

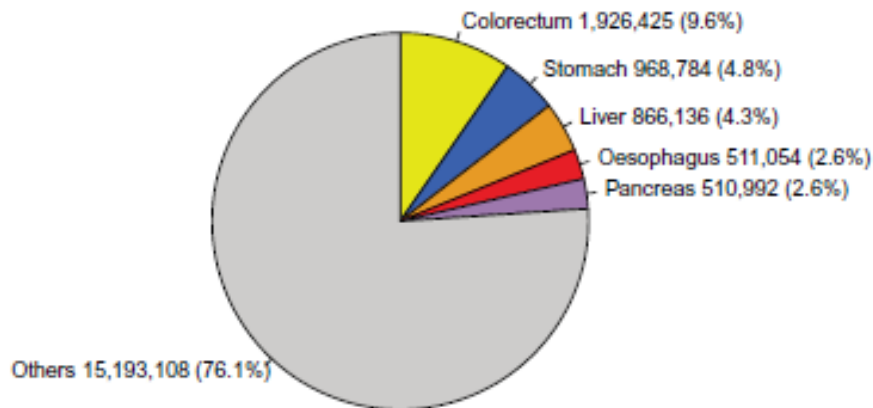
NUOVE FRONTIERE NELLA TERAPIA MEDICA DEI TUMORI DEL TRATTO GASTROENTERICO

**CORSO AGGIORNAMENTO PER IL MEDICO DI BASE
PALAZZO CONGRESSI, LUGANO
15.10.2025**

PD Dr Piercarlo Saletti

GI big killer

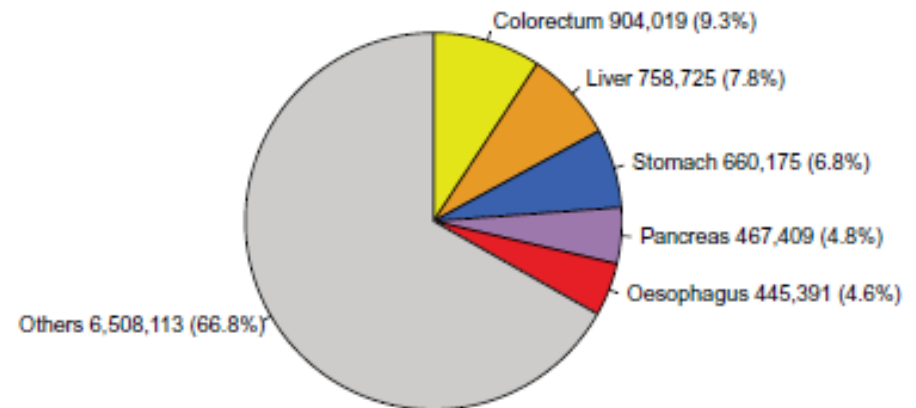
(A) Incidence



All cancers: 19,976,499

All 5 GI cancers: 4,783,391 (23.9%)

(B) Mortality



All cancers: 9,743,832

All 5 GI cancers: 3,235,719 (33.2%)

Evoluzione delle cure



3000 AC-1890



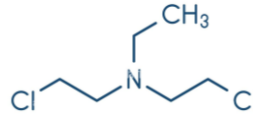
Chirurgia e
cauterizzazioni
le sole opzioni
terapeutiche



1900



Marie e Pierre
Curie danno il
via alla
radioterapia



1940



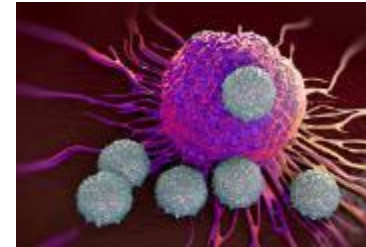
Sviluppo dei
chemioterapici



1980



Avvento dei
farmaci a
bersaglio
molecolare
(anticorpi e
inibitori di
tirosin-chinasi)

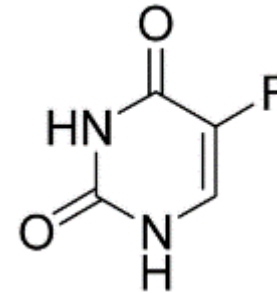


2010



Sviluppo di
anticorpi
monoclonali
capaci di
stimolare la
risposta
immunitaria
(checkpoint
inhibitors)

70 anni fa



CLINICAL EVALUATION OF CANCER CHEMOTHERAPY
WITH 5-FLUOROURACIL

V. K. VAITKEVICIUS, M.D., M. J. BRENNAN, M.D., V. L. BECKETT, M.D., J. E. KELLY, M.D.,
AND R. W. TALLEY, M.D.

CANCER January-February 1961



APRIL 13, 1959. DR. CHARLES H. HARRIS, of the Univ. of Wis. Medical Laboratory, adjusts a Geiger counter to trace the drug 5-fluorouracil which inhibits growth of cancer cells. He announced the drug here 4/3. UNITED PRESS TELE

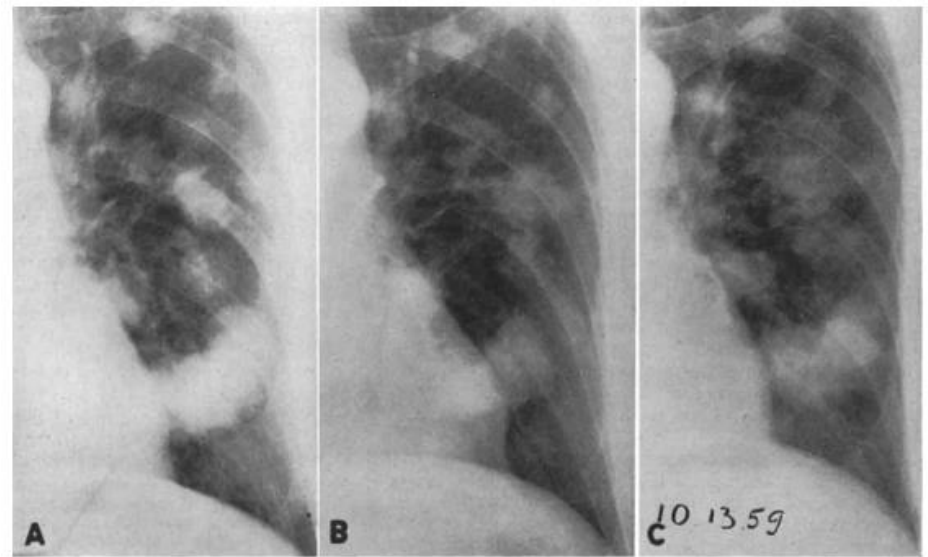


FIG. 8. Case 7. Pulmonary metastasis in a patient with adenocarcinoma of the colon. A, April 3, 1959. B, Sept. 5, 1959. C, Oct. 13, 1959.

