20% of intrahepatic CCAs and rare in other subsites
HER2 (*ERBB2*) overexpression and/or amplification	5%–20% of CCAs, 15%–30% of gallbladder cancer
RET fusion	<1%
KRAS G12C	1%

[e] The rarity of individual subgroups limits precise incidence and frequency estimates. Incidence estimates refer to BTCs across anatomic subsites, unless otherwise stated.

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HERIZON-BTC-01 Trial

- ZW25 Zanidatamab is a biparatopic HER-2 targeted bispecific antibody that binds two non-overlapping epitopes of HER2
- Global, single arm, phase 2b trial recruited at 32 different sites
- Inclusion criteria – gemcitabine based regimen, no prior HER2 treatment,HER2+ by IHC2+ or 3+
- Primary endpoint ORR by ICR assessment, secondary endpoints DOR, DCR, PFS, safety and OS
- Median age 64 years (range 58-70), 51% had gallbladder, 29% intrahepatic cholangiocarcinoma, 20% extrahepatic cholangiocarcinoma

https://doi.org/10.1200/JCO.2023.41.16_suppl.40

HERIZON-BTC-01 Trial

- Phase 2b Herizon-BTC-01 trial (NCT044466891) previously treated patients cohort 1 (n=80) ORR 41.3% (95% CI, 30.4%-52.8%) CR=1.3 PR=40% and SD=30% PD=30%

- Median time to response 1.8 months (95% CI, 1.7-2.0), median DOR 12.9 months, 81.8% experienced duration of response of at least 16 weeks

https://doi.org/10.1200/JCO.2023.41.16_suppl.40

HERIZON-BTC-01 Trial

- Safety most common AE diarrhea (grade 1/2, 32% grade 3 5%), infusion-related grade 1/2 32%, 1%), decreased EF (6%,3%), nausea (8%,1%)

Conclusion:

- Zanidatamab demonstrated meaningful clinical benefit with a manageable safety profile in patients with treatment-refractory, HER2-positive biliary tract cancer. These results support the potential of zanidatamab as a future treatment option in HER2-positive biliary tract cancer

https://doi.org/10.1200/JCO.2023.41.16_suppl.40

Pancreatic Cancer

PRINCIPLES OF SYSTEMIC THERAPY

Metastatic Disease (First-Line Therapy)

- **Patients who progress with metastatic disease are not candidates for radiation unless required for palliative purposes.**

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Good PS 0–1	• FOLFIRINOX (category 1) or modified FOLFIRINOX[e,5] • NALIRIFOX[i,16] (category 1) • Gemcitabine + albumin-bound paclitaxel[6] (category 1) **Only for known *BRCA1/2* or *PALB2* mutations:** • FOLFIRINOX (category 1) or modified FOLFIRINOX[e,5] • Gemcitabine + cisplatin[7,8]	• Gemcitabine (category 1) • Gemcitabine + erlotinib[f,10] (category 1) • Gemcitabine + capecitabine[9] • Gemcitabine + albumin-bound paclitaxel + cisplatin[13,14] • Fluoropyrimidine + oxaliplatin ▸ CapeOx[11] (category 2B) ▸ OFF[12] (category 2B) • GTX[15] (category 2B)	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Selpercatinib (if *RET* gene fusion-positive) • Pembrolizumab[j,21] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive) (category 2B)[19,20]

Maintenance Therapy for Metastatic Disease on PANC-F (7 of 12)
Subsequent Therapy on PANC-F (8 of 12)

[e] Due to the high toxicity of this regimen, bolus 5-FU is often omitted.
[f] Although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.
[i] While NCCN recognizes that there is high-level evidence supporting the use of NALIRIFOX over gemcitabine and albumin-bound paclitaxel, it should be recognized that this regimen does not appear to have an advantage over FOLFIRINOX and adds considerably more expense compared to FOLFIRINOX.
[j] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References
Continued

Pancreatic Cancer

- Tumor/somatic molecular profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations

