NETS and Medical Oncology

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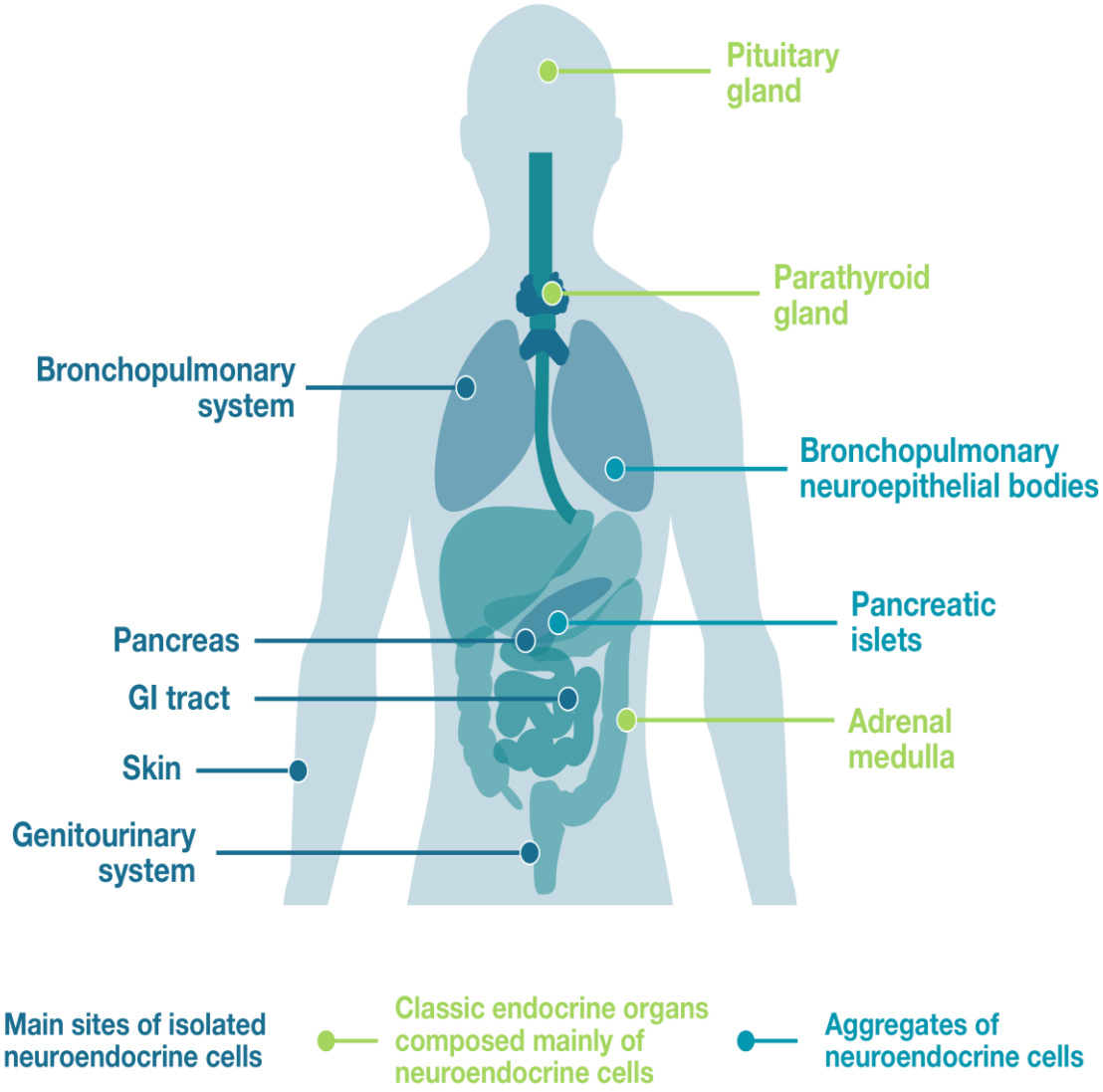
DEFINITION OF NETs

Neuroendocrine tumours (NETs) are a group of neoplasms that originate in secretory cells known as neuroendocrine cells, which are distributed throughout the body.[1,2]
They are located in three broad areas:

1. Isolated neuroendocrine cells scattered throughout most tissues.[1,3]
2. Aggregates of neuroendocrine cells in organs.[3]
3. Classic endocrine glands.[1]

NETs were originally named ‘carcinoid’ (cancer-like) tumours. There have since been other terms coined to describe these lesions and the current term ‘NET’ was first put forward in 1995.[4,5]

The term ‘carcinoid’ is criticised for inaccurately implying that NETs are always benign lesions.[6]



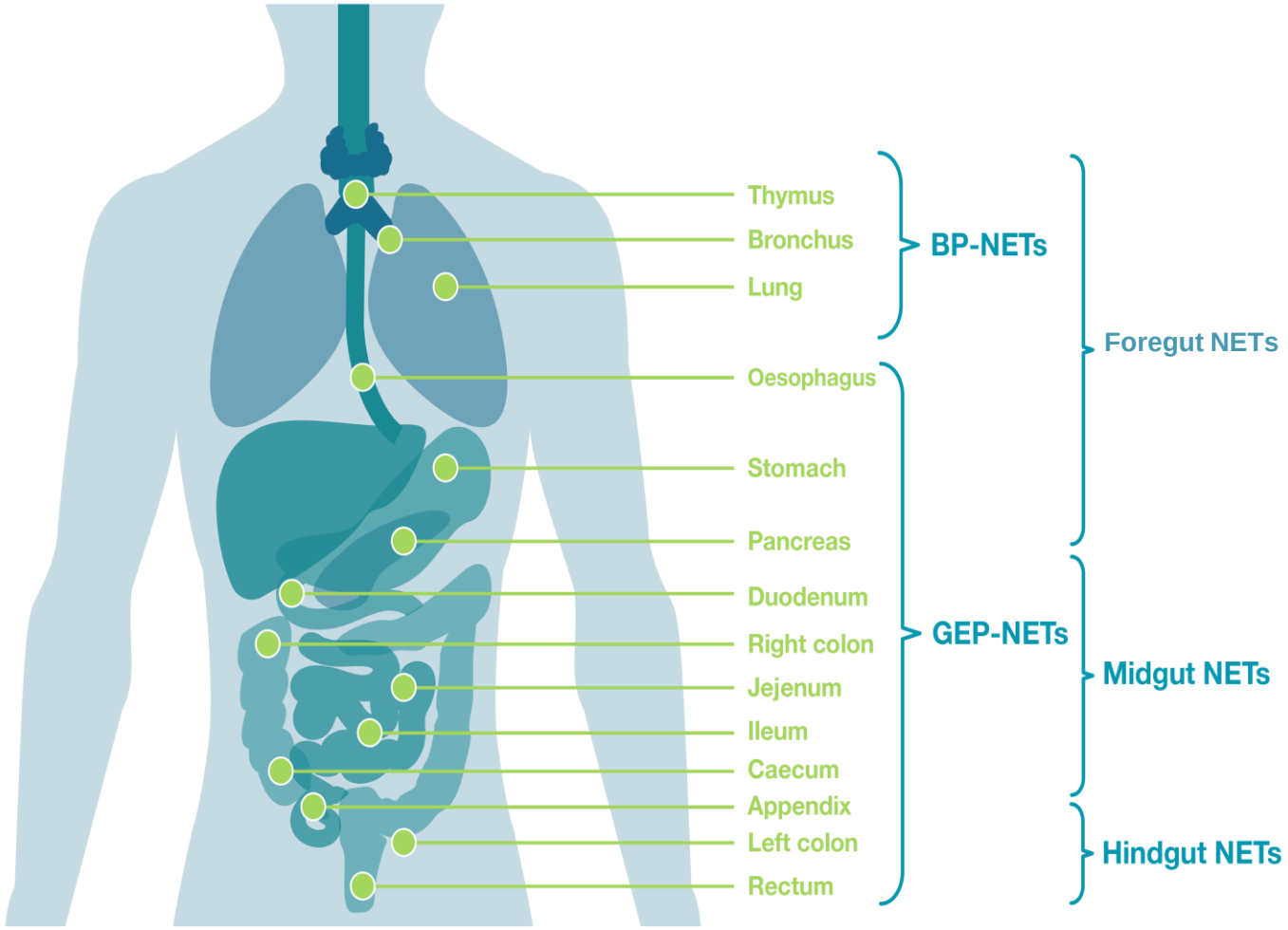
ANATOMICAL DISTRIBUTION OF NETs

NETs are classified according to their anatomical site of origin, with the vast majority arising in the GEP or BP tracts (GEP-NETs and PB-NETs, respectively).[6]