Paradigma: medicina di precisione

- Meccanismi molecolari che regolano la carcinogenesi
- Identificazione di geni «druggable»
 - Next-generation sequencing (NGS), profili molecolari e biomarkers
- Limiti
 - Non per tutti (assenza del bersaglio)
 - Eterogeneità tumorale
 - Resistenza
 - Costi elevati
 - Accessibilità ai farmaci

HER2
Immune-evasion
MMR/MSI
Claudin 18.2
angiogenesi
NTRK
BRAF
TMB-H



Immune-evasion
angiogenesi
MMR/MSI
NTRK
RET



EGFR
BRAF
MMR/MSI
HER2
NTRK
TMB-H
RET
KRAS G12C
PIK3CA



Immune-evasion
IDH1
FGFR2
MMR/MSI
HER2
BRAF
NTRK
TMB-H
RET
KRAS G12C

NRG1
KRAS G12C
HER2
FGFR

Next Generation Sequencing – Analisi TMB

Marcatore	Risultato	Interpretazione
TML (Tumor mutation Load)	9.23 mutazioni/Mb	TML basso

Per i criteri di interpretazione del TML vedi sezione descrizione microscopica/analisi complementari.

Next Generation Sequencing – Analisi Mutazionale

Gene	Risultato
IDH1	Presenza della mutazione p.R132C
FGFR2	Presenza della mutazione p.C382R
TAF1	Presenza della mutazione p.R750VfsTer15

La mutazione identificata nel gene TAF1 è una mutazione frameshift che porta alla formazione di un codone di stop precoce e quindi verosimilmente ad una perdita della funzionalità della proteina codificata. Pertanto tale mutazione è considerata patogena nonostante non sia mai stata descritta in letteratura e nei database specifici.

Sono state individuate mutazioni in altri geni inclusi nel pannello il cui significato clinico e l'impatto sulla funzionalità proteica non è noto (VUS) (tali varianti non sono state descritte, o solo raramente, in letteratura e nei database specifici). Vedi sezione descrizione microscopica/analisi complementari.

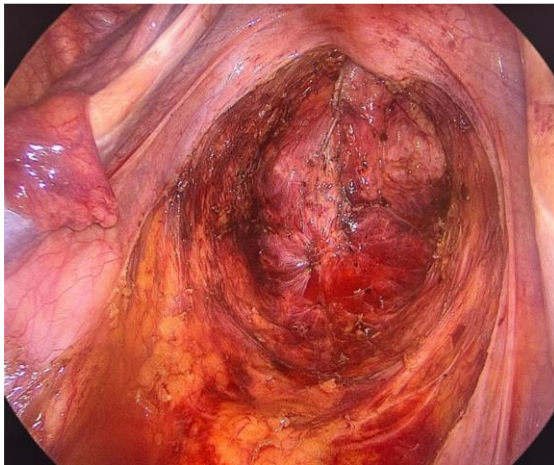
Dati sul campione analizzato

Materiale analizzato	DNA genomico estratto da tessuto fissato in formalina e incluso in paraffina contenente almeno il 30% di cellule tumorali. Il DNA estratto viene sottoposto a trattamento con UDG per ridurre gli artefatti da fissazione.
Rappresentatività del materiale (Patologo)	cellularità neoplastica: 70% (MZ)
Codice identificativo interno	T21-1584

Dati generali della metodica utilizzata

Tecnologia	Next generation sequencing tramite Ion Torrent (ThermoFisher)
Pannello	OncoPrint Tumor Mutation Load Assay (TML, ThermoFisher)
Biomarcatori/Geni inclusi nel pannello	Viene valutata l'intera sequenza codificante di 409 geni (15500 regioni target) comprendenti 1.2 Mb di regione esonica per l'analisi del Tumor Mutation Load (TML) e delle varianti tumorali somatiche. Alcuni geni inclusi nel pannello sono: AKT1, AKT2, AKT3, ALK, AR, ARID1A, ASXL1, ATM, ATR, ATRX, AXL, BAP1, BRAF, BTK, CBL, CCND1, CDK4, CDK6, CDK12, CDKN2A, CDKN2B, CEBPA, CHEK1, CHEK2, CREBBP, CSF1R, CTNNB1, DDR2, DNMT3A, EGFR, ERBB2, ERBB3, ERBB4, ERCC2, ESR1, EZH2, FANCA, FANCD2, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FOXL2, GATA2, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KDR, KIT, KRAS, MAP2K1, MAP2K2, MAP2K4, MAPK1, MDM4, MET, MLH1, MPL, MRE11A, MSH2, MSH6, MTOR, MYC, MYCN, MYD88, NBN, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NPM1, NRAS, NTRK1, NTRK3, PALB2, PDGFRA, PDGFRB, PIK3CA, PIK3CB, PIK3R1, PMS2, PP2R1A, PTCH1, PTEN, PTPN11, RAD50, RAF1, RB1, RET, ROS1, RUNX1, SETD2, SF3B1, SMAD4, SMARCA4, SMARCB1, SMO, SRC, STK11, TET2, TOP1, TP53, TSC1, TSC2, WT1.

