Taipei Veterans General Hospital Practices Guidelines for

Small Intestine

(Duodenal cancer ; Ampulla of Vater cancer)

2014年06月10日制定

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Multidisciplinary Team

- **Surgical Oncologists specialized in Periampullary Cancer**
- **Gastroenterologists**
- **Medical Oncologists**
- **Radiation Oncologists**
- **Pathologists**
- **Diagnostic Radiologists**
- **Hospice Specialists**
- **Pharmacists**
- **Nurses (for specialized)**
- **Social Workers**
- **Dietitians (for Nutrition Support)**

Taipei VGH Periampullary Cancer Panel Members

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- **Nuclear Medicine Specialist**

  林可瀚*

- **Pathologist**

  楊清越*

- **Pharmacist**

  胡晉嘉*

* 核心成員

Pretreatment work-ups

- **History and physical exam**
- **CBC, platelets, chemistry profile and PT/APTT**
- **Abdominal CT with IV contrast**
- **Chest imaging**
- **Tumor markers: CEA, CA19-9**
- **Biopsy confirmation**
- **Optional studies**
  - EUS
  - Endoscopic retrograde cholangiopancreatography (ERCP)
  - MRI/MRCP
  - Whole body bone scan
  - Upper GI panendoscopy
  - PET/CT scan
  - Cardiac function (cardiac ultrasound and/or ejection fraction + wall motion)
  - Pulmonary function test (if age > 65 and prepare for surgery)
  - **Consider genetic testing for inherited mutations**
    - *ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11,* and *TP53*

(patients with positive pathogenic mutation/family history of pancreatic/ampullary cancer)
NCCN V1.2022-March 9, 2022

Duodenal cancer
TNM Staging System: UICC/AJCC 2017 8th Edition

- **Primary Tumor (T)**
  - **TX:** Primary tumor cannot be assessed
  - **T0:** No evidence of primary tumor
  - **Tis:** Carcinoma *in situ*
  - **T1a:** Tumor invades lamina propria
  - **T1b:** Tumor invades submucosa
  - **T2:** Tumor invades muscularis propria
  - **T3:** Tumor invades through the muscularis propria into the subserosa or into the nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration
  - **T4:** Tumor perforates the visceral peritoneum or directly invades other organs or structures (includes other loops of small intestine, mesentery, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct)
- **Regional lymph nodes (N)**
  - **NX:** Regional lymph nodes cannot be assessed
  - **N0**: No regional lymph node metastasis
  - **N1**: Regional lymph node metastasis (1-2)
  - **N2**: Regional lymph node metastasis (> 2)
- **Distant metastasis (M)**
  - **M0:** No distant metastasis
  - **M1**: Distant metastasis

General Notes:

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r“ prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

Duodenal cancer
TNM Staging System: UICC/AJCC 2017 (8th Edition)

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4	N0	M0
Stage IIIA	Any T	N1	M0
Stage IIIB	Any T	N2	M0
Stage IV	Any T	Any N	M1

Ampulla of Vater cancer
TNM Staging System: UICC/AJCC 2017 8th Edition

- **Primary Tumor (T)**
  - **TX:** Primary tumor cannot be assessed
  - **T0:** No evidence of primary tumor
  - **Tis:** Carcinoma *in situ*
  - **T1a:** Tumor limited to ampulla of Vater or sphincter of Oddi
  - **T1b:** Tumor invades beyond the sphincter of Oddi or into the duodenal subucosa
  - **T2:** Tumor invades into the **muscularis propria** of the duodenum
  - **T3a:** Tumor invades pancreas (up to 0.5 cm)
  - **T3b:** Tumor invades pancreas (more than 0.5 cm)
  - **T4:** Tumor invades celiac axis, SMA, or common hepatic artery
- **Regional lymph nodes (N)**
  - **NX:** Regional lymph nodes cannot be assessed
  - **N0**: No regional lymph node metastasis
  - **N1**: Regional lymph node metastasis (1-3)
  - **N2**: Regional lymph node metastasis (> 3)
- **Distant metastasis (M)**
  - **M0:** No distant metastasis
  - **M1**: Distant metastasis

General Notes:

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

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a prefix designates the stage determined at autopsy: aTNM.

Ampulla of Vater cancer
TNM Staging System: UICC/AJCC 2017 (8th Edition)

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage 1B	T1b	N0	M0
	T2	N0	M0
Stage IIA	T3a	N0	M0
Stage IIB	T3b	N0	M0
Stage IIIA	T1a – T3b	N1	M0
Stage IIIB	T4	Any N	M0
	Any T	N2	M0
Stage IV	Any T	Any N	M1