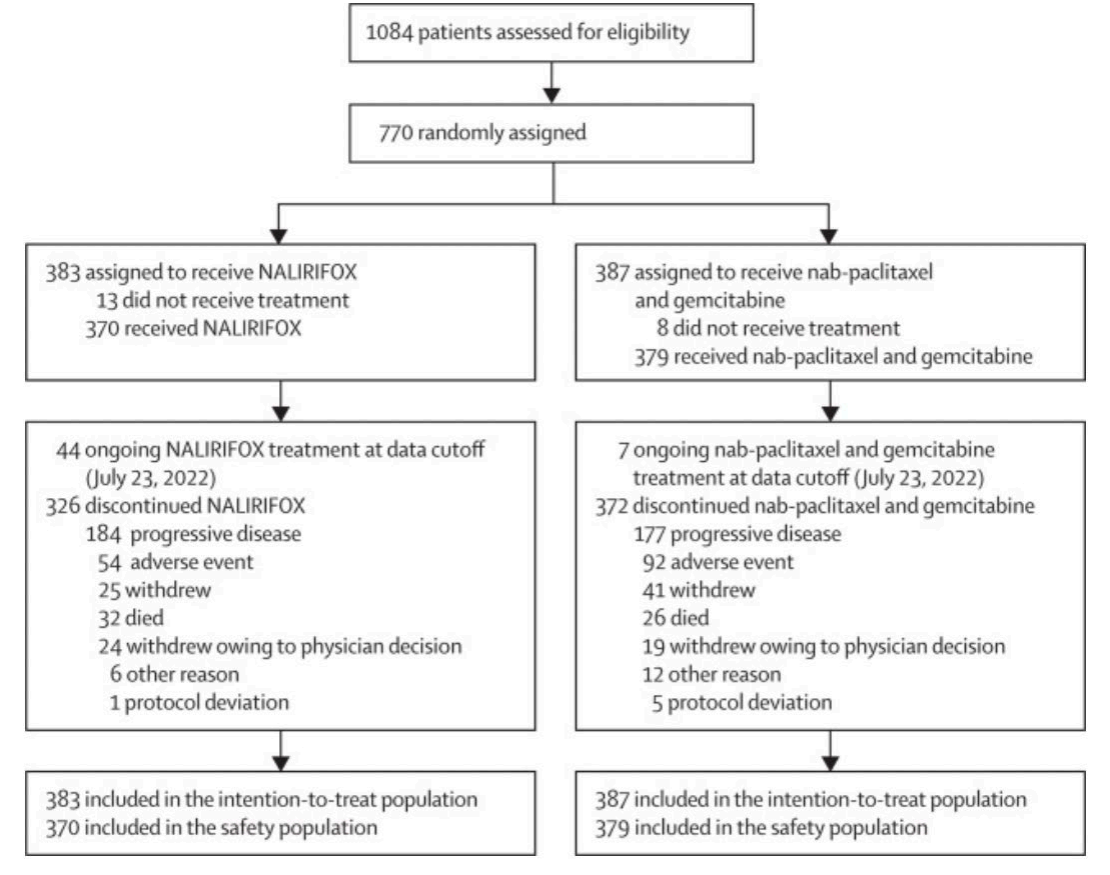
- ALK, NRG1, NTRK, ROS1, FGFR2, and RET), mutations (BRAF, BRCA1/2, KRAS, and PALB2), amplifications HER2, MSI, mismatch repair deficiency, (TMB) RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible.

Pancreatic Cancer
First Line

- Feb. 13 2024 FDA approved NALIFIRFOX – irinotecan liposomal injection,5 FU, leucovorin and oxaliplatin
- Phase III Napoli trial (NCT04083235)
- 770 patients with mPDAC 1:1 ratio to receive NALIRIFOX n=382 or standard nab-paclitaxel plus gemcitabine n=387
- Primary endpoint was overall survival in the intention to treat population

Lancet. 2023 Oct 7;402(10409):1272-1281.