Cura

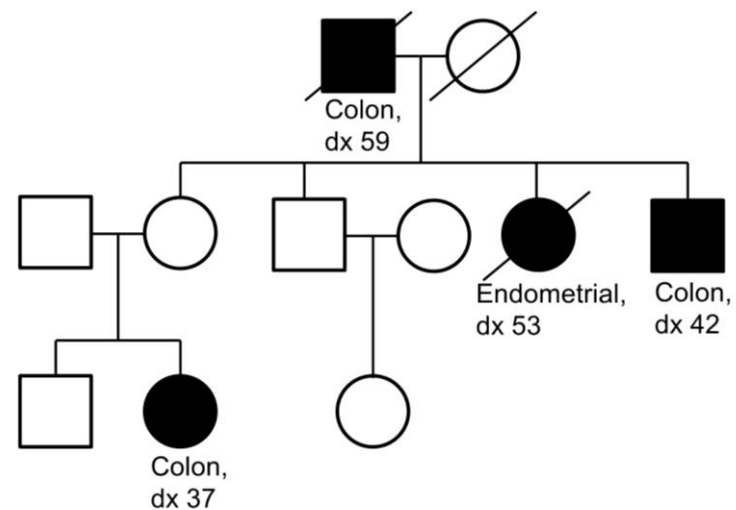
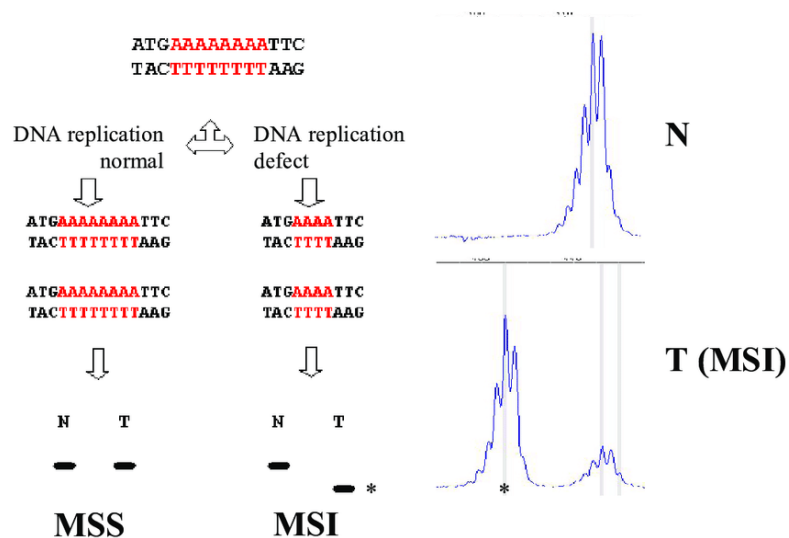


Palliazione



Instabilità genomica: MSI (15-20%)

- Deficit del sistema di riparazione (MMR)
- Sporadico o ereditario (Lynch, 5%)



Colorettale: MSI-H/immuno

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Microsatellite-Instability-High Metastatic Colorectal Cancer

N Engl J Med 2024;391:2014-26

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

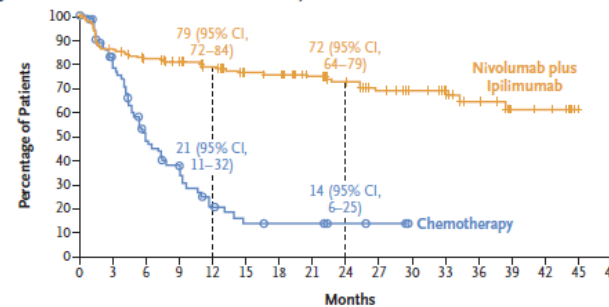
JUNE 23, 2022

VOL. 386 NO. 25

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

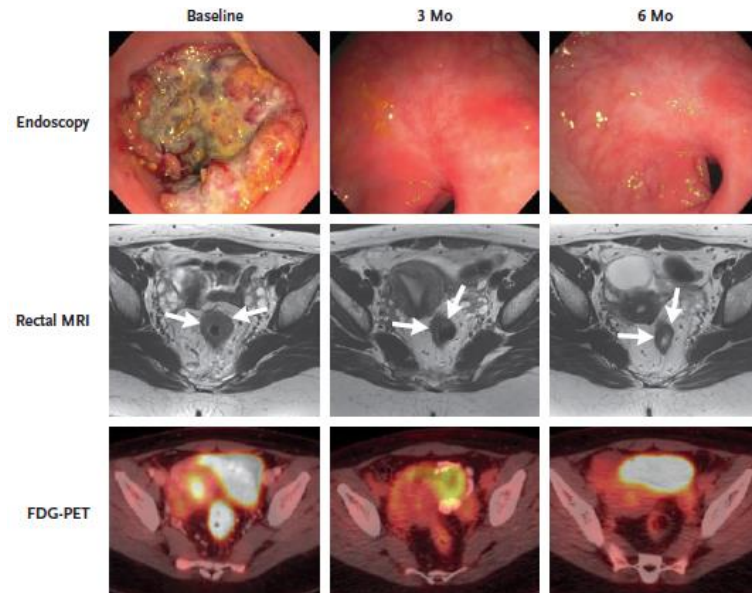
- Dostarlimab
- Fase 2, 30 pazienti
- 100% risposte complete nei primi 12 arruolati

Progression-free Survival in Patients with Centrally Confirmed MSI-H or dMMR Metastatic Colorectal Cancer



No. at Risk

Nivolumab plus ipilimumab	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemotherapy	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0