Histological feature

GX Grade cannot be assessed

G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

G4 Undifferentiated

High Risk Features in stage II duodenal cancer

Histological feature

G3 Poorly differentiated

G4 Undifferentiated

Resection margin

Lymph node status

<5 lymph nodes examined

Tumor perforation

Lympho-vascular or perineural invasion

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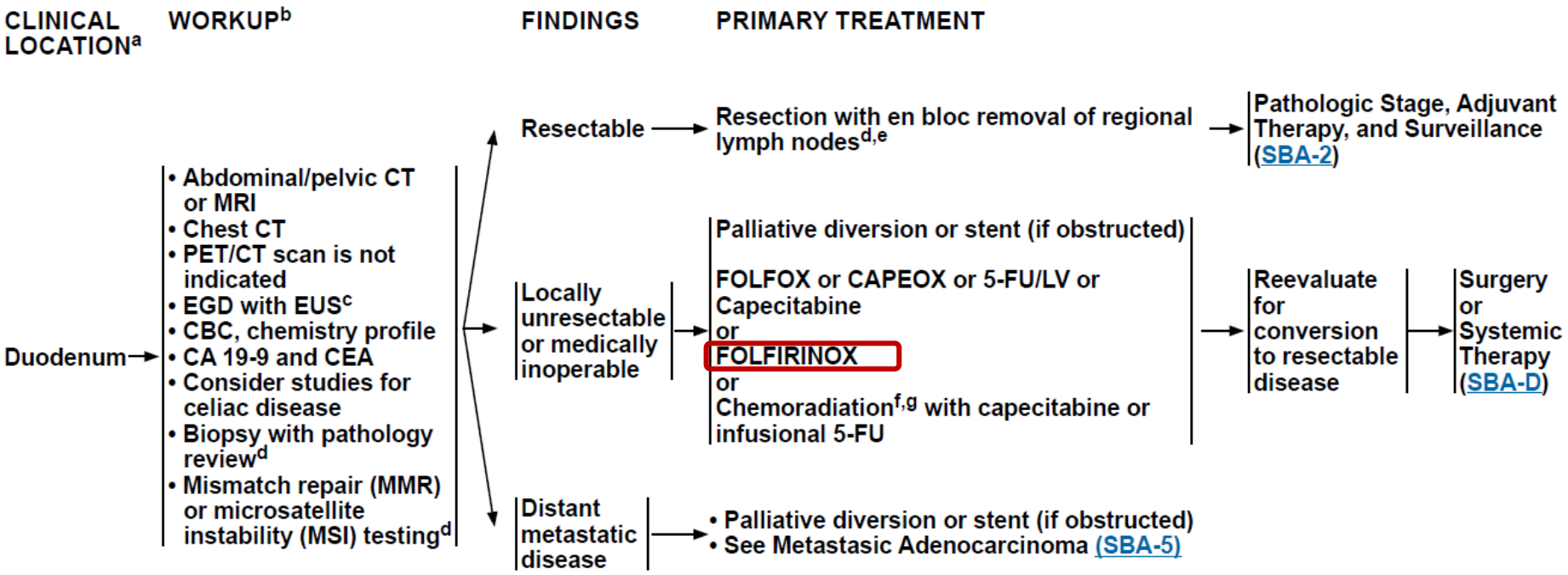
Small Bowel Adenocarcinoma



- General -- FOLFOXIRI replaced with FOLFIRINOX
- Universal MMR or MSI testing is highly suggested in all newly diagnosed patients with SBA

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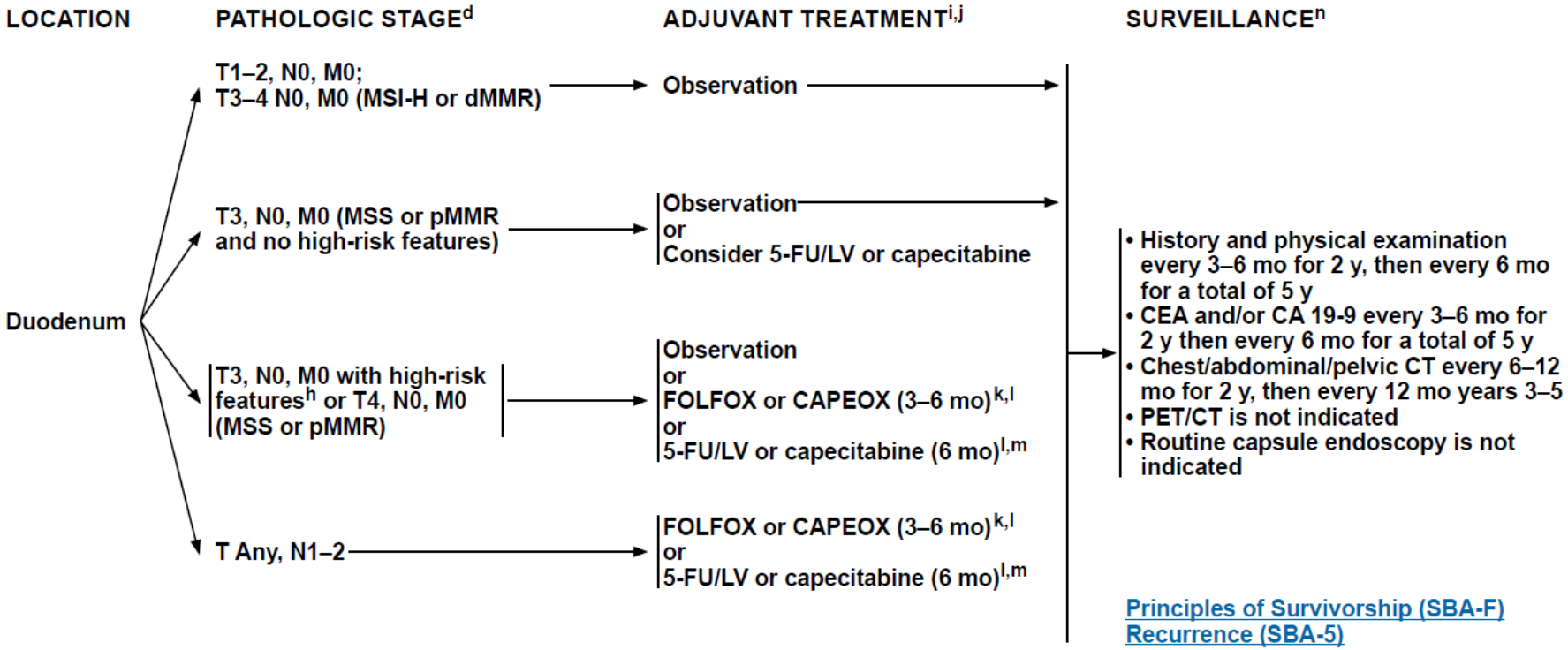

