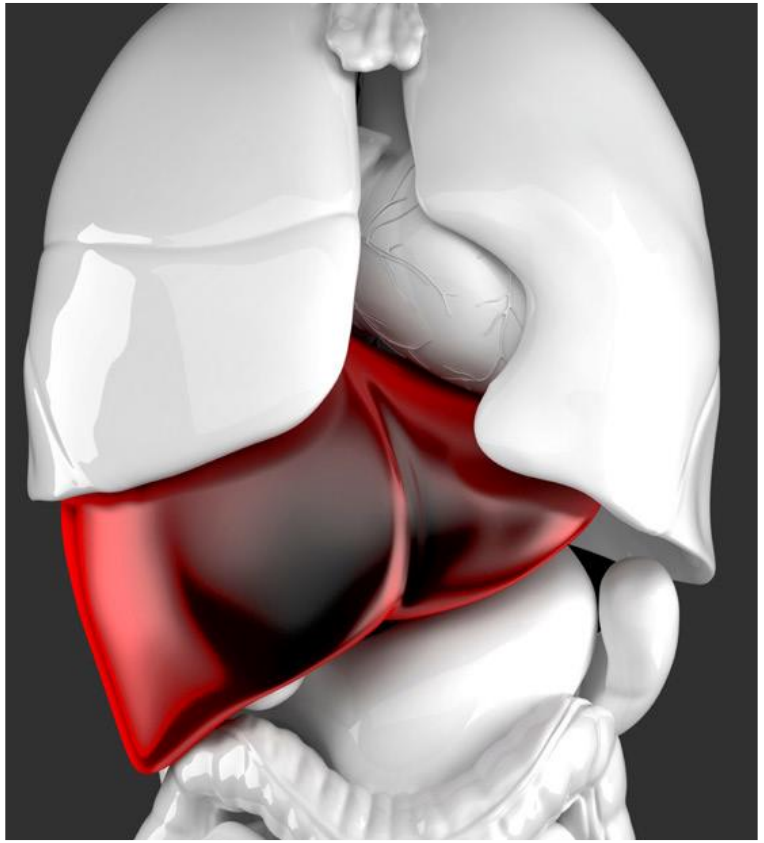
Case Presentation

Dr. Ahmed Refae MD
Consultant Clinical Oncology
International Medical Center-Jeddah
Associate Prof. at Ain- Shams University- Cairo



History

- 47 years old male patient.
- Far Asian Ancestors
- Bipolar disorder (on Depakin & Resperidol),
- 2014: Post Sleeve gastrectomy then bypass operation.

- 2018: Common bile duct mass→ Whipple operation in 11/2018.

- Pathology: CBD intraductal papillary neoplasm of the bile duct (IDPB), with high-grade dysplasia, and focal lamina propria invasion (less than 5-mm depth).
- The proximal and distal bile duct margins are positive for intra-ductal papillary neoplasm**.**

- PORTH: 27 sessions at KAMC.

Intraduct Papillary neoplasm of the bile duct

- IPNB is a variant of bile duct carcinoma presented as ductal mass.
- **40%-80%** of IPNBs contain a component of invasive carcinoma or tubular or mucinous adenocarcinoma, suggesting that IPNB is a disease with high potential for malignancy.
- Biopsy cannot reflect the actual stage in many cases:

  -Different foci may be of different stages

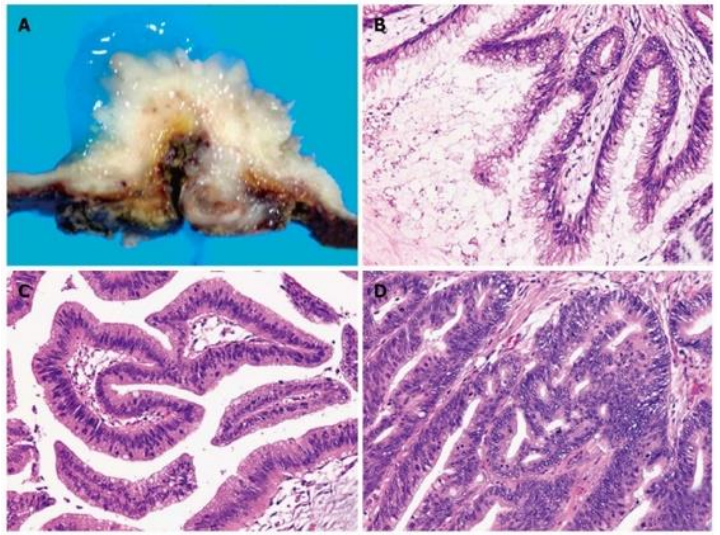
  -Mixed pathologic findings may exist in the same lesion.
- IPNBs are classified into four types.
- IPNB had four stages *(depth of invasion and degree of dysplasia):*

I- low- to intermediate-grade dysplasia

II- High-grade dysplasia

III- Intraductal growth type CCA , AJCC T1

IV- Intraductal growth type CCA, AJCC ≥T2



Histologic subtype	Profile of MUCs			Cytokeratin	
	MUC1	MUC2	MUC5AC	CK7	CK20
Pancreaticobiliary	+	-	+	+	+
Intestinal	-	+	+	+	+
Gastric	-	-	+	+	+
Oncocytic	Focal+	Focal+	+	+	+

Wu XJ Int Med Res. 2018

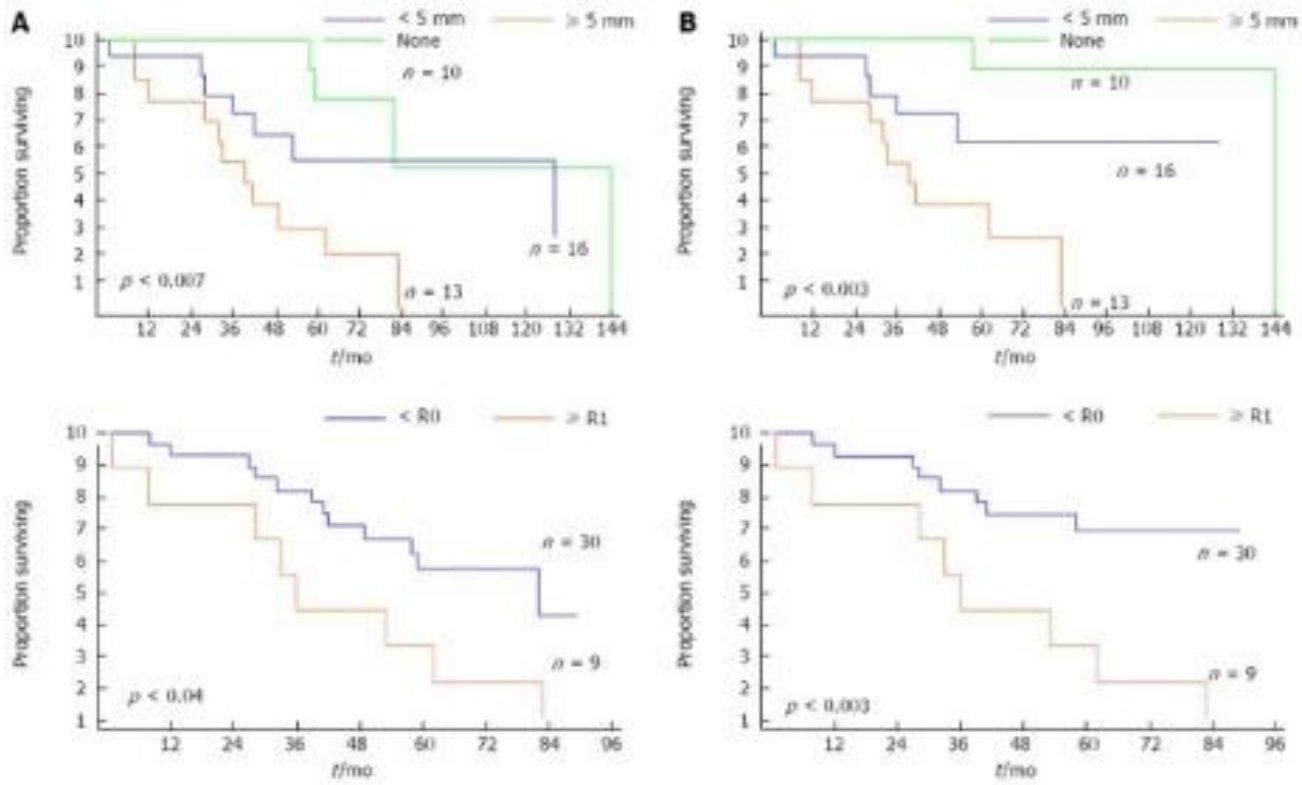
Intraduct Papillary neoplasm of the bile duct

Survival as a function to The depth of invasion, graded as:

- ≥ 5 mm 39m
- < 5 mm 128m
- none 144m ($P < 0.007$).

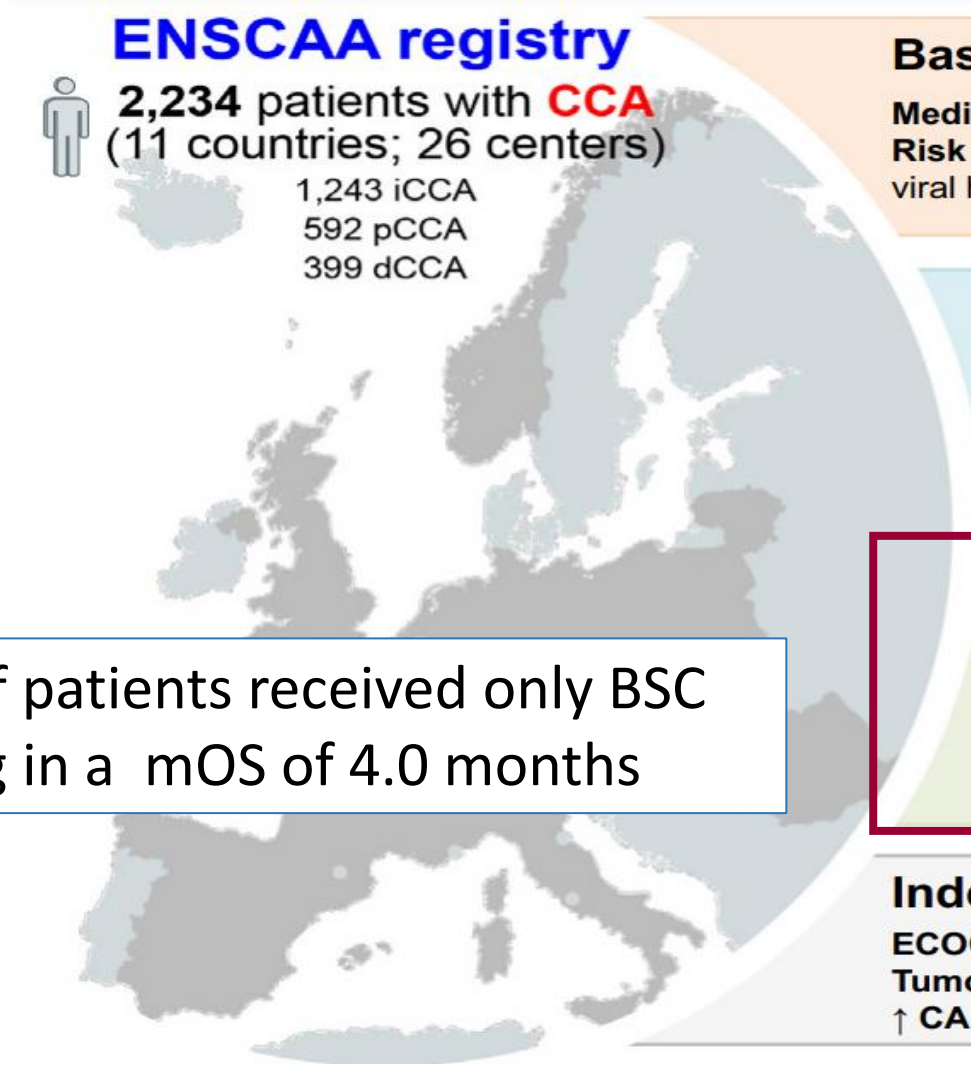
The percentage of invasive carcinoma components, graded as:

- ≥ 10% 42m
- < 10% 128m
- None 144 mo, respectively ($P < 0.03$).