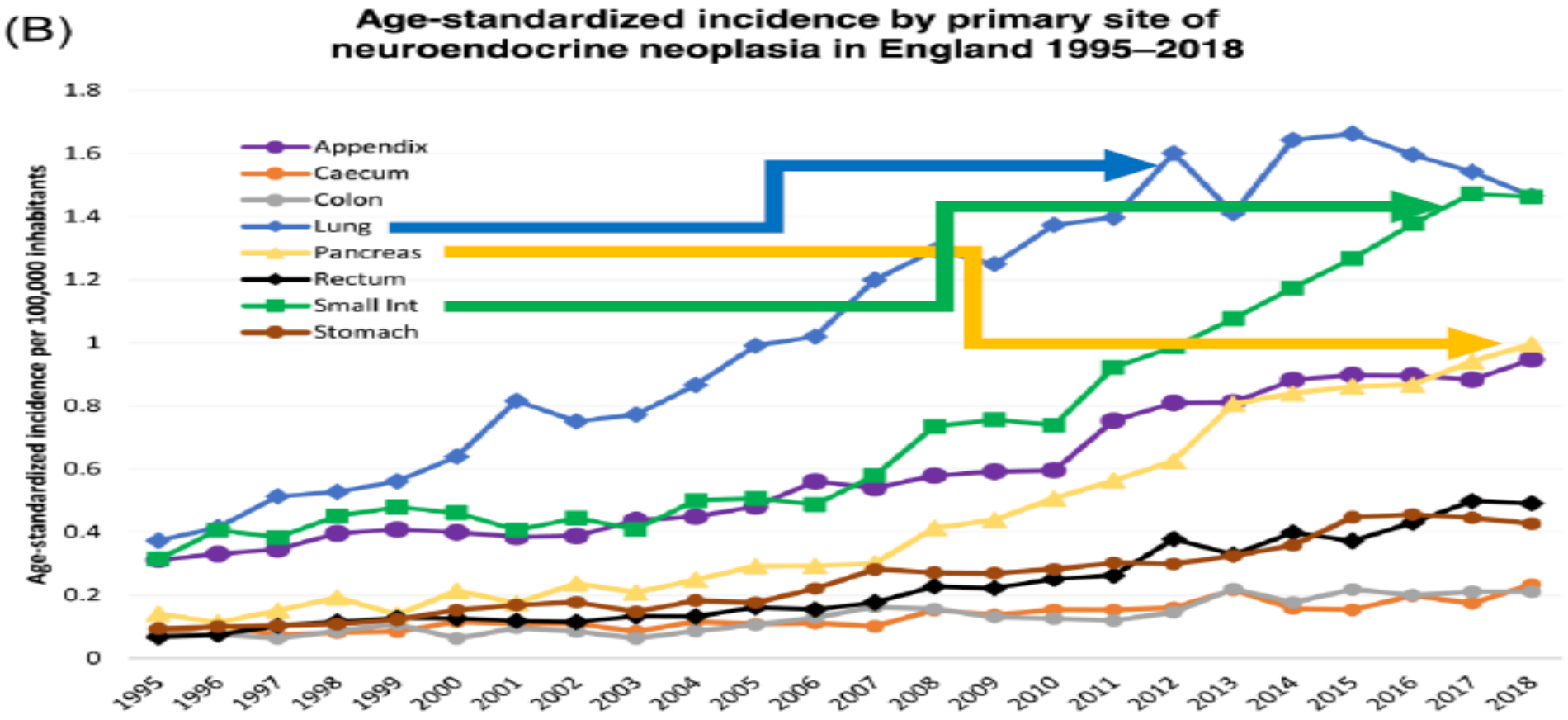
NETs are traditionally subclassified according to the embryological origin of their site:[8]

- Foregut
- Midgut
- Hindgut

Less common NET sites include the genitourinary tract, the adrenal medulla and the parathyroid and pituitary glands.[8,11,12]



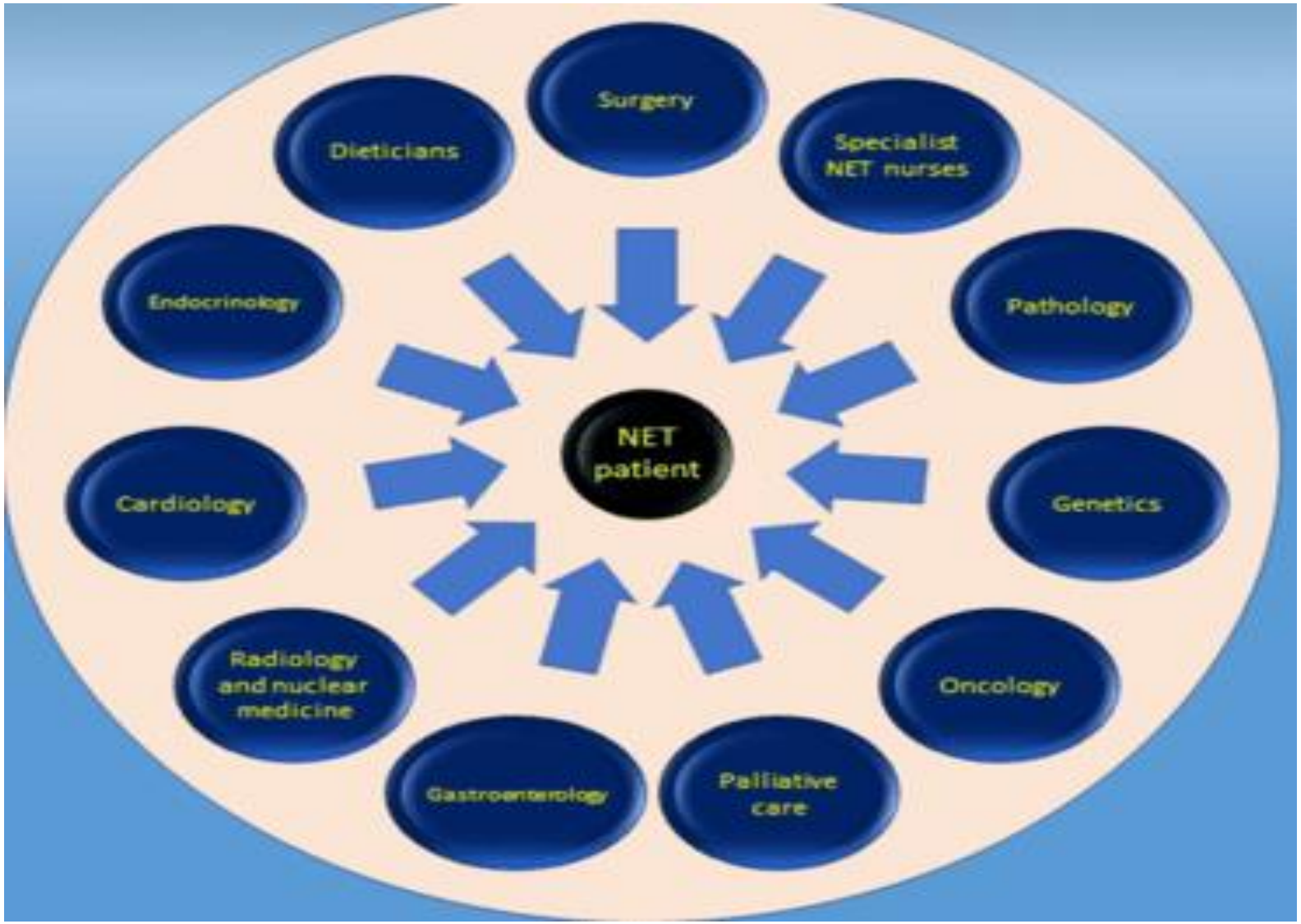
Why bother? ……. NETS are rare…..right?



