Updates in Gastrointestinal Malignancies

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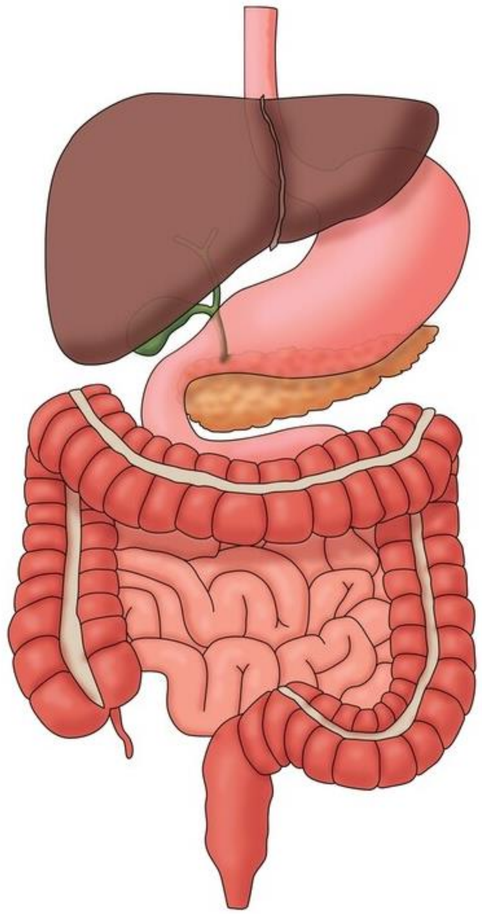
EMPIRE STATE HEMATOLOGY & ONCOLOGY SOCIETY

Disclosure of Conflicts of Interest

Joshua P. Raff, M.D., has no relevant financial relationships to disclose.



Molecular
Therapies

Based upon
results of
molecular profiling

Improvements in
Multidisciplinary
Management

Esophageal / GEJ
Rectal

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Some of the Variables in Molecular Profiling

Organ / Site

Stage

- Early
- Locally Advanced
- Recurrent
- Metastatic

Process

- Driver
- Pathway
- Immune Environment

Technical Aspects

- IHC
- FISH
- NGS
- Tissue vs Liquid
- Prognostic vs Predictive

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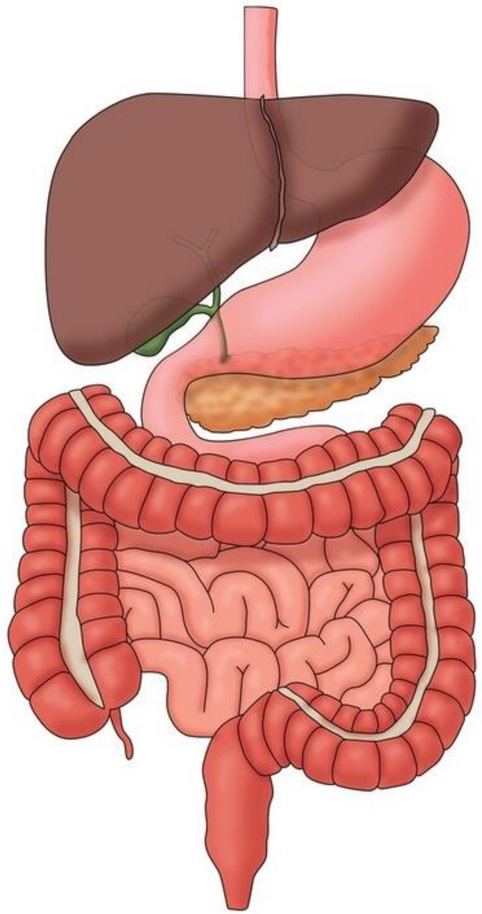
Our Approach is Changing



- Organ of Origin
- Histology
- Stage / Extent of Disease
- Molecular Profiling

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Useful for Advanced Disease – Any Tumor Type

Pembrolizumab
Nivolumab
Dostarlimab

MSI-High
MMR deficient
TMB > 10

Entrectinib
Larotrectinib

NTRK-gene
fusion +

Trastuzumab
or others

HER2

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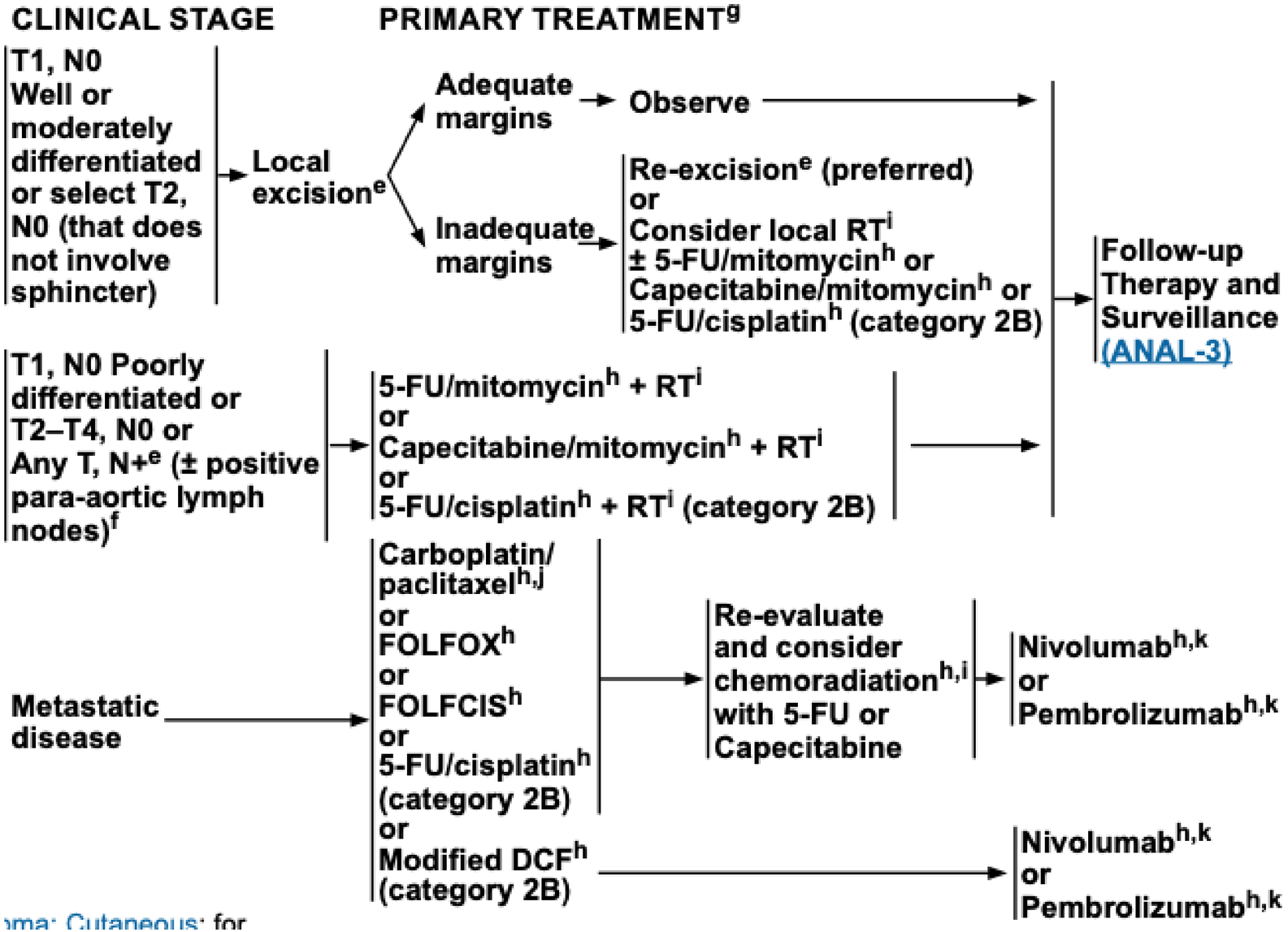
Anal Cancer