Rocha et al Hepatology. 2012;**56**:1352–1360.

Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry



Baseline characteristics

Median age: 66 year **Male:female ratio** = 1.29
Risk factors: obesity (iCCA), diabetes (iCCA, dCCA), cirrhosis (iCCA), viral hepatitis (iCCA), PBC (iCCA), PSC (pCCA), lithiasis (p/dCCA)

Tumor features & biomarkers

Tumor size: iCCA>p/dCCA
Growth pattern: mass-forming (iCCA); peri/intra-ductal (p/dCCA)
CA19-9 (>37 IU/ml): - *Early disease stage*: Low diagnostic sensitivity
- *Advanced disease*: Increased levels

Management

Tumor resection:
R0/N0: mOS = 52.1 **R0/N+**: mOS = 23.3
R1/N0: mOS = 29.3 **R1/N+**: mOS = 21.8
Active palliative therapy: mOS = 10.6
BSC: mOS (months) = 4.0 (iCCA<p/dCCA)

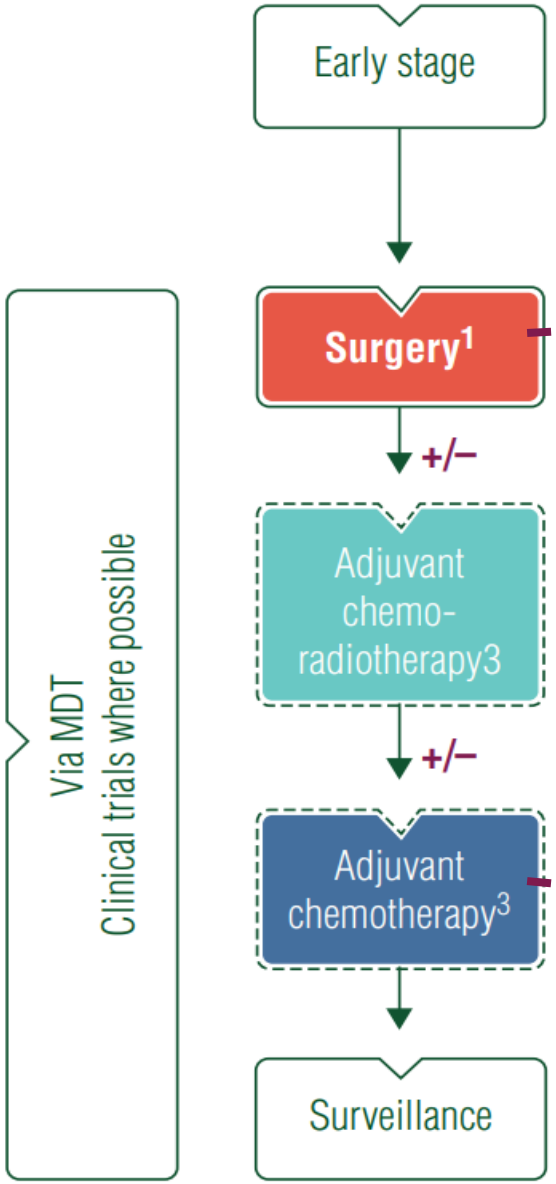
Independent prognostic factor

ECOG-PS (continuous; HR = 1.52)
Tumor metastasis (*vs.* local disease; HR = 4.03)
↑ **CA19-9** (*vs.* <37 IU/ml; HR = 2.79)

20.6% of patients received only BSC resulting in a mOS of 4.0 months

PBC, primary biliary cholangitis; pCCA, perihilar cholangiocarcinoma; PSC, primary sclerosing cholangitis

ESMO guidelines 2016



1 Special considerations:

- Need for pre-operative biliary drainage
- Avoid percutaneous biopsy in resectable disease
- Assess Future Liver Remnant
- Assess need for Portal Vein Embolisation
- Neoadjuvant approach (selected cases)
- Completion surgery for incidental gallbladder cancer of T-stage T1b and above

3 Level of recommendation IV,C

BILCAP: Capecitabine

Japanese Study: S1

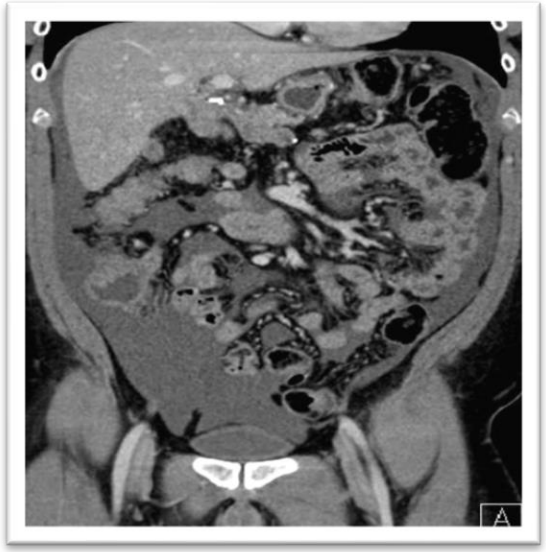
CCA, cholangiocarcinoma; iCCA, intrahepatic CCA; MDT, multidisciplinary team; PS, performance status.

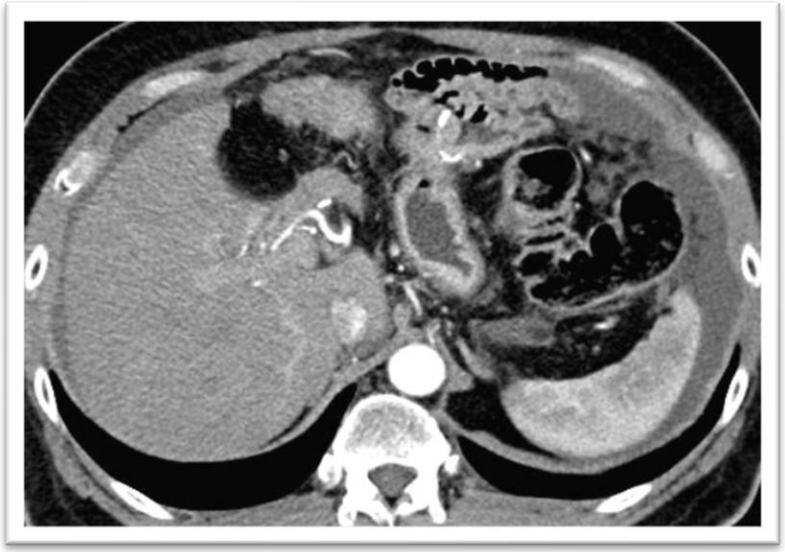
Valle JW, et al. *Ann Oncol.* 2016;27(suppl5):v28–v37.

History

- Follow up: DFI for 22 months
- **10/2020 :** CA19-9 was 136 u/ml
- He was advised initially to follow up in the clinic the month after, but unfortunately because of COVID, he received a message to attend the clinic after 1 year, and he lost FU.
- **8/2022:** CA19-9 was 5504 u/ml
- .

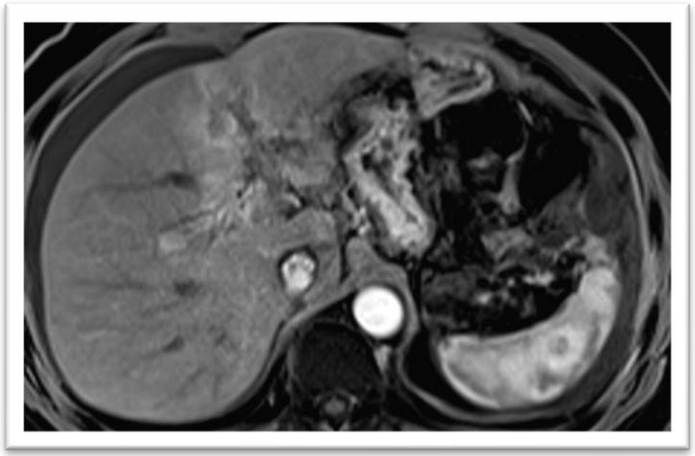
- **9/2022 CT CAP :** Moderate ascites, soft tissue peritoneal & omental deposits with focal liver lesions, circumferential thickening of the colonic wall (Neoplastic process could not be excluded).

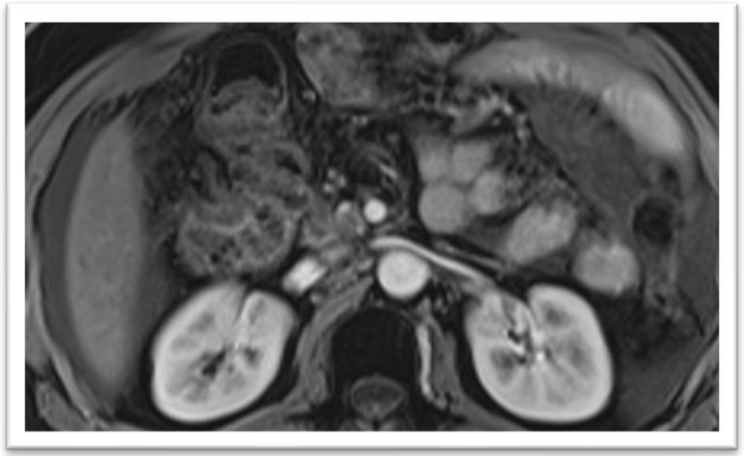




History

• **10/2022 MRI liver:** Segment IV metastatic lesion (1.6x1.3 cm).





•**10/2022 biopsy from the ometum at KAMC**: malignant tumor having cribriform architecture with areas of necrosis.

• Microscopically: Ovoid and hyperchromatic cells , stratified nuclei and have pale eosinophilic cytoplasm. Mitoses and necrosis necrotic debris seen.

• IHC: CK7 negative, CK20 positive, CDX 2 not done, CK 19+, TTF-1 negative, CEA positive, PSA negative, HSA -ve.

• **10/2022 Lower GI endoscopy:** Tubular adenoma, low-grade dysplasia, Cauterized margin is uninvolved.

History

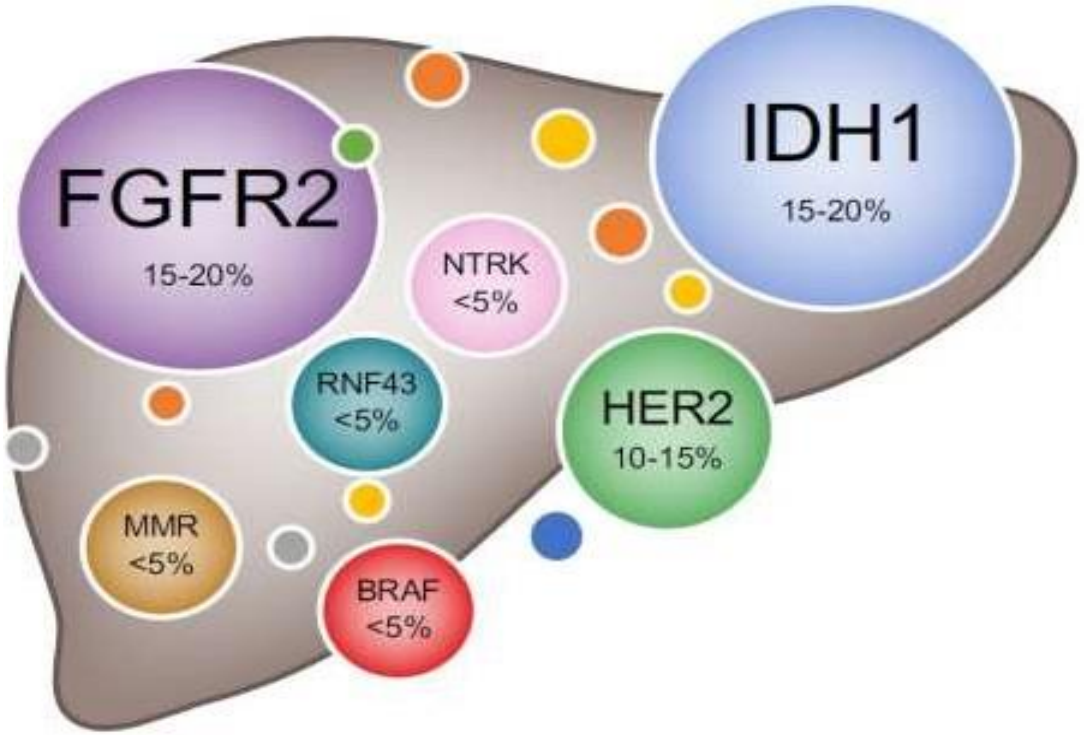
•**Pathology review At IMC revealed the following:**

-***Omental mass biopsy:*** Metastatic adenocarcinoma, consistent with known bile duct primary.