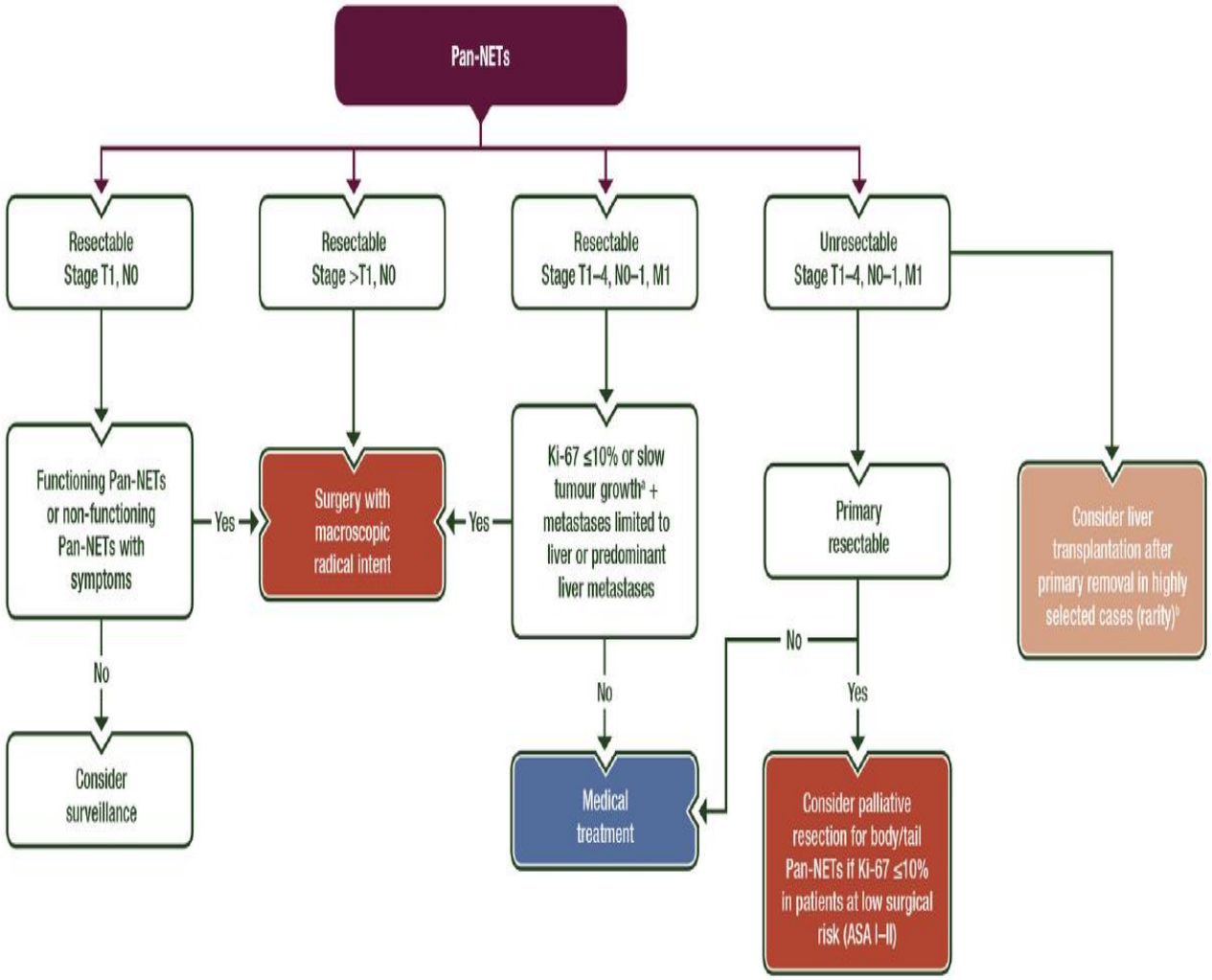
Site	Appendix	Caecum	Colon	Lung	Pancreas	Rectum	Small Int	Stomach
Average change per year	105.2%	107.3%	107.6%	106.6%	110.6%	109.9%	107.5%	107.4%
Absolute increase	304%	305%	287%	393%	705%	725%	466%	453%

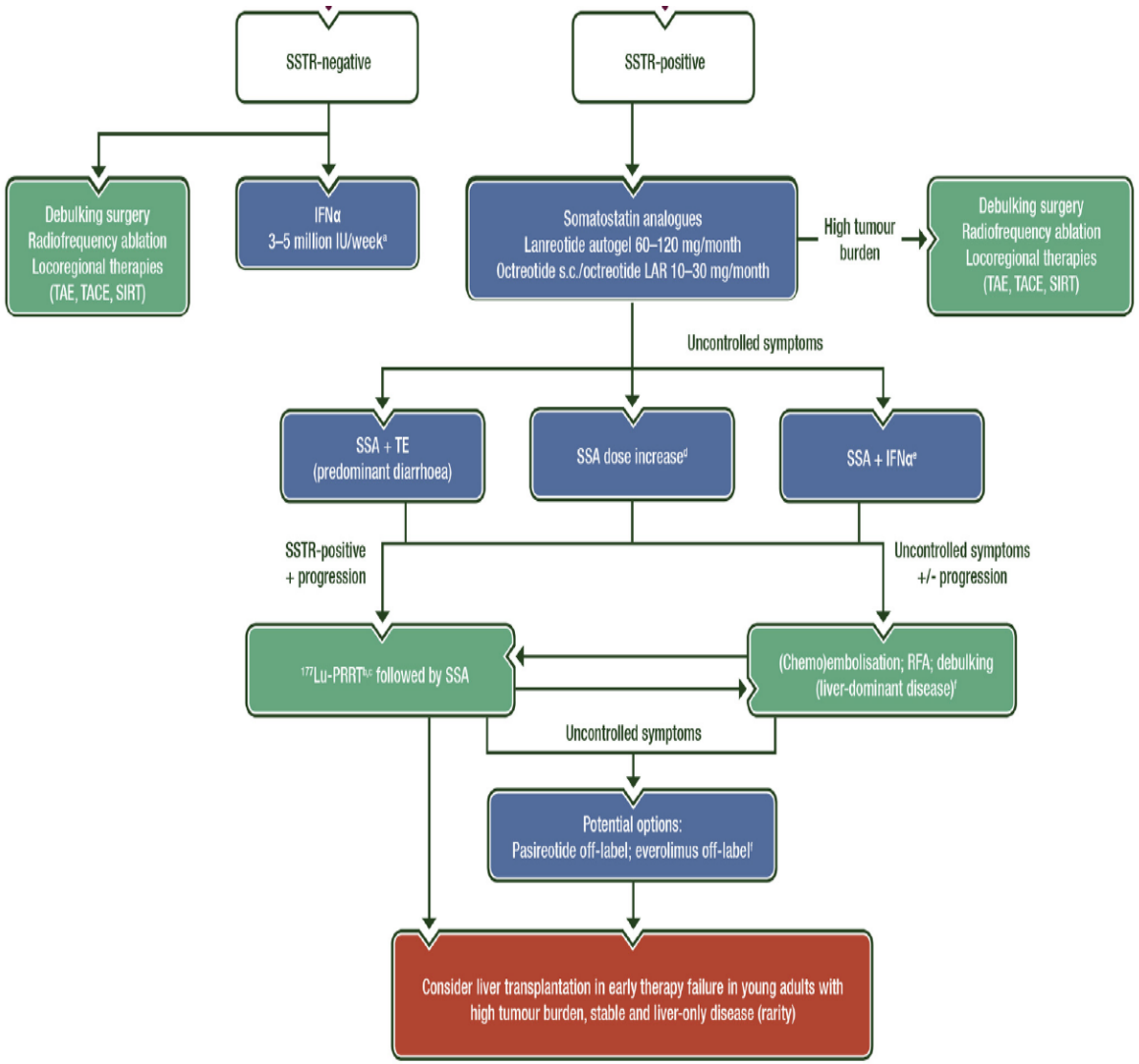
White BE et al. Lancet Reg Health Eur. 2022;23:100510