The NEW ENGLAND JOURNAL of MEDICINE

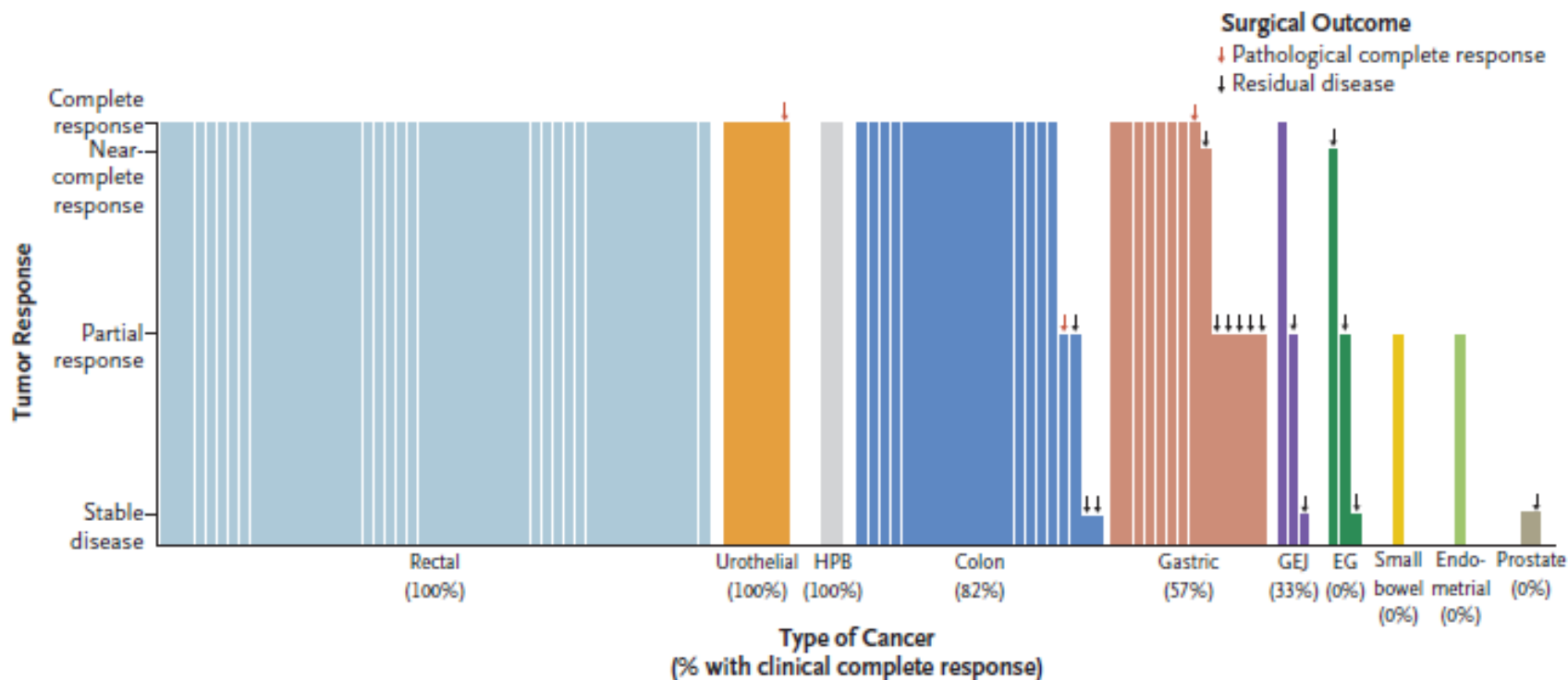
ESTABLISHED IN 1812

JUNE 19, 2025

VOL. 392 NO. 23

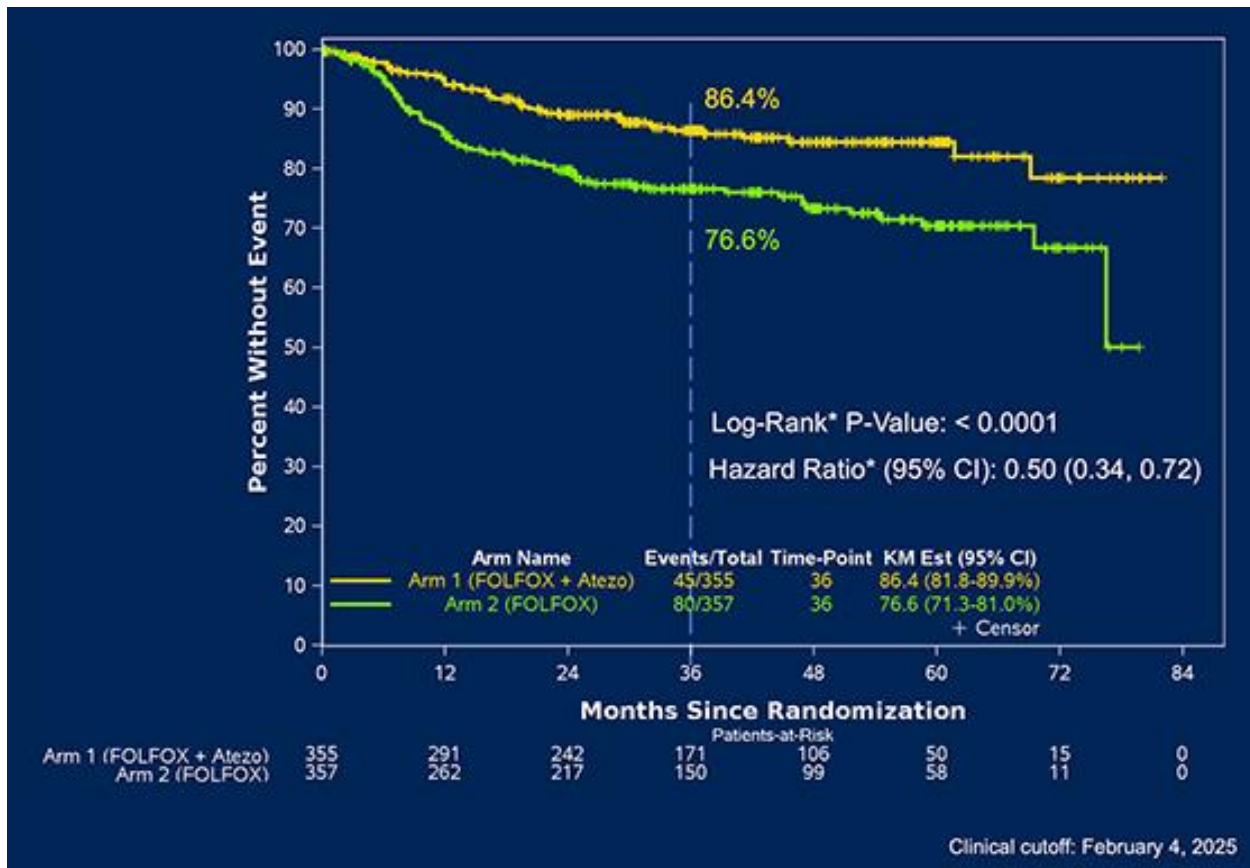
Nonoperative Management of Mismatch Repair–Deficient Tumors

Clinical Response



Colon stadio III, adiuvante: MSI-H/immuno/CxT

ATOMIC Trial: DFS (endpoint primario)



2025 ASCO ANNUAL MEETING

Colorettale, adjuvante: PIK3CA (10-30%)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