Nivo: Ph II, single arm
RR 24%

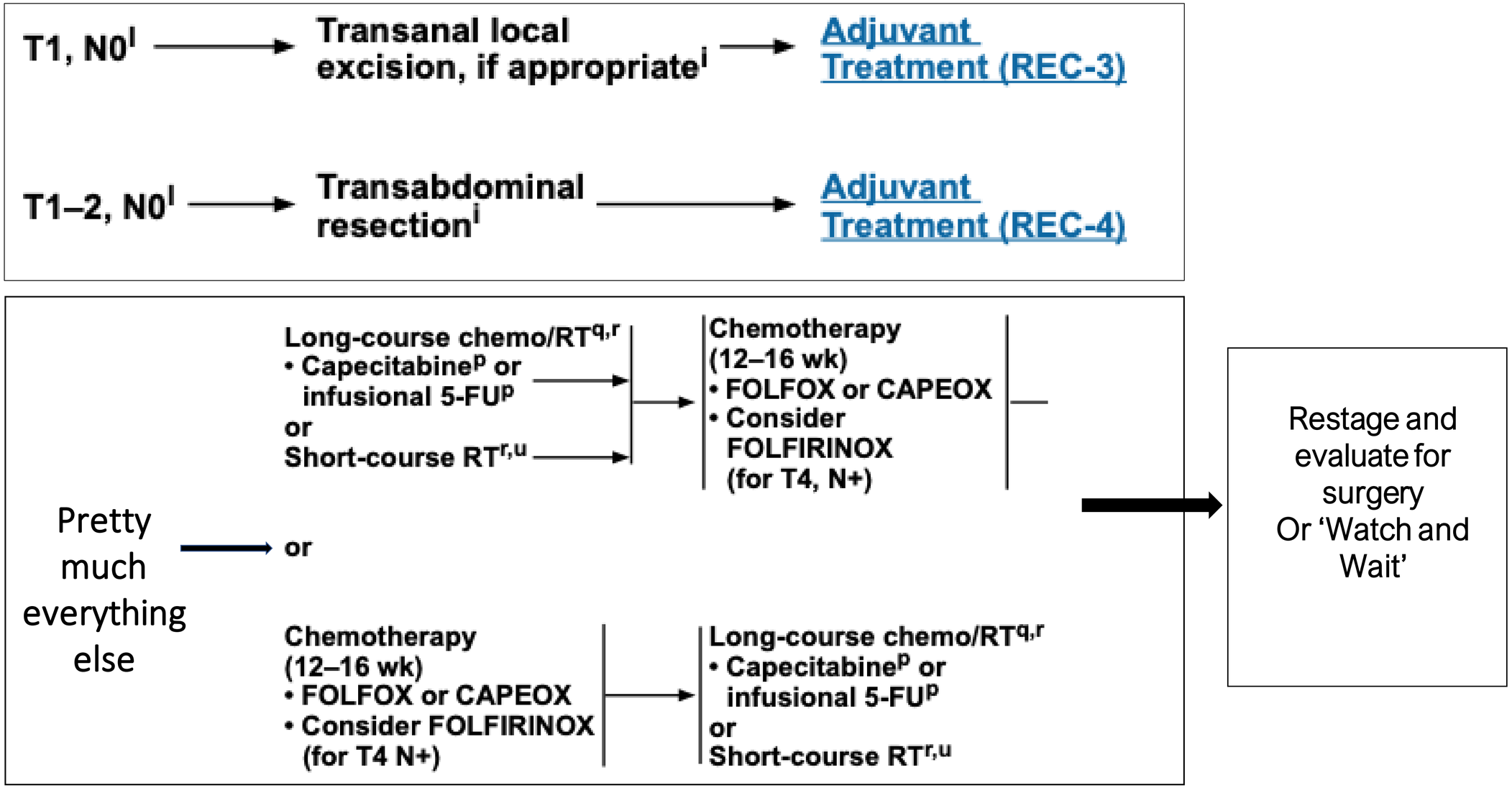
Pembro: Anal Ca cohort
From KN28, PDL1> 1%
RR 17%

NCCN Guidelines Version 2.2022 ANAL-2
Morris Lancet 2017.April.18(4).446
Ott et al. Annal Onc 2017. May.28(5)1036