- ***Ascetic fluid, cytology:*** Positive for malignant cells.

Should we Do Any further Tests?

Advanced Biliary Tract Cancer | Era of Molecular pathology



Lamarca A, et al. *J Hepatol.* 2020;73:170–85.

History

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Bile duct extrahepatic cholangiocarcinoma
NAME [redacted]
DATE OF BIRTH 28 December 1974
SEX Male
MEDICAL RECORD # [redacted]

PHYSICIAN
ORDERING PHYSICIAN Refae, Ahmed
MEDICAL FACILITY International Medical Center - Jeddah
ADDITIONAL RECIPIENT Hisham M. Mahjoub
MEDICAL FACILITY ID 206940
PATHOLOGIST Saleem, Nasir

SPECIMEN
SPECIMEN SITE Omentum
SPECIMEN ID 22SP00731-1
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 02 November 2022
SPECIMEN RECEIVED 18 November 2022

Biomarker Findings

Microsatellite status - Cannot Be Determined [α]
Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

APC V1414fs*7
MYC amplification
SMAD4 W524C
TP53 R337C

2 Disease relevant genes with no reportable alterations: *FGFR2, IDH1*

α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 7)

Genetic Alterations by Site

Intrahepatic Cholangiocarcinoma (CCA)

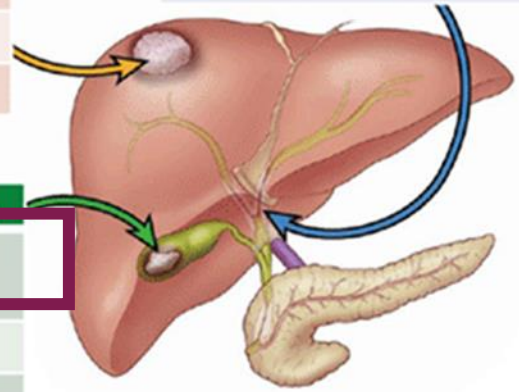
Specific Targetable Mutations	Prevalence, %
FGFR1-3 fusions, mutations, and amplifications	11-45
IDH1/2 mutation	4.9-36
TP53 mutation	2.5-44.4
BAP1 mutation	13
ARID1A mutations	6.9-36
PIK3CA mutations	3-9
KRAS mutation	8.6-24.2

Extrahepatic CCA

Specific Targetable Mutations	Prevalence, %
ERBB2/3 amplification	11-17
ARID1A mutations	12
TP53 mutation	40
IDH1/2 mutation	0-7.4
PIK3CA mutation	7
KRAS mutation	8.3-42

Gallbladder Cancer

Specific Targetable Mutations	Prevalence, %
FGFR1-3 fusions, mutations, and amplifications	3
EGFR mutation	3.9
ERBB2/3 amplification	9.8-19
PIK3CA mutation	5.9-12.5
TP53 mutation	47.1-59
ARID1A mutation	13



1. Javle M et al. *Cancer*. 2016;122:3838-3847. 2. Valle JW et al. *Cancer Discov*. 2017;7:943-962. 3. Rimassa L et al. *J Autoimmun*. 2019;100:17-26.

History

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Bile duct extrahepatic cholangiocarcinoma
NAME [redacted]
DATE OF BIRTH 28 December 1974
SEX Male
MEDICAL RECORD # [redacted]

PHYSICIAN
ORDERING PHYSICIAN Refae, Ahmed
MEDICAL FACILITY International Medical Center - Jeddah
ADDITIONAL RECIPIENT Hisham M. Mahjoub
MEDICAL FACILITY ID 206940
PATHOLOGIST Saleem, Nasir

SPECIMEN
SPECIMEN SITE Omentum
SPECIMEN ID 22SP00731-1
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 02 November 2022
SPECIMEN RECEIVED 18 November 2022

Biomarker Findings

Microsatellite status - Cannot Be Determined α
Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

APC V1414fs*7
MYC amplification
SMAD4 W524C
TP53 R337C

2 Disease relevant genes with no reportable alterations: ***FGFR2, IDH1***

α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

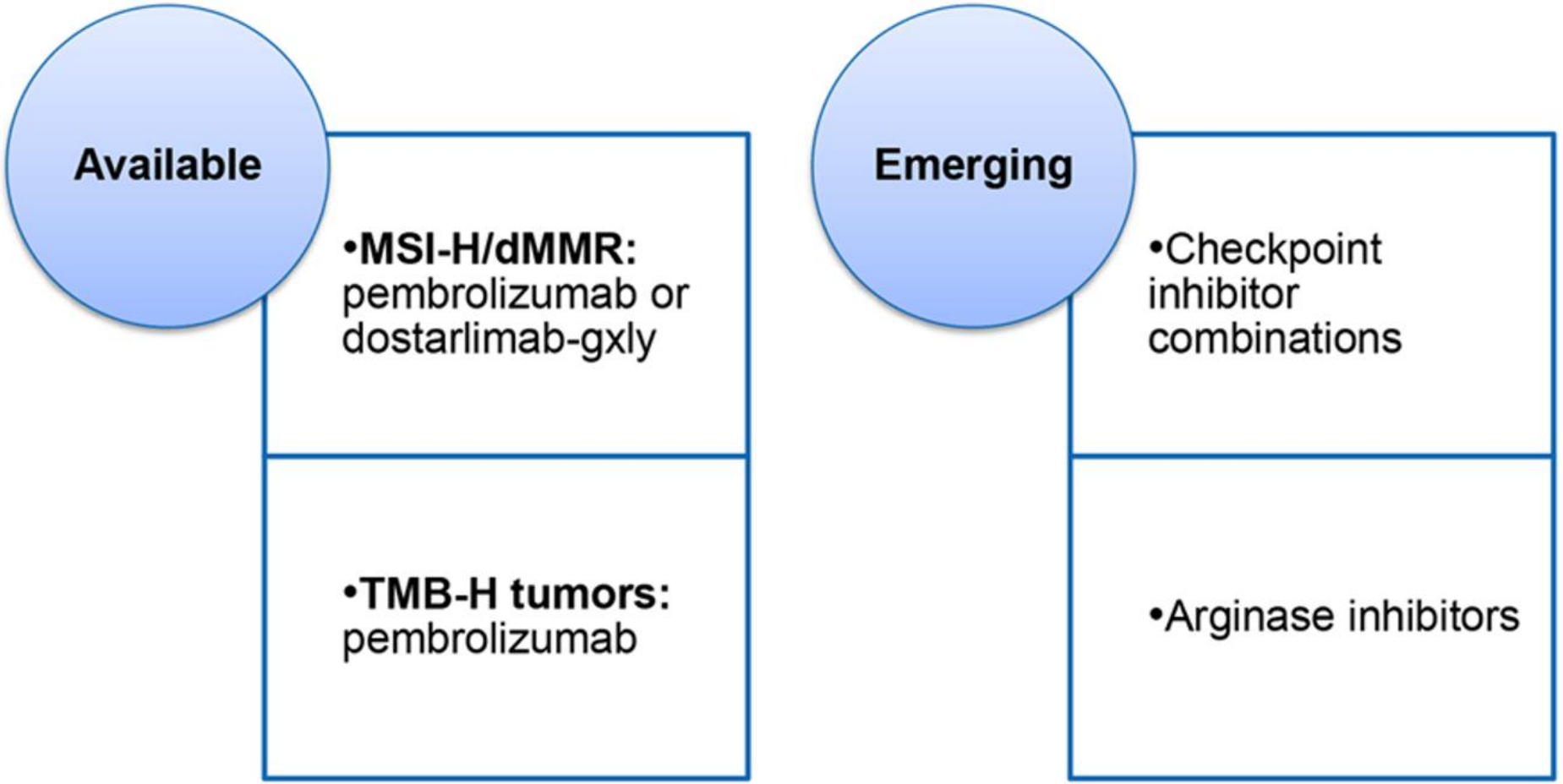
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 7)

PD-L1 IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS (Dako 22C3 pharmDx™)

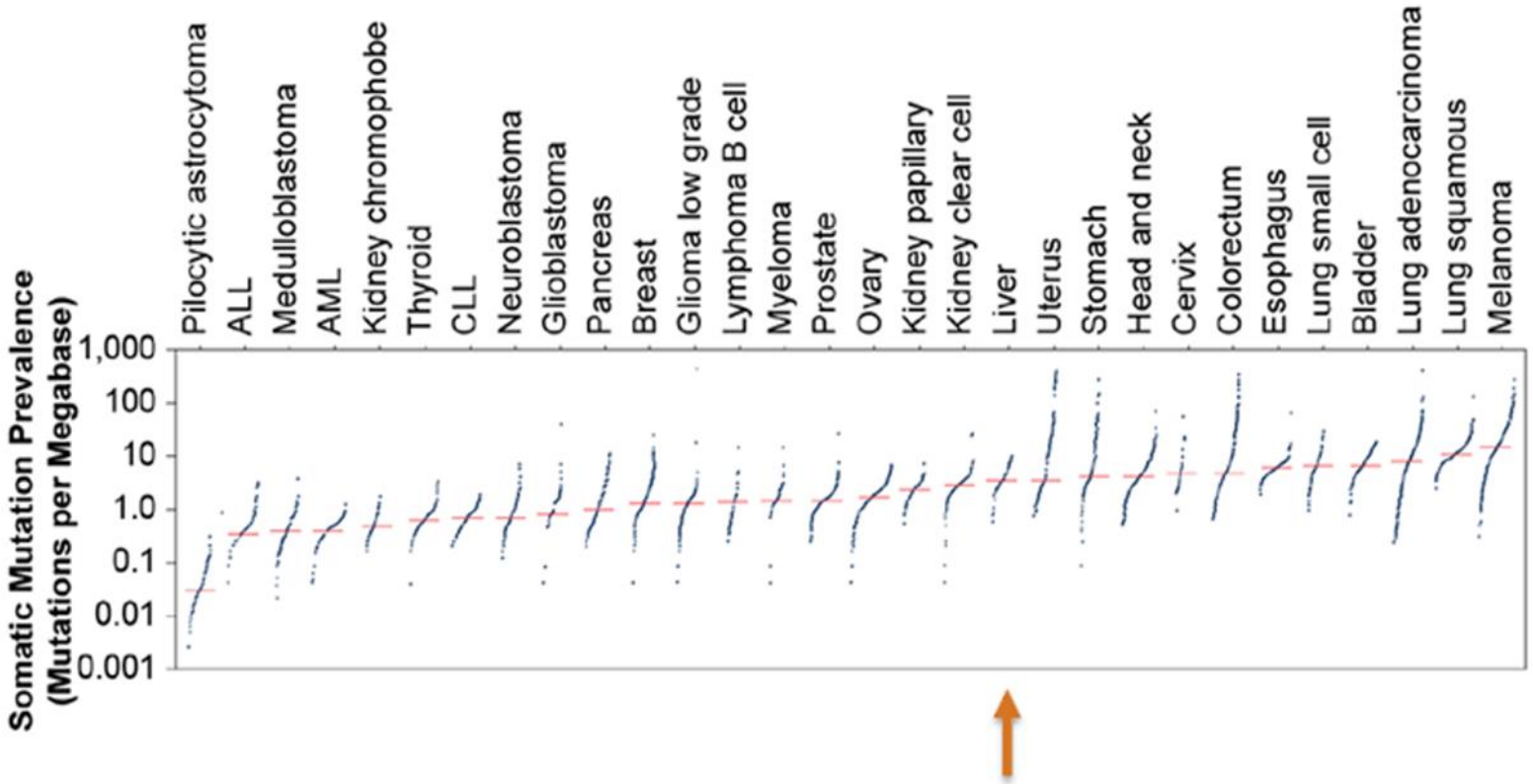
Patient Result	
Tumor Proportion Score (TPS) (%)*	**0**

** See tables 1 and 2 for interpretation.*

Immunotherapy In Biliray Tract cancer



Immunogenicity and Mutational Load



1,327 hepatic CCAs

Median TMB = 2.7 mut/Mb

TMB >10 mut/Mb = 5%

TMB >20 mut/Mb = 2%

MSI high = 1%

Alexandrov LB et al. *Nature*. 2013;500:415-421.