High-risk features in stage II SBA include :

- **Close or positive resection margins,**
  - **Consider sequential chemoradiation with capecitabine or infusional 5-FU if positive margin**
- **<5 lymph nodes examined if duodenal location or <8 lymph nodes examined if jejunal/ileal primary tumor location**
- **Tumor perforation.**

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Small Bowel Adenocarcinoma

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

PATIENT STATUS	INITIAL THERAPY	SUBSEQUENT THERAPY[i]
Intensive therapy recommended	FOLFOX[d] ± bevacizumab[e] or CAPEOX[d] ± bevacizumab[e] or FOLFIRI ± bevacizumab[e,f] or FOLFIRINOX[d] ± bevacizumab[e] or ([Nivolumab ± ipilimumab] or pembrolizumab)[g,h] (dMMR/MSI-H only) See Initial Therapy	FOLFOX[d] ± bevacizumab[e] or CAPEOX[d] ± bevacizumab[e] or FOLFIRI ± bevacizumab[e] or Taxane-based chemotherapy or ([Nivolumab ± ipilimumab] or pembrolizumab)[g,h] or dostarlimab-gxly[g,h] (dMMR/MSI-H only) See Subsequent Therapy → Best supportive care
Intensive therapy NOT recommended[c]	5-FU/LV ± bevacizumab[e] or Capecitabine ± bevacizumab[e] or ([Nivolumab ± ipilimumab] or pembrolizumab)[g,h] (dMMR/MSI-H only) See Initial Therapy	FOLFOX[d] or Irinotecan or ([Nivolumab ± ipilimumab] or pembrolizumab)[g,h] or dostarlimab-gxly[g,h] (dMMR/MSI-H only) See Subsequent Therapy → Taxane-based chemotherapy or Best supportive care

Patient with prior oxaliplatin exposure or contraindication (SBA-D 2 of 7)

Regimen Dosing (SBA-D 4 of 7)

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Small Bowel Adenocarcinoma

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

PATIENT STATUS	INITIAL THERAPY	SUBSEQUENT THERAPY[i]
Patient with prior oxaliplatin exposure in the adjuvant setting or contraindication	FOLFIRI ± bevacizumab[e] or Taxane-based chemotherapy or ([Nivolumab ± ipilimumab] or pembrolizumab)[g,h] or dostarlimab-gxly[g,h] (dMMR/MSI-H only)	Best supportive care See Initial Therapy

High Risk Features in ampulla vater cancer

Histological feature

G3 Poorly differentiated

G4 Undifferentiated

Resection margin

R1 or R2 resection

TNM stage: ≥T2

Lymph node status

Any positive lymph node

<5 lymph nodes examined

Tumor perforation

Lympho-vascular or perineural invasion

Histological type

Pancreato-biliary (CDX-negative, MUC1-positive)

Intestinal(CDX-positive, MUC1-negative)