Rectal Cancer – Principles of MRI reporting

At presentation (before neoadjuvant therapy)	• Distance from the anal verge or anorectal junction to the lower aspect of the tumor • Tumor length • T-stage of primary mass • Tumor deposits within the mesorectum • Involvement of the mesorectal fascia and the smallest distance (mm) between the tumor and the MRF and its location[b] • N-stage • Presence/absence of suspicious extramesorectal lymph nodes • Additional findings that can be provided in synoptic report: ‣ The circumferential location of the tumor ‣ In T3 tumor, the extent (mm) of extramural growth or depth of invasion ‣ Number of suspicious lymph nodes ‣ Presence/absence of extramural vascular invasion (EMVI) ‣ Morphologic pattern of tumor growth (eg, annular, polypoid, mucinous, ulcerated, perforated)
After neoadjuvant therapy	• Distance from the anal verge or anorectal junction to the lower aspect of the remaining tumor • Tumor length • Presence/absence of a residual tumor (high signal on T2-weighted images) • Presence/absence of fibrosis (low signal on T2-weighted images) • yT-stage and any remaining tumor deposits within the mesorectum • yN-stage and number of remaining suspicious lymph nodes • Presence of any remaining suspicious extramesorectal lymph nodes • Persistent involvement/regression from the MRF[b] • The smallest distance (mm) between the remaining tumor and the mesorectal fascia and its location • Additional findings that can be provided in synoptic report: ‣ The circumferential location of the remaining tumor within the wall ‣ In the case of a yT3 tumor, the extent (mm) of extramural growth ‣ The morphologic pattern of tumor growth ‣ Presence/absence of EMVI (no clear consensus on reporting this finding)

Rectal Cancer



Rectal Cancer – the Option of 'Watch and Wait' after TNT

In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative (chemotherapy and/or RT) management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for nonoperative management should involve a careful discussion with the patient of his/her risk tolerance. Surveillance recommendations include DRE, proctoscopy every 3-4 months for 2 years, then every 6 months for a total of 5 years. MRI rectum is recommended every 6 months for at least 3 years to monitor for extraluminal local recurrence.

NCCN Rectal Cancer REC-5

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PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Andrea Cercek, M.D., Melissa Lumish, M.D., Jenna Sinopoli, N.P., Jill Weiss, B.A., Jinru Shia, M.D., Michelle Lamendola-Essel, D.H.Sc., Imane H. El Dika, M.D., Neil Segal, M.D., Marina Shcherba, M.D., Ryan Sugarman, M.D., Ph.D., Zsofia Stadler, M.D., Rona Yaeger, M.D., et al.

Design: A prospective, phase 2, single-group study examined the efficacy and safety of neoadjuvant therapy with the programmed death 1 (PD-1) inhibitor dostarlimab in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma.

Efficacy: 12 of 16 enrolled patients have already completed 6 months of dostarlimab. All 12 had a clinical complete response, with no evidence of tumor on any diagnostic test. During a median follow-up of 12 months, no patient received chemoradiotherapy or underwent surgery, and none had disease progression or recurrence.

CONCLUSIONS

All patients with mismatch repair–deficient, locally advanced rectal cancer who were treated with the PD-1 inhibitor dostarlimab alone for 6 months had a clinical complete response, although longer follow-up is warranted.

Cercek A et al. DOI: 10.1056/NEJMoa2201445

LBA7 - Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: The NICHE-2 study

Pts with ***non-metastatic dMMR CC*** were treated with ***one dose of ipilimumab (1mg/kg) and two doses of nivolumab (3mg/kg)*** and underwent ***surgery ≤6 weeks*** of registration. Co-primary endpoints were safety (ITT) and 3-year DFS (PP). Secondary endpoints included major pathologic response (MPR) and complete response (pCR) rates. Pathologic response was defined as ≤50% residual viable tumor (RVT), and MPR as ≤10% RVT.

A ***total of 112 pts*** were treated. ***Grade 3-4 immune-related adverse events were observed in 3 (3%)*** patients; only 3 pts experienced delay in surgery, meeting the safety primary endpoint. In the PP population (n=107), baseline radiologic assessment revealed 89% stage III, 77% high-risk stage III (Table), and 64% T4 tumors. With a median time from first dose to surgery of 5 weeks, pathologic response was observed in 106/107 (99%) pts, consisting of 102/107 (95%) MPR and 4 (4%) PR. ***pCR was observed in 72/107 (67%) pts***. At a median follow-up of 13 months (range 1-57), none of the pts had disease recurrence.

Advanced Colorectal Cancer

Test or Target	Drug
MSI-High; MMR- deficient TMB > 10*	Pembrolizumab Nivolumab Dostarlimab
BRAF V600E	Encorafenib + either Panitumumab or Cetuximab
NRTK Gene Fusion	Entrectinib or Larotrectinib
HER2	Traztuzumab Lapatinib Pertuzumab Trastuzumab Deruxtecan Tucatinib*
KRAS/NRAS/BRAF wt	Cetuximab or Panitumumab
KRAS G12C	Sotorasib* + Panitumumab
RET Fusion	Selpercatinib
NONE	Fruquintinib*

Pancreatic Cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Pancreatic Cancer Screening

NCCN Guidelines Index
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Discussion

PANCREATIC CANCER SCREENING

- Emerging data have examined the efficacy of pancreatic cancer screening in select individuals at increased risk for exocrine pancreatic cancer. To date, most such studies have restricted pancreatic cancer screening to individuals with:
  1. A known P/LP germline variant in a pancreatic cancer susceptibility gene (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, TP53*; see GENE-A) and a family history of pancreatic cancer (first-degree or second-degree relative) from the same side of the family as the germline P/LP variant; or
  2. A family history of exocrine pancreatic cancer in ≥2 first-degree relatives from the same side of the family, even in the absence of a known P/LP germline variant (many centers would enroll individuals with one affected first-degree relative and one second-degree relative); or
  3. A family history of exocrine pancreatic cancer in ≥3 first- and/or second-degree relatives from the same side of the family, even in the absence of a known P/LP germline variant.
- These studies have typically started screening with contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS) in such high-risk individuals.

Meeting Abstract | 2020 ASCO Annual Meeting I

GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Early detection for pancreatic cancer in individuals at elevated-risk, using endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI) of the abdomen: Feasibility and preliminary outcomes.

Joshua P. Raff, Charles Noyer, Nicole Boxer, Sara Sadan, Dan Costin, Sasan Roayaie, ...