Overview – NETs management

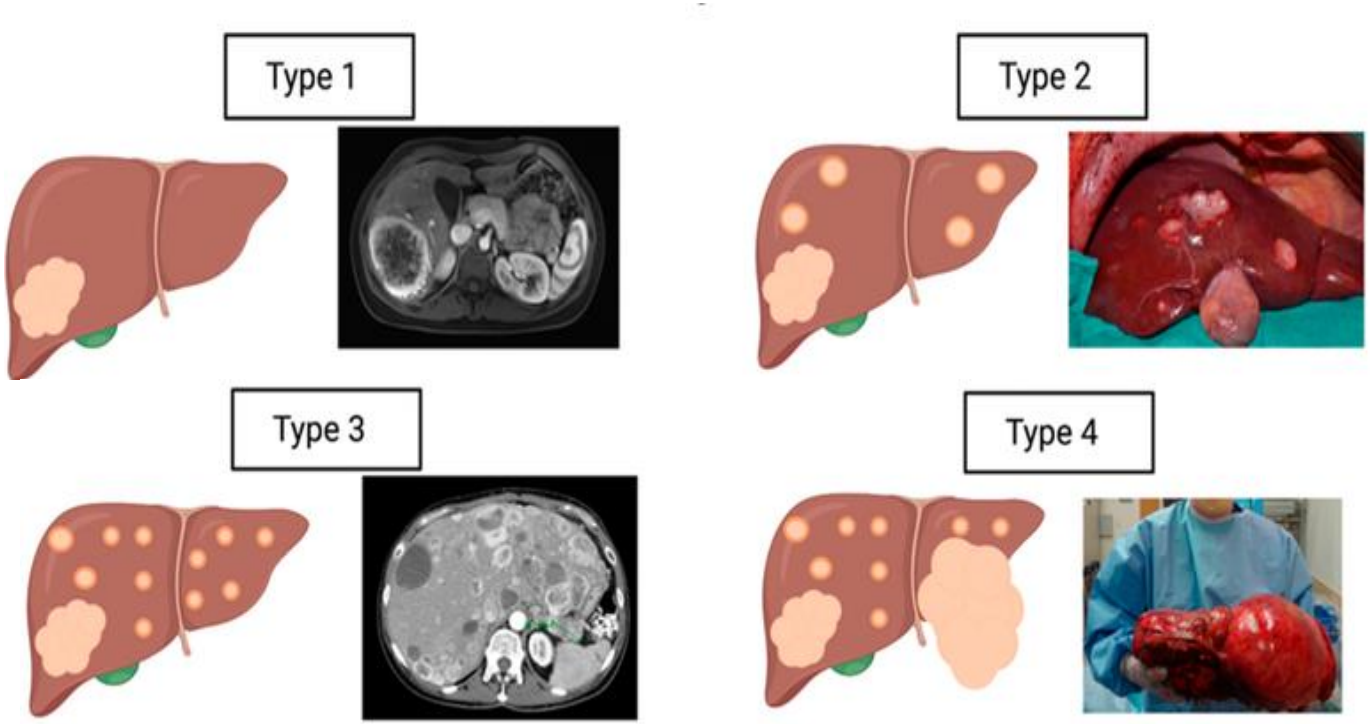


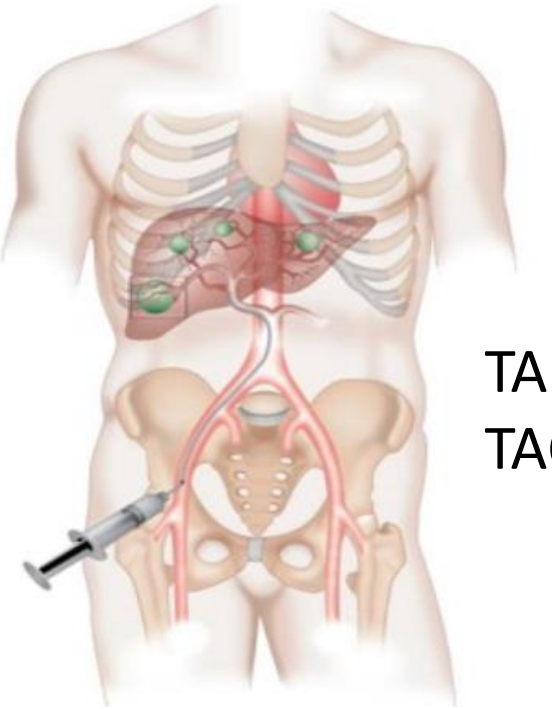
Surgical Decision-making…… Complex!