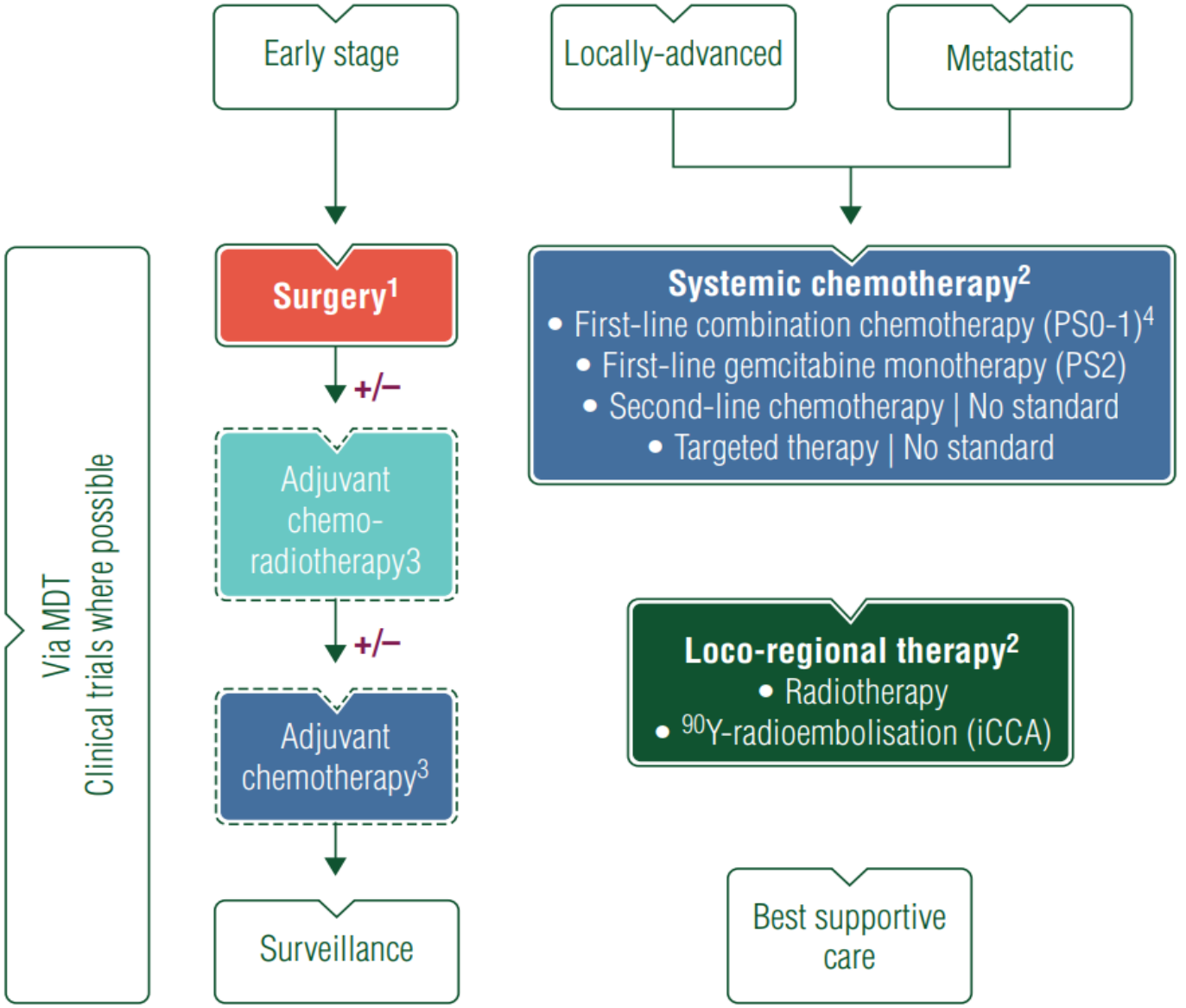
History

•**In Summary**:

- Relpased cholangiocarcinoma
- Liver lesion, Peritoneal Metastases, and ascites
- ECOG PS 0, No functional Derangement.
- PD-L1 0%, low TMB, MSS
- p53, SMAD4,APC mutations, MYC amplification

What is the treatment of choice?

ESMO guidelines 2016



Topaz1:Durvalomab

ABC—06: FOLFOX

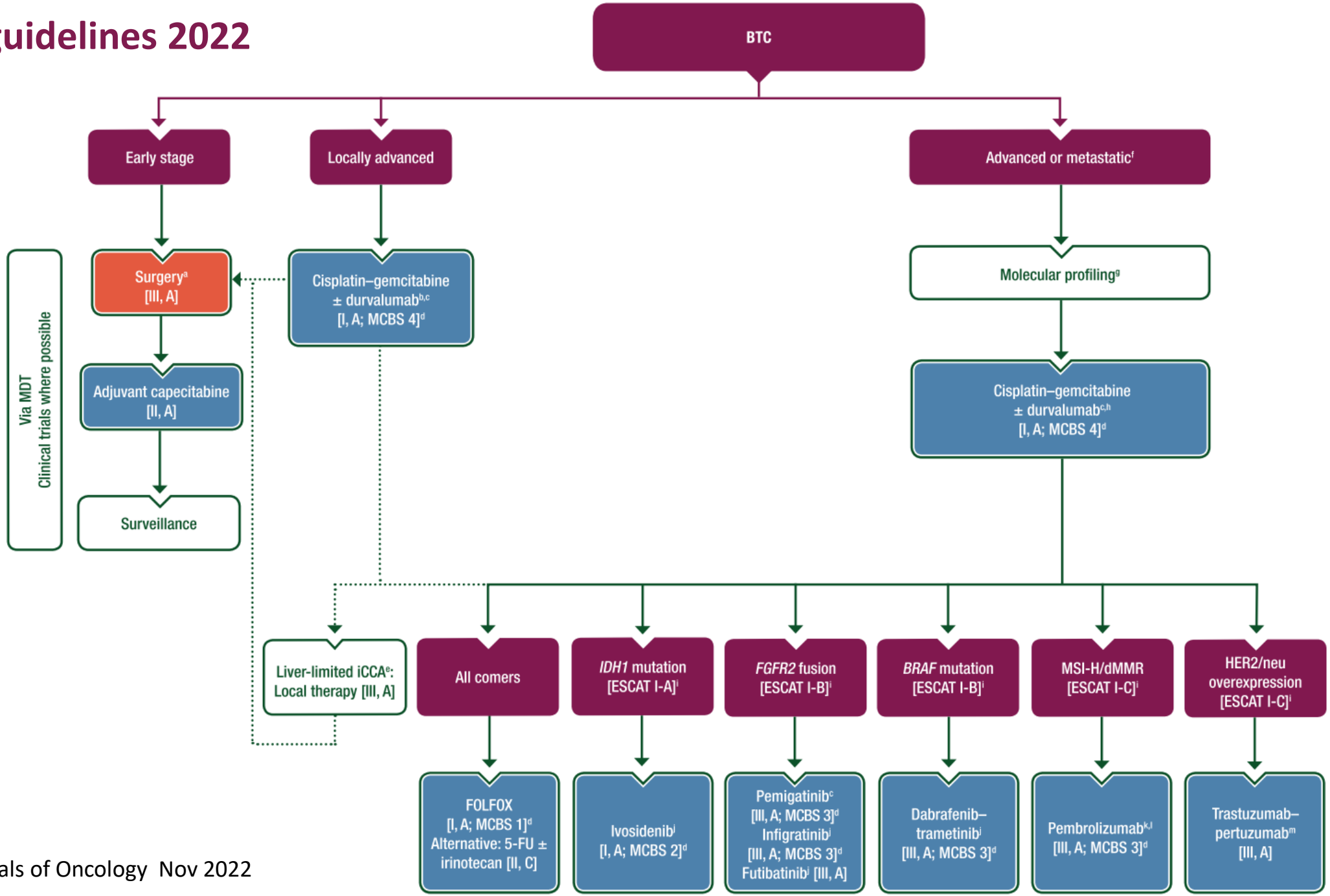
NIFTY: FOLFIRI

Molecular PAthology

CCA, cholangiocarcinoma; iCCA, intrahepatic CCA; MDT, multidisciplinary team; PS, performance status.

Valle JW, et al. *Ann Oncol.* 2016;27(suppl5):v28–v37.

ESMO guidelines 2022

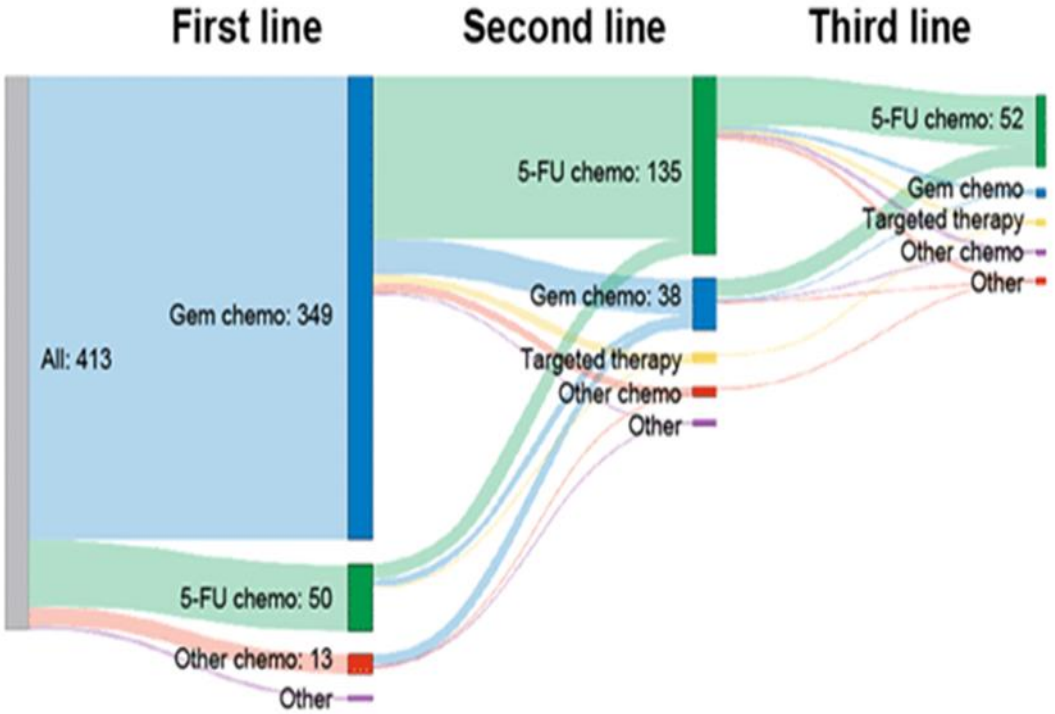


Annals of Oncology Nov 2022

Interesting options in 2nd line but..!!