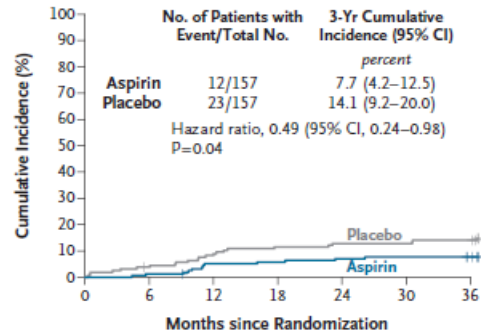
SEPTEMBER 18, 2025

VOL. 393 NO. 11

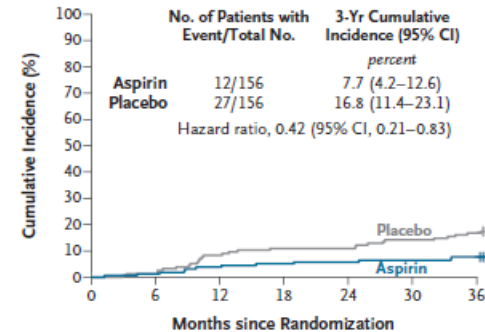
Low-Dose Aspirin for PI3K-Altered Localized Colorectal Cancer

- stage I, II, or III rectal cancer or stage II or III colon cancer
- somatic alterations in PI3K pathway genes
- 160 mg of aspirin or matched placebo once daily for 3 years

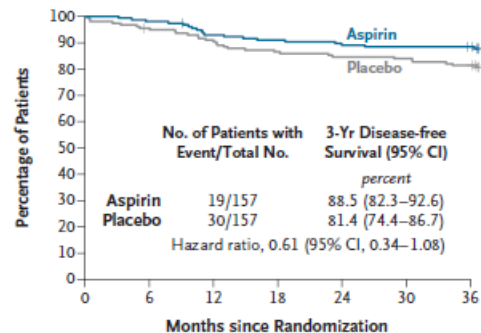
A Colorectal Cancer Recurrence among Patients with Group A Alterations



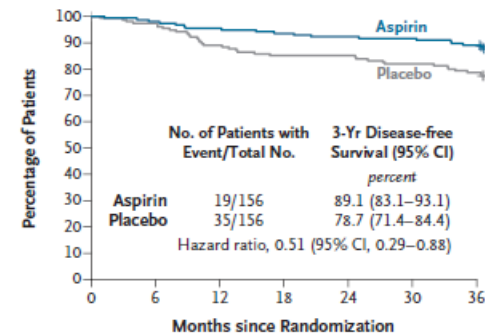
B Colorectal Cancer Recurrence among Patients with Group B Alterations



C Disease-free Survival among Patients with Group A Alterations



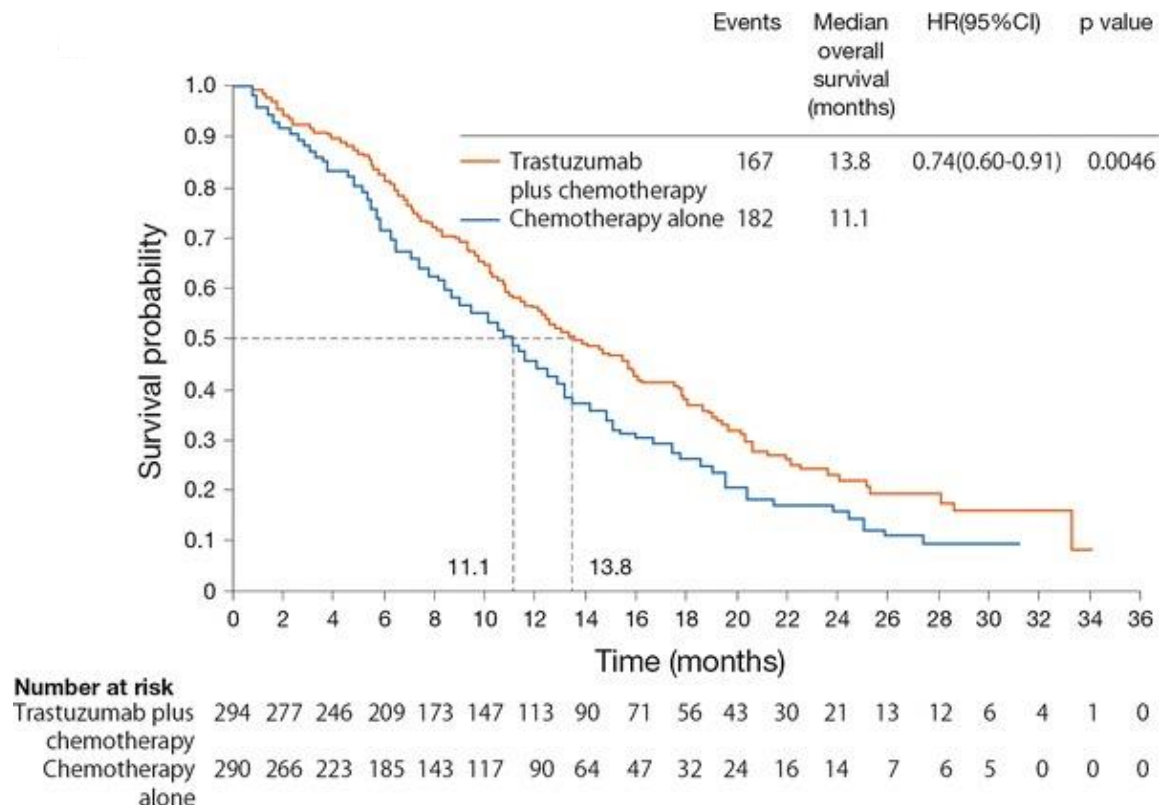
D Disease-free Survival among Patients with Group B Alterations



Esofagogastrico: HER 2 pos (10-15%)

TOGA Trial: OS (endpoint primario)

Bang YJ, Lancet 2010



Esofagogastrico: immuno/CxT

A
D
E
N
O

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ESTABLISHED IN 1812

JULY 17, 2025

VOL. 393 NO. 3

Perioperative Durvalumab in Gastric and Gastroesophageal Junction Cancer

KEYNOTE-859: 4.5-year median follow-up of pembrolizumab plus chemotherapy for previously untreated advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.