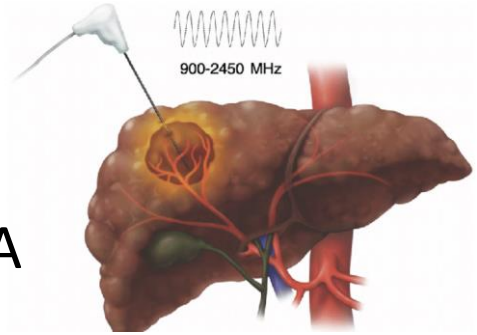


Liver directed therapies

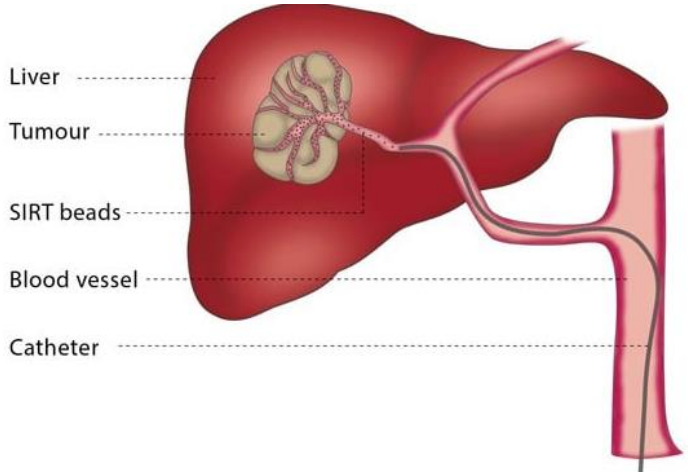




TAE
TACE



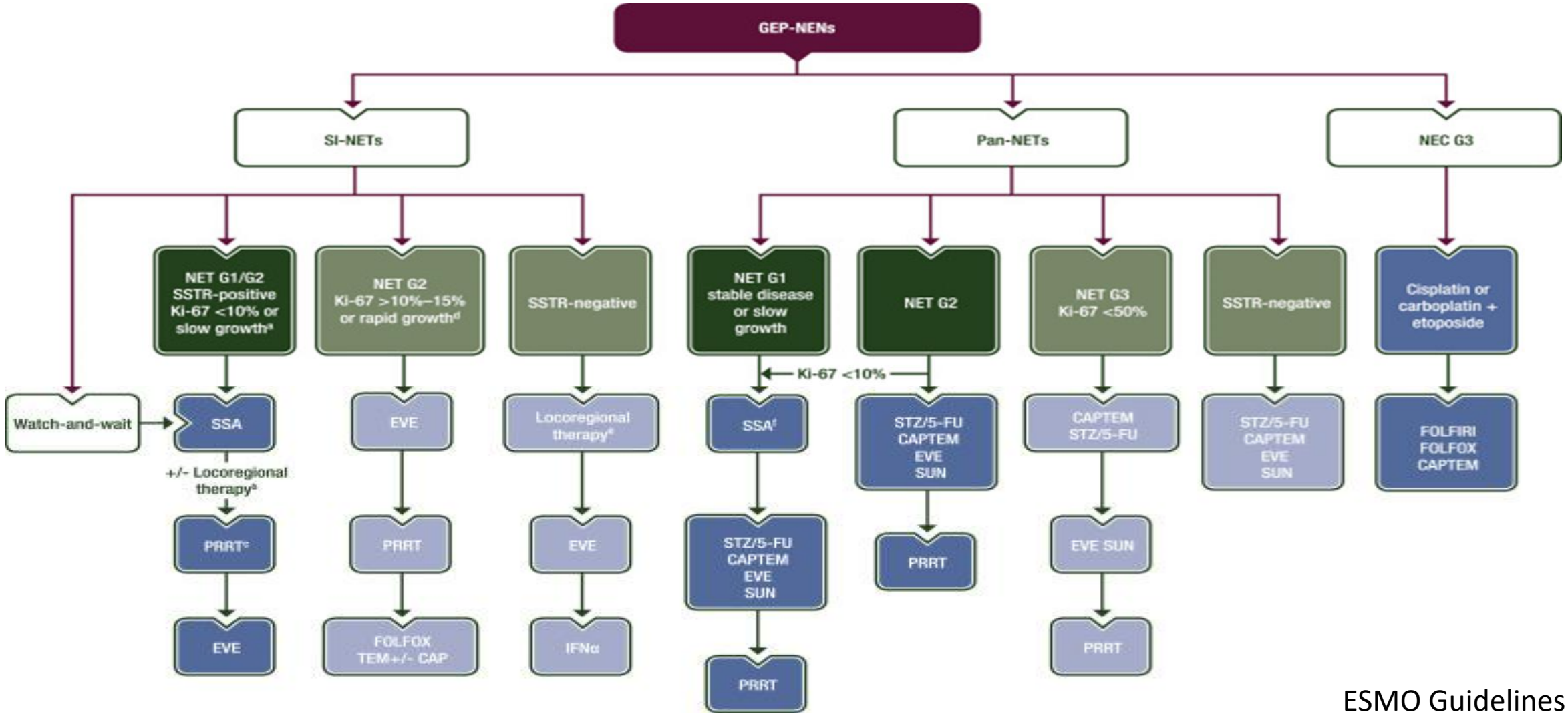
RFA
MWA



SIRT

Transplantation (rare)

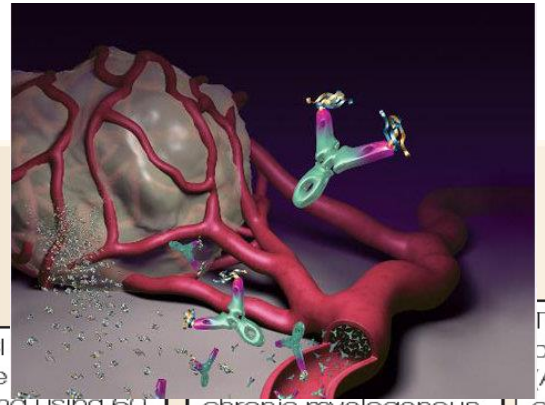
MEDICAL ONCOLOGY……
SACT – systemic anticancer therapy



ESMO Guidelines 2020

Anti-cancer Chemotherapy… A Short History

Anti-cancer Chemotherapy… A Short History



Timeline | Th…erapy

1942 — Louis Goodman and Alfred Gilman use nitrogen mustard to… a patient with non-Hodgkin's lymphoma… demonstrate for the… time that chemotherapy can induce tumour regression.

1948 — …systematic programme for drug screening commences.

1955 — …Food and Drug …ministration (FDA) approves the alkylating agent cyclophosphamide.

1958 — …cure lymphomas with combination chemotherapy

1959 — …as adjuvant treatment for node-positive breast cancer.

1965 — The NCI 'disease… screening using 60 cell lines derived from different types of human tumour.

1970 — …chronic myelogenous leukaemia, a new paradigm for targeted therapy in oncology.

1972 — The FDA approves …bevacizumab (Avastin), the first clinically proven anti-angiogenic agent, for the treatment of colon cancer.

1975 — Syndey Farber uses antifolates to successfully induce remissions in children with acute lymphoblastic leukaemia (ALL).

1978 — Roy Hertz and Min Chiu Li demonstrate that methotrexate as a single…

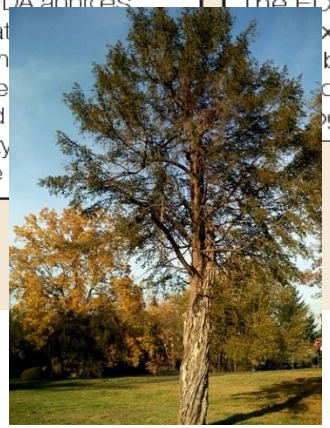
1989 — Combination chemotherapy (POMP regimen) is …long-…ns in …ALL.

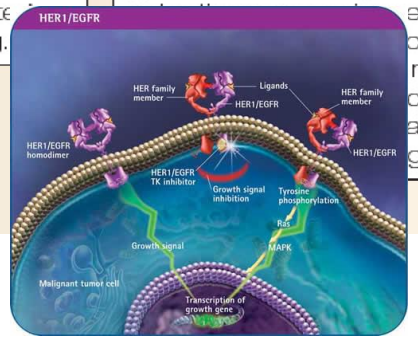
1992 — The FDA appres… cisplat… treatm… cance… would… activity… range…

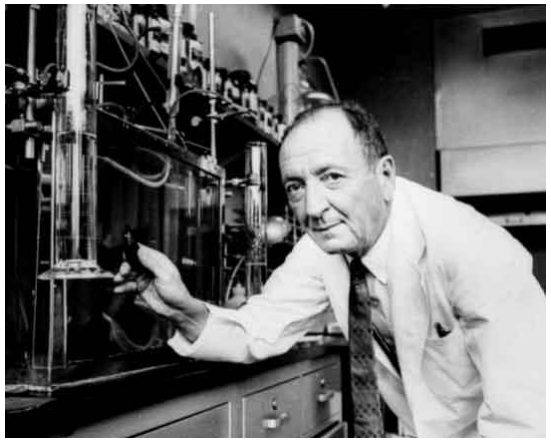
2001 — The FDA approves …xel (Taxol), …becomes the …ockbuste… …gy drug.

2004 — Researchers at Harvard University define mutations in the epidermal growth factor receptor that confer …ess to the …o, indicating …might be …dentify …at will …gents.

George Hitchings an… the purine analogue 6…







Alfred Gilman

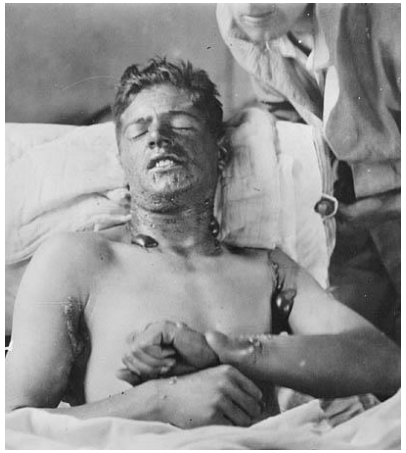
Louis Goodman

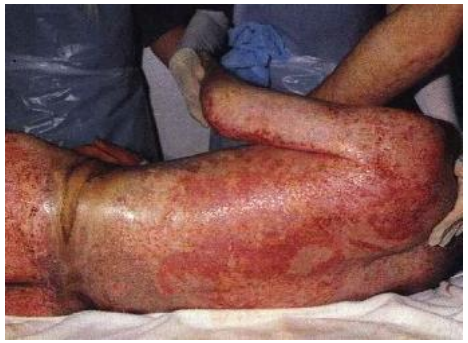
NITROGEN MUSTARD THERAPY

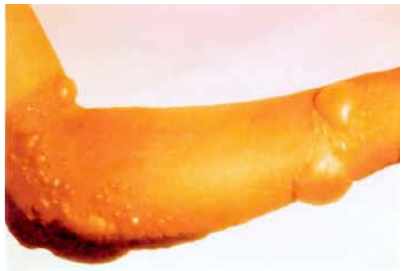
Use of Methyl-Bis(Beta-Chloroethyl)amine Hydrochloride and Tris(Beta-Chloroethyl)amine Hydrochloride for Hodgkin's Disease, Lymphosarcoma, Leukemia and Certain Allied and Miscellaneous Disorders