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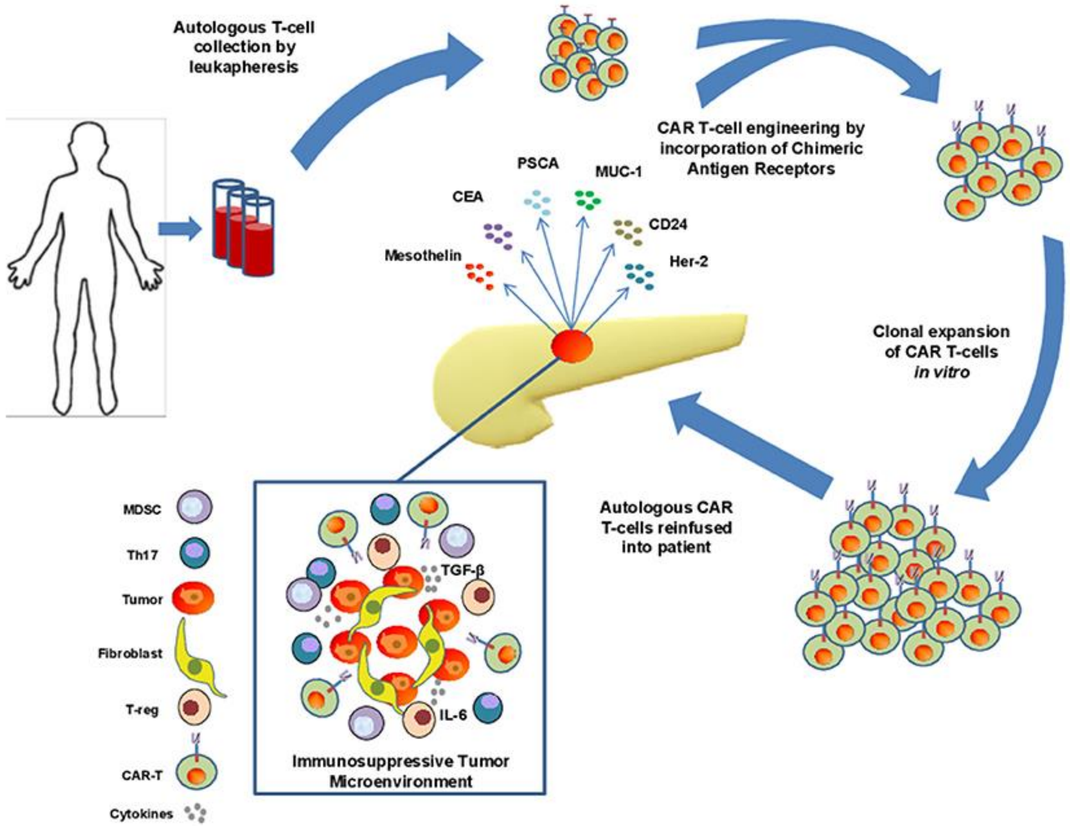
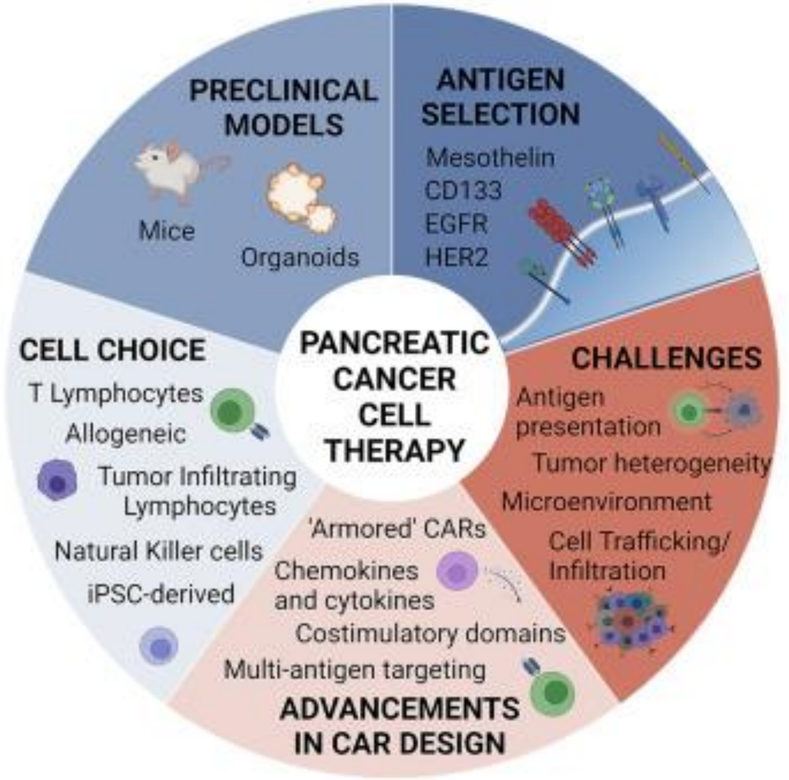
Pancreatic Cancer

Neoantigen T-Cell Receptor Gene Therapy in Pancreatic Cancer

Rom Leidner, M.D., Nelson Sanjuan Silva, B.S., Huayu Huang, M.S., David Sprott, B.S., Chunhong Zheng, Ph.D., Yi-Ping Shih, Ph.D., Amy Leung, B.S., Roxanne Payne, M.N., Kim Sutcliffe, B.S.N., Julie Cramer, M.A., Steven A. Rosenberg, M.D., Ph.D., Bernard A. Fox, Ph.D., et al.

"Novel treatment targeting KRAS G12D expression induces deep and durable response"





N Engl J Med 2022; 386:2112-2119
Akce Front Immunol Front. Immunol., 25 September 2018
Yeo D. Mol Oncol Ther Volume 24, 17 March 2022,