A recent assessment of 1,009 oncology providers managing patients with advanced CCA found that the 81% were not confident in their ability to use targeted therapies in patients with advanced CCA

Moreover…



- 85% of patients initiated gemcitabine-based chemotherapy as their first-line treatment
- About 46% of patients initiated second-line treatments, which were predominantly 5-FU–based chemotherapies
- Few patients (17%) moved to third line of treatment
- Median time on treatment in the first line was 3.2 months and in both the second and third line was 2.7 months

1. Parikh K et al. American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI 2021). Abstract 347. 2. Valderrama A et al. ASCO GI 2022. Abstract 398.

PRINCIPLES OF SYSTEMIC THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Gemcitabine + cisplatin[4] (category 1)
- Durvalumab + gemcitabine + cisplatin (category 1)[d,5]

Other Recommended Regimens

- 5-fluorouracil + oxaliplatin
- 5-fluorouracil + cisplatin (category 2B)
- Capecitabine + cisplatin (category 2B)
- Capecitabine + oxaliplatin
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Gemcitabine + cisplatin + albumin-bound paclitaxel[1] (category 2B)
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,10,11]
- For *RET* fusion-positive tumors:
  - Pralsetinib (category 2B)[12]

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[g]

Preferred Regimens

- FOLFOX[13]

Other Recommended Regimens

- FOLFIRI[14] (category 2B)
- Regorafenib[15] (category 2B)
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)[16]
- Durvalumab + gemcitabine + cisplatin (category 2B)[h,5]
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above

Useful in Certain Circumstances

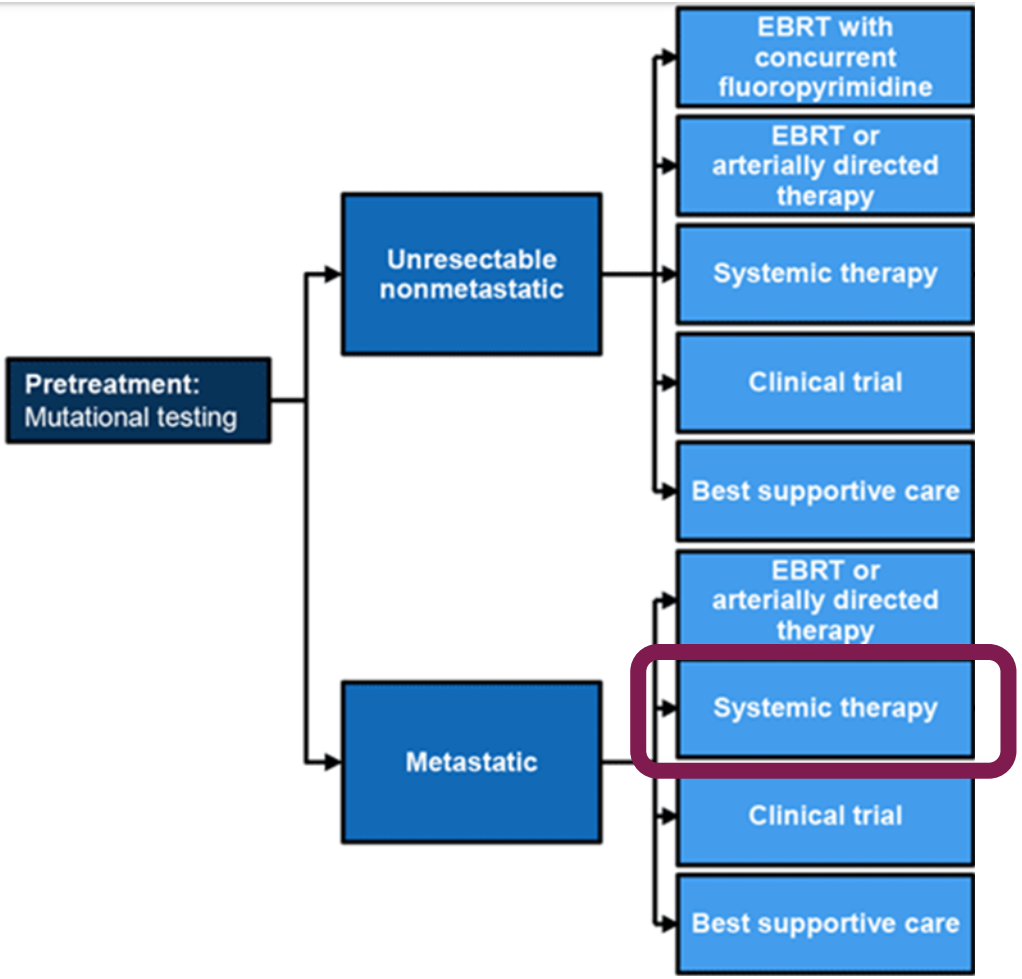
- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[6-8]
  - Larotrectinib[9]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,h,10,11]
  - Dostarlimab-gxly[f,h,i,17,18] (category 2B)
- For TMB-H tumors:
  - Pembrolizumab[e,f,h,19]
- For *BRAF*-V600E mutated tumors
  - Dabrafenib + trametinib[20,21]
- For CCA with *FGFR2* fusions or rearrangements:
  - Pemigatinib[22]
  - Infigratinib[23]
- For CCA with *IDH1* mutations
  - Ivosidenib[24,25]
- For *RET* fusion-positive tumors:
  - Pralsetinib (category 2B)[12]
- For HER2-positive tumors:
  - Trastuzumab[j] + pertuzumab[26]
- Nivolumab[f,h,27] (category 2B)
- Lenvatinib + pembrolizumab[f,h,28] (category 2B)

[d] Durvalumab + gemcitabine + cisplatin is also a recommended treatment option for patients who developed recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy.
[e] There are limited clinical trial data to support pembrolizumab in this setting. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med 2019;25:744-750.
[f] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] Treatment selection depends on clinical factors including previous treatment regimen/agent and extent of liver dysfunction.
[h] For patients who have not been previously treated with a checkpoint inhibitor because there is a lack of data for subsequent use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[i] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
[j] 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.

References
Continued

History



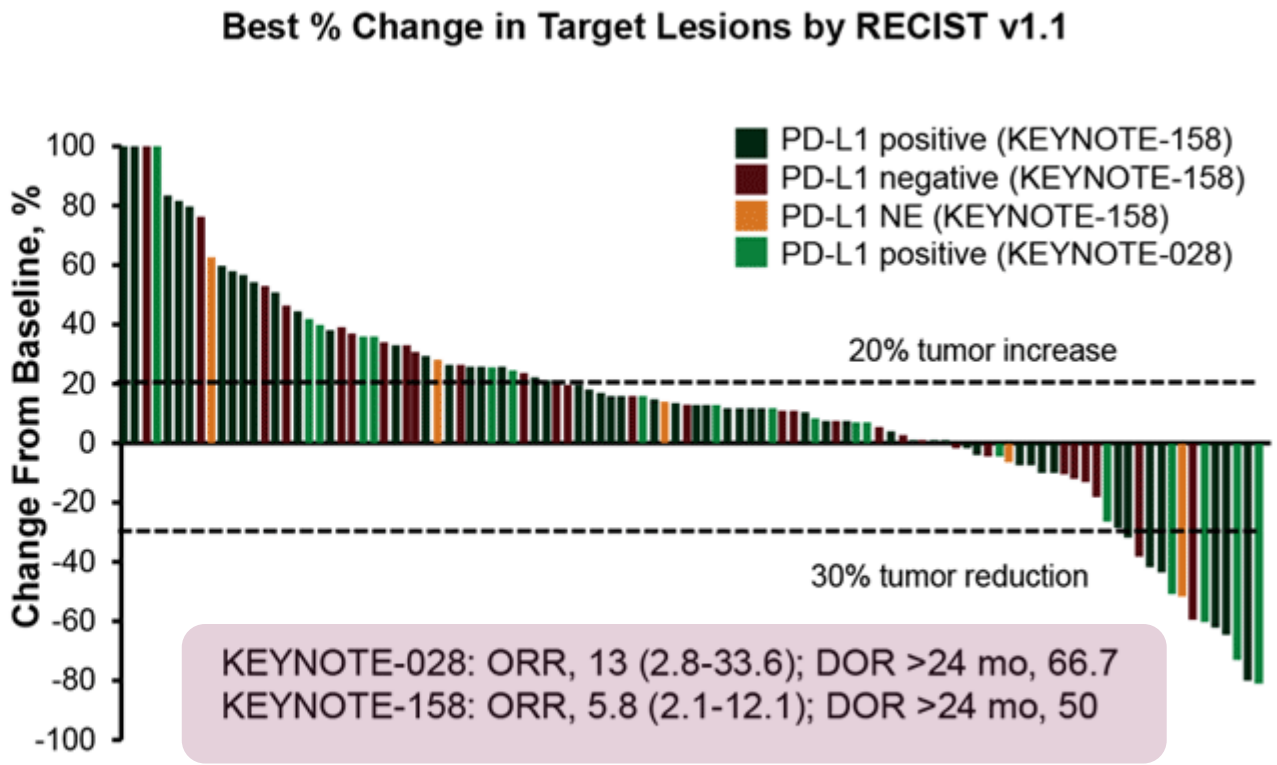
Tumor board Recommendation:

- Gemcitabine/Cisplatin/ Durvalomab x 8 cycles (at least)

→ followed by maintenance Durvalomab

Pembrolizumab In 2nd Line or beyond Biliary Cancer

- KEYNOTE-028: phase 1b biomarker-selected basket; N = 24
- KEYNOTE-158: phase 2 unselected multicohort study; N = 108
- Most heavily pretreated
- Well tolerated
  - 18% had immune-related AEs
  - 6% were grade 3; no grade 4/5 AEs
- Caveats: location of biliary cancer not collected
- At least one patient in KEYNOTE-028 was MSI-H; others missing
- Assays for PD-L1 differed between the two trials
  - KEYNOTE-028: prototype QualTek assay
  - KEYNOTE-158: CPS >1 using IHC 22C3 (Aligent)

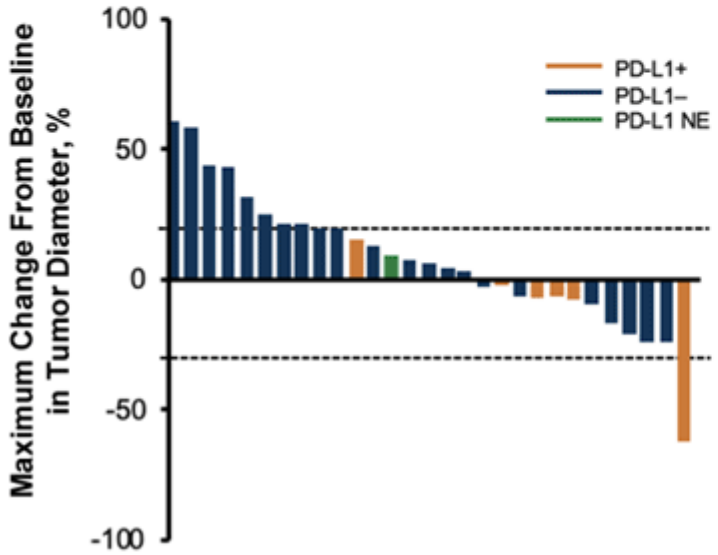


Piha-Paul SA et al. *Int J Cancer*. 2020;147:2190-2198.