Napoli Trial



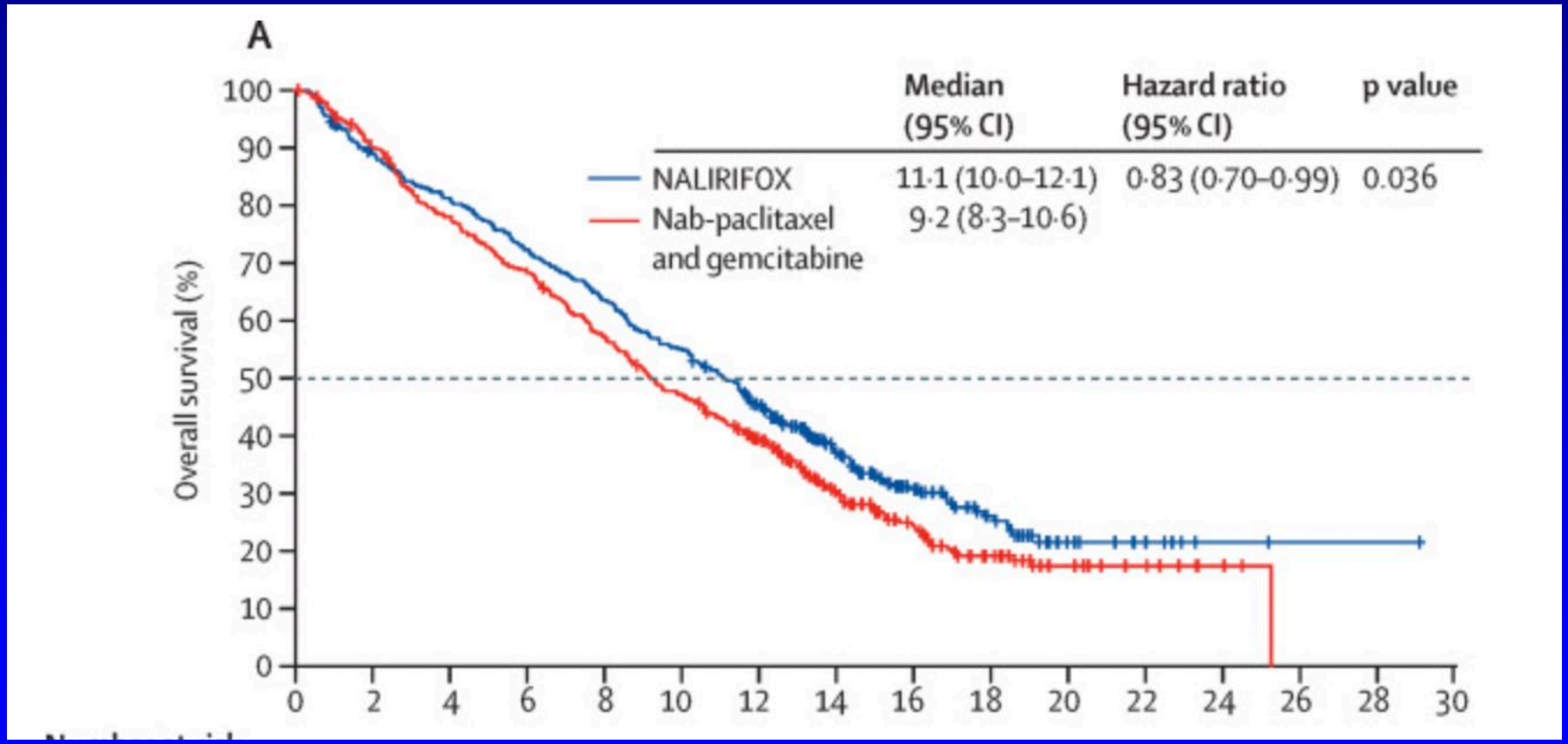
Lancet2023 Oct 7;402(10409):1272-1281.

Efficacy

- Median follow up 16.1 months – NALIRIFOX delivered 11.1 versus 9.2 months (HR 0.83)
- 18 months OS 26.2% (95% CI, 20.9%-31.7) versus 19.3% (95%CI,14.8%-24.2%)
- Median PFS 7.4 months (95% CI,6.0-7.7) versus 5.6 months (95%CI;5.3-5.8)
- NALIRIFOX ORR 41.8% versus 36.2%

Lancet. 2023 Oct 7;402(10409):1272-1281

Efficacy



Lancet. 2023 Oct 7;402(10409):1272-1281

AE

Table 3. Duration of treatment, exposure, and overview of TEAEs in the safety population.

