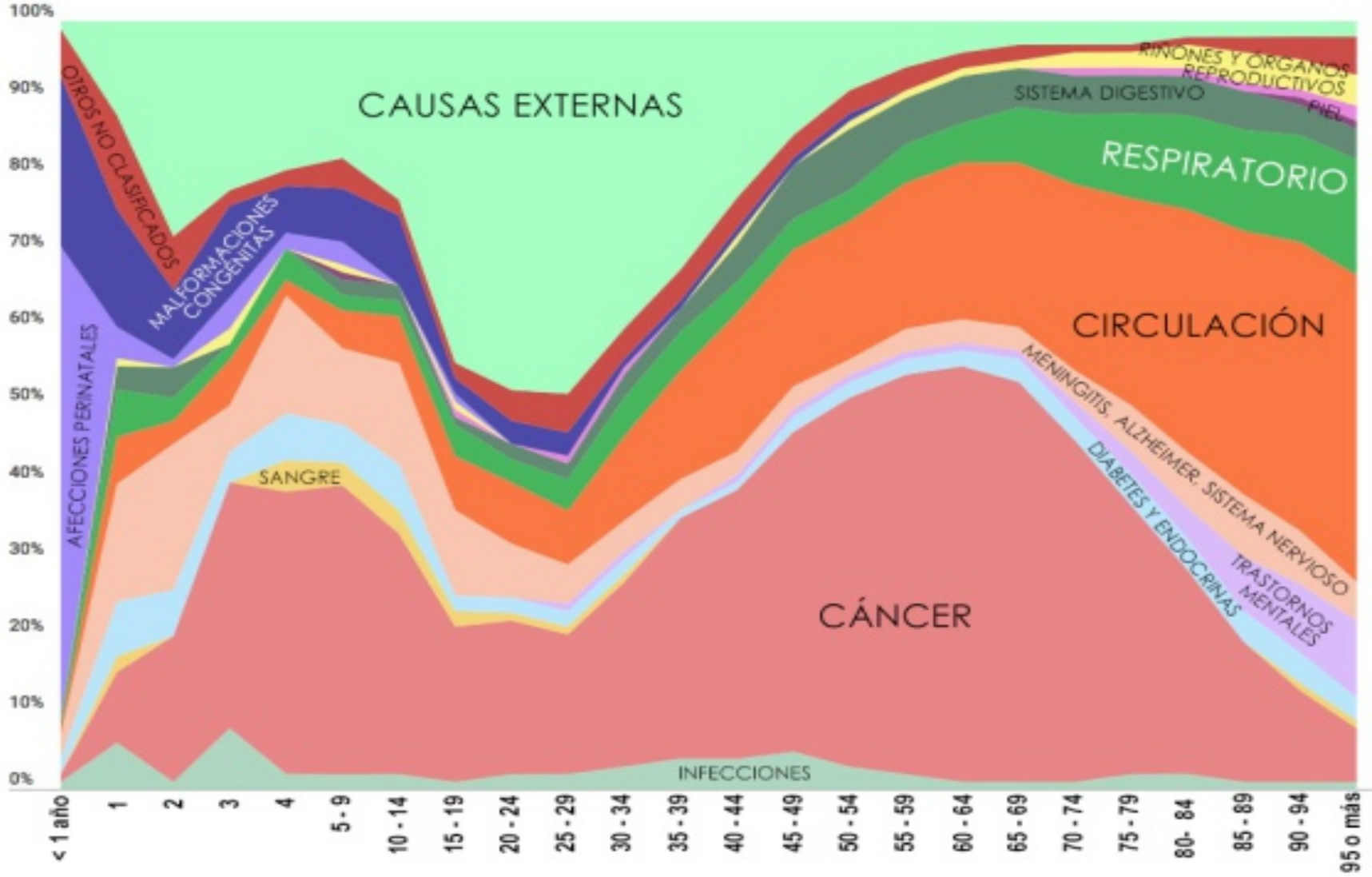
CONGRESO GEPAC 2018

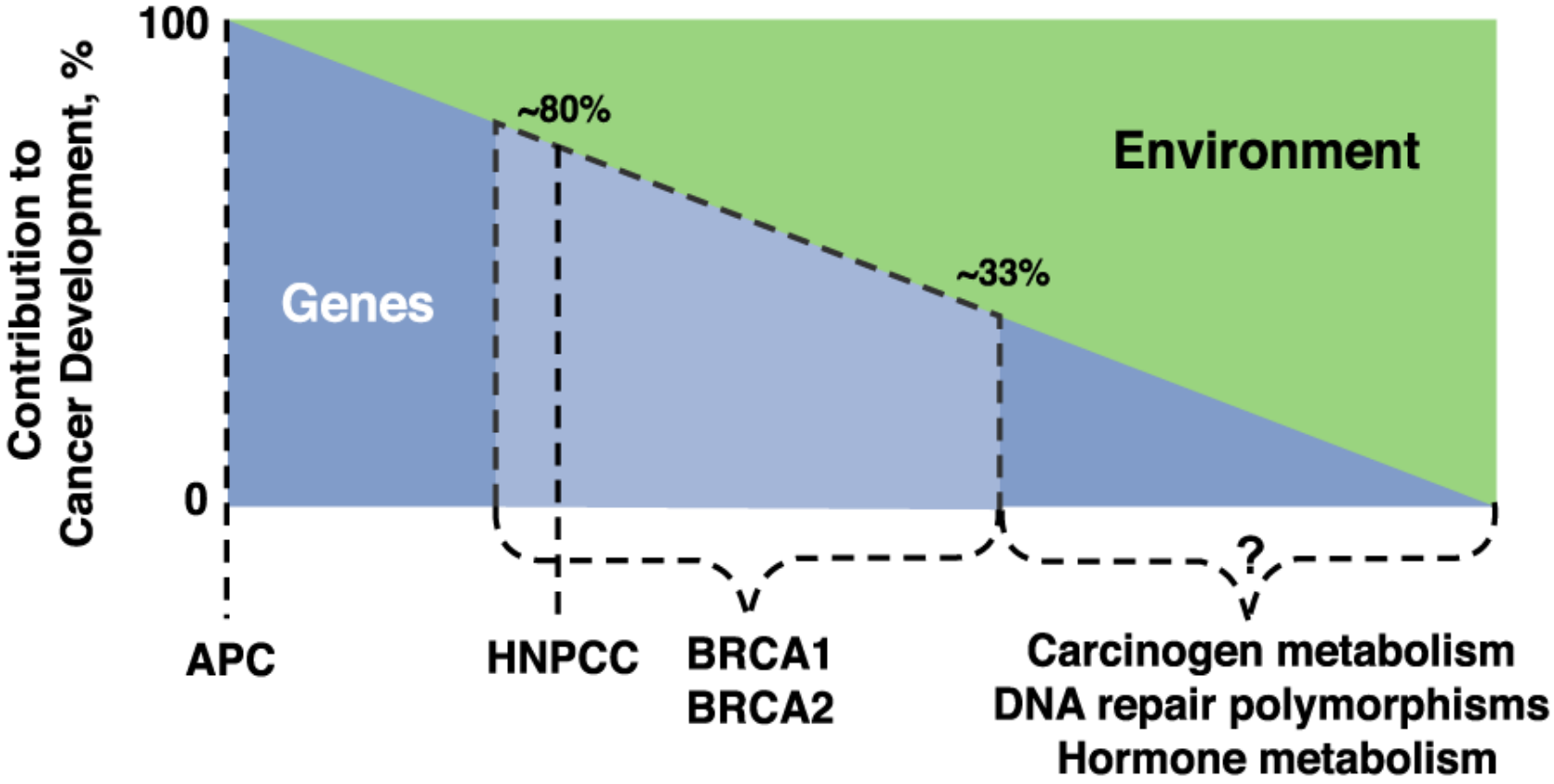
TERAPIA DE PRECISIÓN EN EL CÁNCER DE PÁNCREAS, HÍGADO Y VÍAS BILIARES

Alfredo Carrato
Catedrático y Jefe Servicio de Oncología Médica
Hospital Universitario Ramón y Cajal

De qué mueren los españoles según su edad



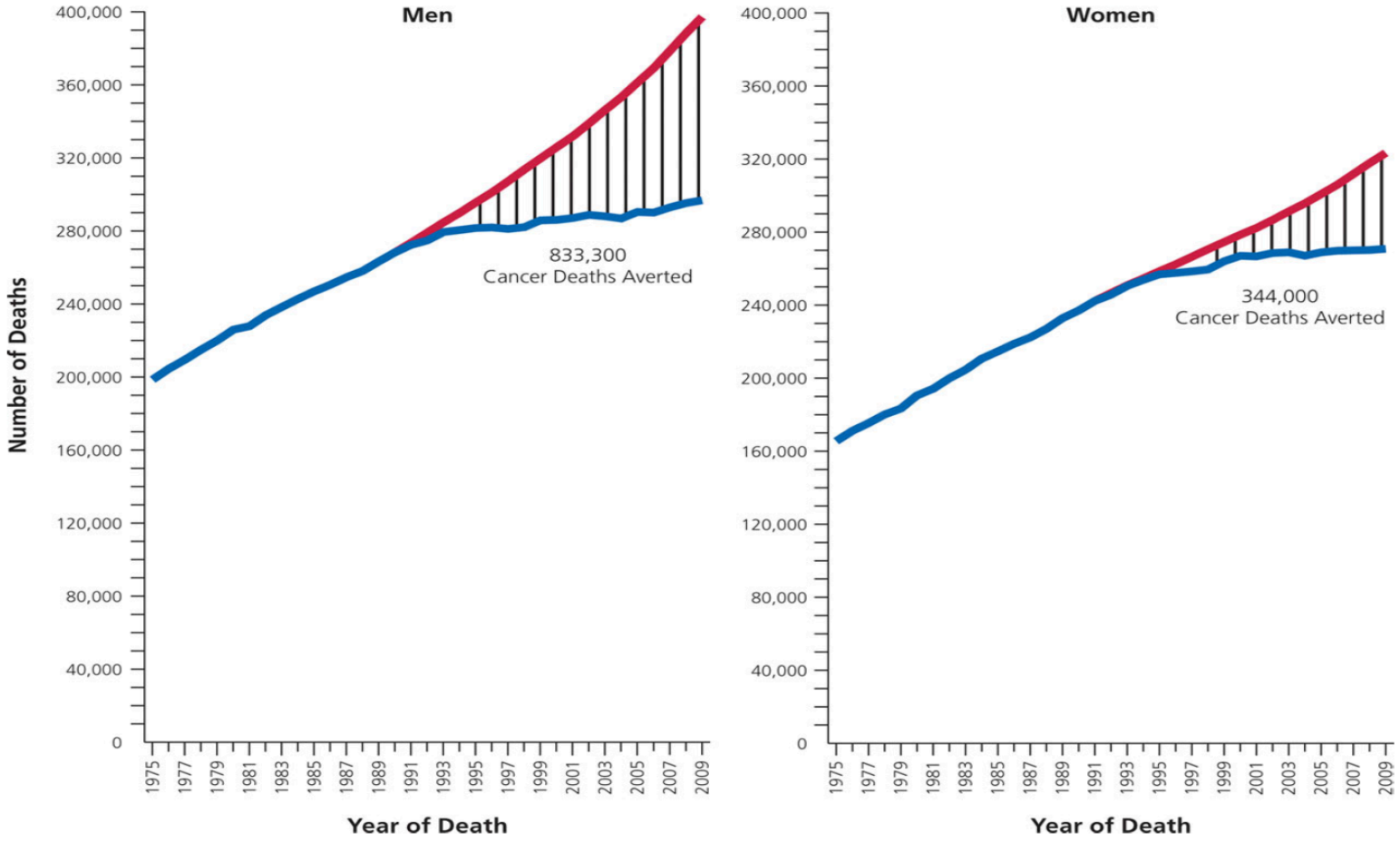
Gene-Environment Interaction and Likelihood of Developing Cancer



A cancer gene could be expressed without any environmental influence or only when activated by environmental factors.

Lichtenstein P. N Engl J Med 2000; 343:78-85

Total number of cancer deaths averted from 1991 to 2009

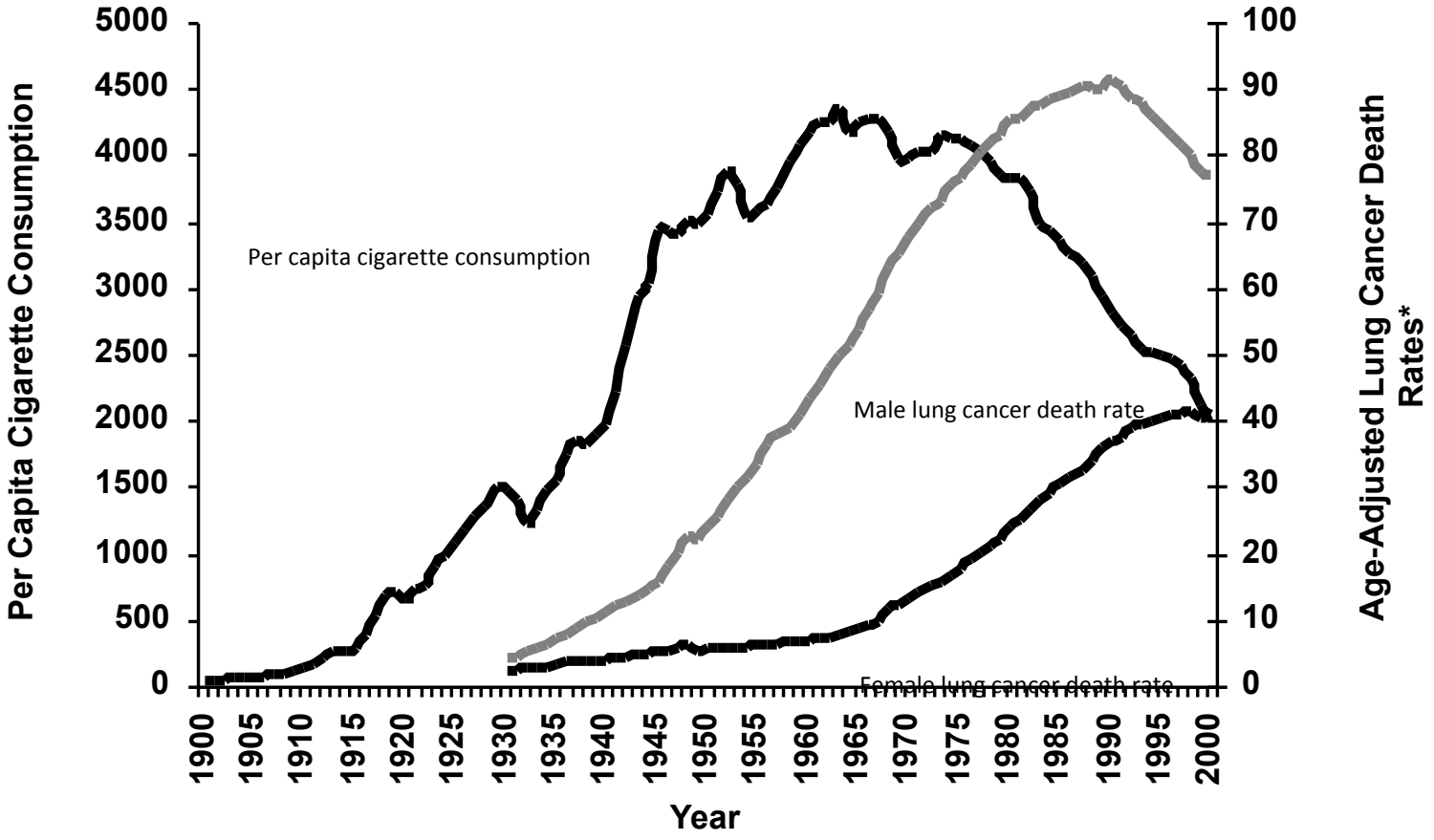


FRENTES EN LA LUCHA CONTRA EL CÁNCER

- Prevención primaria (Hábitos saludables, fármacos, cirugía, etc.)
- Prevención Secundaria (Diagnóstico precoz o screening)
- Mejorando el diagnóstico (Tecnología, Anatomía Patológica)
- Mejorando el tratamiento: (A) Tratamientos individualizados, (B) realizados por profesionales bien entrenados. (C) Trabajo asistencial multidisciplinar. (D) Atención integral del paciente. Cuidados continuos)
- Aumento de conocimientos sobre la biología del cáncer (Incremento de la investigación básica, traslacional y clínica)