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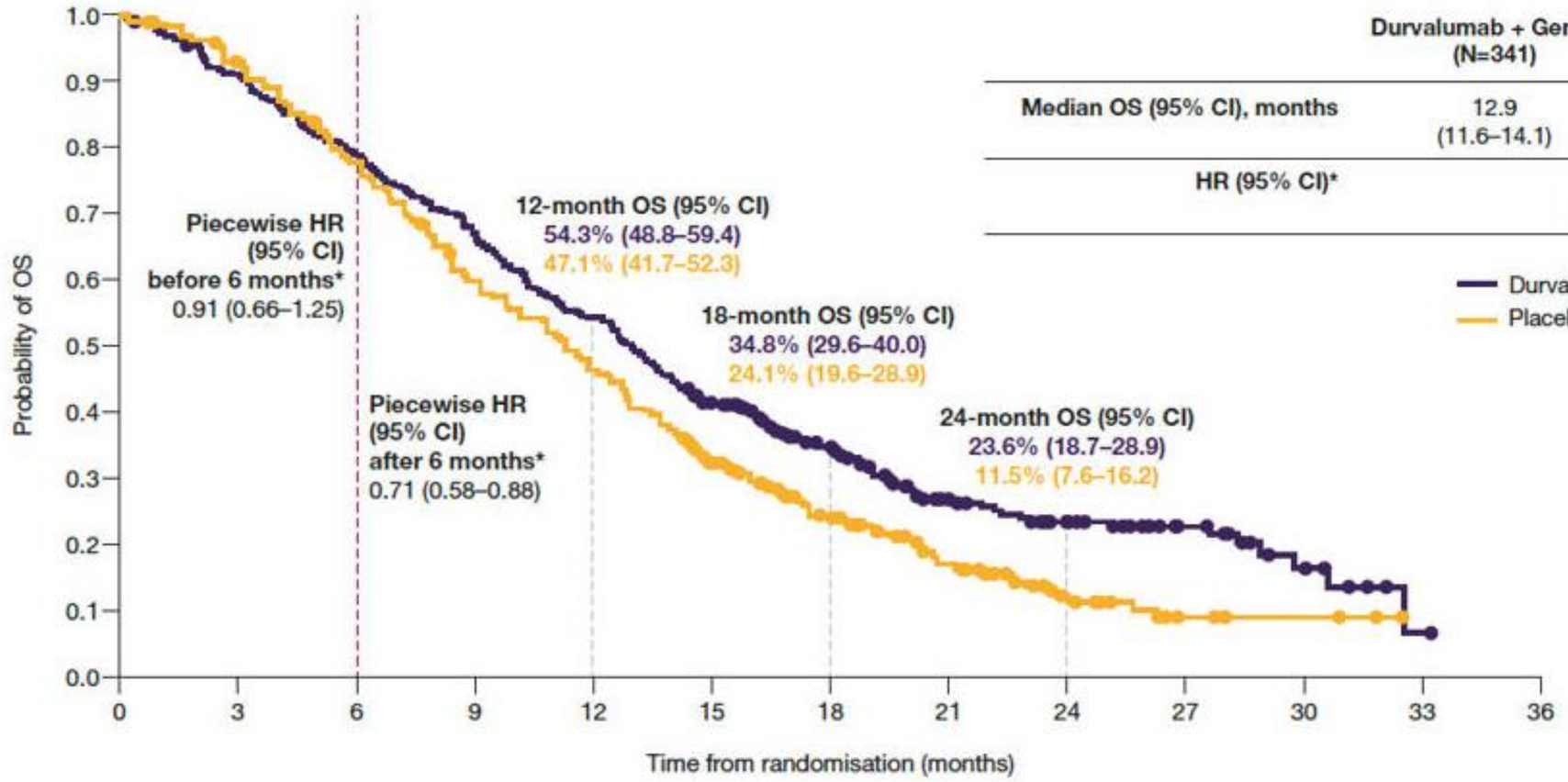
Biliary Tract Cancers (CCA and GB)

Durvalumab plus cisplatin/gemcitabine is now standard of care for patients with advanced/metastatic biliary tract cancer

Kaplan-Meier curve of overall survival



	Durvalumab + GemCis (N=341)	Placebo + GemCis (N=344)
Median OS (95% CI), months	12.9 (11.6–14.1)	11.3 (10.1–12.5)
HR (95% CI)*	0.76 (0.64–0.91)	

ESMO Congress 2022, Abstract 56P

Biliary Tract Cancers (CCA and GB)

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,h,10,11]
  - Dostarlimab-gxly[f,h,i,18,19] (category 2B)
- For TMB-H tumors:
  - Pembrolizumab[e,f,h,20]
- For *BRAF*-V600E mutated tumors
  - Dabrafenib + trametinib[21,22]
- For CCA with *FGFR2* fusions or rearrangements:
  - Pemigatinib[23]
  - Infigratinib[24]
  - Futibatinib[25]
- For CCA with *IDH1* mutations
  - Ivosidenib[26,27]
- For *RET* gene fusion-positive tumors:
  - Selpercatinib for CCA[13]
  - Pralsetinib (category 2B)[12]
- For HER2-positive tumors:
  - Trastuzumab[j] + pertuzumab[28]
- Nivolumab[f,h,29] (category 2B)
- Lenvatinib + pembrolizumab[f,h,30] (category 2B)

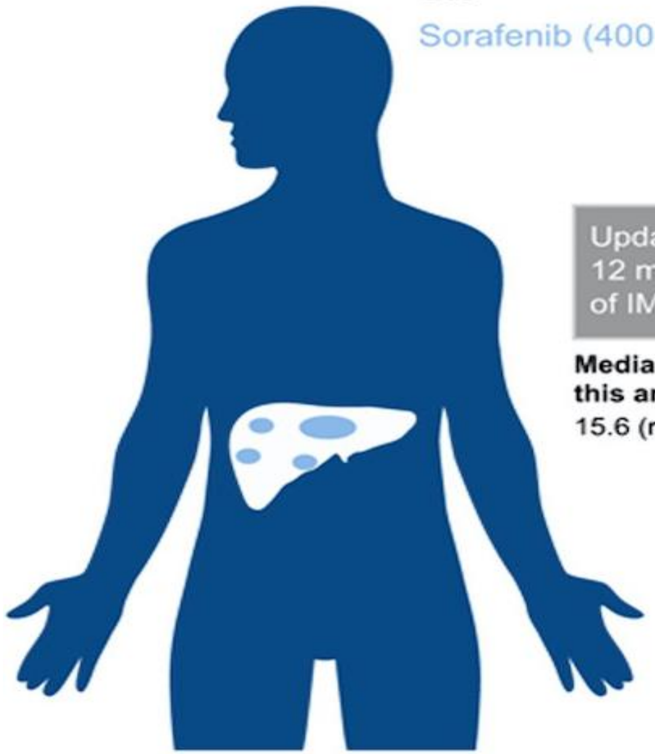
Hepatocellular Carcinoma

IMbrave150: Atezolizumab plus bevacizumab versus sorafenib in patients with unresectable HCC