	NALIRIFOX (n=370)	Nab-paclitaxel and gemcitabine (n=379)
Median duration of treatment, weeks	24·3 (0·4–100·9; 8·4–42·1)	17·6 (0·7–81·7; 8·1–30·1)
Median number of treatment cycles	5·0 (1–24; 2–10)	4·0 (1–20; 2–7)
Any dose reductions	220 (60%)	204 (54%)
TEAEs		
Any TEAE	369 (>99%)	376 (99%)
Any treatment-related TEAE	352 (95%)	352 (93%)
Grade ≥3 TEAE	322 (87%)	326 (86%)
Grade ≥3 treatment-related TEAE	262 (71%)	258 (68%)
Any TEAE leading to discontinuation	118 (32%)	112 (30%)
Any treatment-related TEAE leading to discontinuation	94 (25%)	88 (23%)
Any TEAE leading to dose reduction	208 (56%)	190 (50%)
Any treatment-related TEAE leading to dose reduction	198 (54%)	184 (49%)
Any serious TEAEs	201 (54%)	195 (52%)
Any treatment-related serious TEAEs	98 (27%)	72 (19%)
TEAEs leading to death	22 (6%)	23 (6%)

Lancet. 2023 Oct 7;402(10409):1272-1281.

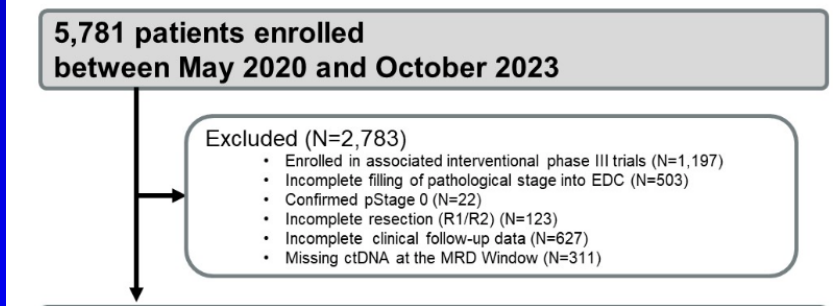
Colorectal Cancer

ctDNA as a Prognostic Marker in CRC

GALAXY: Analysis of ctDNA Dynamics in Resected CRC With MRD

- Prospective, observational study designed to assess association between postsurgical ctDNA and DFS in patients with stage I to IV resectable CRC

- A personalized, tumor-informed assay (Signatera™, Natera, Inc.) was used for the detection and quantification of ctDNA in serial plasma samples collected at 1, 3, 6, 9, 12, 18, and 24 months after surgery until recurrence.
- We investigated the association between ctDNA status and recurrence.