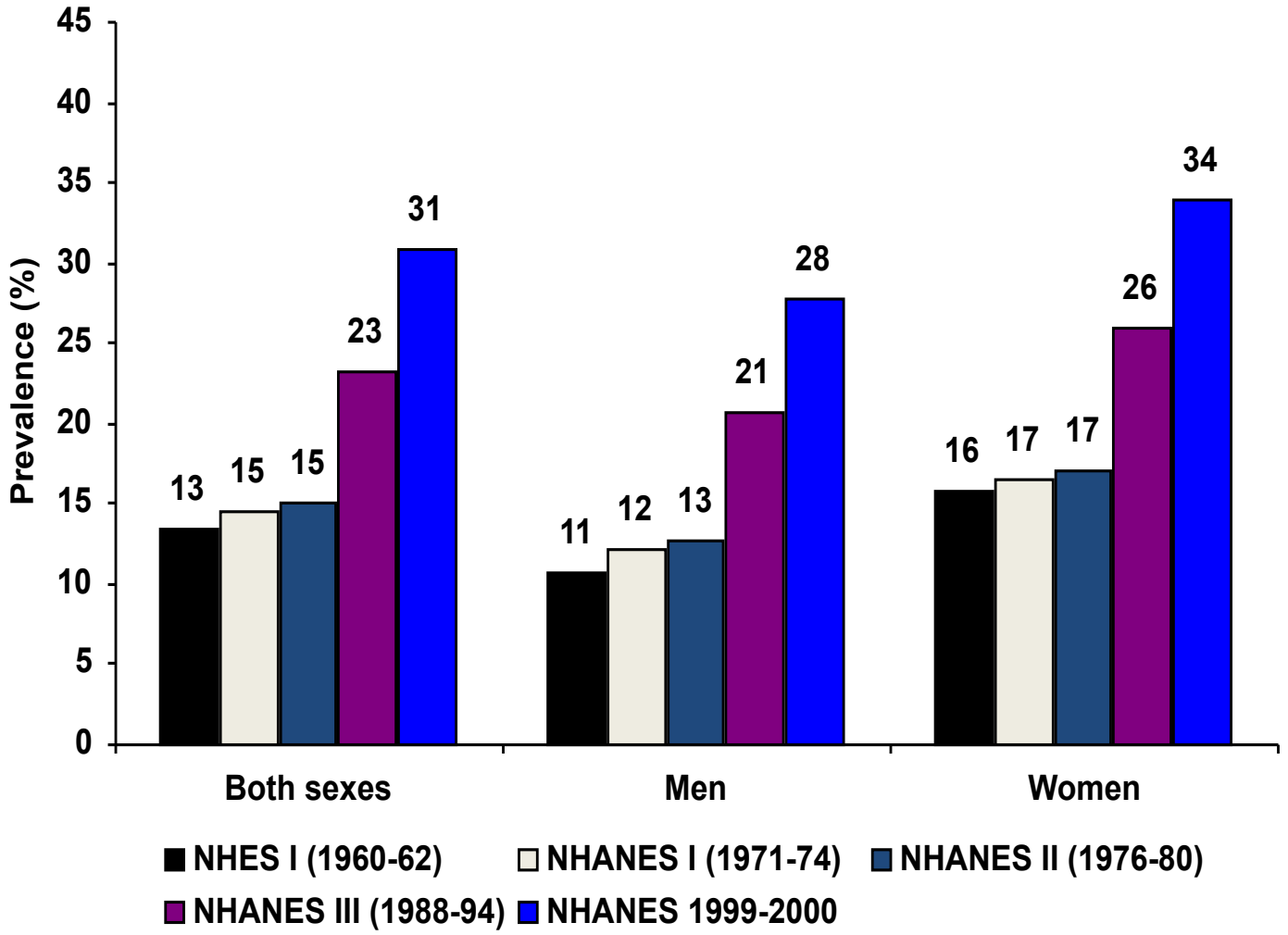
Evitar el hábito de fumar

Tobacco Use in the US, 1900-2000



***Age-adjusted to 2000 US standard population. Source: Death rates: US Mortality Public Use Tapes, 1960-2000, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2002. Cigarette consumption: US Department of Agriculture, 1900-2000.**

Trends in Obesity* Prevalence (%), By Gender, Adults Aged 20 to 74, US, 1960-2000



*Obesity is defined as a body mass index of 30 kg/m^2 or greater. Source: National Health Examination Survey 1960-1962, National Health and Nutrition Examination Survey, 1971-1974, 1976-1980, 1988-1994, 1999-2000, National Center for Health Statistics, Centers for Disease Control and Prevention, 2002.

Evitar el sobrepeso y la obesidad

Hacer ejercicio físico

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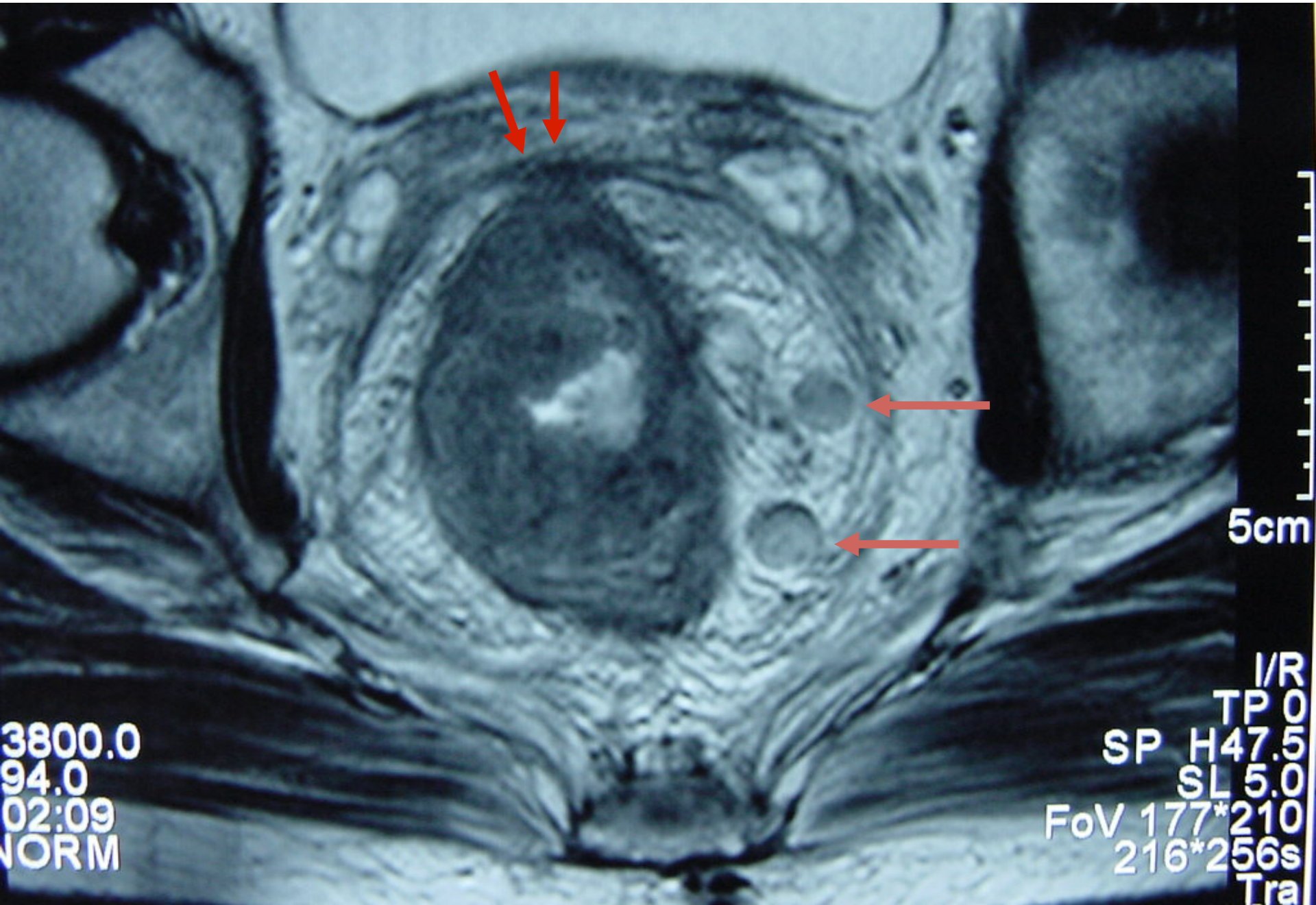
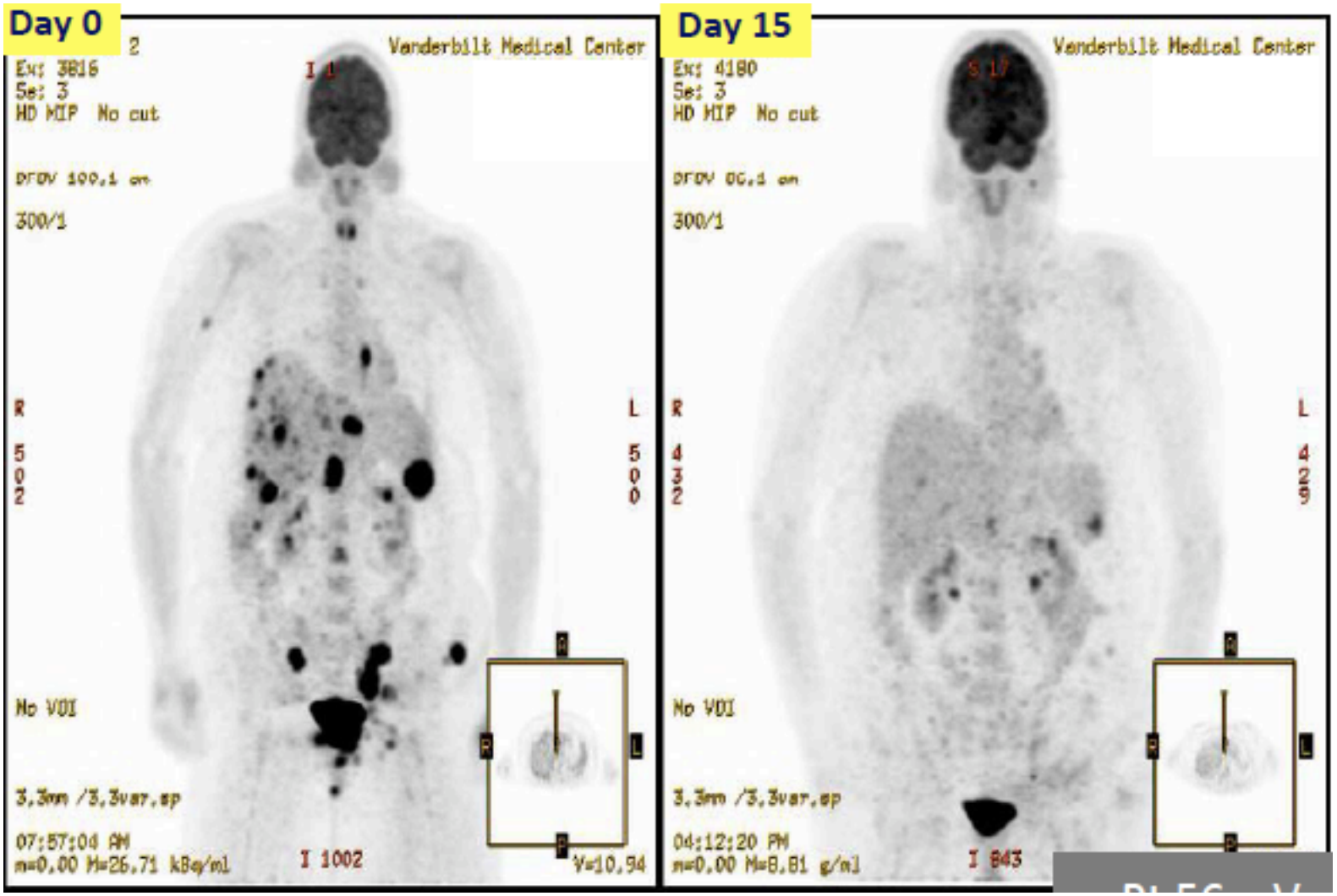
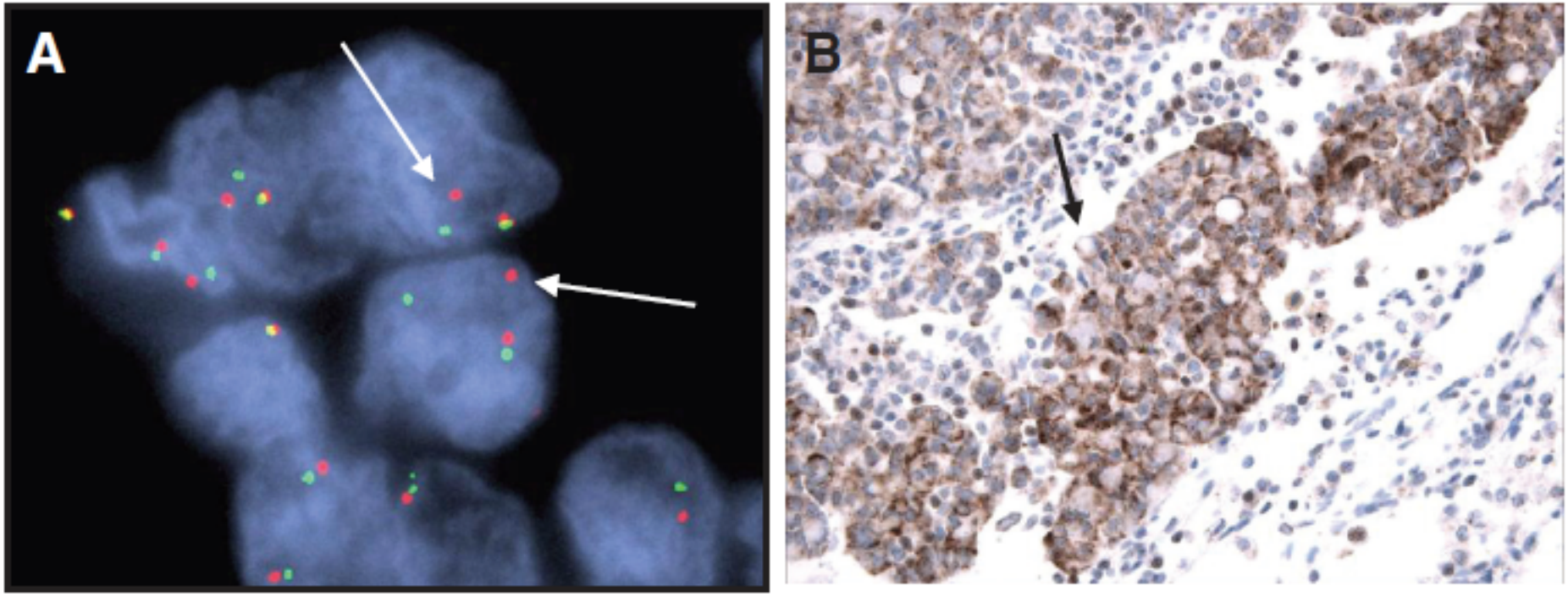
Tecnología punta en el diagnóstico por la imagen



BRAFV600E melanoma patient PET scan at baseline and day +15 after PLX4032 treatment at 720 mg BID



Tecnología punta en Anatomía Patológica



Diagnostic features of EML4-ALK-positive NSCLC (A: FISH. B: IHC)