Atezolizumab (1,200 mg) plus bevacizumab (15 mg/kg) every 3 weeks

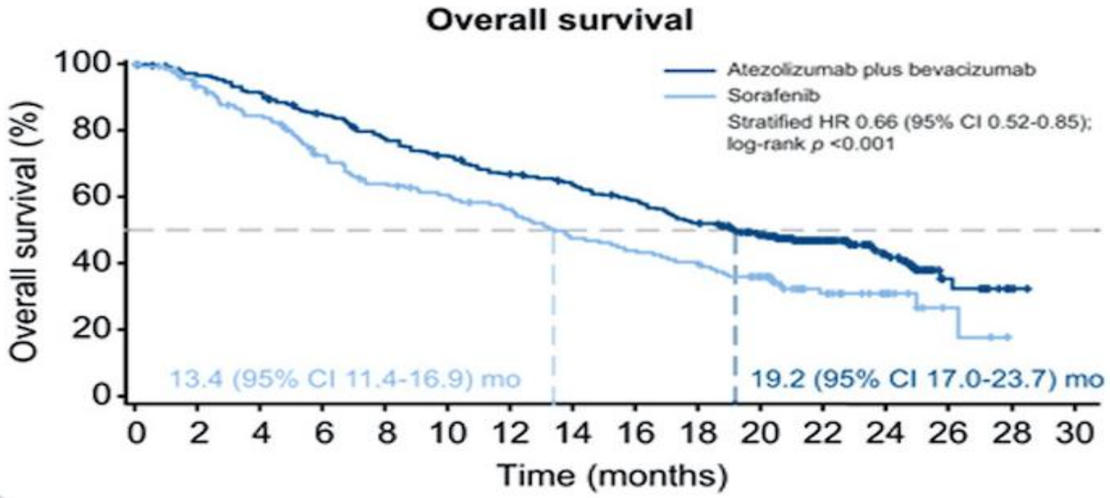
OR

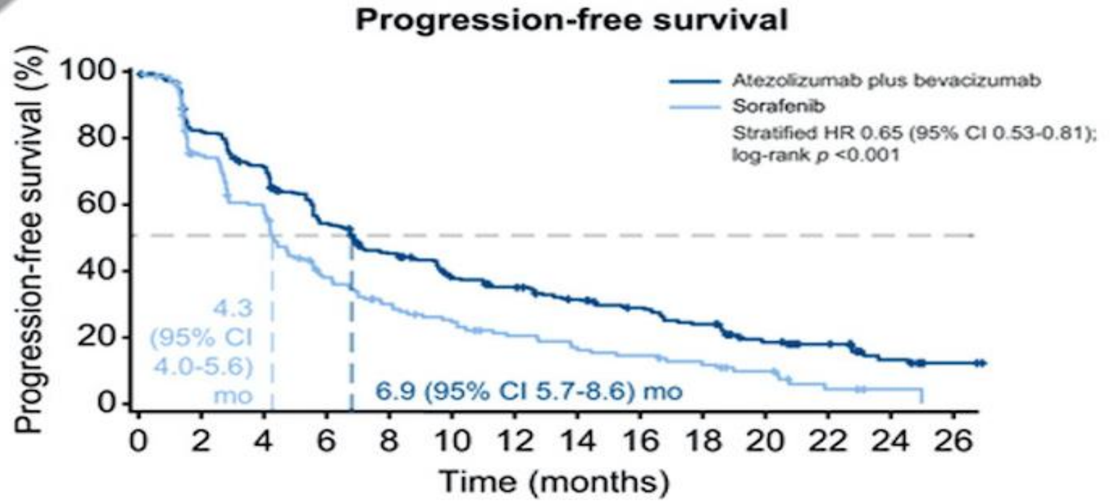
Sorafenib (400 mg twice daily)



Updated analysis
12 months after primary analysis of IMbrave150 study

Median follow-up for this analysis:
15.6 (range, 0-28.6) mo





Confirmed objective response rate: 30% with atezolizumab plus bevacizumab, 11% with sorafenib

Llovet JM, Villanueva A, Marrero JA, et al. AASLD Consensus Conference. Hepatology 2021; 73 Suppl 1:158-191
Cheng AL J Hepatol. 2022:76(4):862. Epub 2021 Dec 11

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Esopghageal / GEJ / Gastric Cancer – The Basics

Histology: Squamous vs Adenoca

If not M1 by CT, then EUS and PET

If Tis, T1a, *T1b, then consider ER/ Ablation or Surgery

For Stage II – III: Multimodality Chemo+Radiation -> Surgery

If Recurrent, locally advanced, or metastatic then check: MMR/MSI; HER2; PDL1

https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

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Following NeoAdjuvant Chemo-Radiation:
Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