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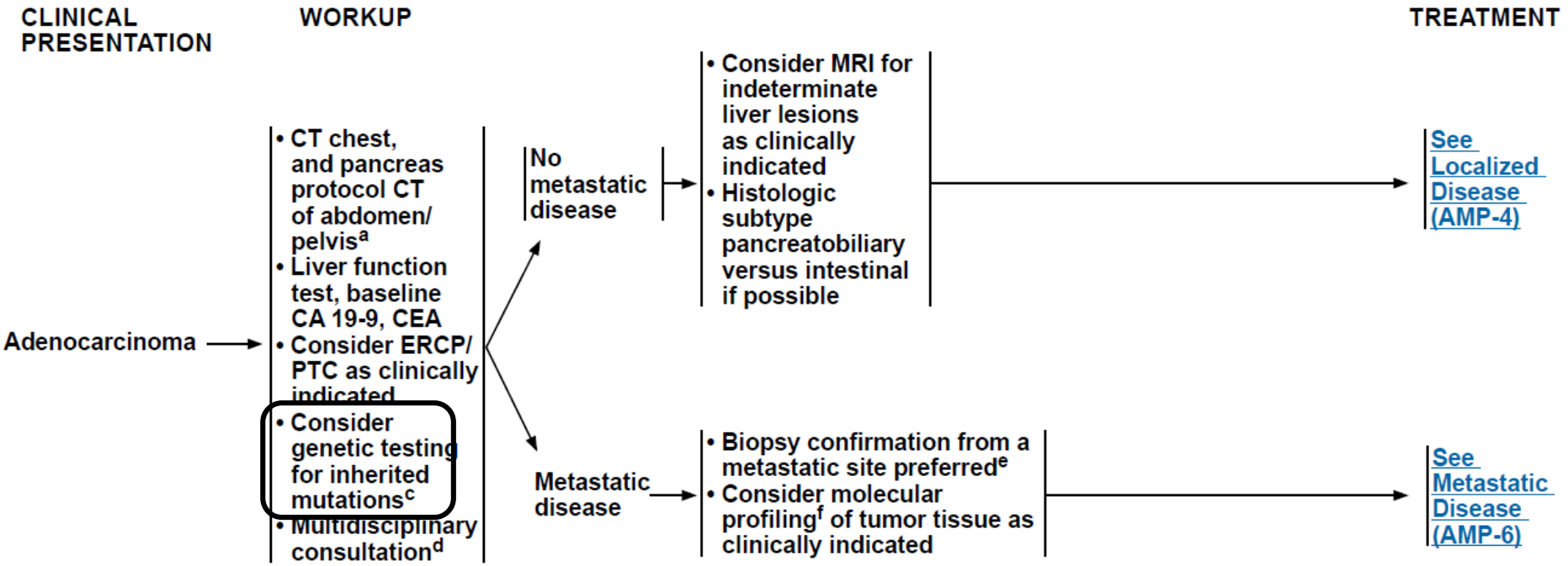
Ampullary Adenocarcinoma



Genetic counseling (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11,* and *TP53*) is recommended:

- Patients who test positive for a pathogenic mutation
- Patients with a positive family history of cancer, especially pancreatic/ampullary cancer, regardless of mutation status.

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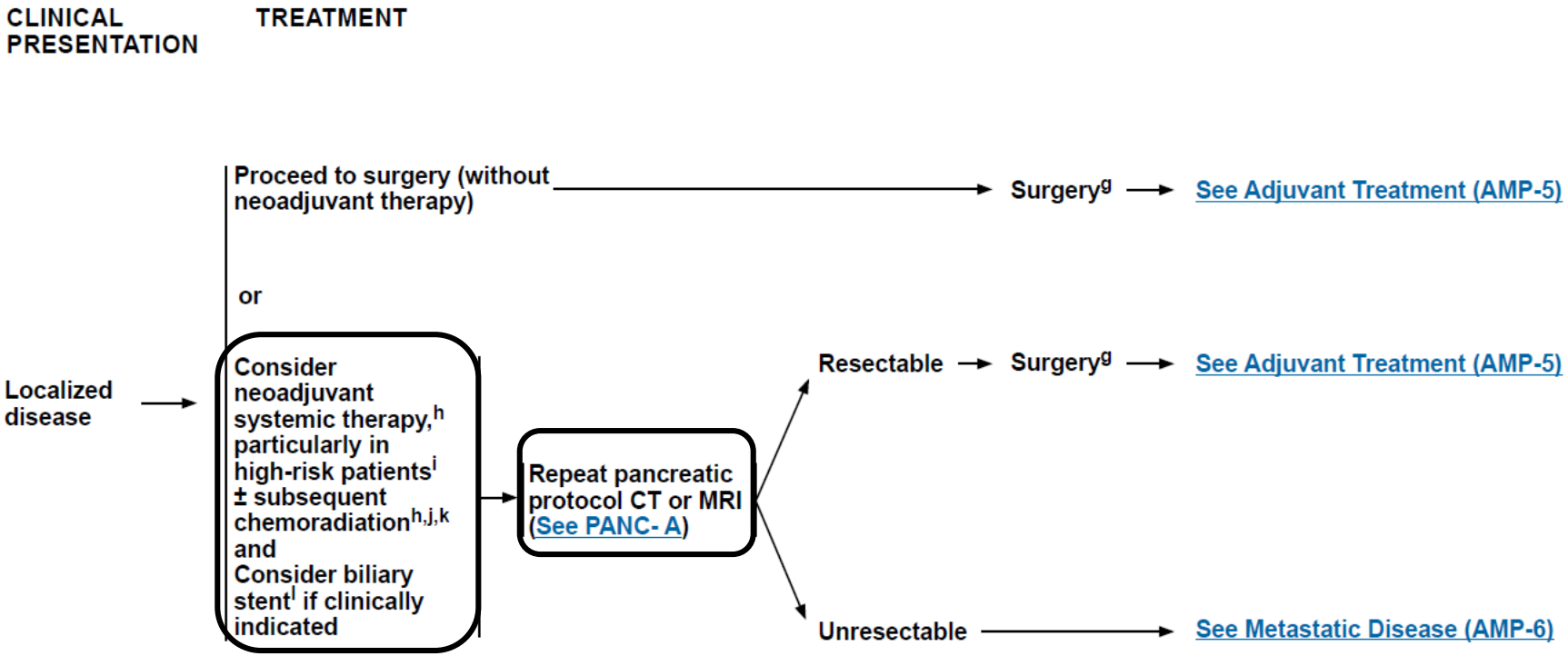
Ampullary Adenocarcinoma