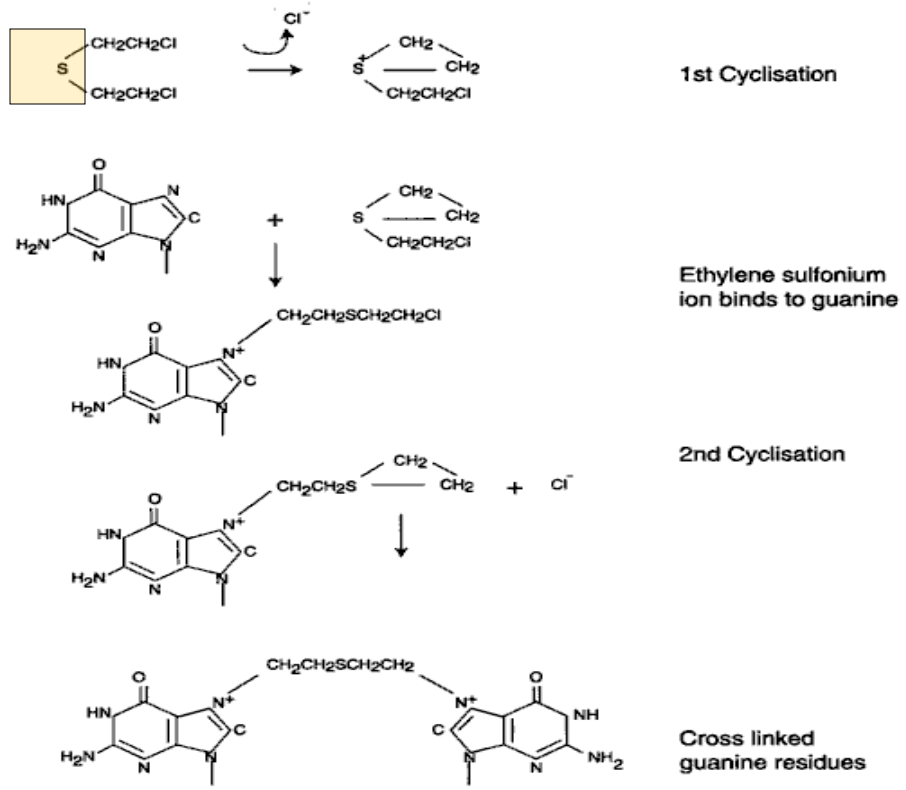
LOUIS S. GOODMAN, M.D.; MAXWELL M. WINTROBE, M.D.; WILLIAM DAMESHEK, M.D.; MORTON J. GOODMAN, M.D.; MAJOR ALFRED GILMAN; MARGARET T. McLENNAN, M.D.

***J Am Med Assoc.* 1946;132(3):126-132.**

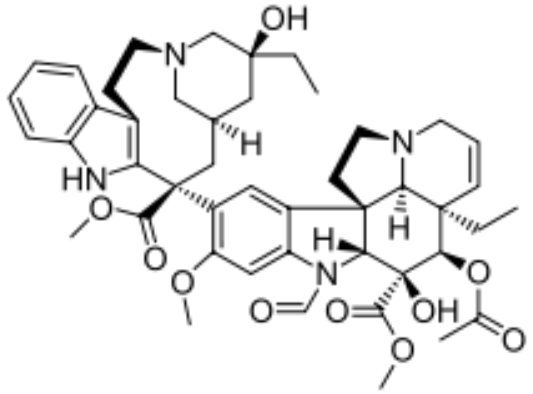




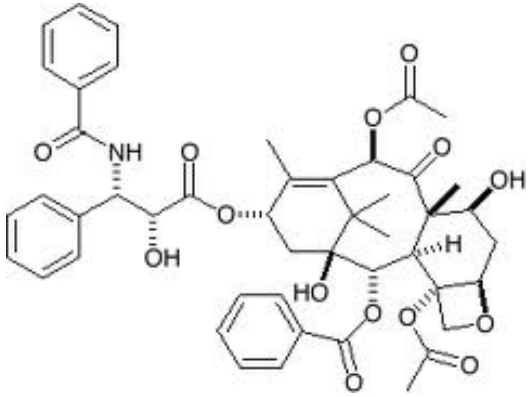




Mitotic Inhibitors

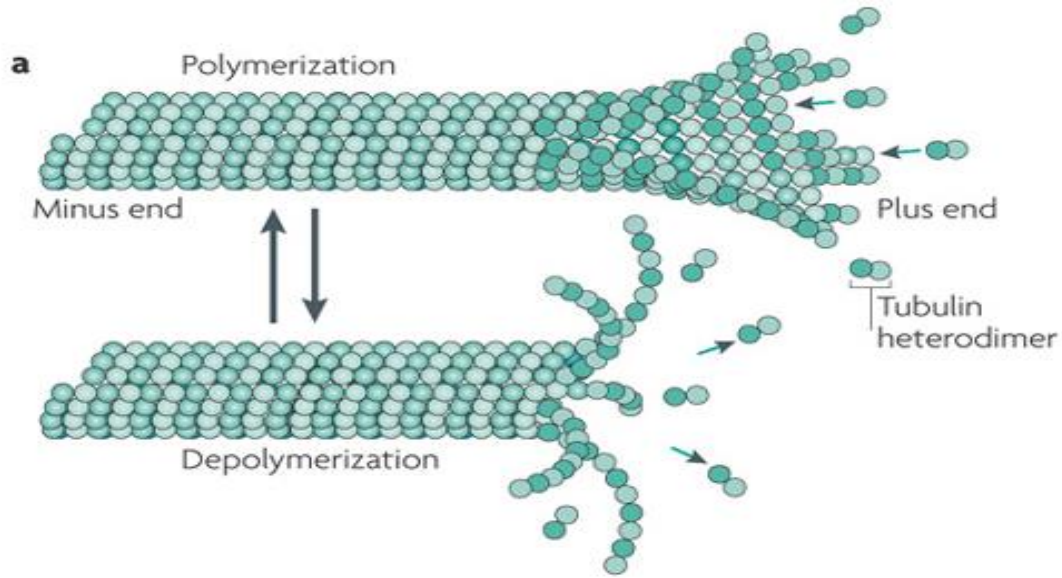


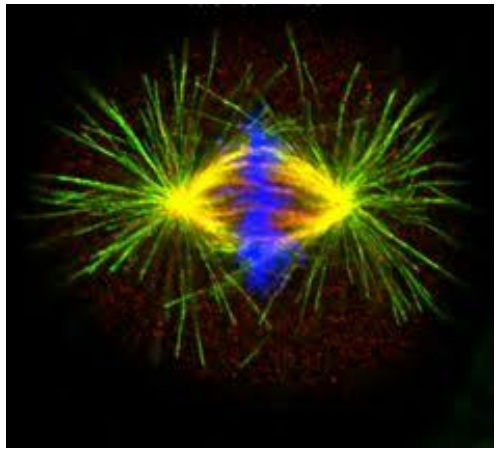
Vinca alkaloids (eg Vincristine) – natural product isolated from the periwinkle plant

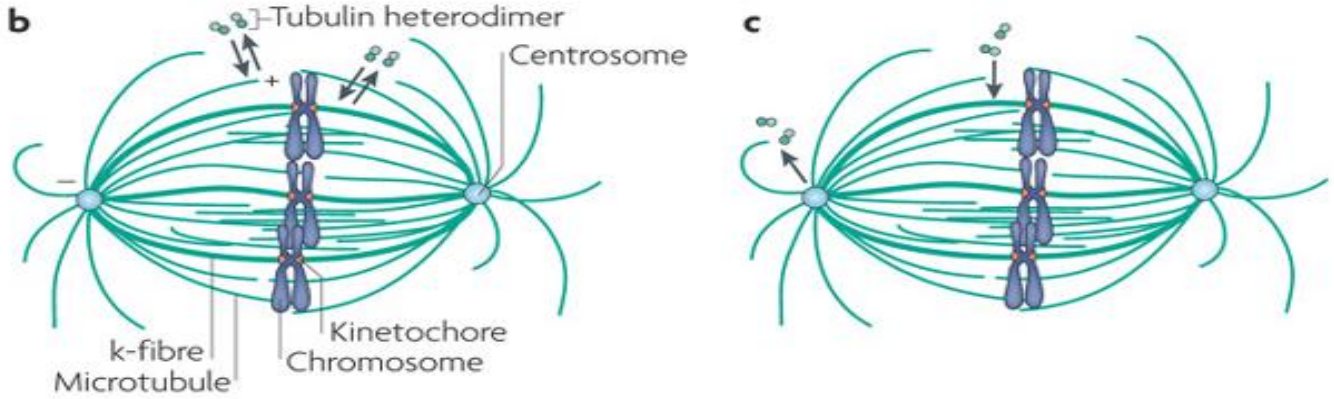


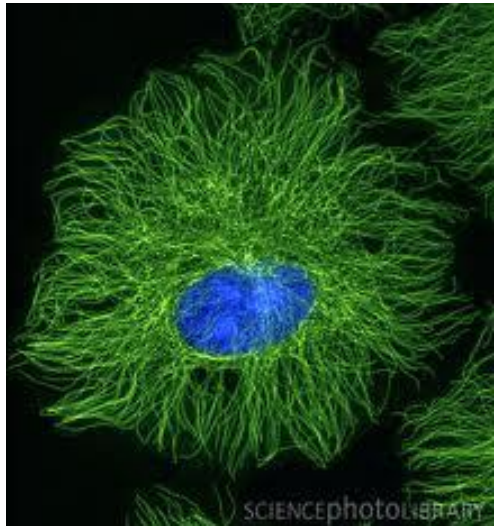
Taxanes (eg taxol) – natural product isolated from the bark of the pacific yew tree