Kelly RJ et al. DOI: 10.1056/NEJMoa2032125

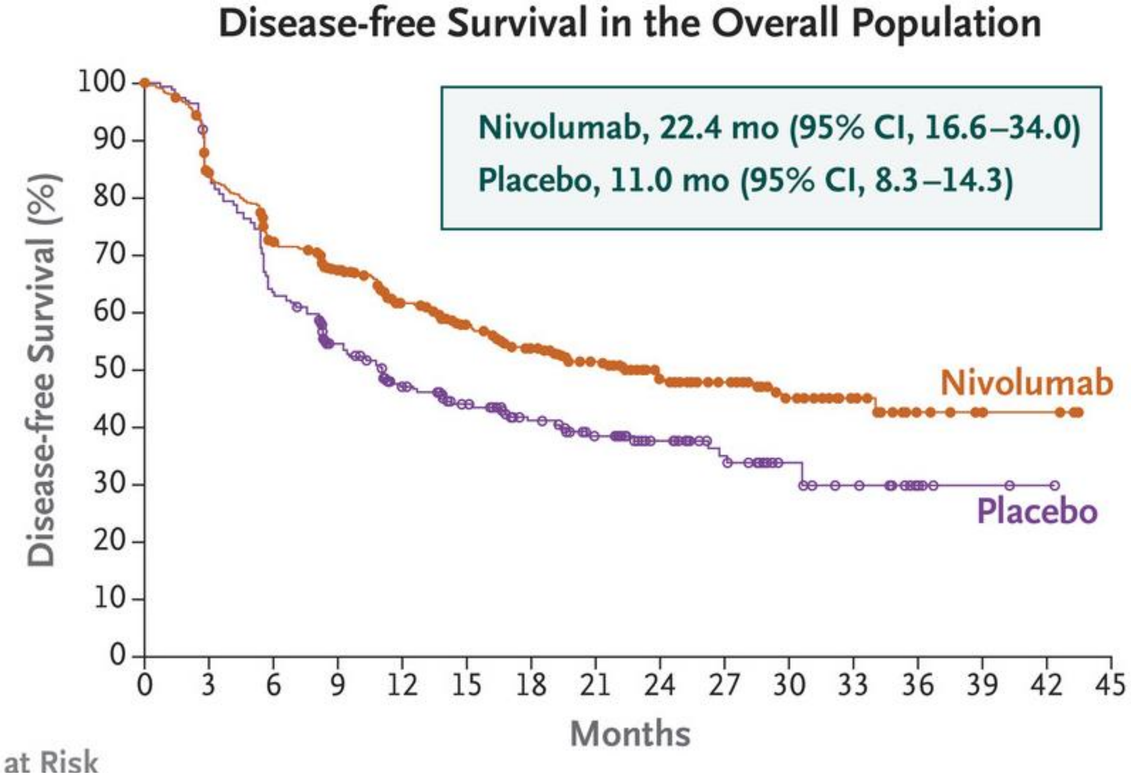
RESULTS

Efficacy:

Median disease-free survival was 22.4 months with nivolumab and 11.0 months with placebo. Adjuvant nivolumab was also associated with longer metastasis-free survival.

Safety:

The safety profile of nivolumab was similar to that seen in other types of solid tumors. The most common high-grade nivolumab-related adverse events with potential immunologic cause were pneumonitis and rash.



CM 648 - R III Open Chemo +/- Nivolumab 1L M Esoph Squamous

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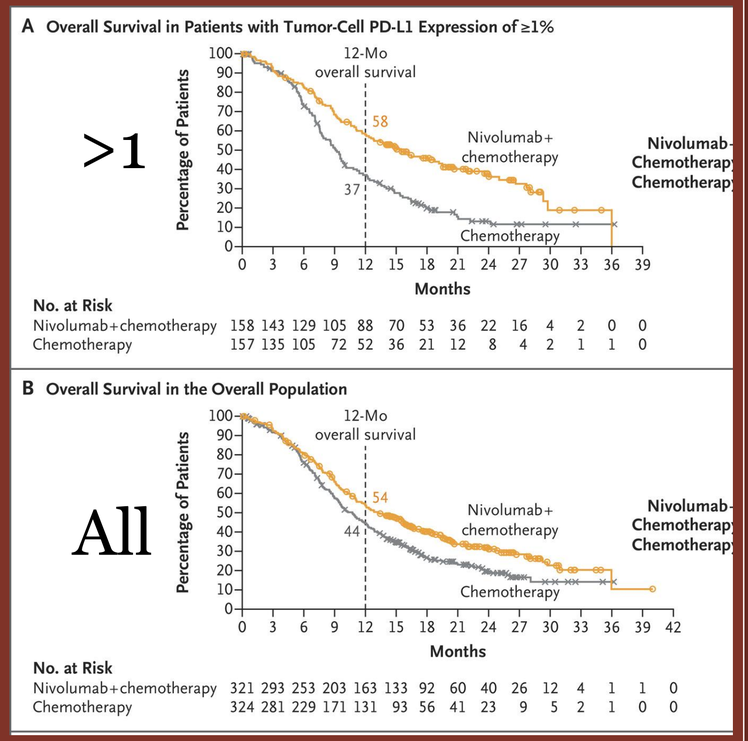

All

OS

KN 590- R III P/C Chemo +/- Pembro 1L M Esoph Squamous

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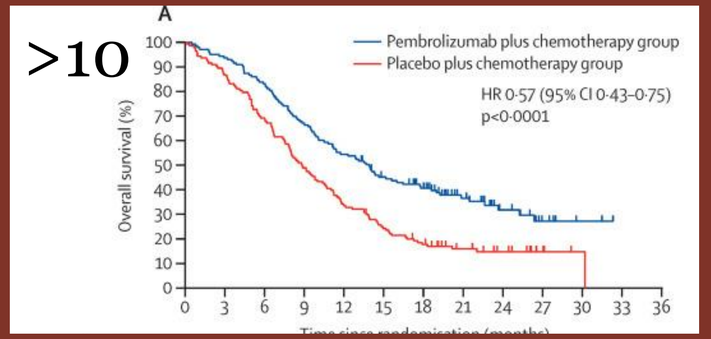

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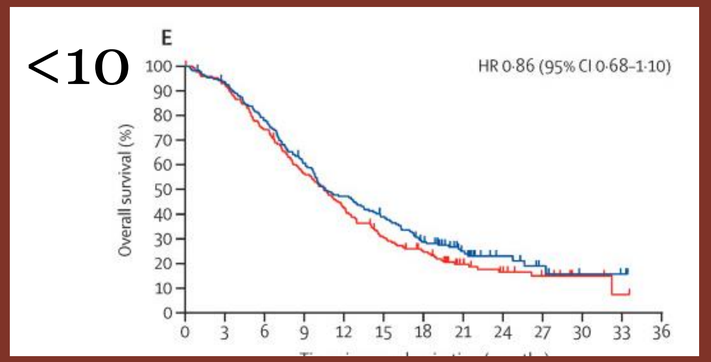
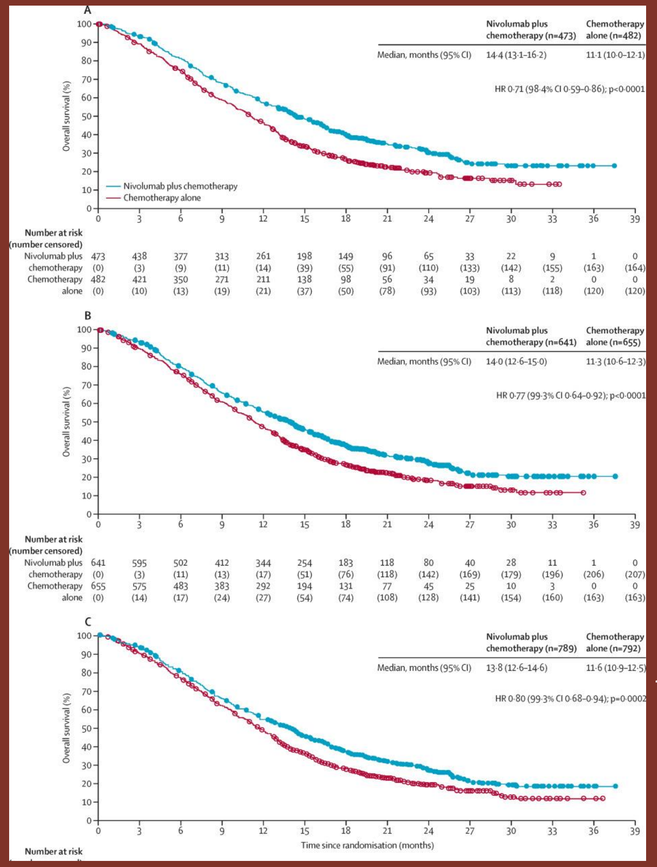