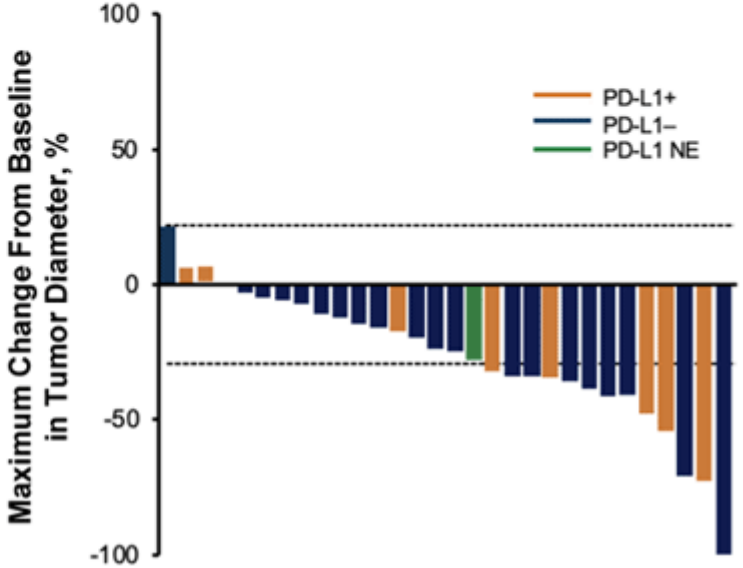
Nivolumab In 2nd line or beyond Biliary Cancer

- 46 evaluable patients from United States
- ORR was 22% by investigator review; 11% by BICR
- PD-L1 (≥1% of tumor cells) expressed on tumor cells in nine of 10 (90%) investigator-assessed responders and all five centrally reviewed responders
- All responders were MSS

Maximum Change in Tumor Diameter With Monotherapy

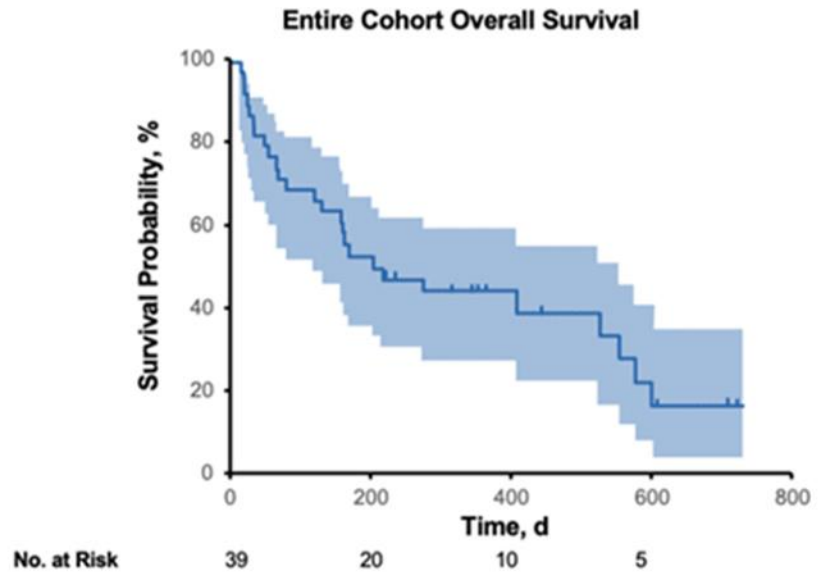


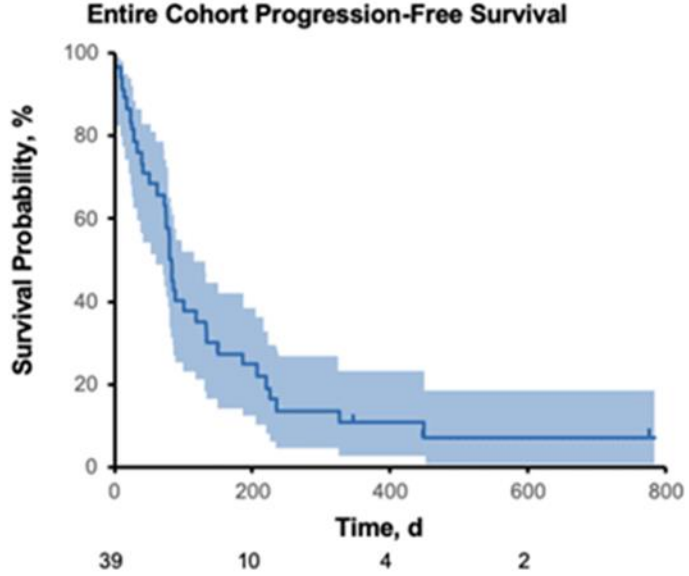
Maximum Change in Tumor Diameter With Combination Therapy



1. Kim RD et al. *JAMA Oncology*. 2020;6:888-894. 2. Ueno M et al. *Lancet Gastro Hepatol*. 2019;4:611-621.

Nivo/Ipilimumab In advanced Biliary Cancer: Phase II trial





- Subgroup analysis of 39 patients with advanced biliary cancers; most (n = 33) had disease progression after ≥1 lines of therapy
- Responses were exclusively observed in patients with intrahepatic CCA and gallbladder carcinoma
  - ORR was 23% (n = 9) with a DCR of 44% (n = 17)
  - Median DOR was not reached (range, 2.5 to ≥23 mo)
  - Median PFS was 2.9 mo (95% CI, 2.2-4.6 mo)
  - OS was 5.7 mo (95% CI, 2.7-11.9 mo)

Results compared favorably to single-agent anti–PD-1 therapy, warranting further investigation

Klein O et al. *JAMA Oncology*. 2020;6:1405-1409.

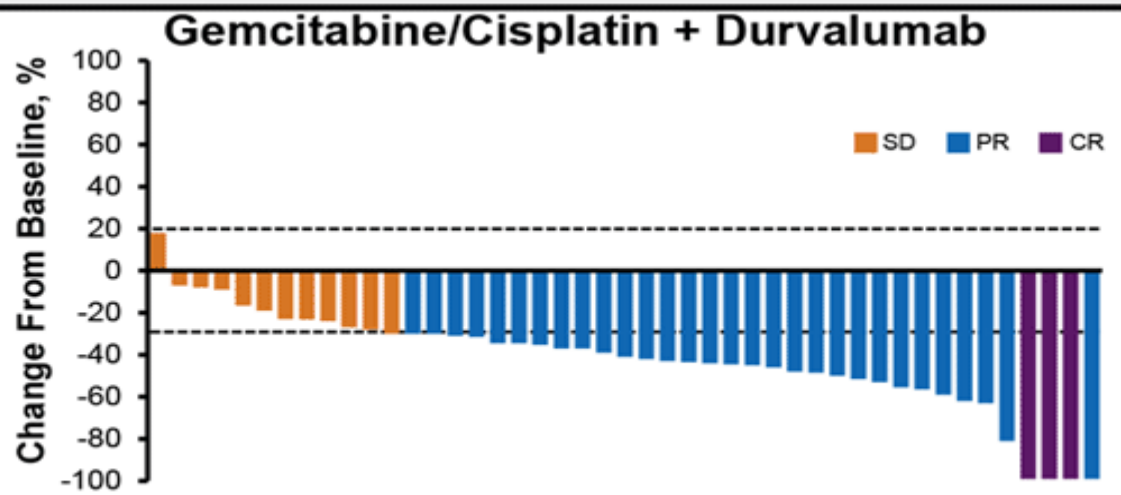
Durvalumab/Tremelimumab

Outcomes	Durvalumab (n = 42)	Durvalumab + Tremelimumab (n = 65)
ORR, %	5	11
DCR, %	16.7	32
mDOR, mo	9.7	8.5
OS, mo	8.1	10.1
AEs grade ≥3, %	19	23

Ioka T et al. *J Clin Oncol*. 2019;37(4 suppl):387-387.

Phase II trial: 1st Line GC+Durvalumab

Characteristic	Biomarker Cohort (n = 30)	Gemcitabine/Cisplatin + Durvalumab Cohort (N = 45)
ORR, % (95% CI)	50.0 (32.1-67.9)	73.4 (60.5-86.3)
Complete response	6.7 (0-15.6)	6.7 (0-14.0)
Partial response	43.3 (25.6-61.0)	66.7 (52.9-80.5)
Stable disease	46.7 (28.8-64.6)	26.7 (13.8-39.6)
Disease progression	3.3 (0-9.7)	0
DCR, % (95% CI)	96.7 (90.3-100)	100 (100-100)
Median DOR, mo (95% CI)	11.0 (3.9-18.1)	9.8 (8.1-11.4)



mPFS:11.9m

mOS:20.7m

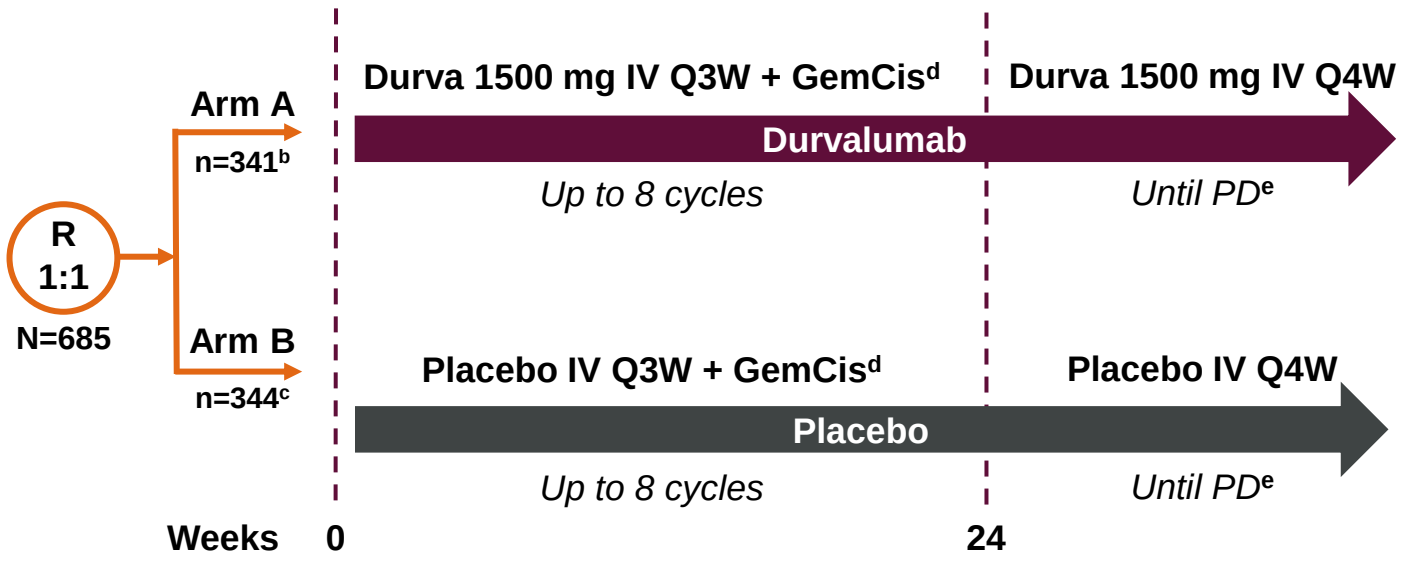
Oh D-Y et al. ASCO 2020. Poster 128.