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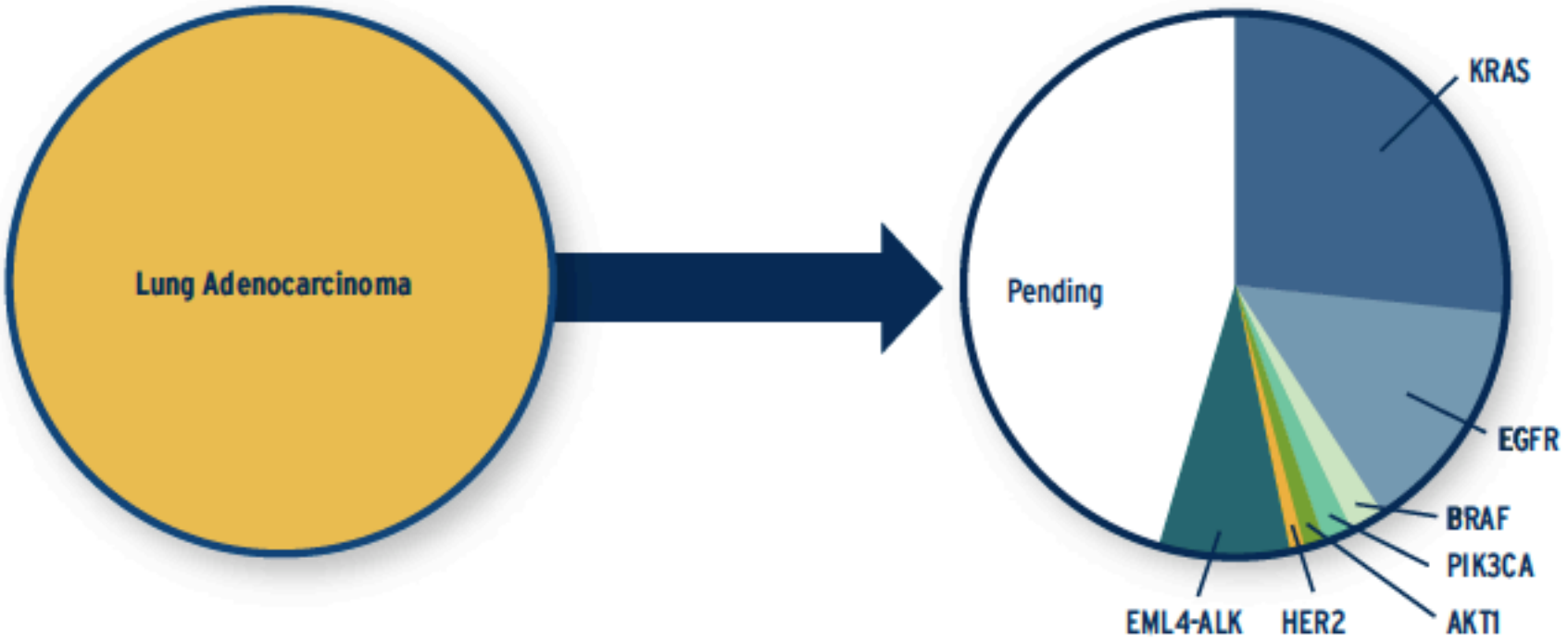
Cancer in the Molecular Era: Identifying the Drivers of Lung Cancer

BEFORE: One Disease

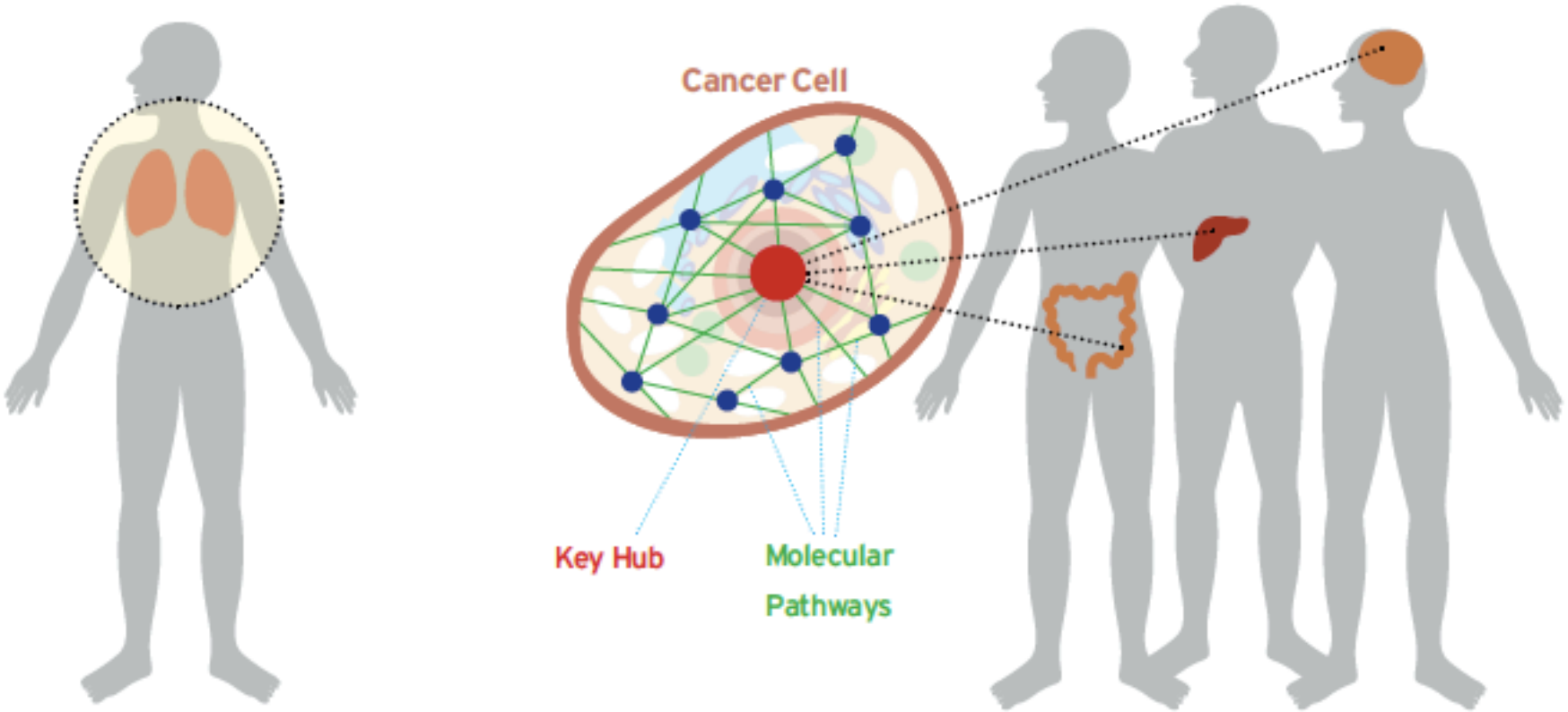
TODAY: Many different forms of lung cancer driven by different molecular defects – with more yet to be identified



A New Model for Therapeutic Development

OLD MODEL: Treatment is determined by a tumor's location in the body, without regard to the molecular charateristics of the patient or the tumor.

NEW MODEL: Treatment is determined by key molecular "hubs" that must be targeted within the cells, and is only administered to patients whose tumors are found to have those hubs – potentially without regard to the tumor's location in the body.



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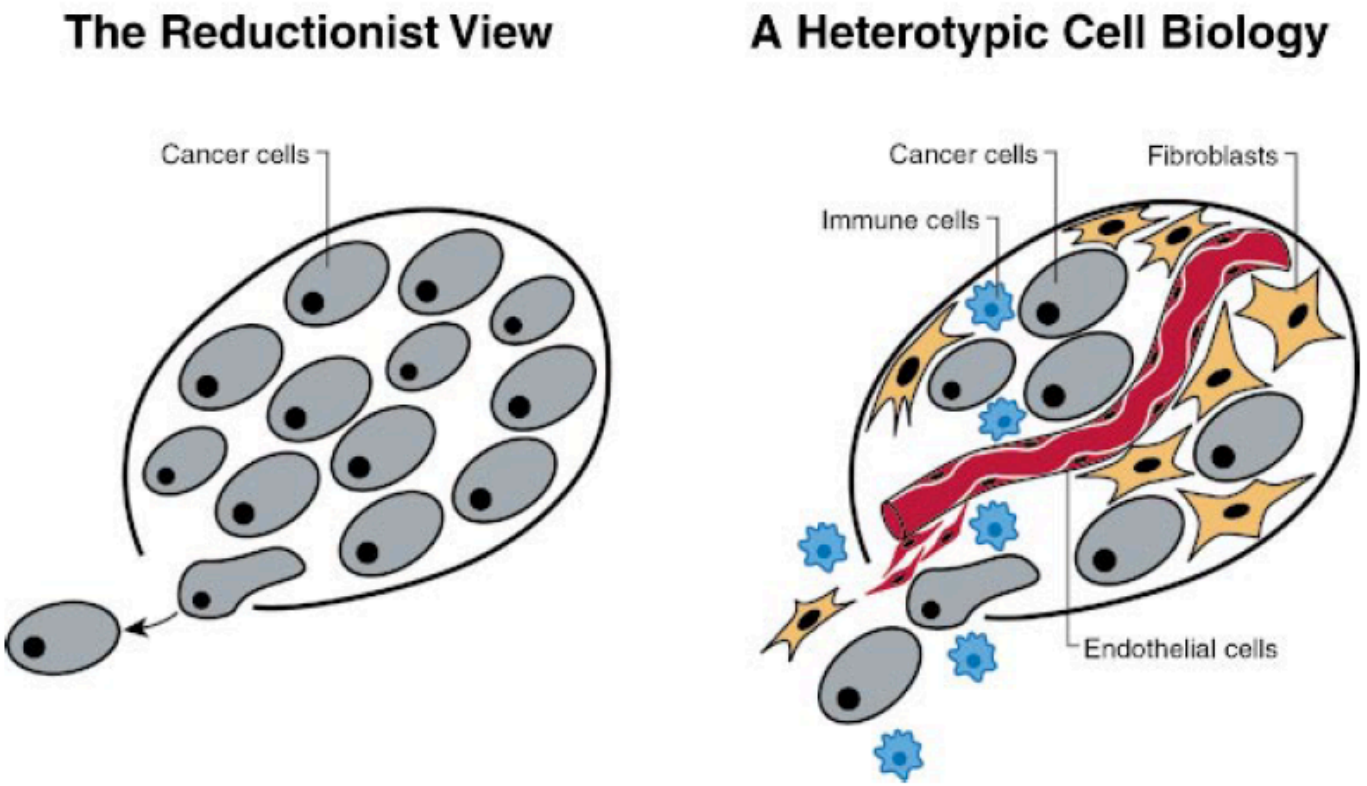
Investigación Traslacional

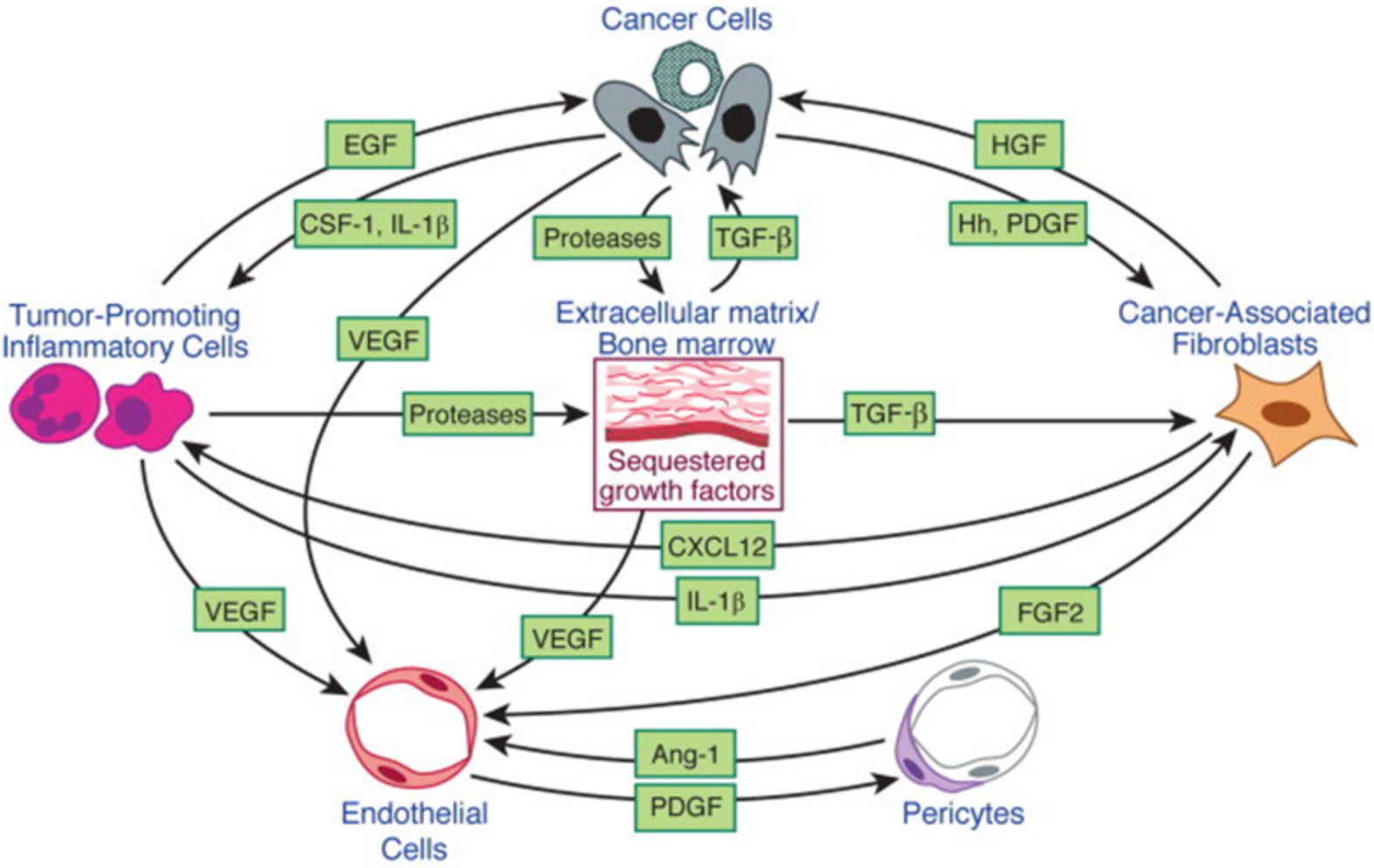
Investigación Traslacional

Investigación en Cáncer



Hanahan and Weinberg. Cell 2000;100:57-70

Pathways: Tumor Microenvironment



Reproduced from Hanahan D, et al. *Cell*. 2011;144(5):646-674. © 2011, with permission from Elsevier.

Cáncer de Páncreas

Exocrine Pancreatic Ductal Adenocarcinoma (PDAC)

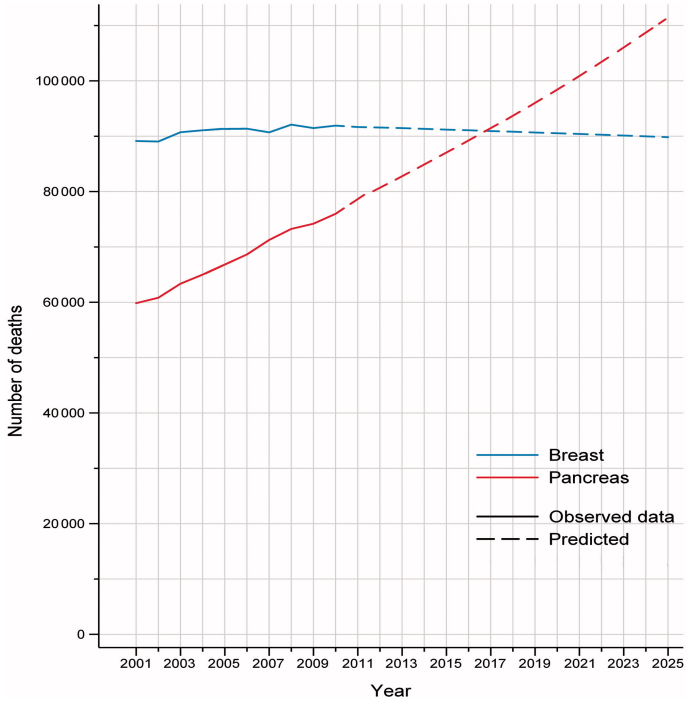
- PDAC is a very tough disease!
- Progress in pancreatic ductal adenocarcinoma has been very slow
- 80% of patients are diagnosed with advanced unresectable disease
- 70% of patients who have resection and adjuvant therapy, relapse
- “Cure” rate is only 5-7%
- Median survival of patients with metastases without treatment is only about 3 months

Pancreatic adenocarcinoma statistics

- High recurrence rate after surgery (80% in the first year)
- Prevention must be a primary strategy target
- 5-year overall survival:
  - All Stages (7%), Local (26%), Regional (10%), Distant (2%)

Stage	Percentage of patients at diagnosis	Median overall survival, months
Metastatic	60	6-9
Locally advanced	25	9-12
Resectable	15	15-20

[1]Geer RJ, Brennan MF. Am J Surg 1993; 165:68-72; [2]Willett CG, et al. J Clin Oncol. 2005;23:4538-4544.



Recorded (2001–2010) and projected (up to 2025) number of breast and pancreatic cancer deaths (both males and females) in the EU.

J. Ferlay; C. Partensky; F. Bray; More deaths from pancreatic cancer than breast cancer in the EU by 2017. *Acta Oncologica* **2016,** 55, 1158-1160.

Table 1 of 2

Table 1. Recorded (2010) and estimated number of cancer deaths in the EU in 2017 and 2025.