Targeting Microtubules



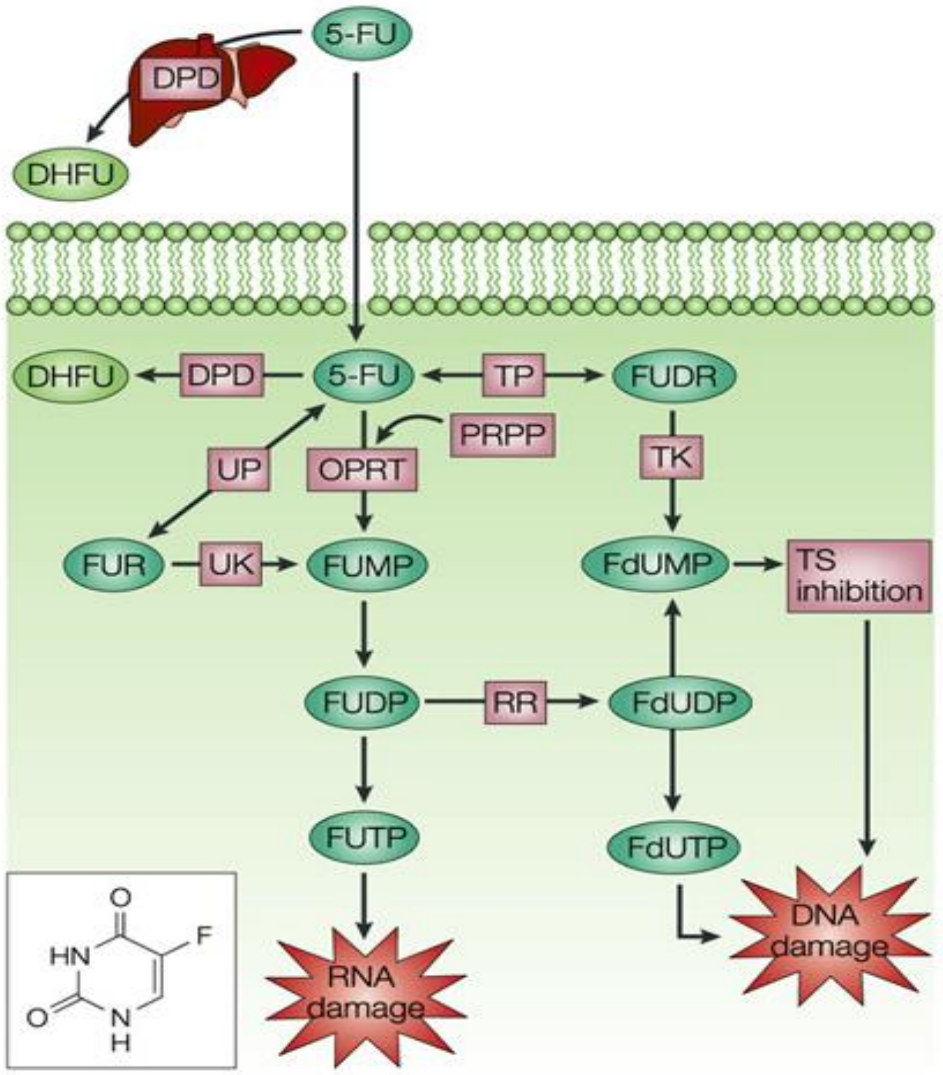






***Nature Reviews Molecular Cell Biology* 11, 91-102**
(February 2010)

5FU /Capecitabine



- 5-Fluorouracil is converted to three main active metabolites:
  - fluorodeoxyuridine monophosphate (FdUMP),
  - fluorodeoxyuridine triphosphate (FdUTP) and
  - fluorouridine triphosphate (FUTP).
- Main mechanism: Conversion of 5FU to fluorouridine monophosphate (FUMP), either directly by orotate phosphoribosyltransferase (OPRT) with phosphoribosyl pyrophosphate (PRPP) as the cofactor, or indirectly via fluorouridine (FUR) through the sequential action of uridine phosphorylase (UP) and uridine kinase (UK).
- FUMP is phosphorylated to fluorouridine diphosphate (FUDP), which can be further phosphorylated to the active metabolite fluorouridine triphosphate (FUTP), or converted to fluorodeoxyuridine diphosphate (FdUDP) by ribonucleotide reductase (RR).
- In turn, FdUDP can either be phosphorylated or dephosphorylated to generate the active metabolites FdUTP and FdUMP, respectively.
- An alternative activation pathway involves the thymidine phosphorylase catalysed conversion of 5-FU to fluorodeoxyuridine (FUDR), which is then phosphorylated by thymidine kinase (TK) to FdUMP.

Toxicity… in DPD deficient, 5% population

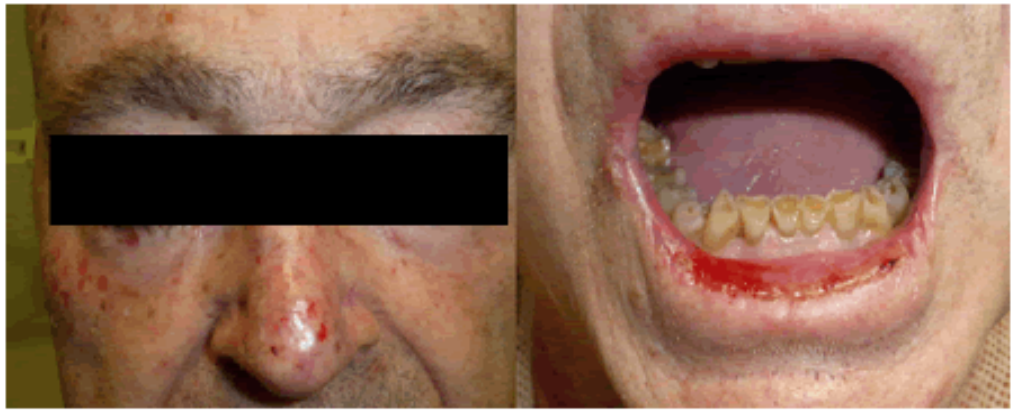
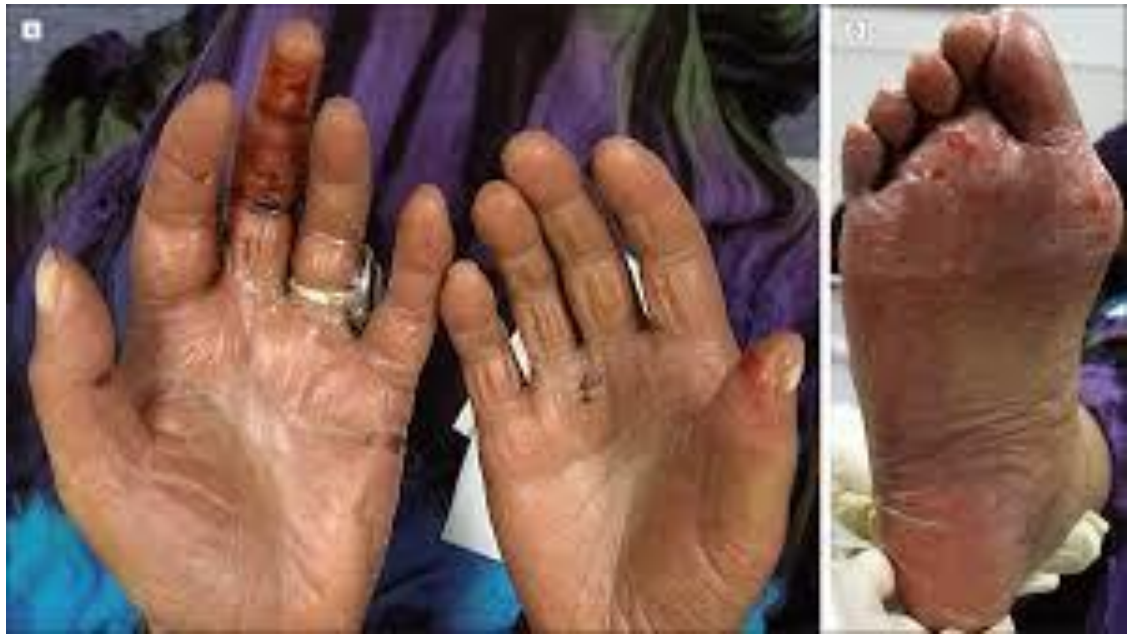
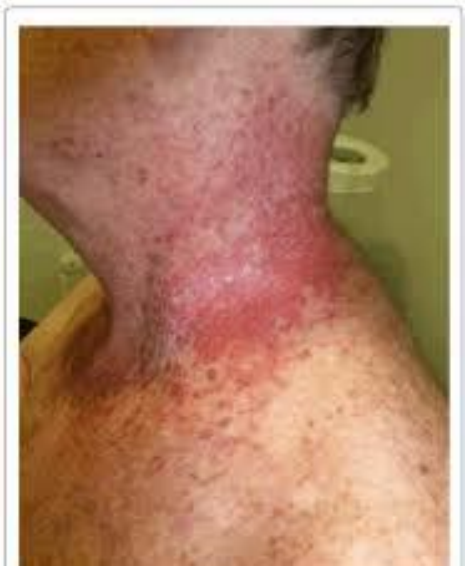