High-risk features:
imaging findings, markedly elevated CA 199, markedly elevated carcinoembryonic antigen (CEA), large primary tumors, large regional lymph nodes, excessive weight loss, and extreme pain.

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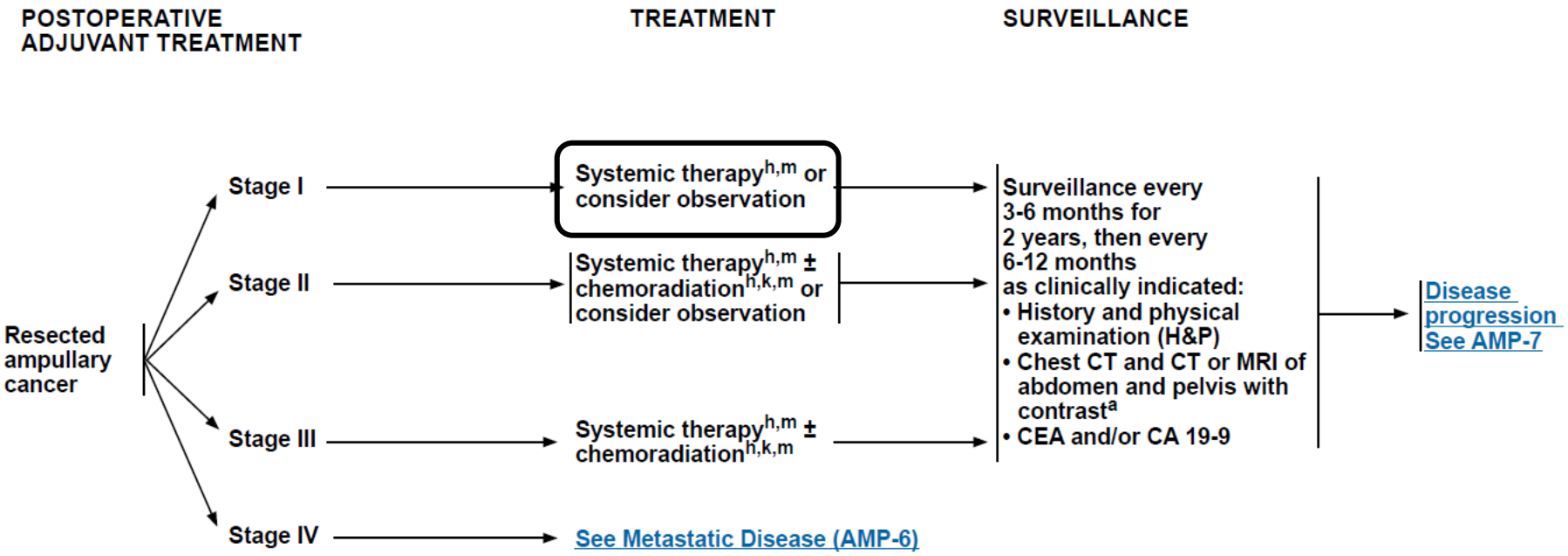

- **Stage I with high-risk feature: consider systemic therapy**
  - **See page 16**
- **Initiation of adjuvant systemic therapy is recommended within 12 weeks of surgery if the patient is medically fit.**
- **The optimal duration of treatment is 4 to 6 months.**