	Pancreas			Breast		
Year	Both male and female	Male	Female	Both male and female	Male	Female
2010	76000	38000	38000	92000	1000	91000
2017	91500	45500	46000	91000	1000	90000
2025	111500	55000	56500	90000	1000	89000

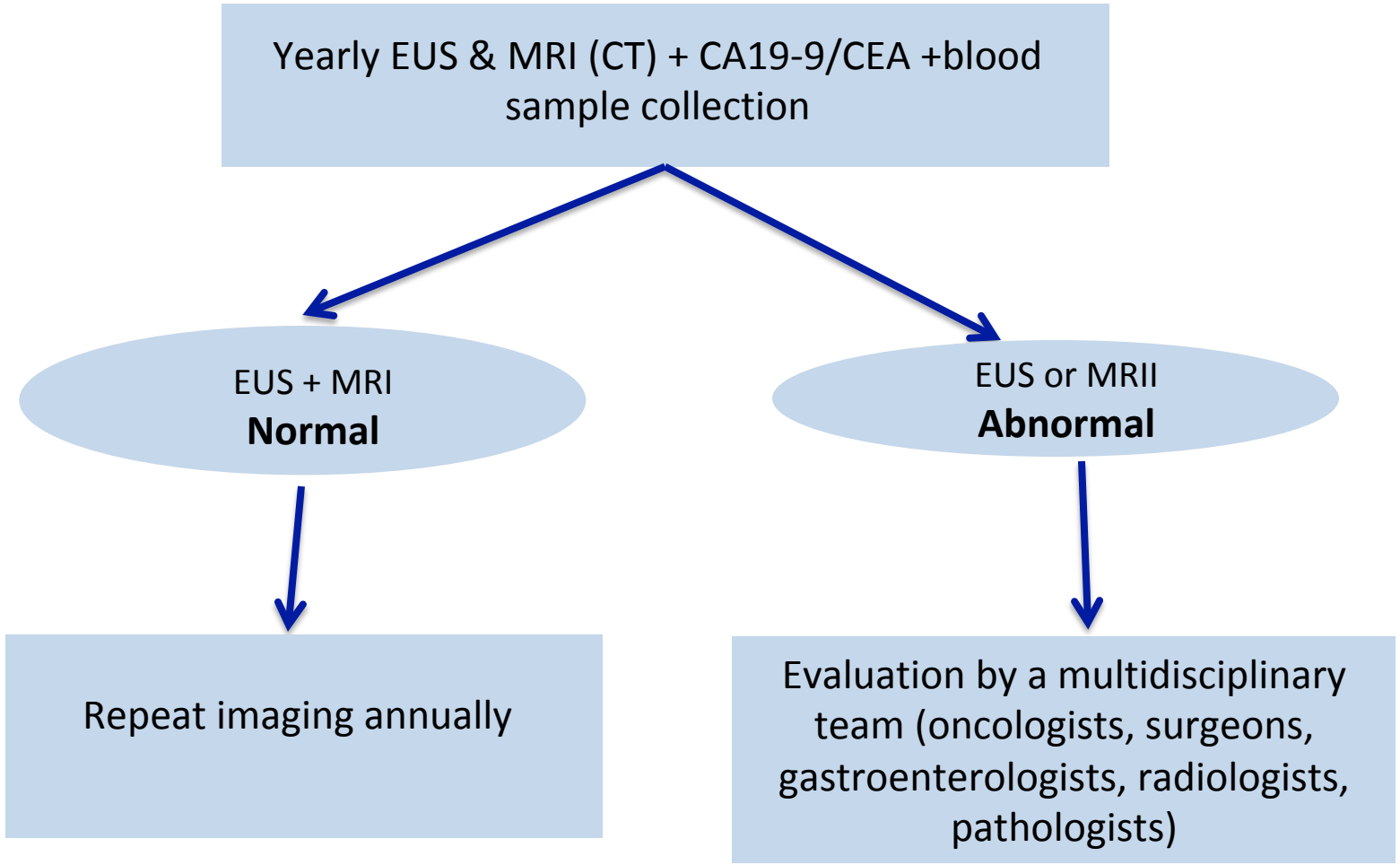
Exocrine Pancreatic Ductal Adenocarcinoma (PDAC) unmet needs

- Primary prevention and PDAC awareness
- Lack of screening programs for an earlier diagnosis
  - no high-risk population defined yet
  - Non invasive methods should be advisable (liquid bx)
- Improvement in diagnosis
  - Some patients are diagnosed only by imaging
  - Cytology is performed in >50% of cases, with mistakes
- Non existence of a health plan for assistance
  - Networking & reference centers
- Non existence of a health program for research
  - No professionalized biobanks
  - Networking research 6 clinical centers
- Research funds for PDAC are scanty at the EU
  - 2% of cancer research funds
  - $5.26 billion for the National Cancer Institute for FY 2015;

Pancreatic cancer screening

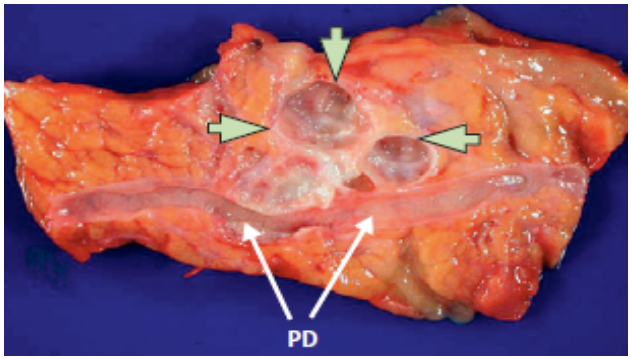
- Non-invasive precursors and early disease stages can be identified by screening high-risk individuals:
  - First-degree relatives of individuals with several family members affected by pancreatic cancer
  - Persons with an inherited predisposition harboring early curable diseases, such as pancreatic intraepithelial neoplasms, noninvasive intraductal papillary mucinous neoplasms and mucinous cystic neoplasms
- Endoscopic ultrasound is widely used as a screening test due to its ability to detect small pre-invasive lesions (~1 cm)
- An ideal screening test would be a highly accurate blood marker that could be measured non-invasively

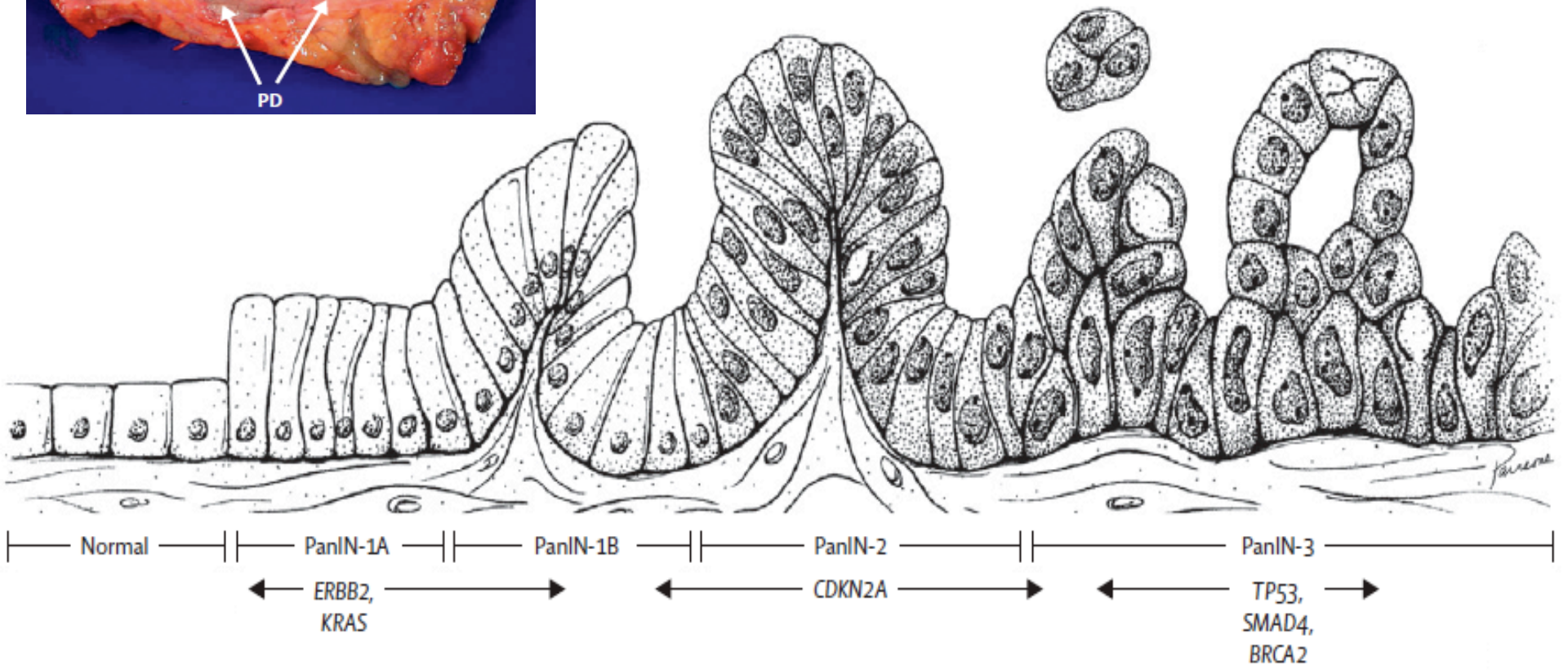
Familial Pancreatic Cancer Screening Protocol

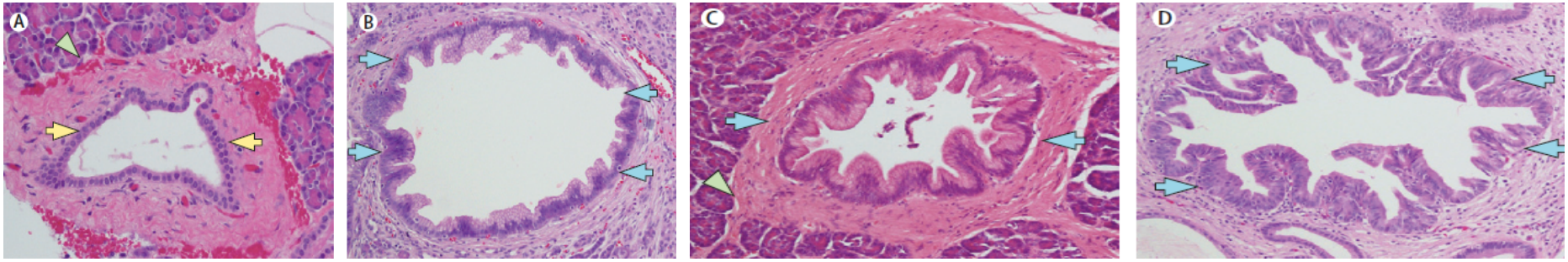


PANCREATIC CANCER PROGRESSION MODEL

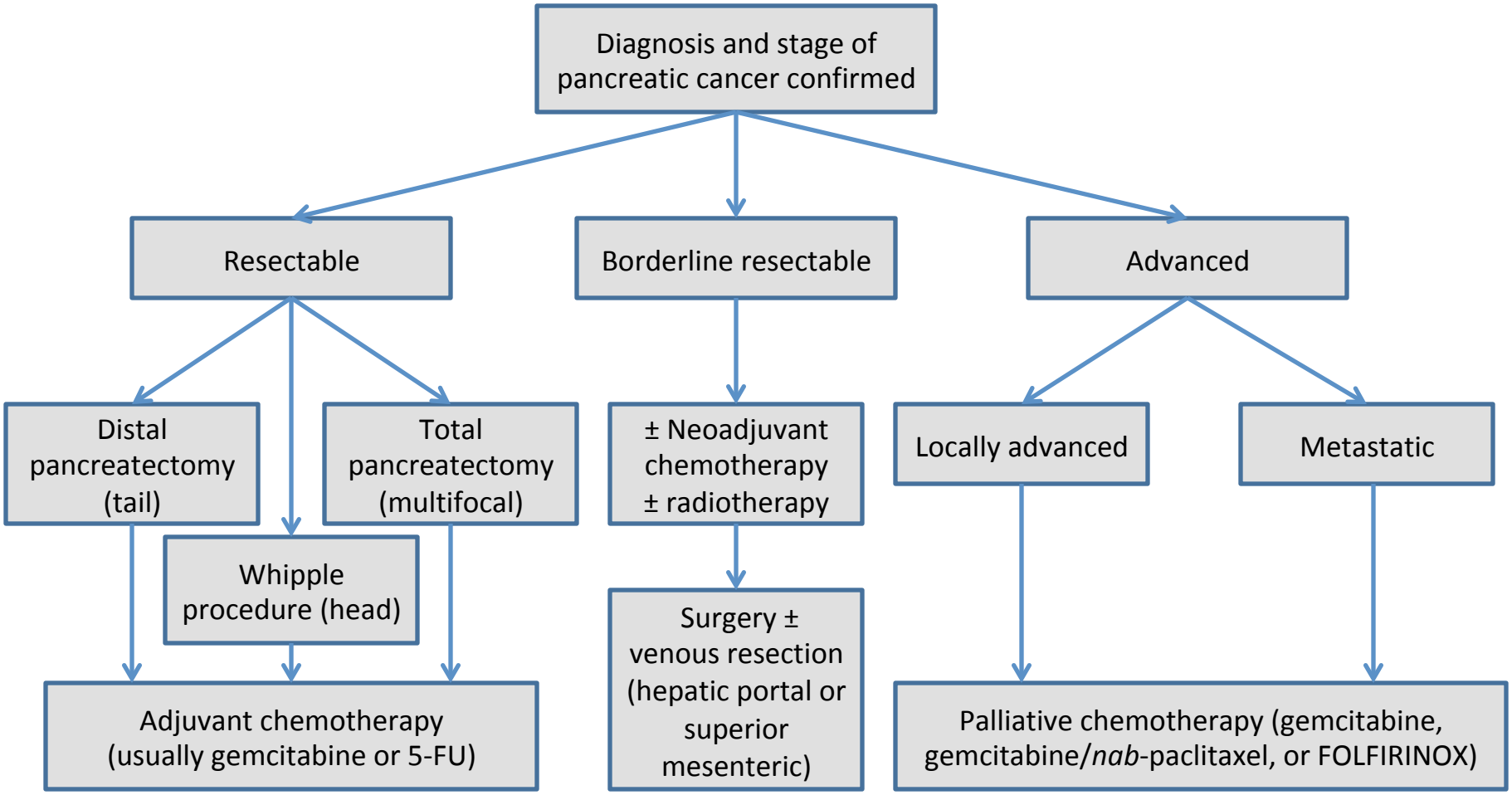
Vincent A et al. Lancet 2011; 378: 607–20







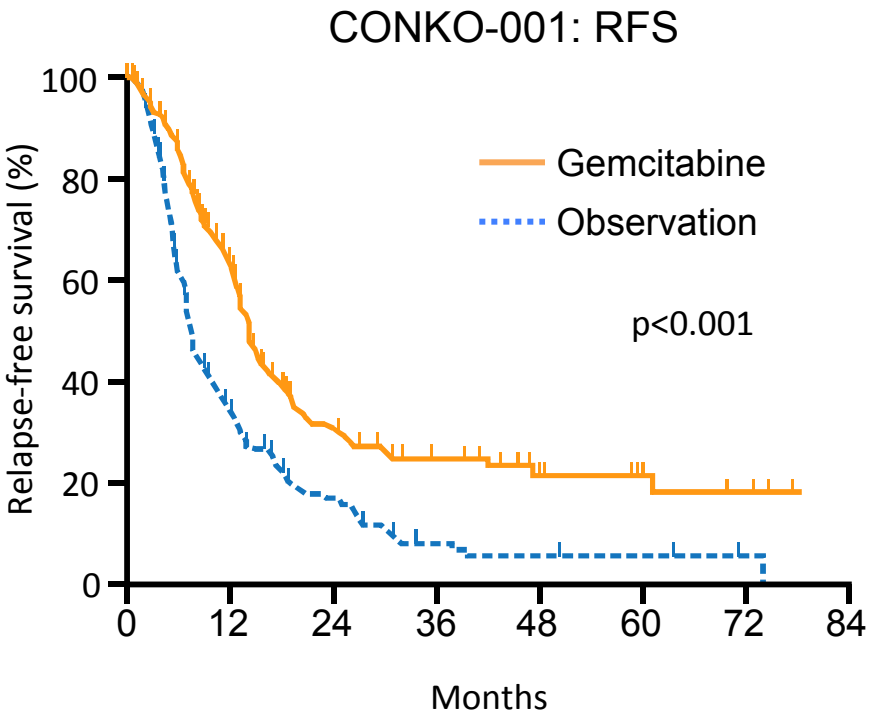
Treatment Algorithm Overview

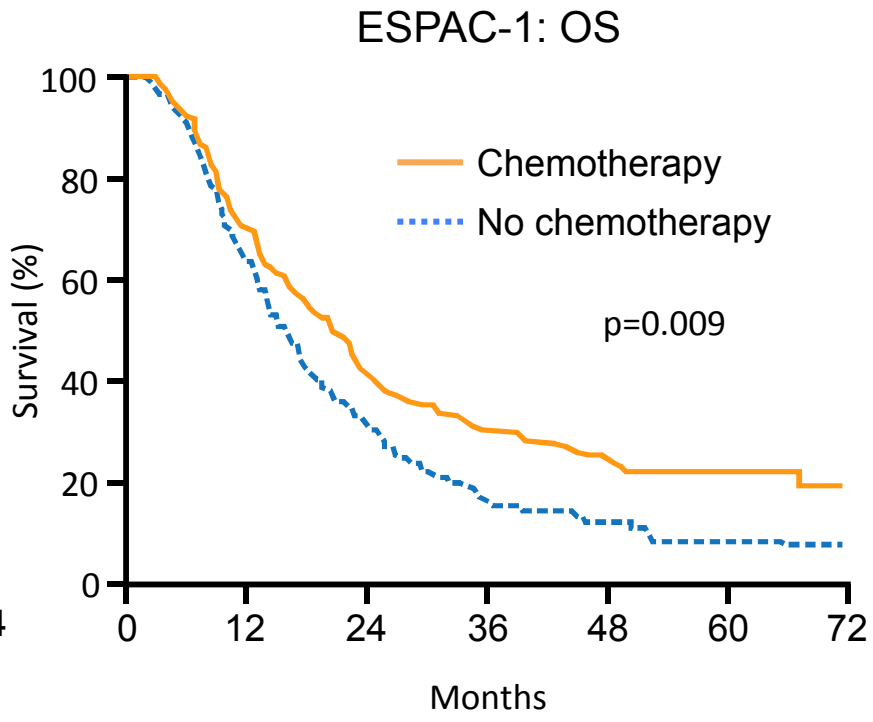


5-FU, 5-fluorouracil; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin.