TOPAZ-1: Study Design[1,2]

Phase III, randomized, double-blind, placebo-controlled, multicenter global study for first-line treatment in patients with advanced biliary tract cancer (BTC)

Study population

- Previously untreated, unresectable, locally advanced or metastatic BTC (ICC, ECC and GBC) at initial diagnosis
- Recurrent disease >6 months after curative surgery or completion of adjuvant therapy [a]
- ECOG PS of 0 or 1



Primary endpoint[1,2]

- OS

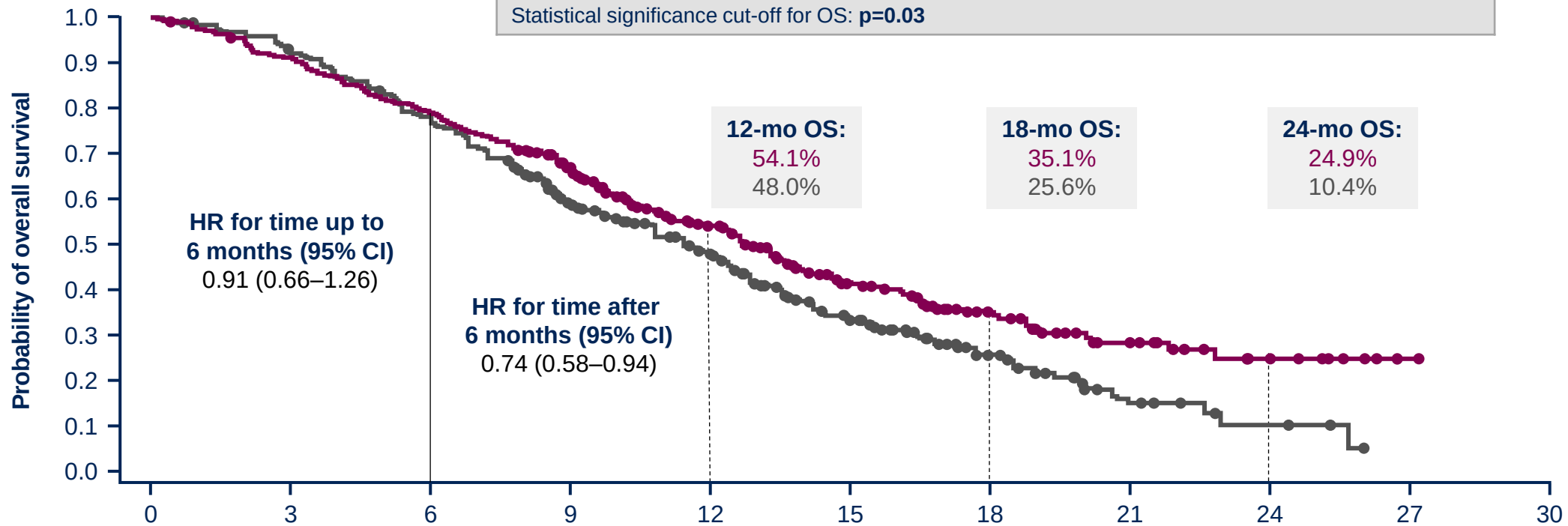
Key secondary endpoints[1,2]

- PFS[f]
- ORR[f]
- DoR[f]
- DCR[f]
- Serum concentration of durvalumab
- Tiered results of ADAs for durvalumab
- HRQoL[g]
- Safety and tolerability[1]

[a]Chemotherapy and/or radiation; [b]338 received treatment; [c]342 received treatment; [d]Cisplatin (25 mg/m^2) followed by gemcitabine (1000 mg/m^2), each administered on Days 1 and 8, q3w for up to 8 cycles (SoC chemotherapy) [e]Until confirmed PD, withdrawal of consent, or another discontinuation criteria is met; [f]Measured according to RECIST 1.1 using investigator assessments and OS by PD-L1 expression; [g]Measured with EORTC QLQ-C30 and EORTC QLQ-BIL21.
Abbreviations and references in slide notes.

TOPAZ-1: Durvalumab + GemCis Improved OS vs. GemCis Alone

	Median OS, months (95% CI)	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis[a] (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis[a] (n=344)	11.5 (10.1–12.5)		
Statistical significance cut-off for OS: **p=0.03**			



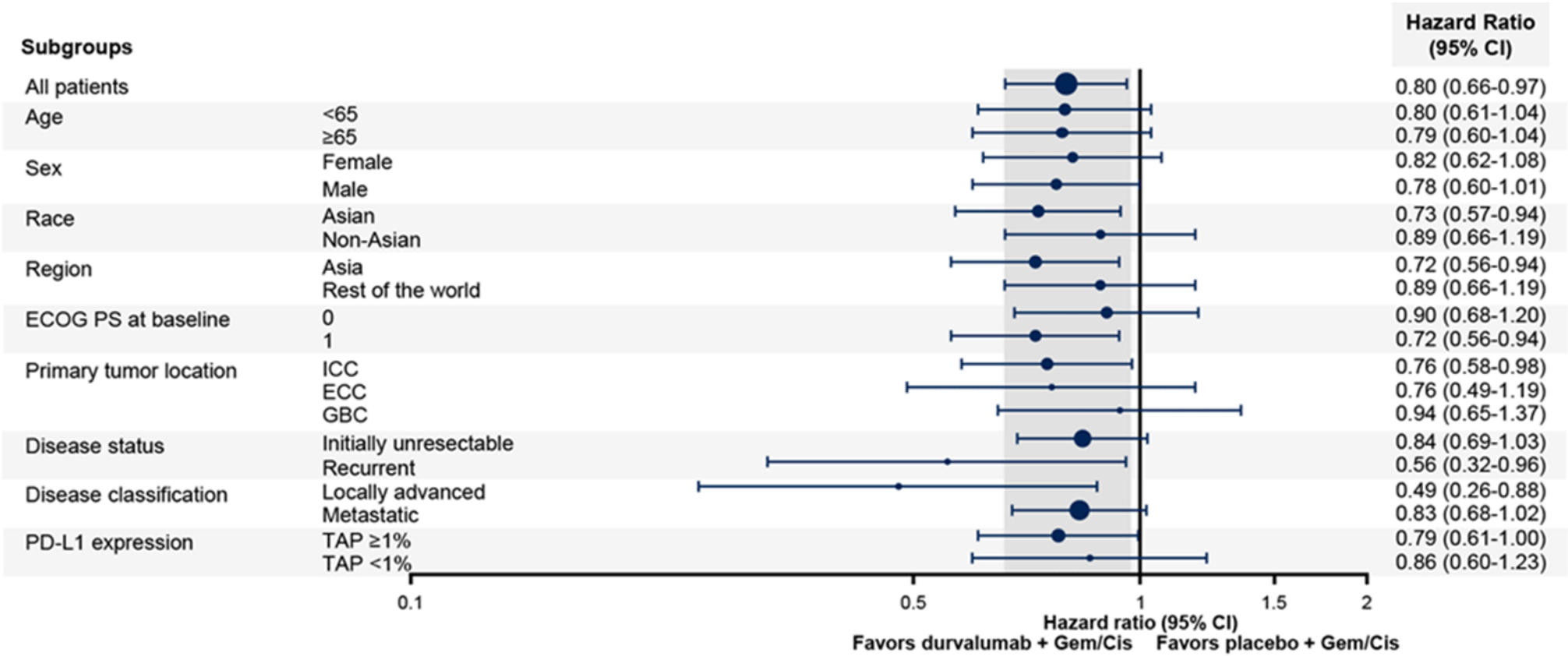
Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

[a]Median duration of follow-up (95% CI) was 16.8 (14.8–17.7) months with durvalumab + GemCis and 15.9 (14.9–16.9) months with placebo + GemCis.

CI = confidence interval; GemCis = gemcitabine + cisplatin; HR = hazard ratio; mo = month; OS = overall survival.

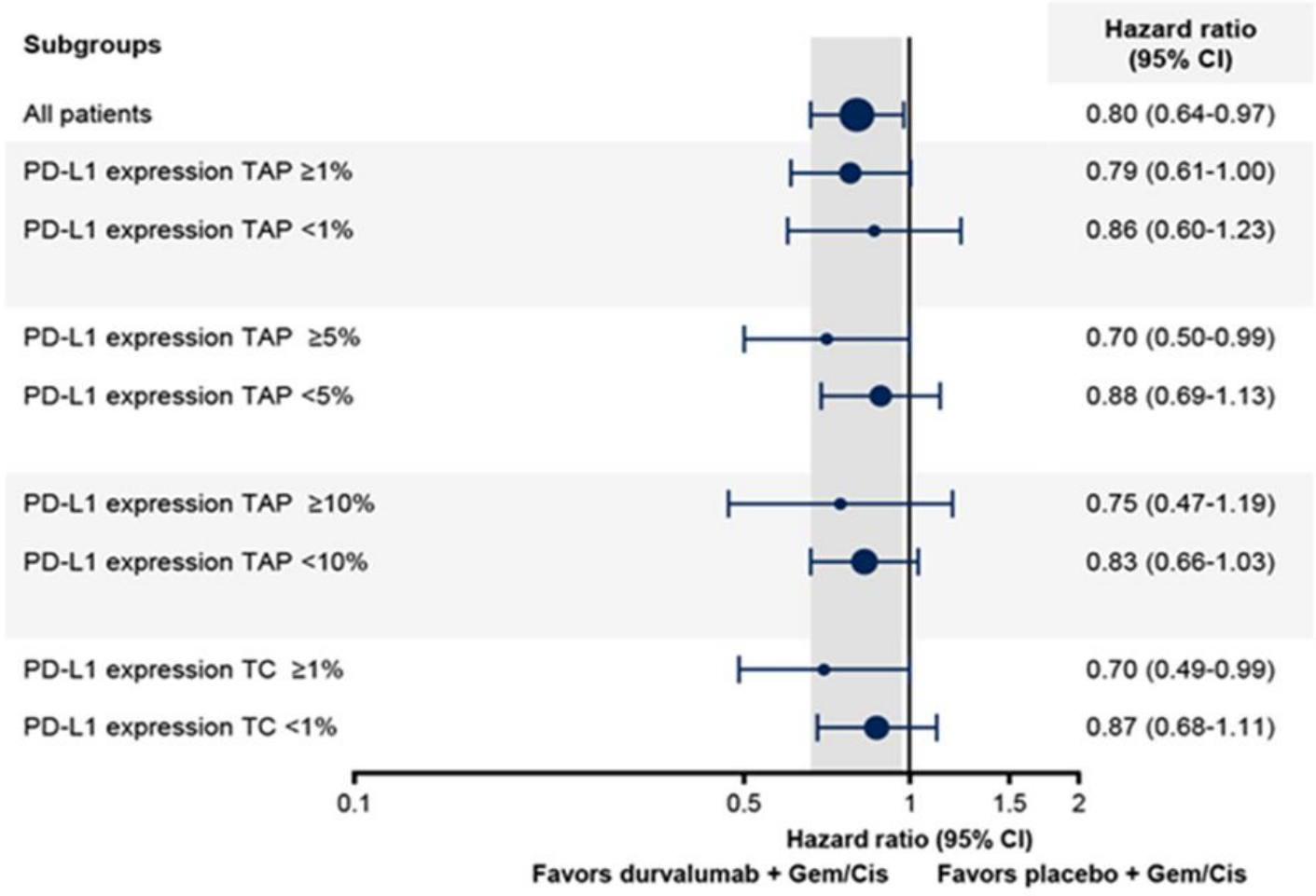
Oh D-Y, et al. Presented at: ASCO GI Congress; January 20-22, 2022; San Francisco, CA.