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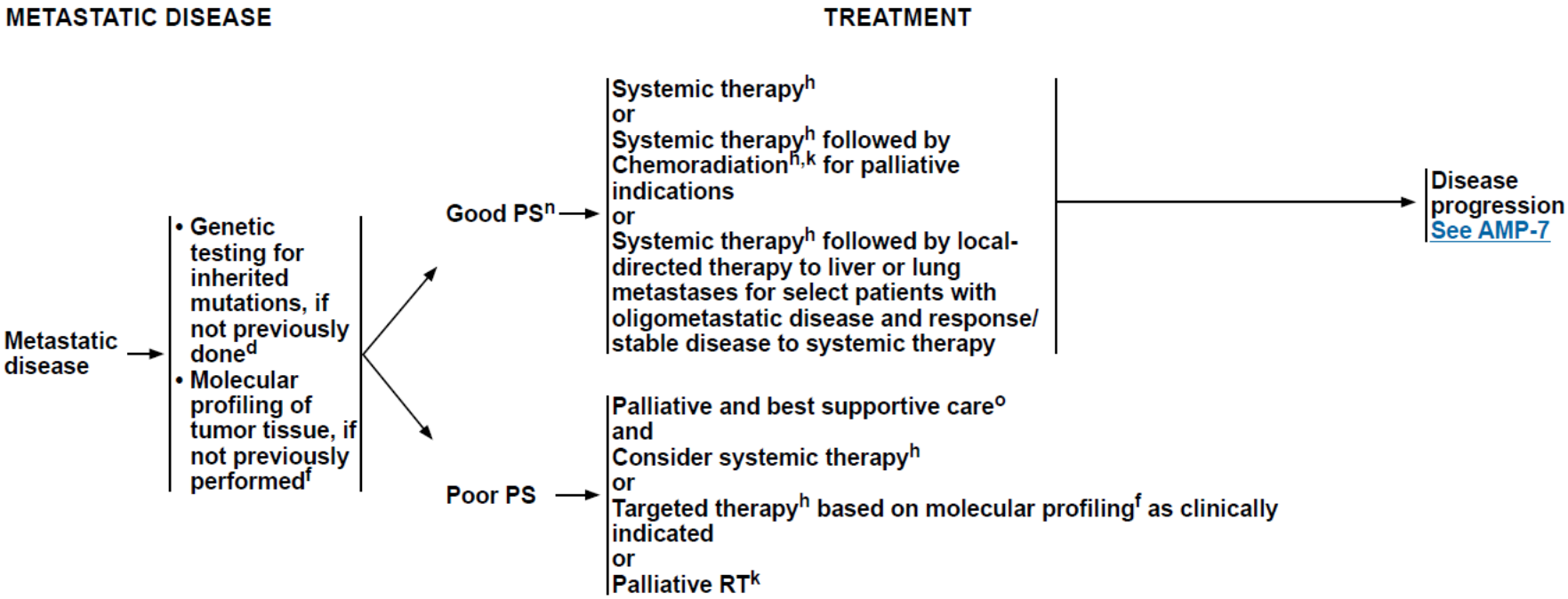
Ampullary Adenocarcinoma



Good PS is defined as :

- **ECOG 0–1**
- **Good biliary drainage**
- **Adequate nutritional intake**

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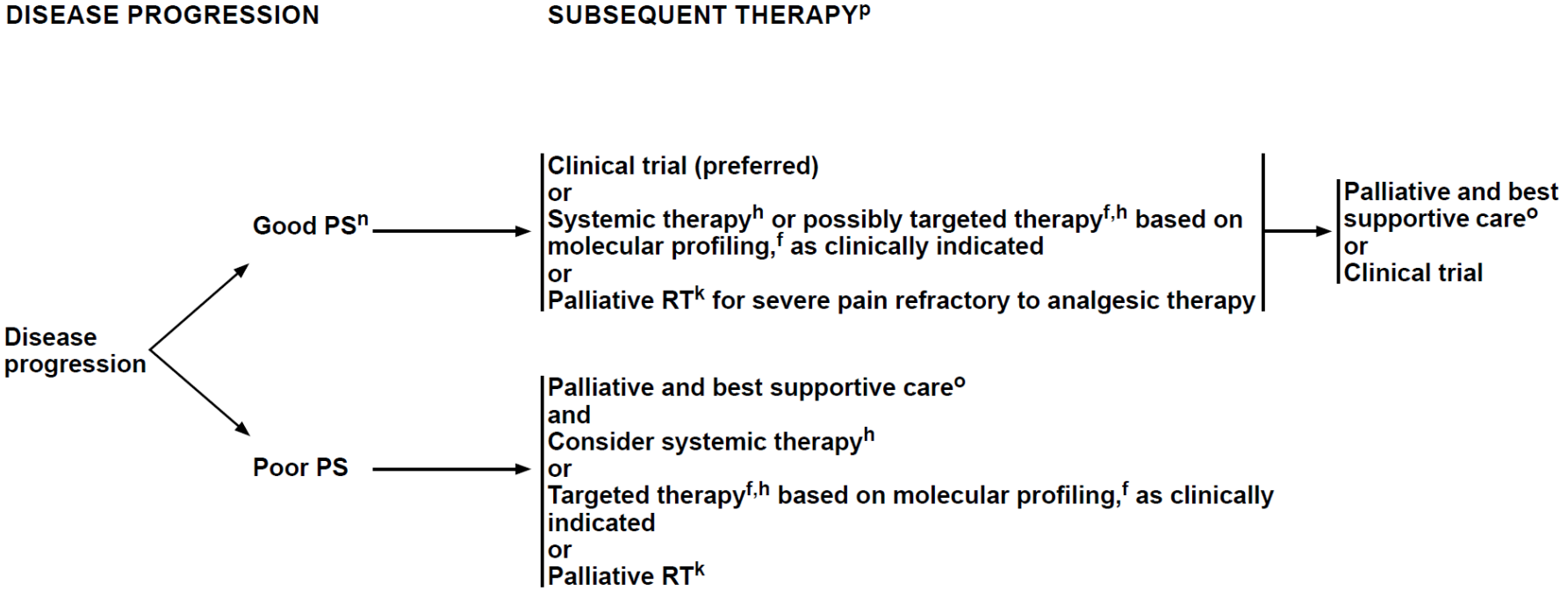
Ampullary Adenocarcinoma