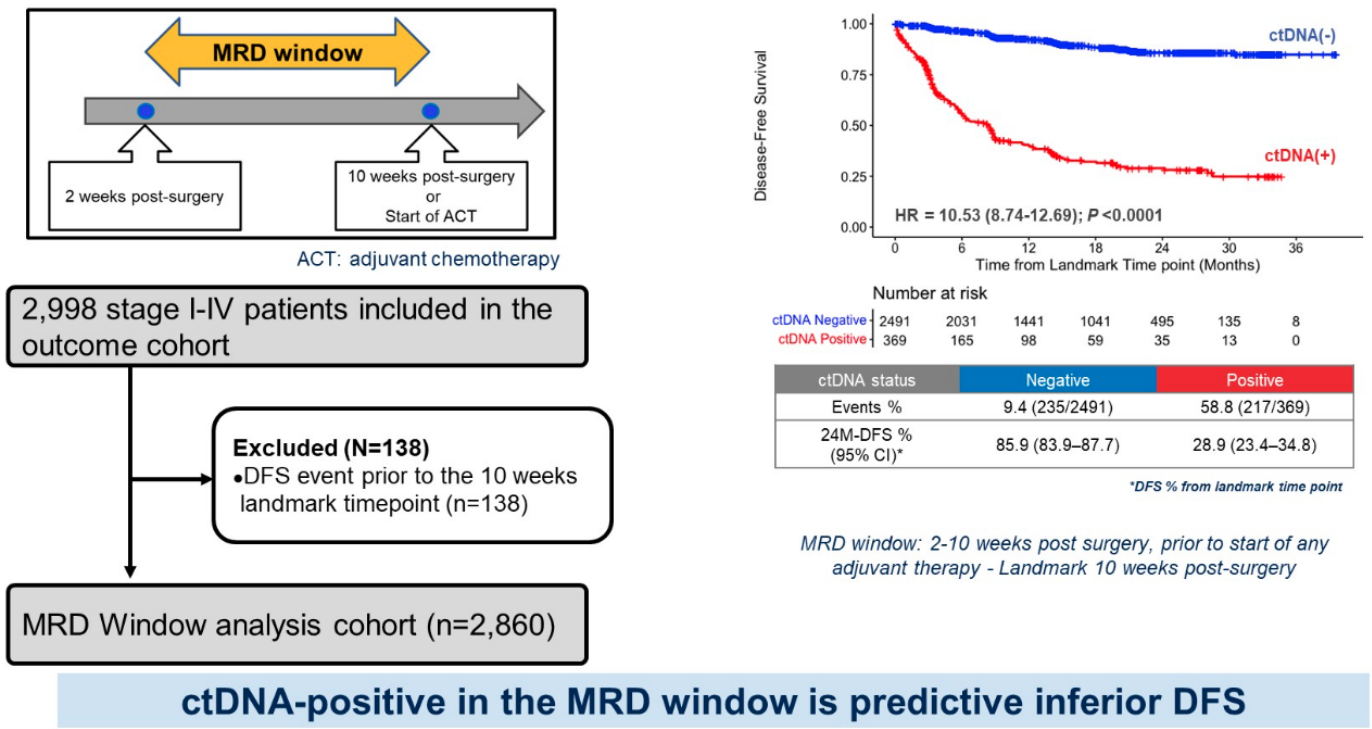
Characteristic	N = 2,998[1]
Age	69 (23 - 95)
Gender	
Male	1,622 (54%)
Female	1,376 (46%)
Performance Status	
0	2,700 (90%)
1	298 (10%)
Tumor Location	
Right-sided colon	938 (33%)
Left-sided colon	1,376 (48%)
Rectum	553 (19%)
Unknown	131
Pathological T Stage	
T1-T2	592 (20%)
T3-T4	2,351 (80%)
Unknown	55
Pathological N Stage	
N0	1,449 (49%)
N1-N2	1,493 (51%)
Unknown	56
Pathological Stage	
I	415 (14%)
II	901 (30%)
III	1,231 (41%)
IV	451 (15%)

Characteristic	N = 2,998[1]
Neoadjuvant Treatment	
Neoadjuvant Chemotherapy	315 (11%)
Upfront Surgery	2,683 (89%)
Adjuvant Treatment	
Adjuvant Chemotherapy	1,130 (38%)
Observation	1,868 (62%)
Adjuvant Treatment Duration	
3 months	361 (32%)
6 months	458 (40%)
<3 or >6 months	311 (28%)
***BRAF* status**	
BRAF^{wt}	2,638 (93%)
BRAF^{V600E}	205 (7%)
Unknown	155
***RAS* status**	
RAS^{wt}	1,622 (57%)
RAS^{mut}	1,231 (43%)
Unknown	145
MSI status	
MSS or MSI-Low	2,686 (91%)
MSI-High	280 (9%)
Unknown	32
Clinical or Radiological Recurrence	
Recurrence	530 (18%)
No Recurrence	2,468 (82%)
Total Follow-up (months)	16.1 (0.2 - 42)

[1]Median (Range); n (%)

Yukami. ASCO GI 2024. Abstr 6

GALAXY: DFS by ctDNA Status, All Stages (MRD Window)



Yukami. ASCO GI 2024. Abstr 6.