Adapted from: Kanji ZS, et al. *CMAJ.* 2013;185(14):1219-1226.

Adjuvant chemotherapy





[1]Oettle H, et al. JAMA 2007; 297:267-77; [2]Neoptolemos JP, et al. N Engl J Med 2004; 350:1200-10.

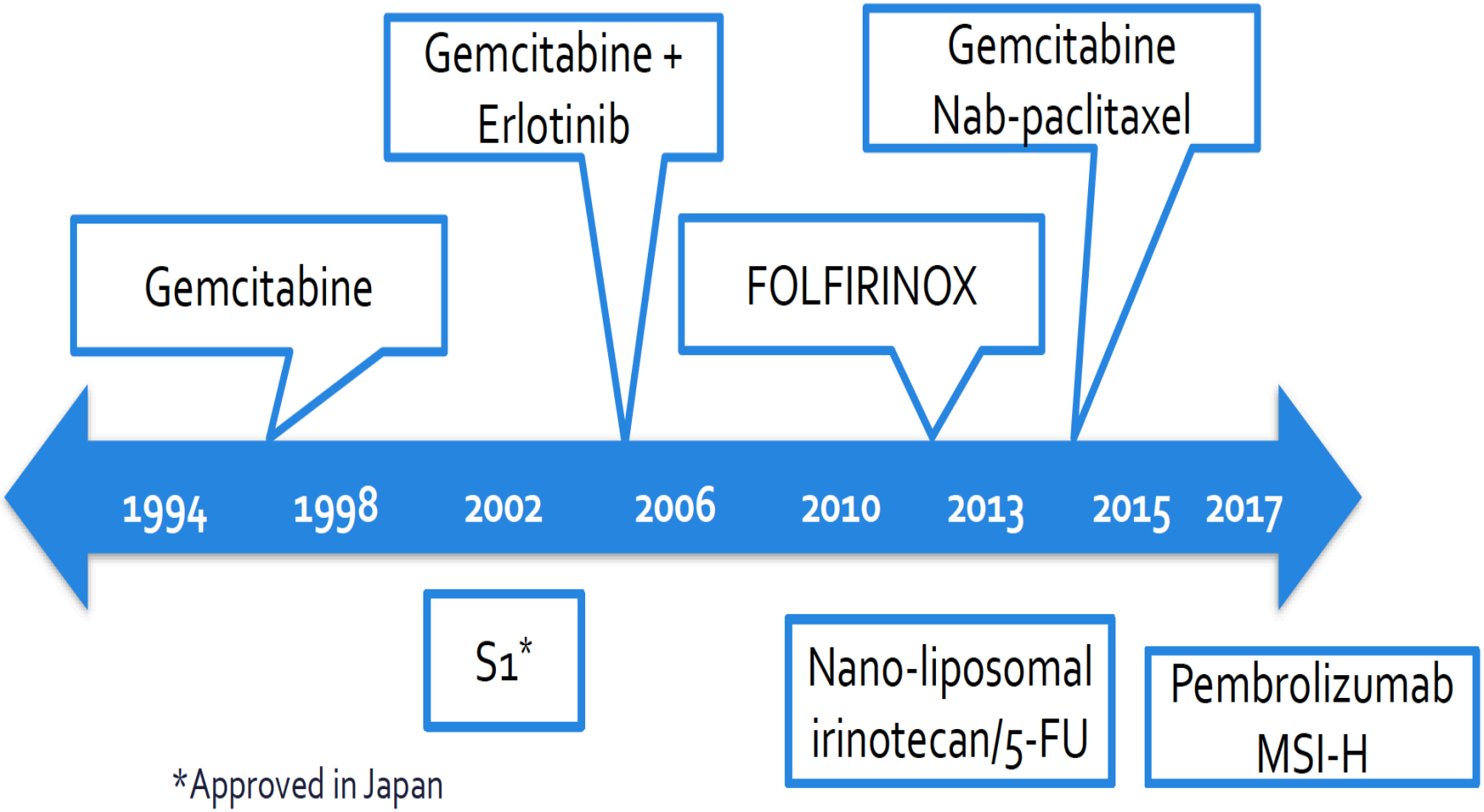
Cáncer de Páncreas avanzado y metastásico

Advanced pancreatic cancer treatment story

- Pre-1997: 5-fluorouracil monotherapy (FU)
- 1997: GEM monotherapy shown to improve survival,[1] becomes standard of care for advanced PC
- 2000s: GEM-based combinations demonstrate clinically significant survival benefit in good PS patients
- 2007: Erlotinib/GEM shows significant survival benefit vs GEM,[2] not clinically significant, approved in Europe
- 2011: **FOLFIRINOX** shows significantly improved survival vs GEM,[3] but is associated with greater toxicity
- 2013: MPACT Trial of **Nab-paclitaxel-GEM** vs GEM shows significantly improved survival[4]
- 2016: **Nal-Iri + FU/LV** shows significantly improved survival vs FU in 2nd-line treatment[5]

1. Burris HA, et al. *J Clin Oncol*. 1997;15:2403–2413; 2. Moore MJ, et al. *J Clin Oncol*. 2007;25:1960–1966; 3. Conroy T, et al. *N Engl J Med*. 2011;364:1817–1825.
[4] *N Engl J Med*. 2013:369(18):1691-703. 5Lancet 2016;387:545-57. GEM, gemcitabine; FOLFIRINOX, oxaliplatin, irinotecan, fluorouracil, leucovorin; PC, pancreatic cancer
The FOLFIRINOX regimen has not been approved by the EMA for treatment of pancreatic cancer.

Approved Therapies In Pancreas Adenoca (PDAC)



NCCN Guidelines Version 2.2018
Pancreatic Adenocarcinoma

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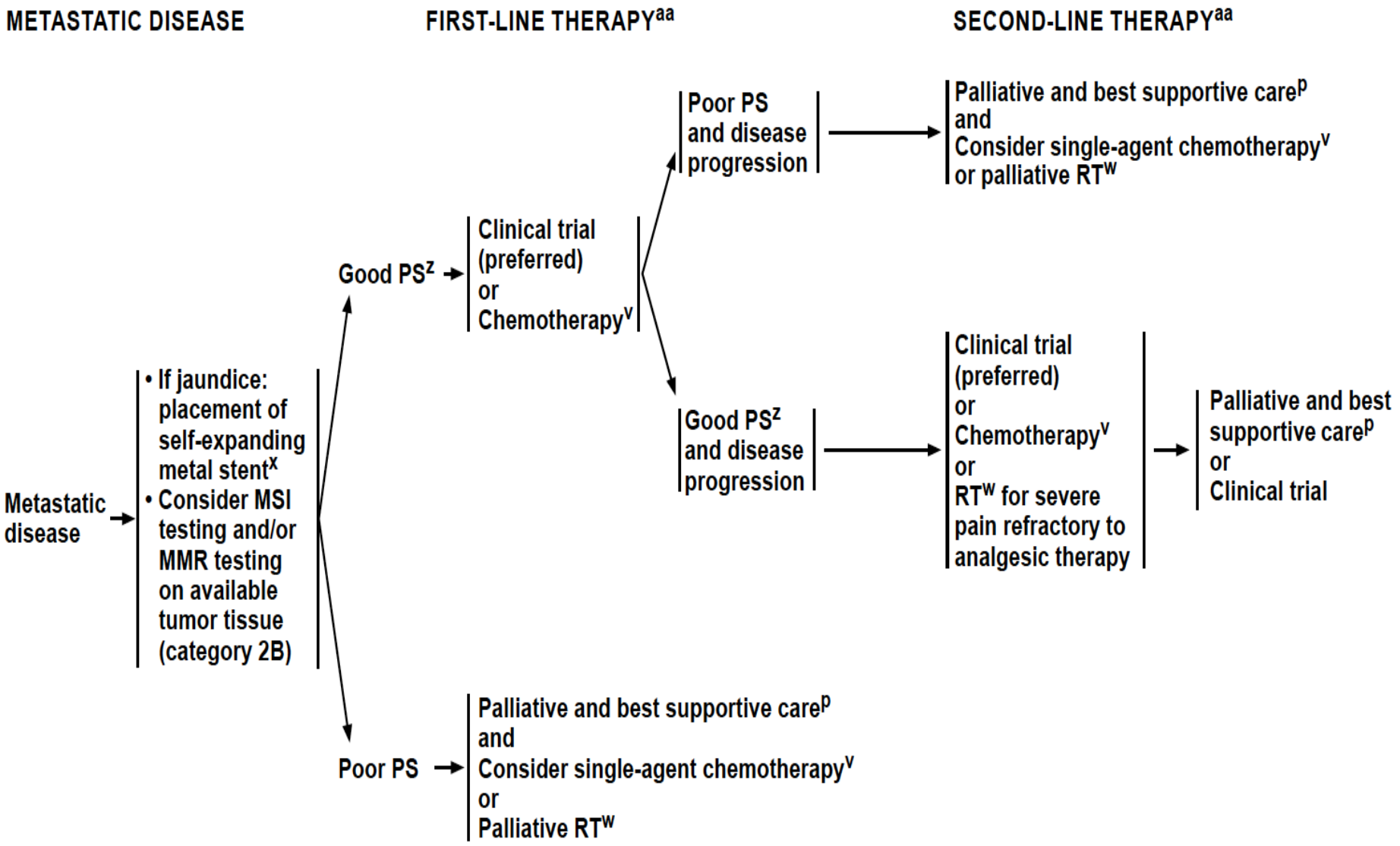


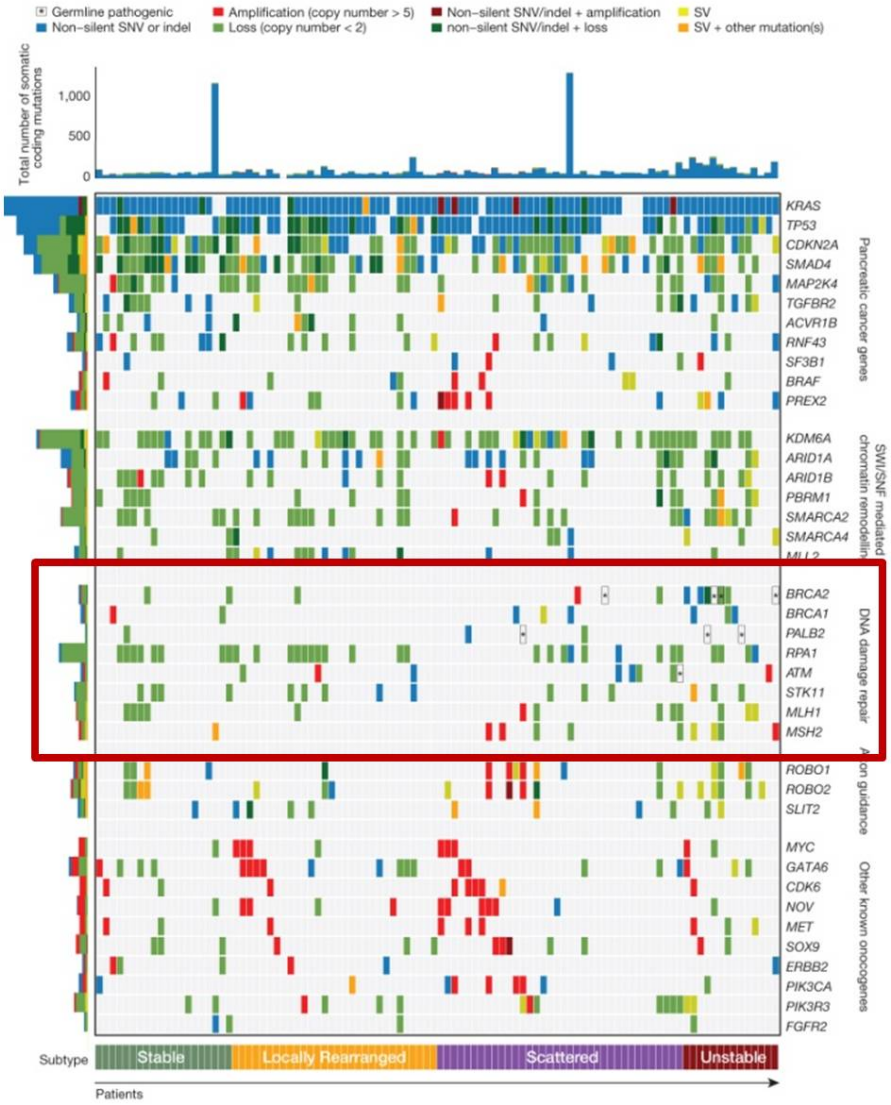
What have we learnt from our negative results?

- Clinical trials do not always match the molecular and clinicopathological complexity of PDAC
- Drug resistance limits the benefits of cytotoxics
- Targeting single gene pathway is unlikely to succeed
- RAS remains unchecked
- Opportunity may exist outside the cancer cell

Promising approaches:

- DNA damage repair strategies
- Stromal alterations approaches
- Immune therapy
- RAS?