Good PS: Defined as ECOG 0–1, with good biliary drainage and adequate nutritional intake.

Consider specifically testing for potentially actionable somatic findings including, but not limited to:

- **Fusions (*ALK, NRG1, NTRK, ROS1, FGFR2, RET*), mutations (*BRAF, BRCA1/2, KRAS, PALB2*)**
- **Amplifications (*HER2*)**
- **Microsatellite instability (MSI) and/or mismatch repair (MMR) deficiency.**

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Ampullary Adenocarcinoma

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.

	Pancreatobiliary/Mixed Type	Intestinal Type	Useful in Certain Circumstances
Good PS[f]	• FOLFIRINOX[a] or modified FOLFIRINOX[a,g,7] • Gemcitabine + albumin-bound paclitaxel[8] • Gemcitabine + cisplatin[5] • Gemcitabine + capecitabine • FOLFOX	• FOLFOXIRI ± bevacizumab[h] • FOLFOX ± bevacizumab[h] • FOLFIRI ± bevacizumab[h] • CapeOx ± bevacizumab[h]	• Pembrolizumab[j] (if MSI-H, dMMR or TMB-H [≥10 mut/Mb]) • Nivolumab + ipilimumab[j] (if MSI-H or dMMR, for intestinal type only)
Poor PS	• Gemcitabine • Capecitabine • 5-FU + leucovorin For select patients with ECOG 2 consider multi-agent regimens[i]: • FOLFOX • Gemcitabine + albumin-bound paclitaxel	• 5-FU + leucovorin For select patients with ECOG 2 consider multi-agent regimens[i]: • FOLFOX ± bevacizumab[h] • FOLFIRI ± bevacizumab[h] • 5-FU ± bevacizumab[h] • Capecitabine ± bevacizumab[h] • CapeOx ± bevacizumab[h]	Pembrolizumab[j,10] (if MSI-H, dMMR or TMB-H [≥10 mut/Mb]) • Nivolumab + ipilimumab[e] (if MSI-H or dMMR, for intestinal type only) • Larotrectinib (if *NTRK* gene fusion positive) • Entrectinib (if *NTRK* gene fusion positive)

Chemoradiation

Preferred Regimens: (Pancreatobiliary, Mixed, and Intestinal Types)	Other Recommended Regimens: (Pancreatobiliary only)
• Capecitabine + concurrent RT • 5-FU + concurrent RT	• Gemcitabine + concurrent RT[16]

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Ampullary Adenocarcinoma

Subsequent Therapy for Disease Progression

	Pancreatobiliary/Mixed Type		Intestinal Type	Useful in Certain Circumstances
Good PS[f]	If prior gemcitabine based therapy: • 5-FU + leucovorin + liposomal irinotecan[11] • 5-FU + leucovorin + irinotecan (FOLFIRI)[12-15] • FOLFIRINOX[a] or modified FOLFIRINOX[a,g,7] • Oxaliplatin + 5-FU + leucovorin (OFF)[14] • FOLFOX • CapeOx • Capecitabine • 5-FU + leucovorin	If prior fluoropyrimidine based therapy: • Gemcitabine • Gemcitabine + albumin-bound paclitaxel • Gemcitabine + capecitabine • FOLFIRI or 5-FU + leucovorin + liposomal irinotecan (if no prior irinotecan) If prior oxaliplatin therapy: • FOLFIRI or 5-FU + leucovorin + liposomal irinotecan (if no prior irinotecan)	If prior oxaliplatin-based therapy: • FOLFIRI ± bevacizumab[h]	• Pembrolizumab[e,10] (if MSI-H, dMMR or TMB-H [≥10 mut/Mb]) • Dostarlimab-gxly[e,k,9] (if MSI-H or dMMR) • Nivolumab + ipilimumab[e] (if MSI-H or dMMR) • Larotrectinib (if *NTRK* gene fusion positive) • Entrectinib (if *NTRK* gene fusion positive) • Gemcitabine + cisplatin[5] (only for known *BRCA1/2* mutations)
Poor PS	• Gemcitabine • Capecitabine (category 2B) • 5-FU + leucovorin (category 2B) For select patients with ECOG 2 consider multi-agent regimens[i]: • FOLFOX • CapeOX • FOLFIRI • Gemcitabine + albumin-bound paclitaxel		• 5-FU + leucovorin For select patients with ECOG 2 consider multi-agent regimens[i]: • Capecitabine ± bevacizumab[h] • 5-FU ± bevacizumab[h] • FOLFOX ± bevacizumab[h] • FOLFIRI ± bevacizumab[h] • FOLFOXIRI ± bevacizumab[h] • CapeOx ± bevacizumab[h]	• Pembrolizumab[e] (if MSI-H, dMMR or TMB-H [≥10 mut/Mb]) • Dostarlimab-gxly[e,k,9] (if MSI-H or dMMR) • Nivolumab + ipilimumab[e] (if MSI-H or dMMR) • Larotrectinib (if *NTRK* gene fusion positive) • Entrectinib (if *NTRK* gene fusion positive)

Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-1281.

Recommended treatment of Ampullary adenocarcinoma

- Ampullary cancer patients with T2 or above stage or lymph node-positive tumors are associated with increased recurrence risk and therefore, could be benefitted from adjuvant treatment. A common strategy in the United States is adjuvant chemotherapy with gemcitabine plus capecitabine or fluoropyrimidine for 6 months if systemic therapy alone is chosen and excellent performance status.
- For most patients with resected ampullary cancer stage T2N0 or higher, the addition of concurrent infusional FU-based chemoradiotherapy to adjuvant chemotherapy was usually suggested in the United States.
- The commonly used dose is 50.4 grays given in 4 to 6 weeks concurrently with fluoropyrimidine or gemcitabine-based treatment in adjuvant setting either sandwiched between chemotherapy or after 4 to 5 months of chemotherapy.

Recommended regimens of Periampullary adenocarcinoma

- **FOLFOX**: Oxaliplatin 85 mg/m^2 iv, leucovorin, 400 mg/m^2; Fluorouracil, Fluorouracil, 400 mg/m^2, then 1200 mg/m^2 for 2 days, repeat every 2 weeks
- **FOLFIRI**: Irinotecan 180 mg/m^2 iv, leucovorin, 400 mg/m^2; Fluorouracil, Fluorouracil, 400 mg/m^2, then 1200 mg/m^2 for 2 days, repeat every 2 weeks
- FL: Fluorouracil, 2200 mg/m^2 and leucovorin, 150 mg/m^2; given as a 24-hour continuous infusion, every 2 weeks
- **Gemcitabine** at 1000 mg/m^2 over 30 minutes, weekly for 3 weeks every 28 days ± oxaliplatin 85 mg/m^2 iv for 2 hours
- **GEMOX**: Gemcitabine at 1000 mg/m^2 over 30 minutes , weekly for 7 weeks and rest 1 week, then weekly for 3 weeks every 28 days ± oxaliplatin 85 mg/m^2 iv for 2 hours
- **EEPFL**: Epirubicin, 10 mg/m^2; etoposide, 50 mg/m^2; cisplatin, 20 mg/m^2; leucovorin, 150 mg/m^2; and fluorouracil, 2200 mg/m^2 given as a 24-hour continuous infusion, every 2 weeks
- PFL: Cisplatin, 20 mg/m^2; leucovorin, 150 mg/m^2; and fluorouracil, 2200 mg/m^2 given as a 24-hour continuous infusion, every 2 weeks
- **CAPEOX**: Capecitabine 1000 mg/m^2 PO bid for 10 days and ± oxaliplatin 85 mg/m^2 iv for 2 hours every 14 days
- TS-1 orally twice daily at a dose according to the body surface area (BSA) (< 1.25 m^2, 80 mg/d; ≥ 1.25 to < 1.5 m^2, 100 mg/d; ≥ 1.5 m^2, 120 mg/d) on days 1 through 28 of a 42-day cycle

Recommended Immunotherapy of Periampullary adenocarcinoma

For dMMR/MSI-H only

- **Pembrolizumab**
  Pembrolizumab 2 mg/kg IV every 3 weeks, or
  Pembrolizumab 200 mg IV every 3 weeks, or
  Pembrolizumab 400 mg IV every 6 weeks

  N Engl J Med 2020; 383:2207-2218(KEYNOTE-177)

- **Nivolumab**
  Nivolumab 3 mg/kg every 2 weeks, or
  Nivolumab 240 mg IV every 2 weeks, or
  Nivolumab 480 mg IV every 4 weeks

  Lancet Oncol 2017; 18: 1182–91(CHECKMATE-142)

- Ipilimumab + nivolumab
  Nivolumab 3 mg/kg (30-minute IV infusion)
  Ipilimumab 1 mg/kg (30-minute IV infusion)
  Once every 3 weeks for four doses, then
  Nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks

  Journal of Clinical Oncology 2018 36:8, 773-779(CHECKMATE-142)

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