GALAXY: Investigator Conclusions

- In this analysis of the GALAXY study, ctDNA detection had prognostic value and predicted lower DFS after adjuvant chemotherapy at 24 mo in patients with stage I to IV resectable CRC (N = 2998)
  - Sustained ctDNA clearance after adjuvant chemotherapy associated with >90% DFS; transient ctDNA clearance and noncleared ctDNA after adjuvant chemotherapy associated with poorer prognosis
  - In patients of transient ctDNA clearance who experienced clinical or radiographic recurrence, 98% experience molecular recurrence by 18 mo
- Patients with post surgery ctDNA had significantly lower DFS vs ctDNA-negative patients at 24 mo (29% vs 86%)
- ctDNA concentration reduction (MTM/mL) at 6 mo a predictor of clinical outcomes
- Ongoing trials underway to further assess value of ctDNA-guided adjuvant therapy strategies

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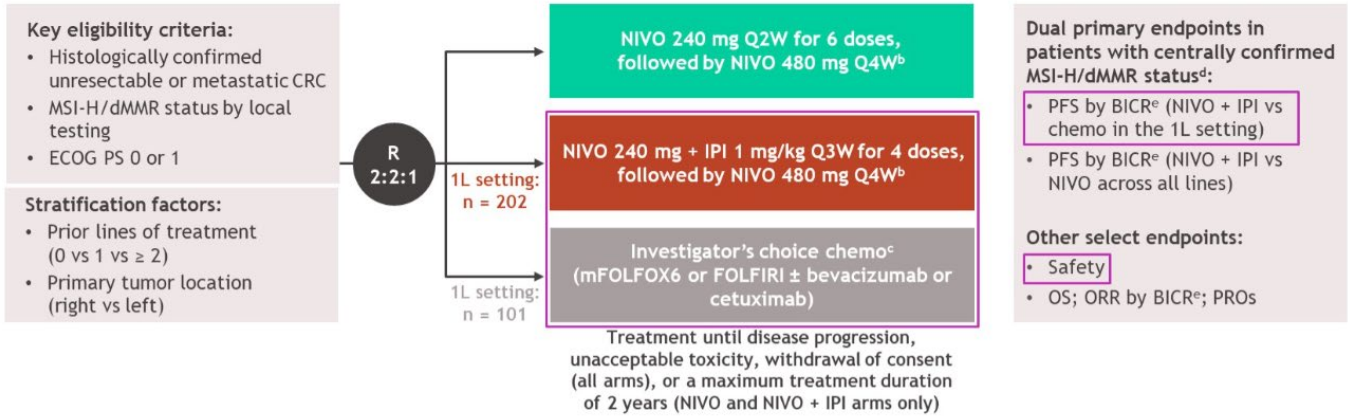
CheckMate 8HW: Nivolumab + Ipilimumab vs CT for Advanced MSI-H/dMMR CRC

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]



- At data cutoff (October 12, 2023), the median follow-up[f] was 24.3 months

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients receiving investigator's choice of chemotherapy are eligible to receive NIVO + IPI upon progression (crossover treatment). [d]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [e]Evaluated using RECIST v1.1. [f]Time between randomization and last known date alive or death.