Defects of DNA Damage Response Mechanisms



WGS/CNV

from Waddell et al., Nature 2015

DNA repair system

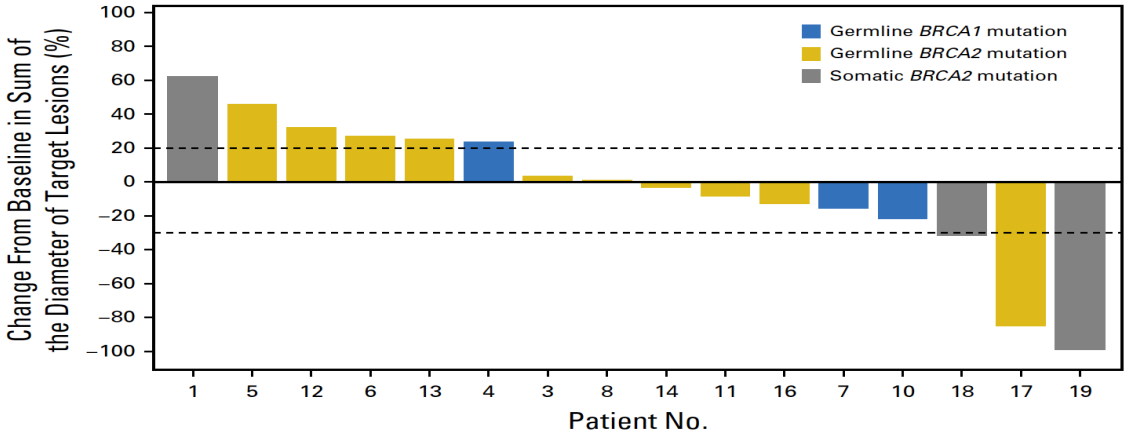
- 9-10% of PDAC pts have germline or somatic *BRCA* mutations
- In total 24 % have defects in DDR (mutations in BRCA1/2, PALB2, ATM, CHK1/2…) and/or show a genomic instable phenotype with DDR insufficiency

- Accumulation of genetic alterations
- Promotion of genomic instability
- Enhance therapeutic resistance

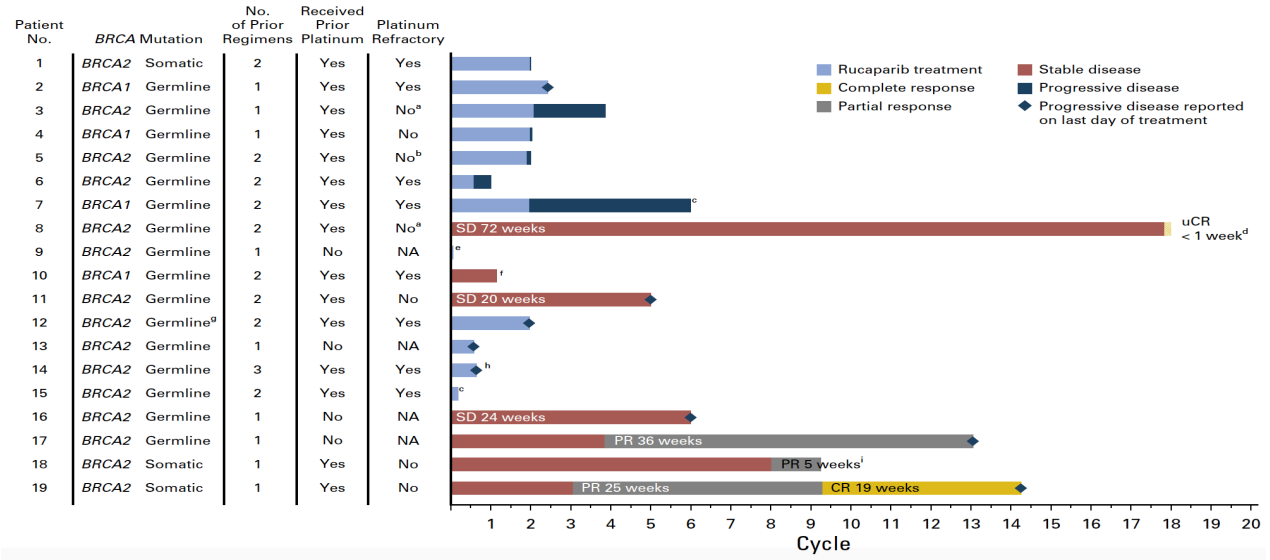
Biankin et al.; 2012, Sausen et al.; 2015; Witkiewicz et al.; 2015, Ying et al.; 2016

Rucaparib Monotherapy in Patients With Pancreatic Cancer and a Known Deleterious BRCA Mutation. Rachna T. Shroff et al.

JCO™ Precision Oncology 2018



Patient No.	BRCA Mutation		No. of Prior Regimens	Received Prior Platinum	Platinum Refractory
1	*BRCA2*	Somatic	2	Yes	Yes
2	*BRCA1*	Germline	1	Yes	Yes
3	*BRCA2*	Germline	1	Yes	No[a]
4	*BRCA1*	Germline	1	Yes	No
5	*BRCA2*	Germline	2	Yes	No[b]
6	*BRCA2*	Germline	2	Yes	Yes
7	*BRCA1*	Germline	2	Yes	Yes
8	*BRCA2*	Germline	2	Yes	No[a]
9	*BRCA2*	Germline	1	No	NA
10	*BRCA1*	Germline	2	Yes	Yes
11	*BRCA2*	Germline	2	Yes	No
12	*BRCA2*	Germline[g]	2	Yes	Yes
13	*BRCA2*	Germline	1	No	NA
14	*BRCA2*	Germline	3	Yes	Yes
15	*BRCA2*	Germline	2	Yes	Yes
16	*BRCA2*	Germline	1	No	NA
17	*BRCA2*	Germline	1	No	NA
18	*BRCA2*	Somatic	1	Yes	No
19	*BRCA2*	Somatic	1	Yes	No

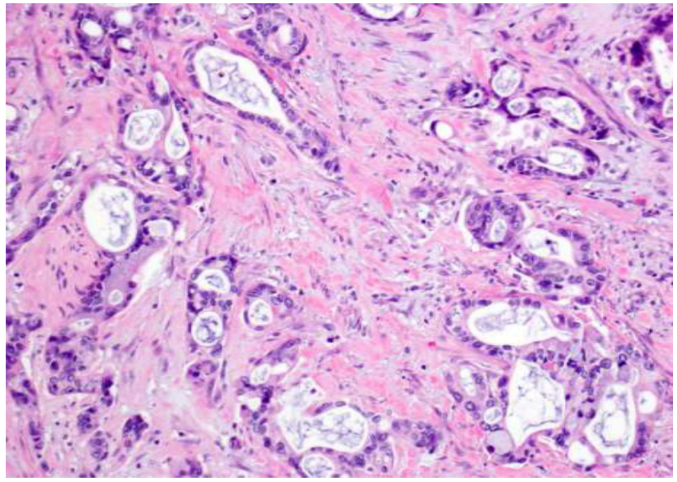


PDAC and MSI-H/MMR-D

	Germline Mutations in MMR Genes
Frequency	5/ 608 (0.8%)
Mutation burden IMPACT NGS	5/5 (100%) ≥ 10 mutations 4/5 (80%) ≥ 50 mutations
Status	4/5 (80%) alive 30- 314+ months Ongoing checkpoint inhibitor therapies

Microenvironment in PDAC

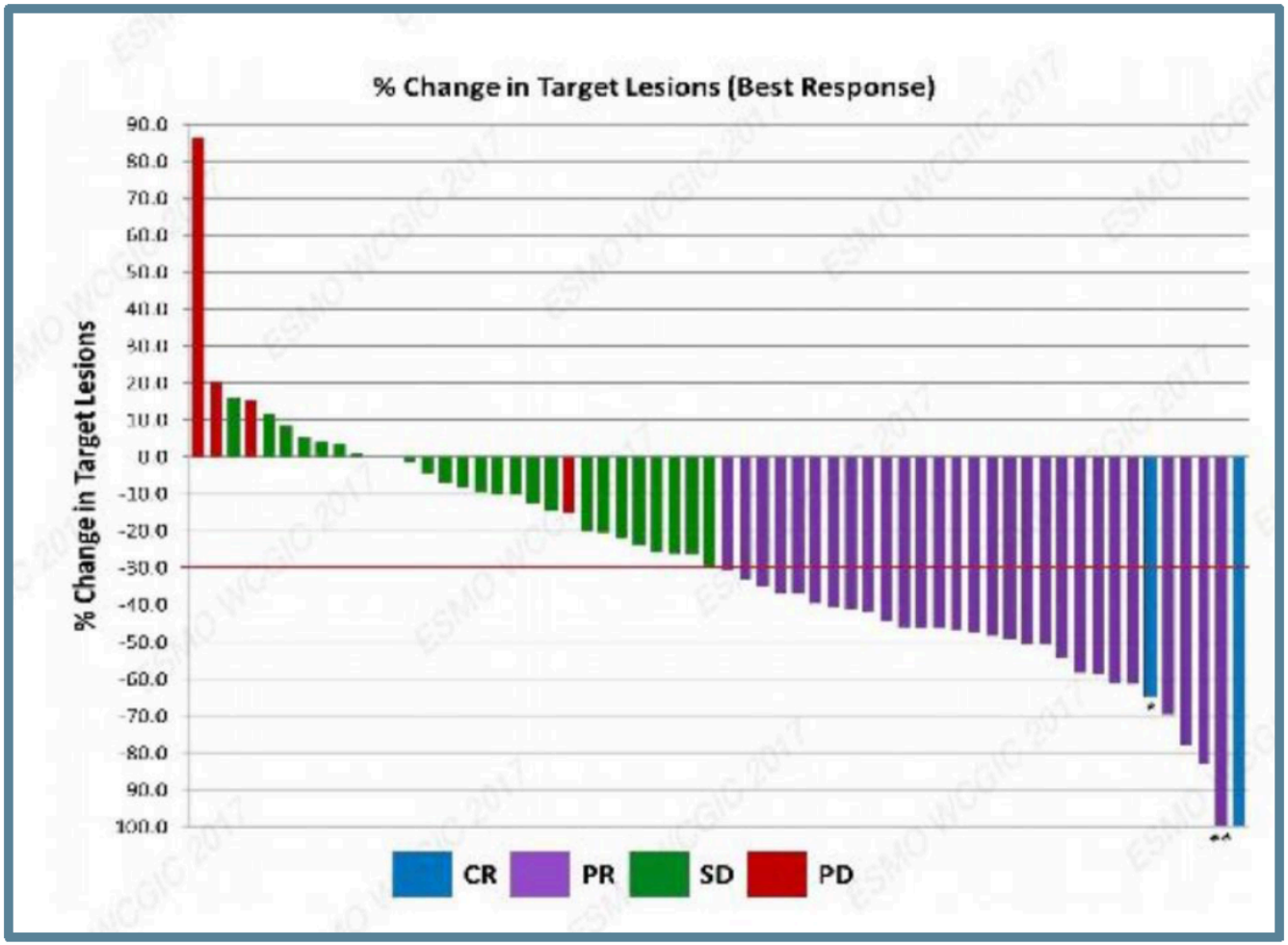
- Hypovascular, hypoxic
- Physical stromal barrier
  - Hyaluronan (HA) glycosaminoglycans
  - Increased EMT, chemoresistance
- PEGPH20 rhuman hyaluronidase
  - Depletes HA in stroma
  - Improves drug delivery



PEGPH20: Ongoing Development

- Randomized phase II trial
  - FOLFIRINOX +/- PEGPH20 (SWOG-NCI)
    Closed by DSMB as futility likely to be met
    Not biomarker selected; Retrospective analysis underway
- Phase III trial underway
  - Nab-P + gemcitabine +/- PEGPH20 (HALO-301); N= 420
  - Biomarker selected: Hyaluronan-high
  - Primary endpoints: PFS, OS