Phase III TOPAZ-1 study : Subgroups OS Analysis



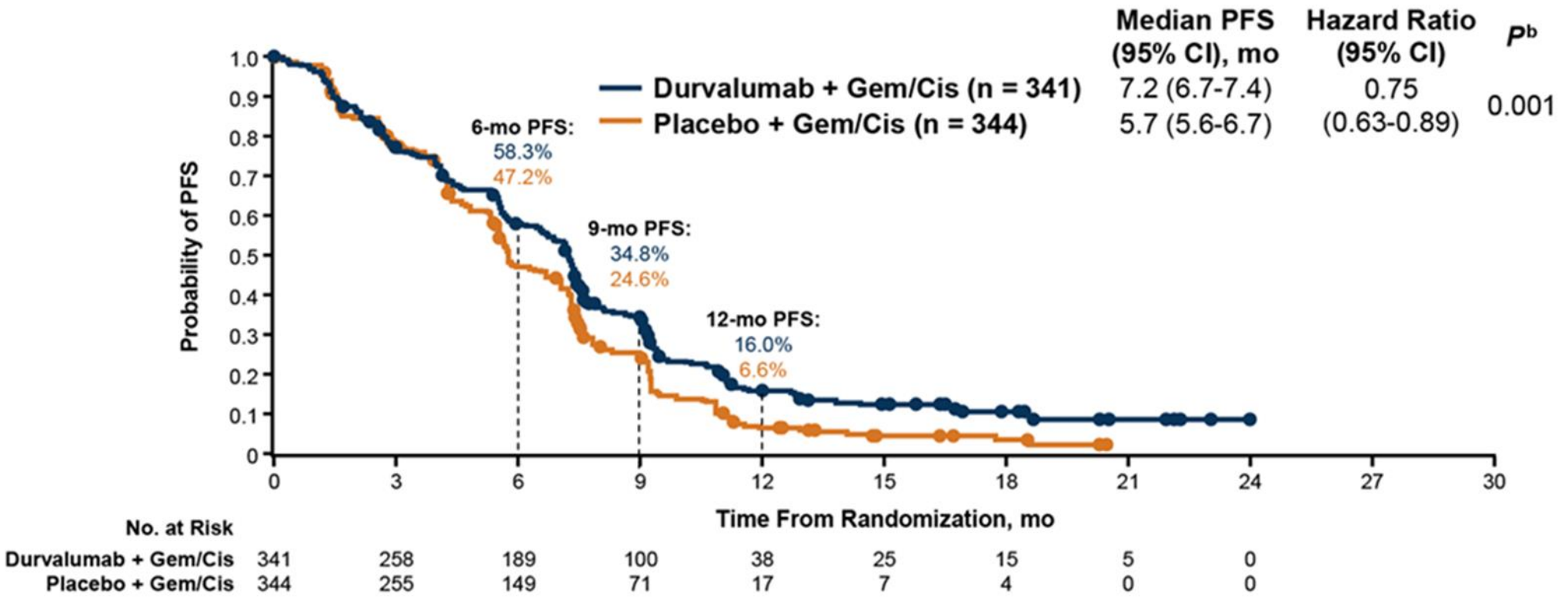
Oh D-Y, et al. ASCO GI Congress; January 2022

Phase III TOPAZ-1 study : PD-L1 % Subgroups OS Analysis



Oh D-Y, et al. ASCO GI Congress; January 2022

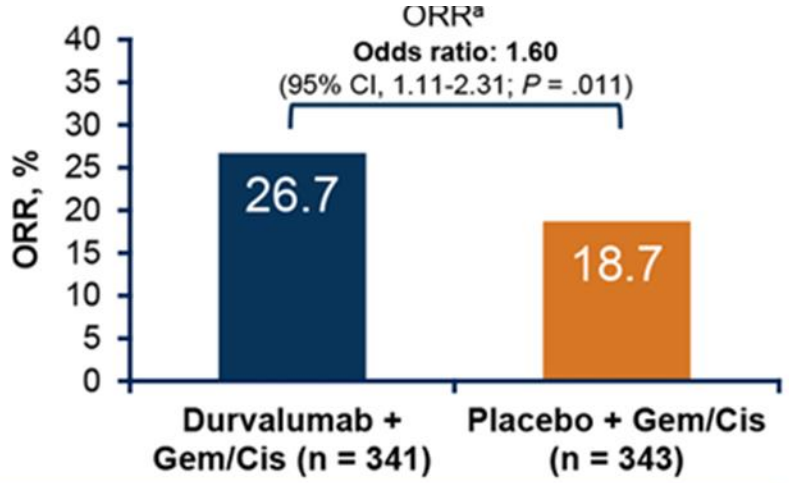
Phase III TOPAZ-1 study : PFS



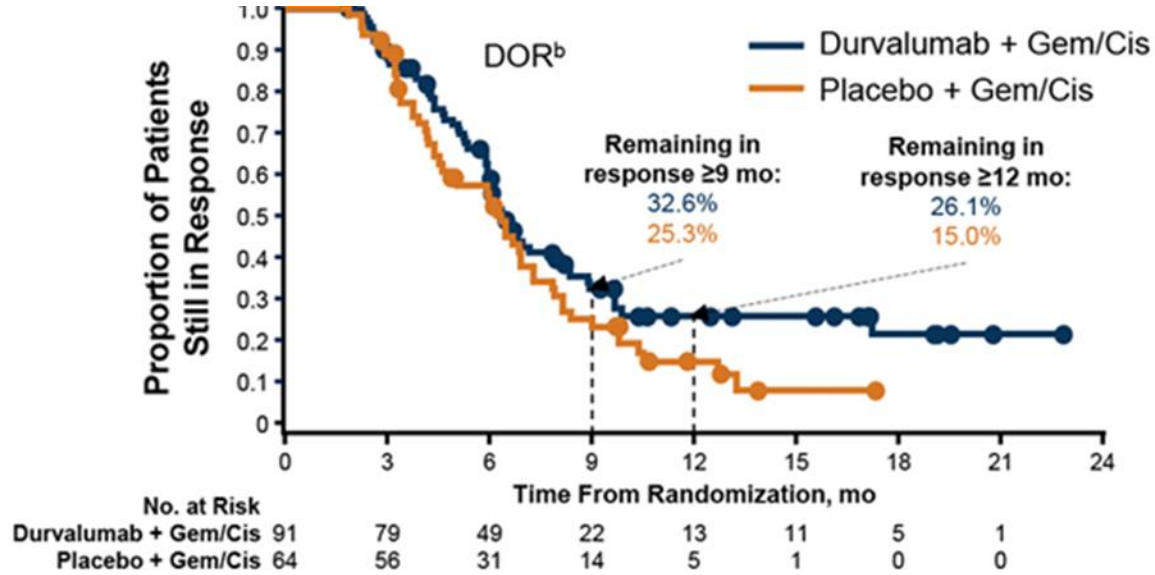
[a] Median duration of follow-up (95% CI) was 9.2 (0-24.0) months with durvalumab + Gem/Cis and 6.9 (0-20.4) months with placebo + Gem/Cis.
[b] Statistical significance cut-off for PFS: $P = .0481$.

Oh D-Y, et al. ASCO GI Congress; January 2022

Phase III TOPAZ-1 study :Response Rate, and DOR



	Durvalumab + Gem/Cis (n = 341)	Placebo + Gem/Cis (n = 343)
ORR, n (%)	91 (26.7)	64 (18.7)
CR, n (%)	7 (2.1)	2 (0.6)
PR, n (%)	84 (24.6)	62 (18.1)
DCR, n (%)[c]	291 (85.3)	284 (82.6)



	Durvalumab + Gem/Cis (n = 91)	Placebo + Gem/Cis (n = 64)
Median DOR (quartile 1-3), mo	6.4 (4.6-17.2)	6.2 (3.8-9.0)
Median time to response (quartile 1-3), mo	1.6 (1.3-3.0)	2.7 (1.404.1)

[a] By investigator assessments using RECIST v1.1 based on patients in the final analysis set who had measurable disease at baseline. [b] Analysis of DOR was based on patients in the full analysis set who had an objective response and measurable disease at baseline. [c] Analysis of DCR was based on all patients in the full analysis set.

Oh D-Y, et al. ASCO GI Congress; January 2022

History

- **2/2023:** patient received so far 3 doses of GC/durvalumab

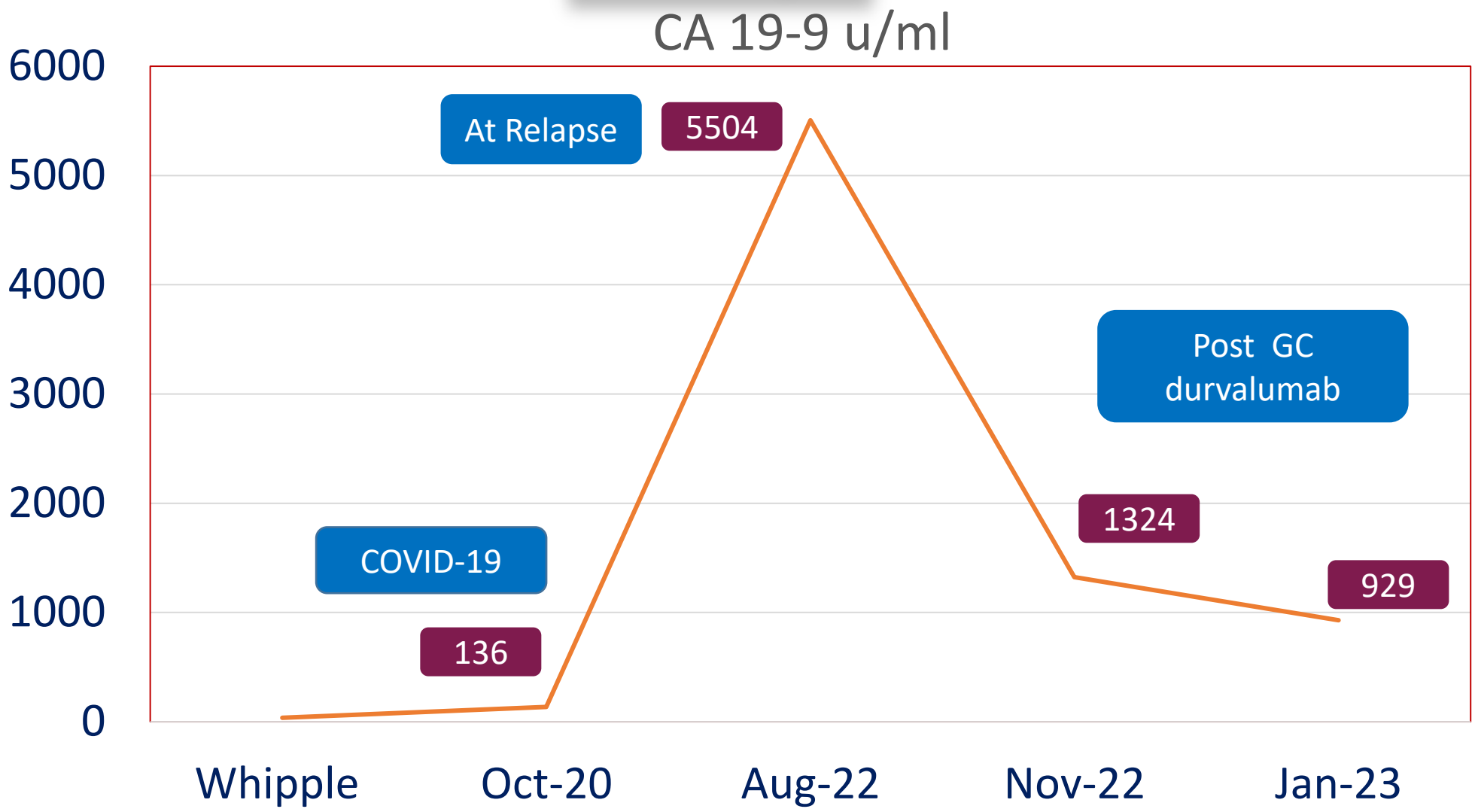
•Clinically:

- Patient is completely asymptomatic

- No reported side effects except mild alopecia

- Increase in body weight, excellent performance status

History


CA 19-9 u/ml
6000
5000
4000
3000
2000
1000
0
At Relapse
5504
COVID-19
136
Post GC durvalumab
1324
929
Whipple
Oct-20
Aug-22
Nov-22
Jan-23

Thank You