CM 649 - R III Open Chemo +/- Nivolumab 1L M Esoph / GEJ/ Gastric Adeno



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All

Doki NEJM N Engl J Med 2022; 386:449-46
Janjigian, : The Lancet 2021 Volume: 398 Issue: 10294 Page: 27
Sun. The Lanet 2021 Volume 398 10302 Page 759.

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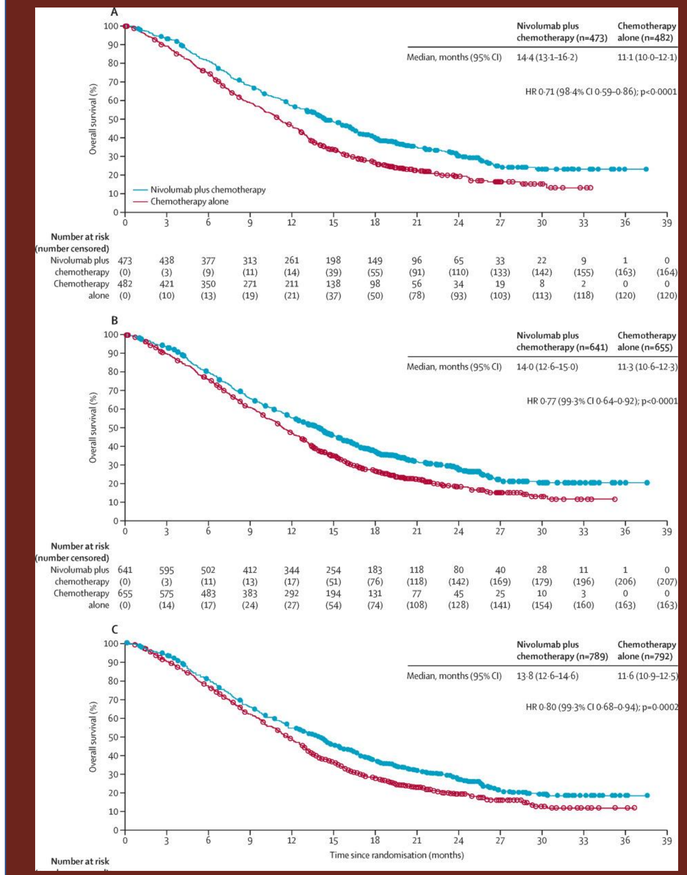
CM 649 - R III Open
Chemo +/- Nivolumab
1L M Esoph / GEJ/ Gastric Adeno



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All

KN -062
Pembro Vs Chemo Vs Pembro + Chemo
Gastric / GEJ Adeno
PDL1 >1
Pembro non inferior

KN 859
Chemo +/- Pembro
Gastric / GEK adeno
PDL1 >1
Ongoing

Janjigian, : The Lancet 2021 Volume: 398 Issue: 10294 Page: 27
Shitara JAMA Oncology 2020 6(10)1570

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KN811: Trastuzumab + Chemo + (Pembrolizumab Vs Placebo) for 1L M HER2+

N 264; median follow-up was 12.0 mo (range, 8.5-19.4).
ORR was 74.4% for Pembro + SOC vs 51.9% for placebo + SOC (*P* = 0.00006);
CR rate was 11.3% vs 3.1% SOC

Phase 2 DESTINY-Gastric02 study Gastric / GEJ, HER2

Trastuzumab deruxtecan
N= 79, all previously treated with trastuzumab
Median follow-up of 10 months (range, 0.7-22.1), OS = 12mo
ORR was 41.8% (95% CI, 30.8%-53.4%)
CR in 4 patients (5.1%) and PR in 29 patients (36%).

Jangigian YY ASCO GI 2021 Abstract #4013
Ku G ESMO 2022; Annals of Oncology (2022) 33 (suppl_7): S555-S580. 10.1016/annonc/annonc1065

Questions for Esophageal / GEJ / Gastric ca:

- Role of neoadjuvant checkpoint inhibitors ? (R Ph II DANTE trial: Atezo/FLOT)
- How to use PDL1 results to guide use of checkpoint inhibitors ?
- What is the best approach for HER2 ?
- When to Consider Nivo / Ipo?
- How will new targeted agents fit in? (FGFR2b / Bemari)

https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

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Does Everyone Require a Multidisciplinary Approach ?

Pathologists
Radiologists
Gastroenterologist: EUS, ERCP, Spyglass, RFA, biliary and enteral stents, ESD
Surgeons
Interventional Radiologist: Biopsies, biliary stents, drains
Radiation Oncologists
Dieticians
Genetic Counselors
Ostomy Team

Wrap Up

- Lots of moving parts / Need multidisciplinary relationships
- Molecular Profiling (and targeting) for LA, recurrent, or metastatic
- CPI emerging in peri-op setting of GEJ
- Treatment for MMRd/MSI-H moving to neoadjuvant for CRC
- Newer agents targeting HER2 (n.b. CRC and Esoph/Gastr Adeno)
- Chemo + CPI established in BTC, and Esoph/Gastric AC and SCC
- Pancreatic cancer screening for individuals at risk
- Lots of combinations emerging for HCC
- ctDNA is here – how to best apply in practice?

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Thank you!

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