EFFICACY: NAPABUCASIN PLUS GEMCITABINE AND NAB-PACLITAXEL



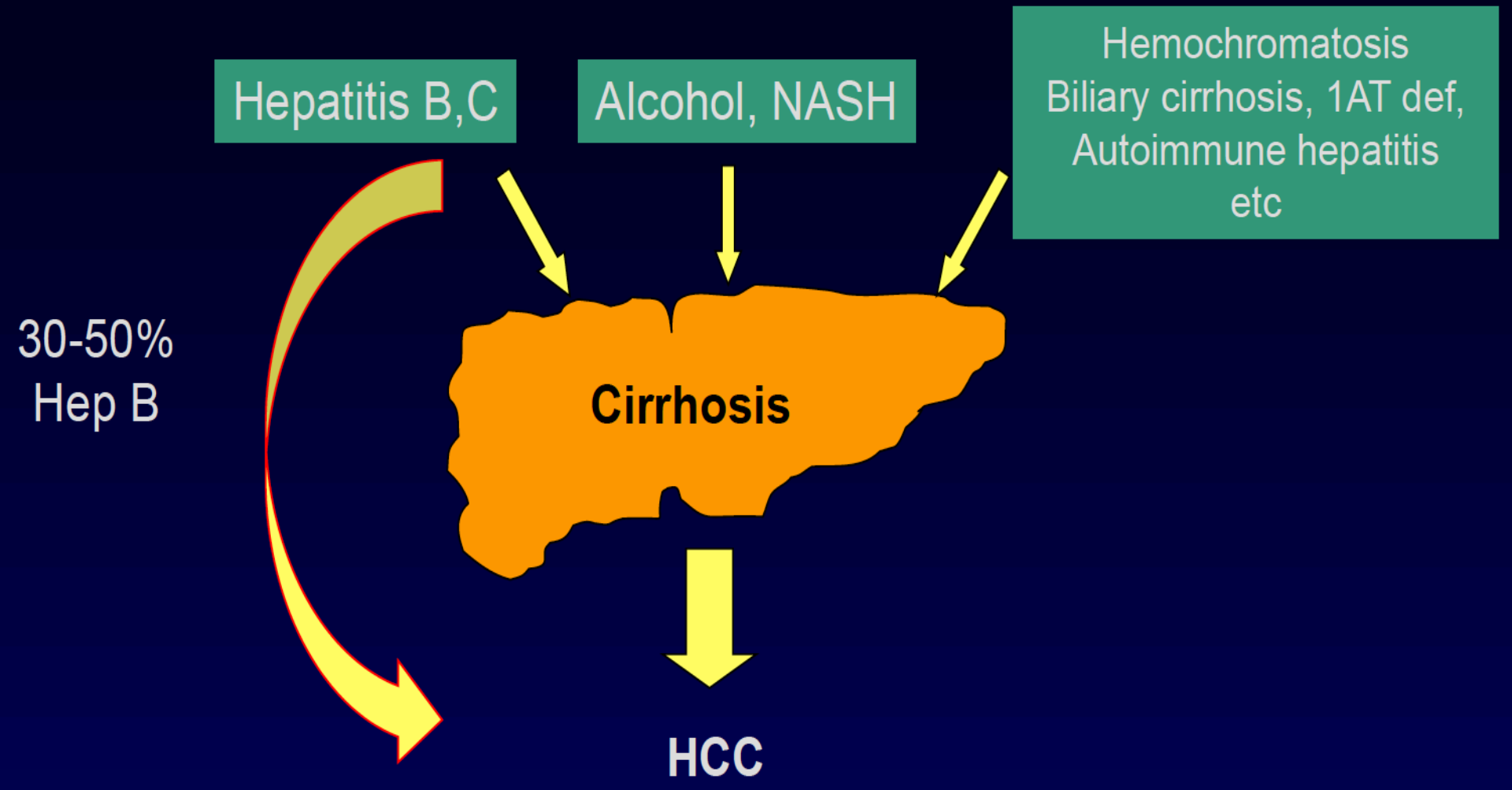
Cancer cell stemness inhibitor

N=66
mPFS: 7.1 months
mOS: 10.7 months
DCR: 93%

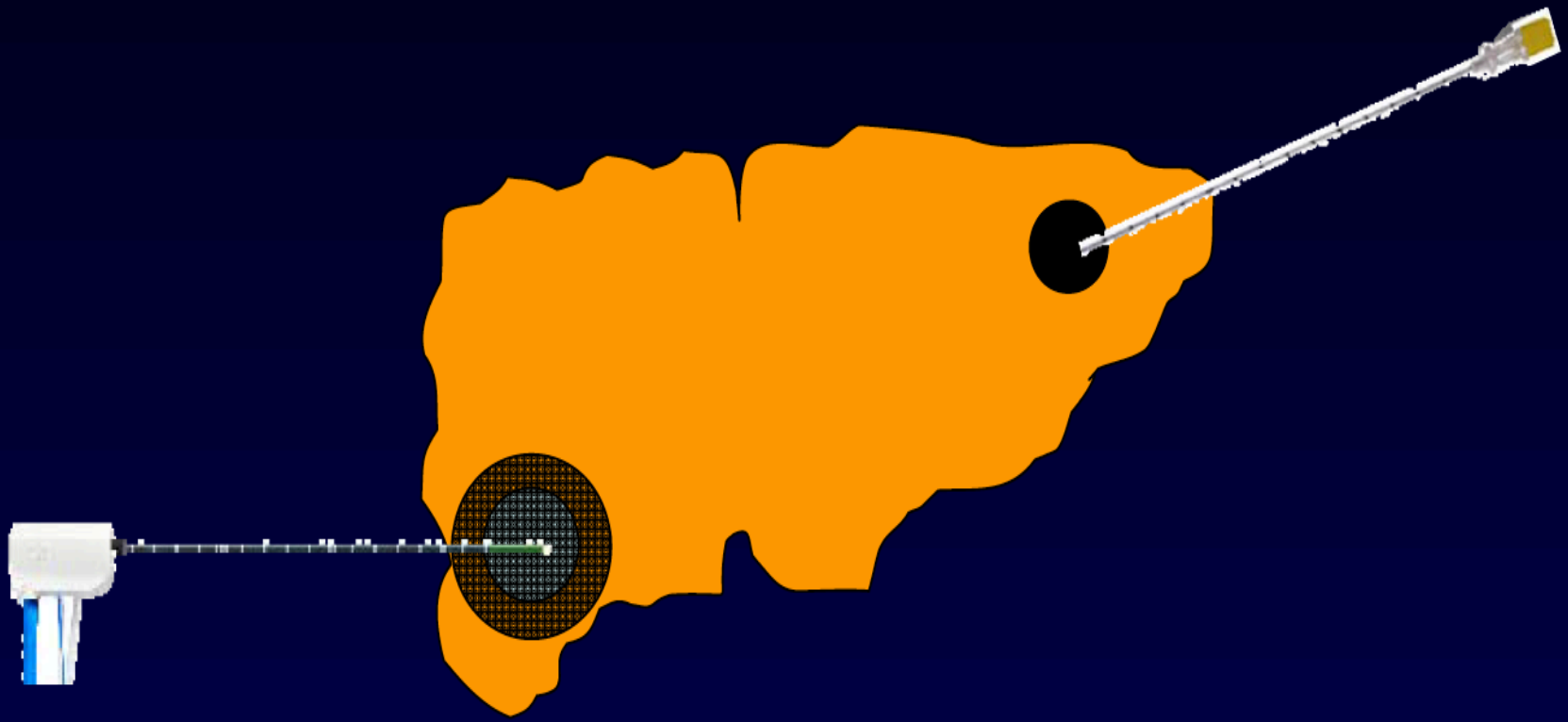
Bekaii-Saab T et al. WCGIC 2017

Cáncer de Hígado

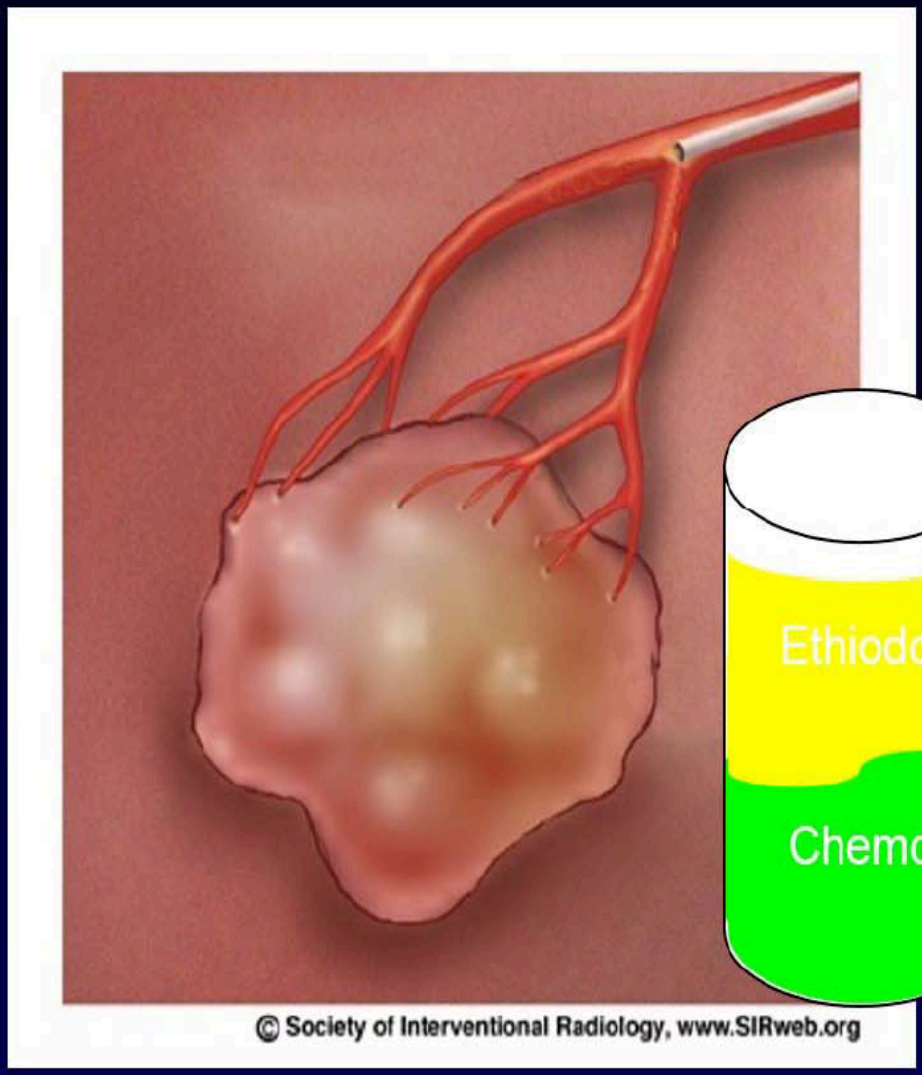
Hepatocellular carcinoma most commonly occurs in the setting of underlying liver disease



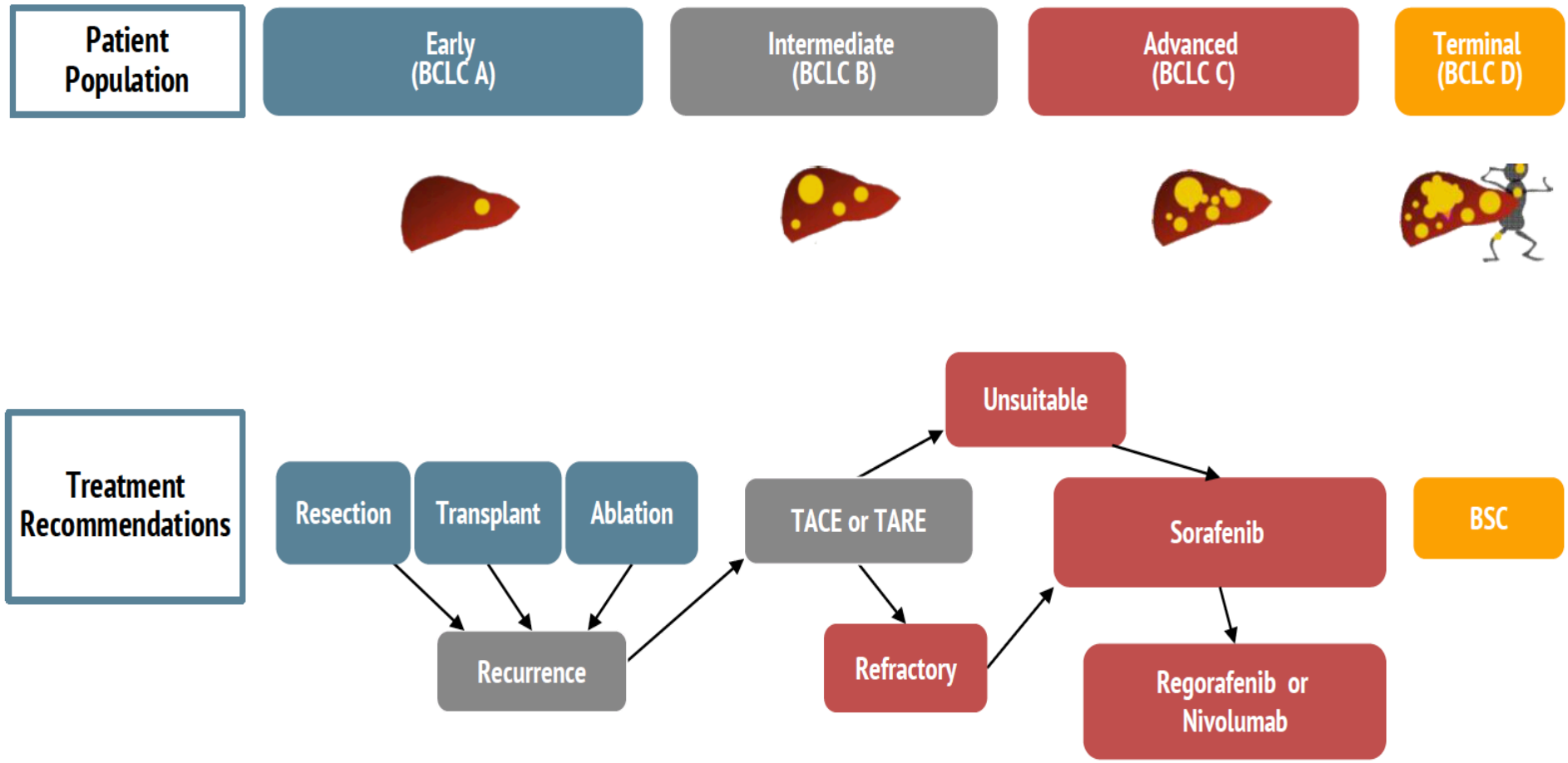
Ablation is potentially curative for accessible tumors < 3 cm in size and up to 3 in number



Transarterial chemoembolization (TACE)



New perspective of HCC landscape



POSITIVE PHASE 3 TRIALS

Arms	Targets	N of Patients	Median Overall Survival
Sorafenib vs placebo (SHARP)[1]	VEGFR1-3, PDGFRβ, RAF1, BRAF	602	10.7 vs 7.9 months HR 0.69 (0.55-0.87), p<0.001
Sorafenib vs placebo (Asia-Pacific)[2]	VEGFR1-3, PDGFRβ, RAF1, BRAF	226	6.5 vs 4.2 months HR 0.68 (0.50-0.93), p=0.041
Lenvatinib vs sorafenib (REFLECT)[3]	VEGFR1-3, FGFR1-4, PDGFRα, RET, KIT	954	13.6 vs 12.3 months HR 0.92 (0.79-1.06), p=NR
Regorafenib vs placebo (RESORCE)[4]	RAF, KIT, RET, PDGFR, VEGFR1-3, TIE2	573	10.6 vs 7.8 months HR 0.63 (0.50-0.79), p<0.0001
Cabozantinib vs placebo (CELESTIAL)[5]	VEGFR, MET, AXL	703	10.2 vs 8.0 months HR 0.76 (0.63-0.92), p=0.0049
Ramucirumab vs placebo (REACH-2)[6]	VEGFR2	292	8.5 vs 7.3 months HR 0.71 (0.53-0.95), p=0.0199

1. Llovet JM et al, NEJM 2008; 2. Cheng AL et al, Lancet Oncol 2009; 3. Kudo M et al. Lancet 2018; 4. Bruix J et al, Lancet 2017; 5. Abou-Alfa GK et al. NEJM 2018; 6. Zhu AX et al. ASCO 2018

FUTURE PERSPECTIVES

New key signaling pathways, molecular mechanisms, and oncogenic addiction loops could be promising targets (e.g., MET, TGF-β, FGF19/FGFR4)

Biomarkers identification is crucial to define, stratify, **select subgroups** of patients in clinical trials and in clinical practice

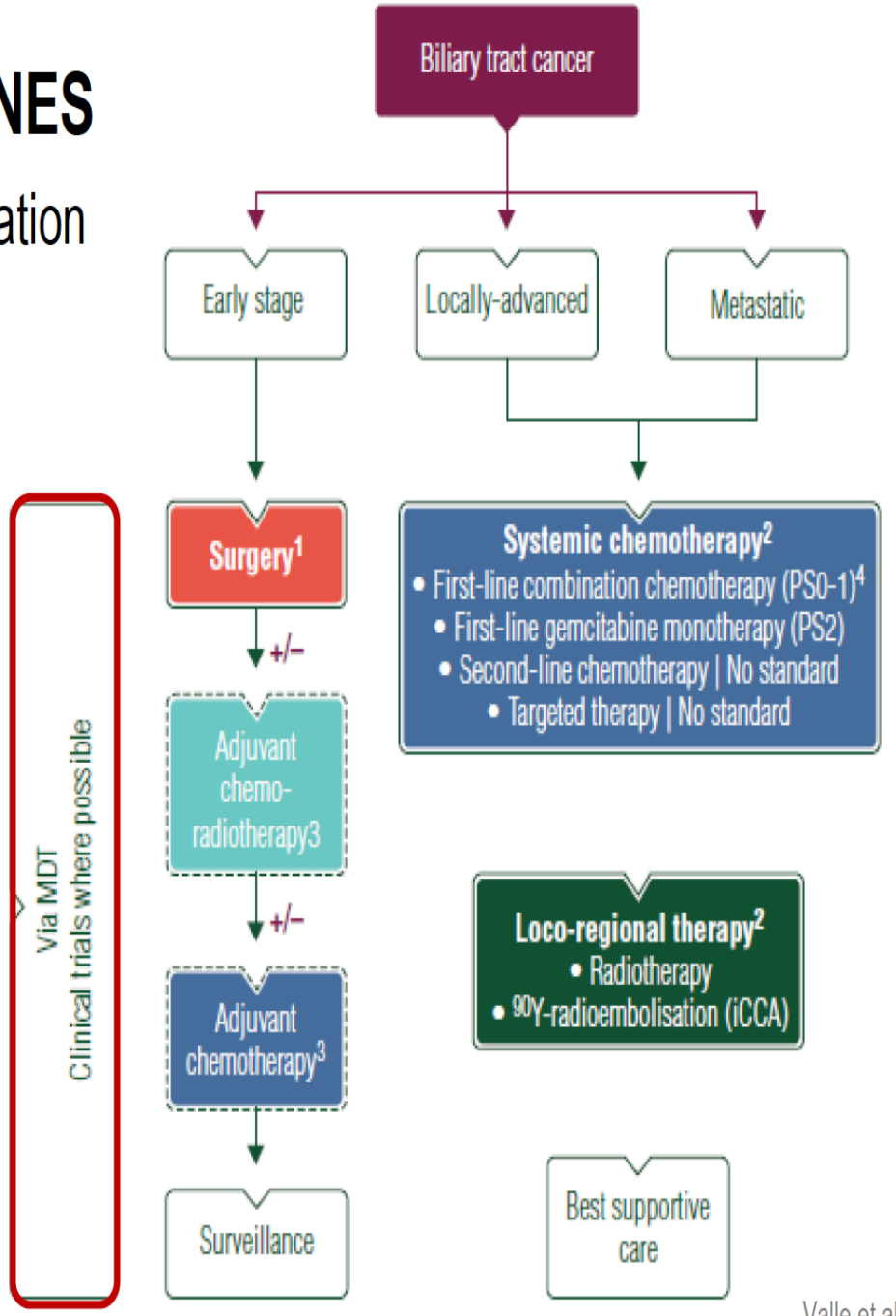
Collection of **biologic samples** and, in the future, **liquid biopsy** should be mandatory to identify and validate **prognostic and predictive biomarkers**

HRQoL assessment should be included in clinical trials and utilized to select drugs in clinical practice

Cáncer de Vía Biliar

ESMO GUIDELINES

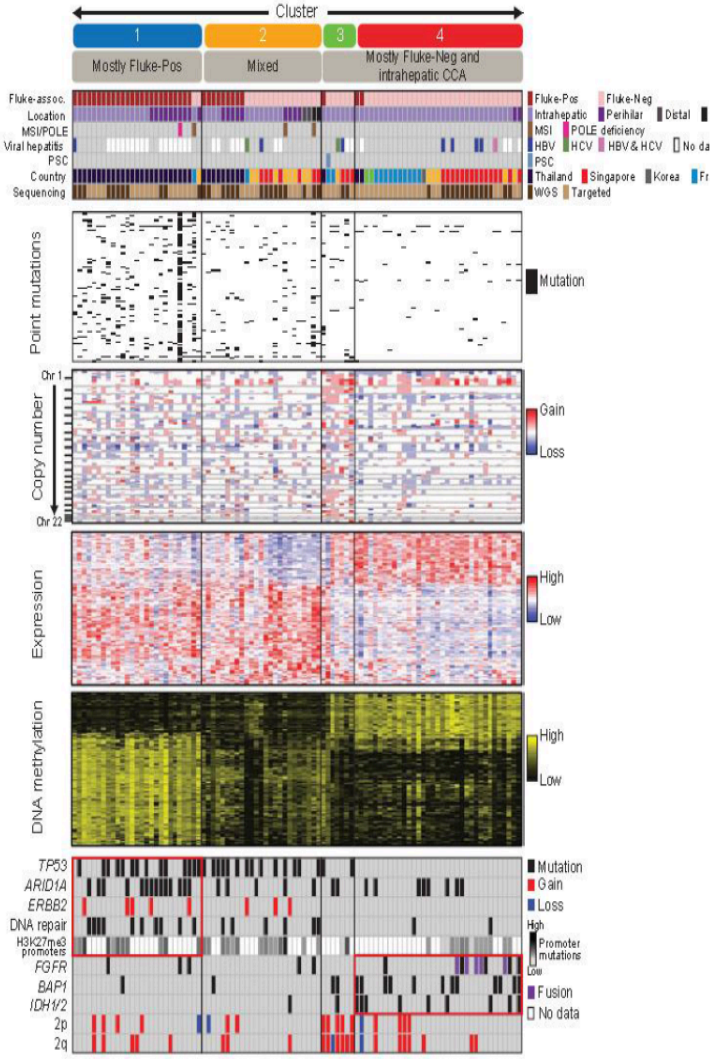
Encourages participation in clinical trials