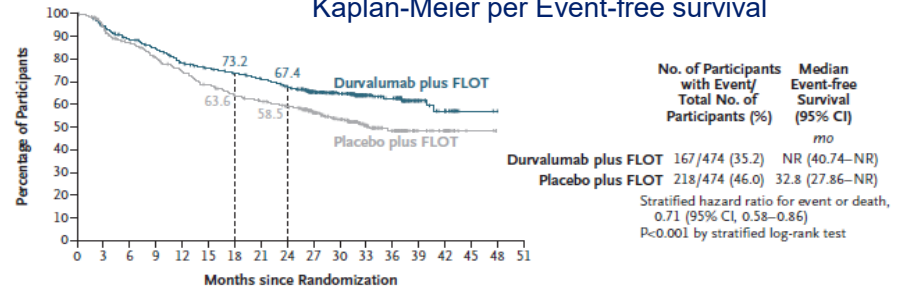
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma

S
C
C

Kaplan-Meier per Event-free survival

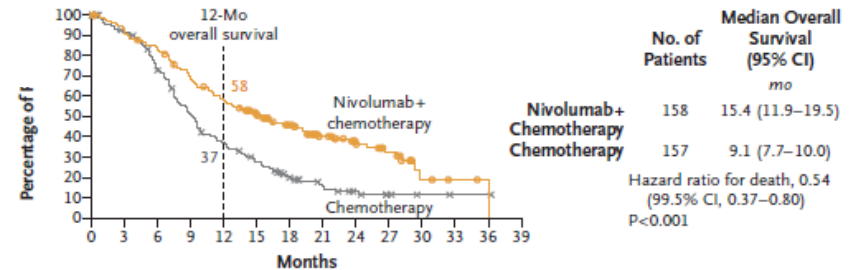


No. at Risk

Durvalumab plus FLOT	474	436	404	381	351	334	320	307	288	234	187	107	88	33	20	2	1	0
Placebo plus FLOT	474	429	392	360	329	302	278	264	249	202	160	89	65	26	21	2	1	0

	All pts N = 1579		PD-L1 CPS ≥1 n = 1235		PD-L1 CPS ≥10 n = 553	
	Pembro + chemo n = 790	Pbo + chemo n = 789	Pembro + chemo n = 618	Pbo + chemo n = 617	Pembro + chemo n = 280	Pbo + chemo n = 273
OS, median (95% CI), mo	12.9 (11.9–14.0)	11.5 (10.6–12.1)	13.0 (11.6–14.2)	11.4 (10.5–12.0)	15.8 (14.0–19.3)	11.8 (10.3–12.7)
HR (95% CI)	0.78 (0.70–0.86)		0.74 (0.66–0.84)		0.64 (0.53–0.77)	
PFS, median (95% CI), mo	6.9 (6.3–7.2)	5.6 (5.5–5.7)	6.9 (6.0–7.2)	5.6 (5.4–5.7)	7.8 (6.8–8.5)	5.6 (5.4–6.7)
HR (95% CI)	0.76 (0.68–0.85)		0.72 (0.64–0.82)		0.62 (0.51–0.76)	
ORR, % (95% CI)	51.1 (47.6–54.7)	42.0 (38.5–45.5)	51.9 (47.9–55.9)	42.6 (38.7–46.6)	60.4 (54.4–66.1)	43.2 (37.3–49.3)
DOR, median (range), mo	8.0 (1.2+ to 66.3+)	5.7 (1.3+ to 58.1+)	8.3 (1.2+ to 66.3+)	5.6 (1.3+ to 58.1+)	10.0 (1.2+ to 66.3+)	5.7 (1.4+ to 55.0+)

Overall Survival in Patients with Tumor-Cell PD-L1 Expression of ≥1%



No. at Risk

Nivolumab + chemotherapy	158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemotherapy	157	135	105	72	52	36	21	12	8	4	2	1	1	0

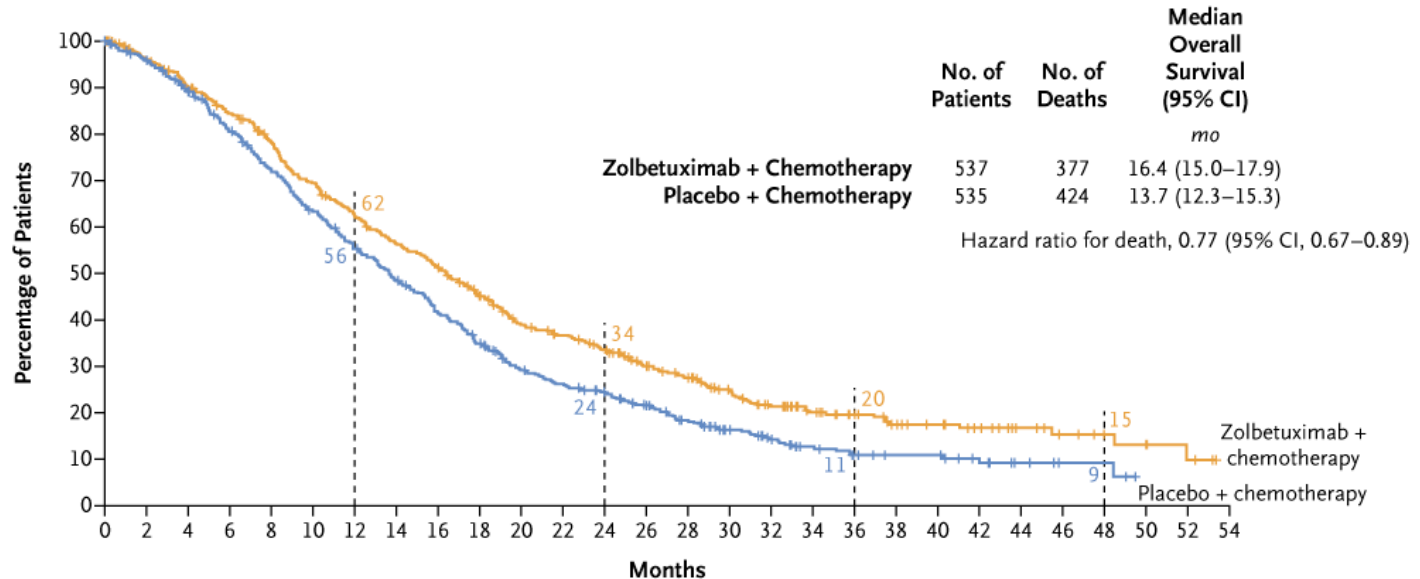
Esofagogastrico HER2 neg: Claudin 18.2

THE LANCET

Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial

Volume 401, Issue 10389, P1655-1668, May 20, 2023

Overall Survival



No. at Risk

Zolbetuximab	537	497	462	427	387	343	303	273	249	213	174	159	140	109	96	75	60	47	39	30	25	20	14	10	7	6	3	0
Placebo	535	506	463	409	362	317	278	239	204	169	135	119	102	85	65	50	38	28	21	17	17	11	6	3	3	0	0	0