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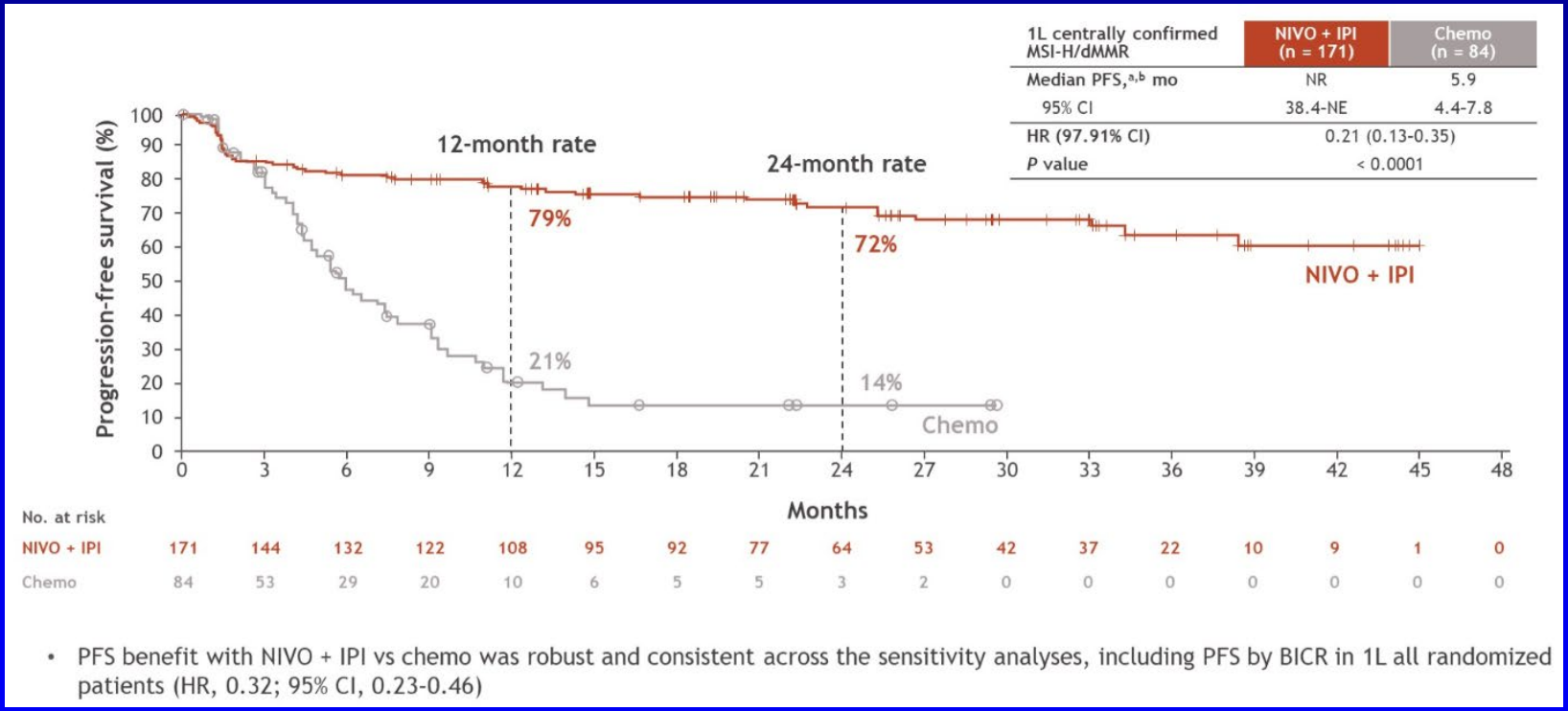
CheckMate 8HW: PFS



- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23-0.46)

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CheckMate 8HW: Baseline Characteristics

Characteristic (1L all randomized patients)	Category	NIVO + IPI (n = 202)	Chemo (n = 101)
Age	Median (range), years	62 (21-86)	65 (26-87)
	< 65 years	117 (58)	46 (46)
Sex	Male	95 (47)	45 (45)
Region	US/Canada/Europe	133 (66)	71 (70)
	Asia	19 (9)	11 (11)
	Rest of world	50 (25)	19 (19)
ECOG PS	0	111 (55)	52 (51)
Disease stage at initial diagnosis[a]	Stage IV	85 (42)	49 (49)
Tumor sidedness	Right	138 (68)	68 (67)
Sites of metastases[b,c]	Liver	76 (38)	42 (42)
	Lung	44 (22)	25 (25)
	Peritoneum	84 (42)	43 (43)
Centrally confirmed MSI-H/dMMR status	Yes	171 (85)	84 (83)
	No	31 (15)	17 (17)
Tumor cell PD-L1[d,e]	< 1%	145 (72)	80 (79)
	≥ 1%	43 (21)	12 (12)
BRAF, *KRAS*, *NRAS* mutation status[e,f]	*BRAF*/*KRAS*/*NRAS* all wild-type	47 (23)	23 (23)
	BRAF mutant	52 (26)	24 (24)
	KRAS or *NRAS* mutant	43 (21)	21 (21)
	Unknown	55 (27)	31 (31)
Clinical history of Lynch syndrome[e,g]	Yes	22 (11)	17 (17)
	No	135 (67)	49 (49)
	Reported as unknown	44 (22)	30 (30)
Prior surgery related to current cancer	Yes	174 (86)	84 (83)
	No	28 (14)	17 (17)