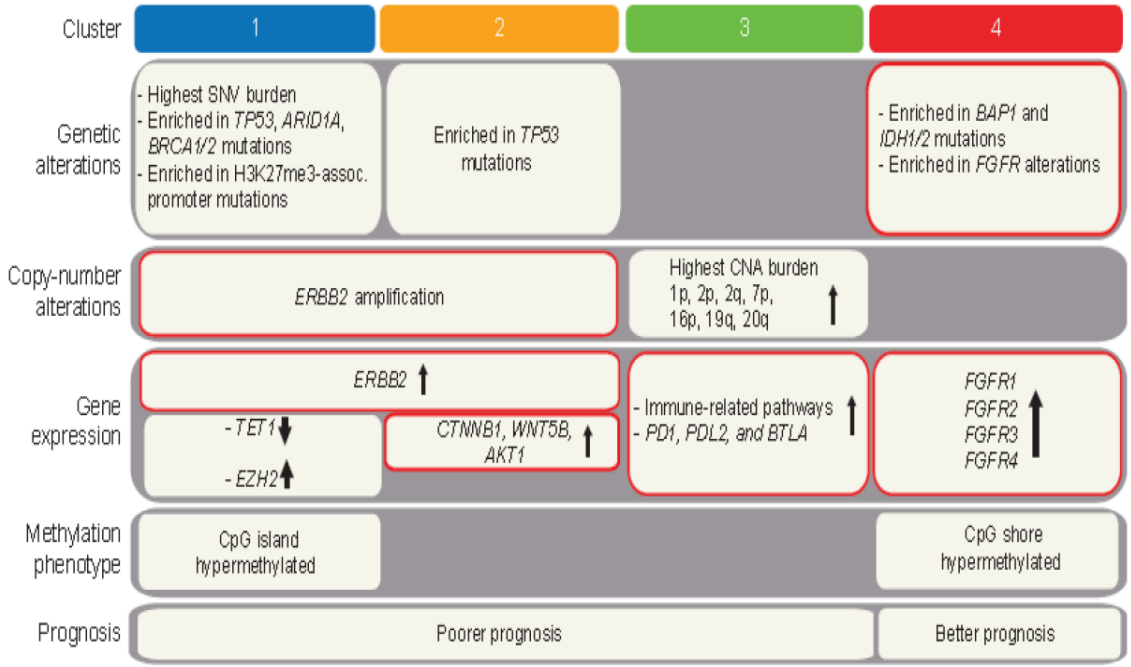


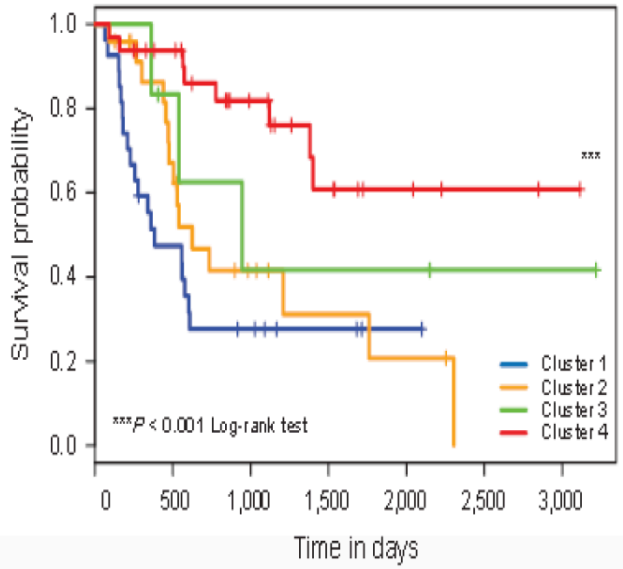
[4] Cisplatin and gemcitabine [category IA], other gemcitabine-based combination [category IIB]

Valle et al Annals of Oncology 2016;27 (Suppl 5): v28–v37)

MOLECULAR SUBGROUPS OF CHOLANGIOCARCINOMA







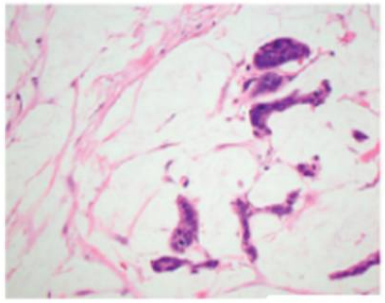
Jasakul A et al. *Cancer Discov* 2017;7(10);1116–35.

MUNICH 2018 ESMO congress

Subtypes of Pancreatic Cancer

Pancreatic Progenitor

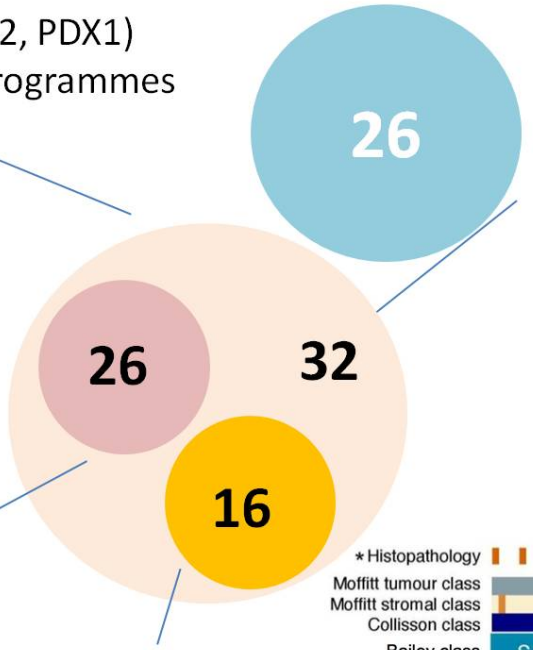
Progenitor genes activation (FoxA2, PDX1)
Upregulation of developmental programmes



Colloid Carcinoma

Squamous

p53 inactivation,
Chromatin modifiers inactivation
EGFR, PDGFR, Myc and MET signaling
Poor Survival

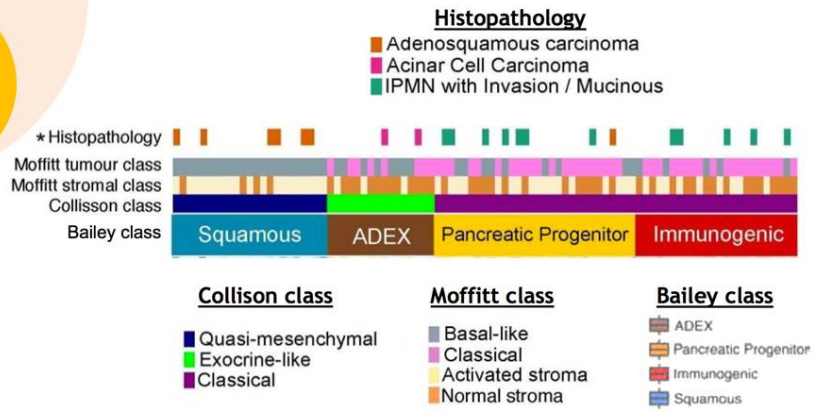


Immunogenic

High expression of immunoregulatory genes
Upregulation of immune avoidance networks

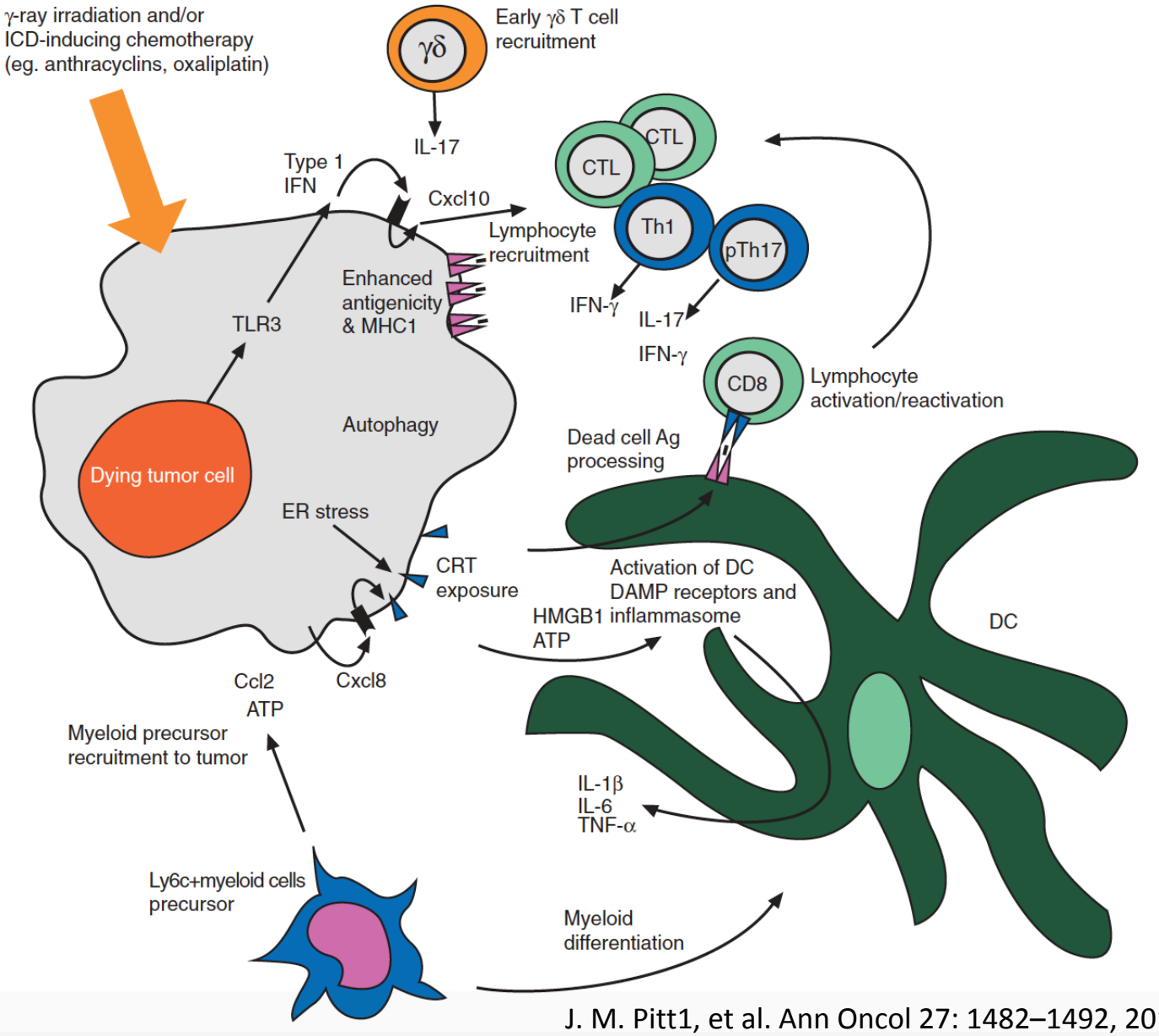
ADEX

Acinar and endocrine differentiation genes



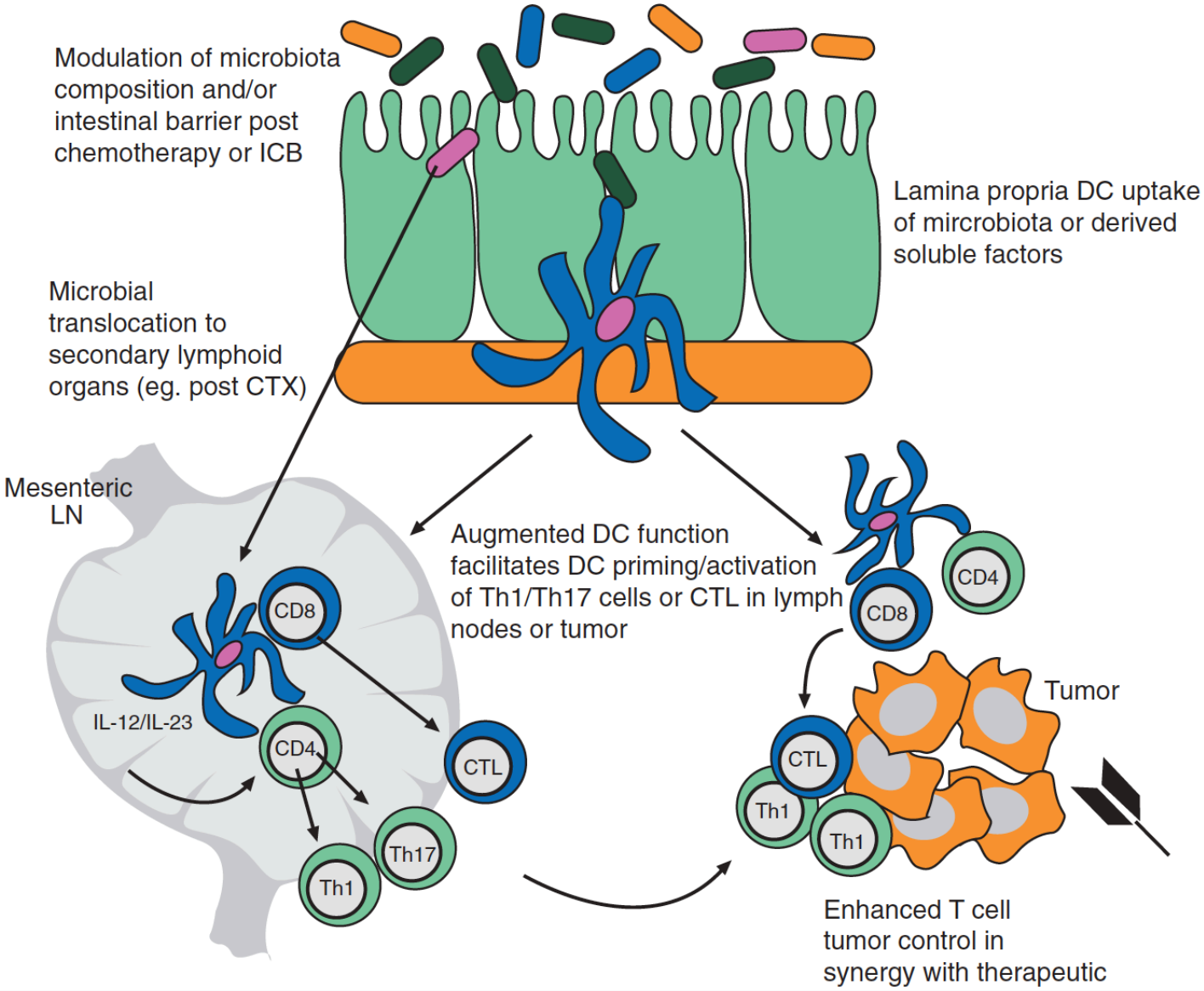
Collison et al., *Nature Medicine* 2011
Moffitt et al., *Nature Genetics* 2015
Bailey et al., *Nature* 2016

Immunogenic ChT and RT to restore the tumor microenvironment



J. M. Pitt1, et al. Ann Oncol 27: 1482–1492, 2016

Microbiota can ↑ DC function and contribute to anticancer immunity



J. M. Pitt1, et al. Ann Oncol 27: 1482–1492, 2016

The Pancreatic Cancer Microbiome Promotes Oncogenesis by Induction of Innate and Adaptive Immune Suppression

Smruti Pushalkar et al. *Cancer Discov; 8(4);1–14. ©2018 AACR*

A distinct and abundant microbiome drives suppressive monocytic cellular differentiation in pancreatic cancer via selective Toll-like receptor ligation leading to T-cell anergy.

Targeting the microbiome protects against oncogenesis, reverses intratumoral immune tolerance, and enables efficacy for checkpoint-based immunotherapy.

The Physician's Attitude

- To cure sometimes
- To relieve often
- To comfort always

—*Traditional saying*

A multidisciplinary approach and molecular pathology are changing cancer patient management

- Right patient
- Right tumor
- Right drug
- Right time

- Increased efficacy
- Improved safety
- Increased Cost-efficacy

¡¡¡Muchas gracias!!!