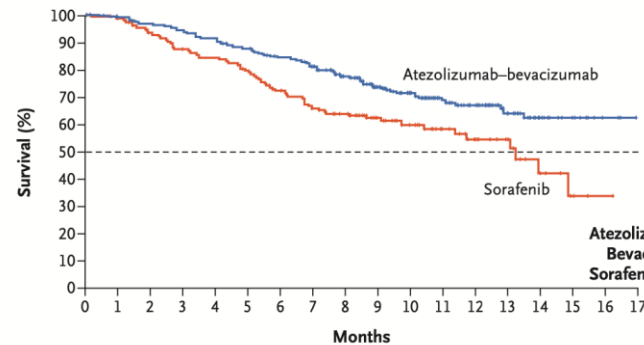
Epatocellulare: immuno combo

N Engl J Med 2020;382:1894-905.

ORIGINAL ARTICLE

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

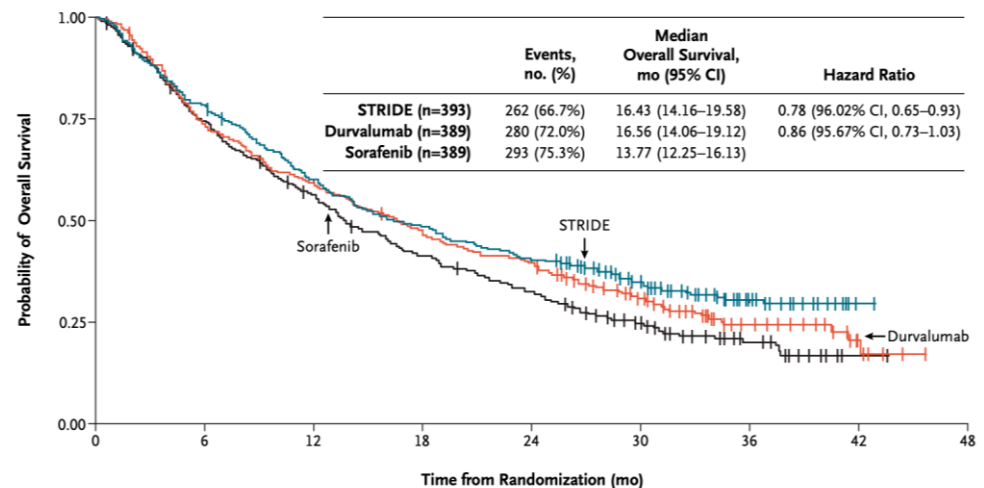
Overall Survival



No. at Risk

Atezolizumab-bevacizumab	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

Update (J Hepatol 2022): OS + 5.8 mesi



NEJM
Evidence

Published June 6, 2022

NEJM Evid 2022; 1 (8)

DOI: 10.1056/EVIDea2100070

ORIGINAL ARTICLE

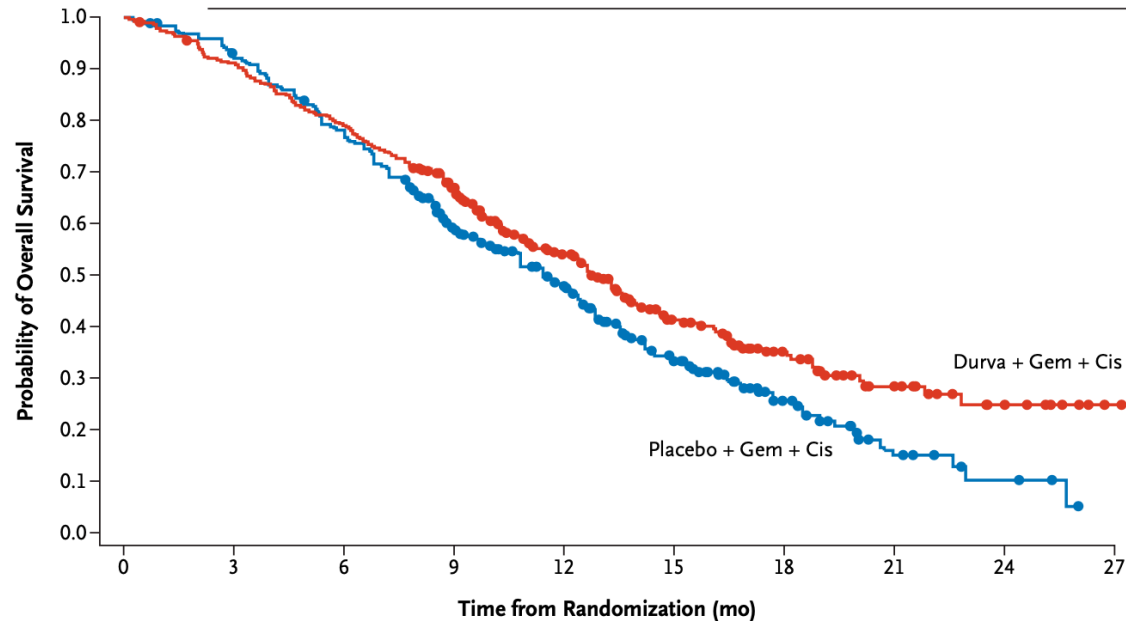
Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma

Vie biliari: immuno/CxT

ORIGINAL ARTICLE

Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

	Median Overall Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + Gem + Cis (n=344)	11.5 (10.1–12.5)		



Update (J Hepatol 2025): 36-month OS: 17% vs. 7.6%

Vie biliari: IDH (15-20%) / FGFR2 (10-15%)