Data are shown as n (%) unless otherwise noted. [a]All patients had stage IV disease at study entry. [b]Per BICR. [c]Metastases not reported in 3 patients in the NIVO + IPI arm. [d]Tumor cell PD-L1 expression indeterminate, not evaluable, or not available: NIVO + IPI, n = 14; chemo, n = 9. [e]Percentages may not add up to 100% due to rounding. [f]*BRAF* and *KRAS*/*NRAS* mutant: NIVO + IPI, n = 5; chemo, n = 2. [g]Patients with Lynch syndrome not reported: NIVO + IPI, n = 1; chemo, n = 5.

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CheckMate 8HW: Investigator Conclusions

- In the phase III CheckMate 8HW study in patients with advanced MSI-H/dMMR CRC, first-line nivolumab + ipilimumab was associated with improved PFS vs chemotherapy + bevacizumab or cetuximab (HR 0.21, *P* <.0001)
  - 24-mo PFS rates: 72% vs 14%
  - Sustained PFS curve separation beginning at 3 mo
  - PFS improvement observed with all subgroups assessed, including *RAS*-mutated CRC
- Nivolumab + ipilimumab associated with a lower rate of grade ≥3 TRAEs; no new safety signals identified
- Investigators concluded that data support first-line nivolumab + ipilimumab as an SOC for advanced MSI-H/dMMR CRC
  - Study ongoing to assess OS and PFS comparison with nivolumab

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Botensilimab (AGEN1181) with Balstilimab (AGEN2034)

- Phase 1a/1b trial (NCT03860272) showed that the Fc-enhanced, next-generation CTLA-4 inhibitor botensilimab in combination with the PD-1 inhibitor balstilimab inhibitor generated a response rate of 23% (95% CI, 14%-34%) in patients with heavily pretreated pMMR/MSS metastatic CRC.
- A total of 67% of patients with microsatellite stable (MSS) CRC (n = 9) experienced pathologic responses, defined as tumor reduction of at least 50%, and 100% of patients with microsatellite instability–high (MSI-H) CRC (n = 3) experienced major pathologic responses, defined as tumor reduction of at least 90%

Oncogene. 2023; 42(44): 3252–3259

Summary

- Gastric cancer early stage benefit from immunotherapy pending further results (Matterhorn)
- Metastatic setting immunotherapy benefit confirmed in PDL1 expression > 1 (Keynote 859 and CheckMate 649)
- New agents on horizon Zolbetuximab (CLDN18.2 inhibitor) and cadonilimab (human bispecific antibody PD-1/CTLA) show benefit
- In HER2 positive hepatobiliary zanidatamab is a biparatopic HER-2 targeted bispecific antibody shows efficacy
- In metastatic pancreatic NAPOLI trial established benefit of NALIFIRFOX and now NCCN recommended in first line

Summary

- Galaxy showed that ctDNA detection had prognostic value and predicted lower DFS after adjuvant chemotherapy at 24 mo in patients with stage I to IV resectable CRC
- Phase III CheckMate 8HW study in patients with advanced MSI-H/dMMR CRC, first-line nivolumab + ipilimumab was associated with improved PFS vs chemotherapy + bevacizumab or cetuximab
- Fc-enhanced, next-generation CTLA-4 inhibitor botensilimab in combination with the PD-1 inhibitor balstilimab inhibitor shows promising responses in MSS heavily pretreated patients