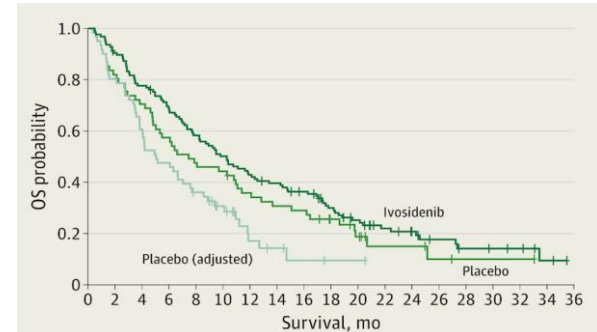
Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With *IDH1* Mutation

The Phase 3 Randomized Clinical ClarIDHy Trial

JAMA Oncol

Published Online: September 23, 2021

2021;7;(11):1669-1677. doi:10.1001/jamaoncol.2021.3836



Median overall survival:

Ivosidenib, 10.3 mo (95% CI, 7.8-12.4)

Placebo, 7.5 mo (95% CI, 4.8-11.1)

HR, 0.79 (95% CI, 0.56-1.12); 1-sided $P = .09$;

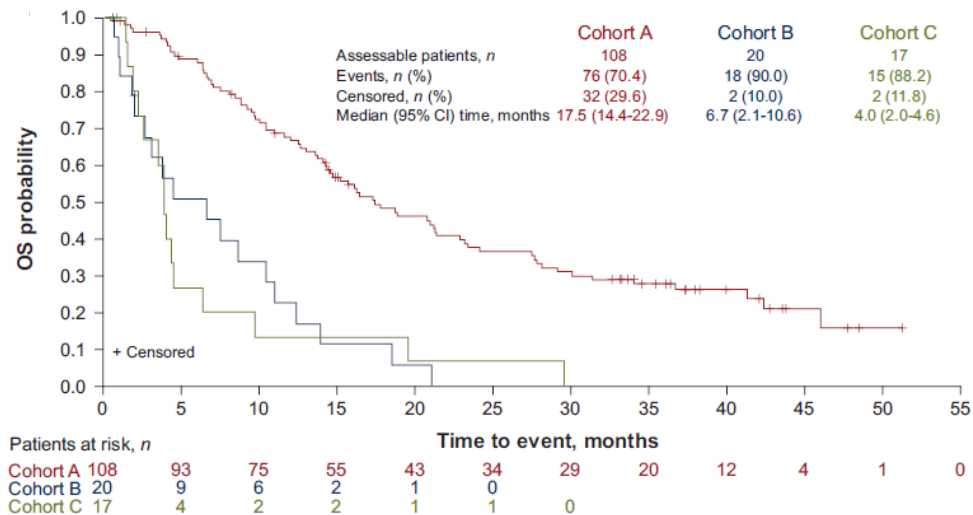
after adjustment for crossover from placebo to ivosidenib:

HR, 0.49 (95% CI, 0.34-0.70); 1-sided $P < .001$



ORIGINAL RESEARCH

An open-label study of pemigatinib in cholangiocarcinoma: final results from FIGHT-202



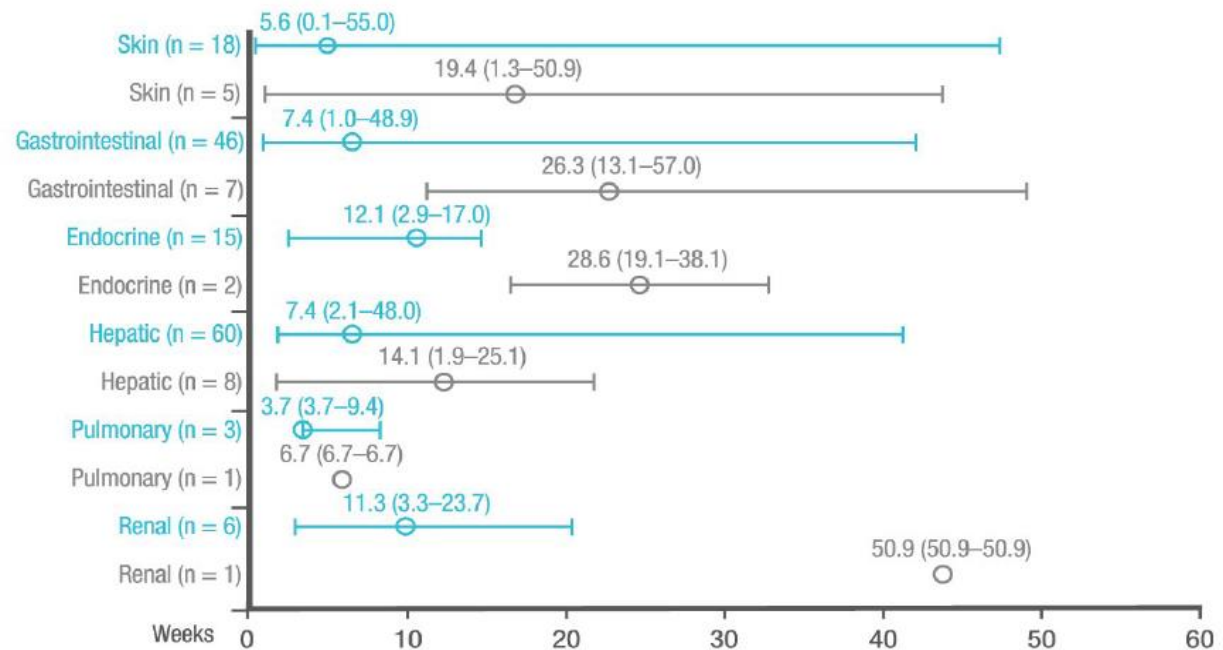
«La medicina di questo secolo
ha fatto enormi progressi:
pensate solo a quante malattie
ha saputo inventare»



CLINICAL PRACTICE GUIDELINES

Incidence and epidemiology

Time to onset of grade 3-4 treatment-related
select adverse events



Circles represent medians; bars signify ranges

—●— Combination ipilimumab + nivolumab

—○— Single agent nivolumab

Riassumendo

- Sempre più verso una medicina di precisione
- Impatto variabile sulla sopravvivenza
- Strada ancora lunga (eterogeneità e complessità tumorale, ottimizzazione-sequenze dei regimi, resistenza, microbiota, ..)
 - Al..
- Sostenibilità (& equità)
- Lavoro multi- e interdisciplinare