Figure 2: Appearance of new erosive lesions on the face and mucositis with predominance in lips.

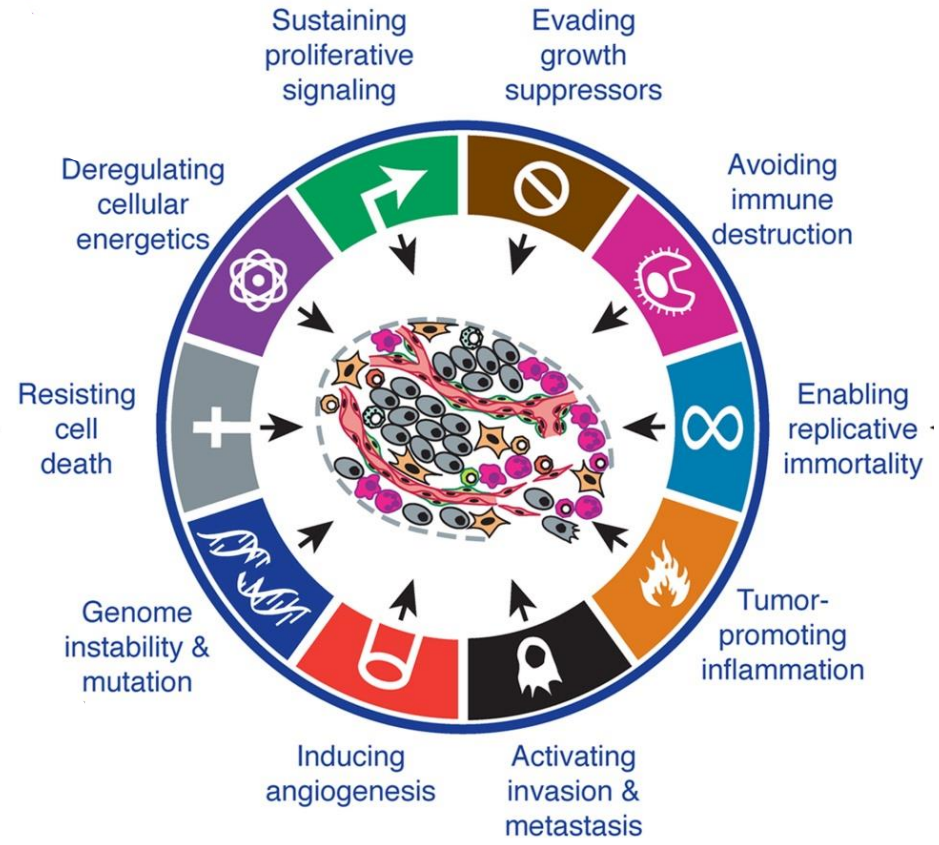




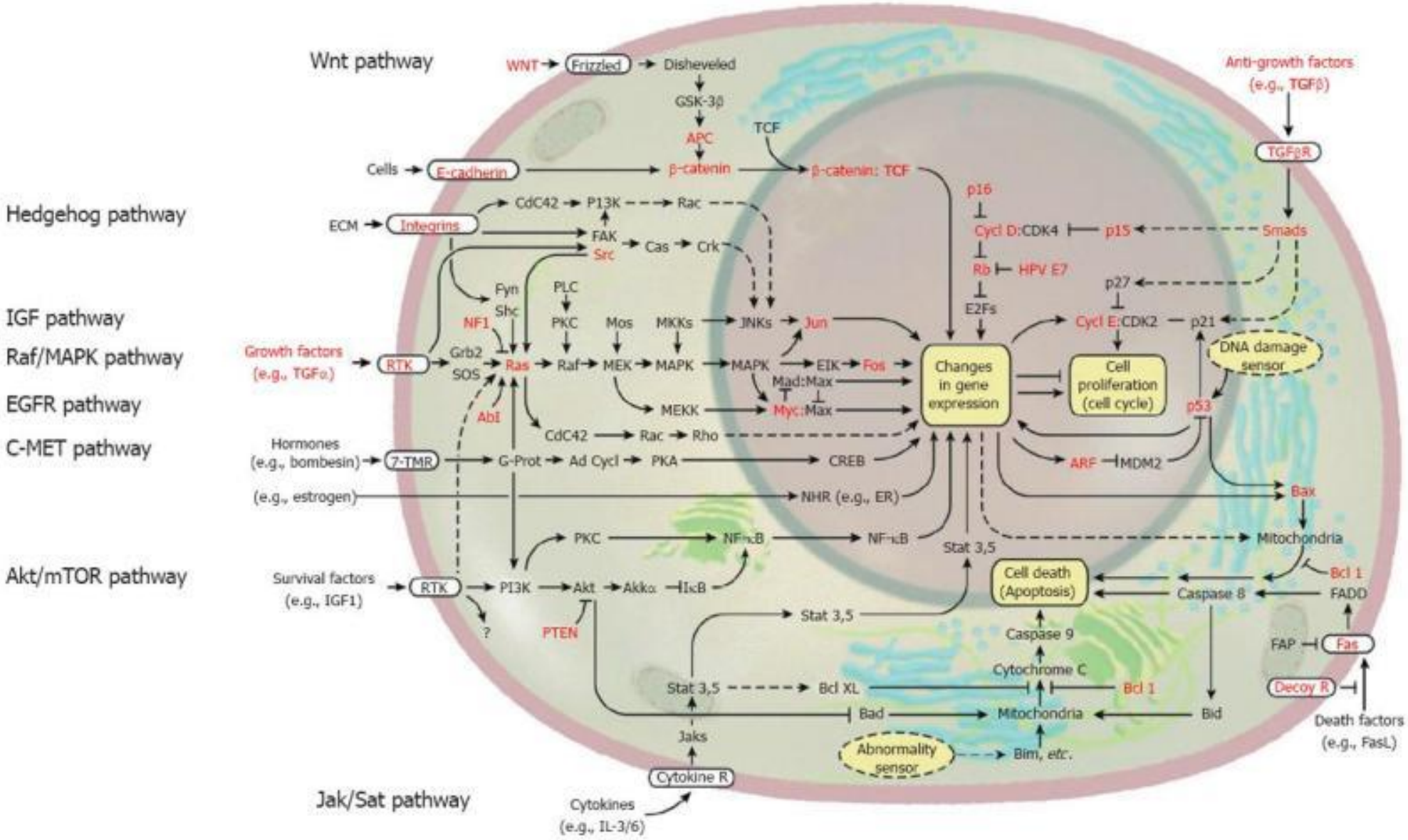
Targetted Drug Therapy

Hallmarks of Cancer: The Next Generation

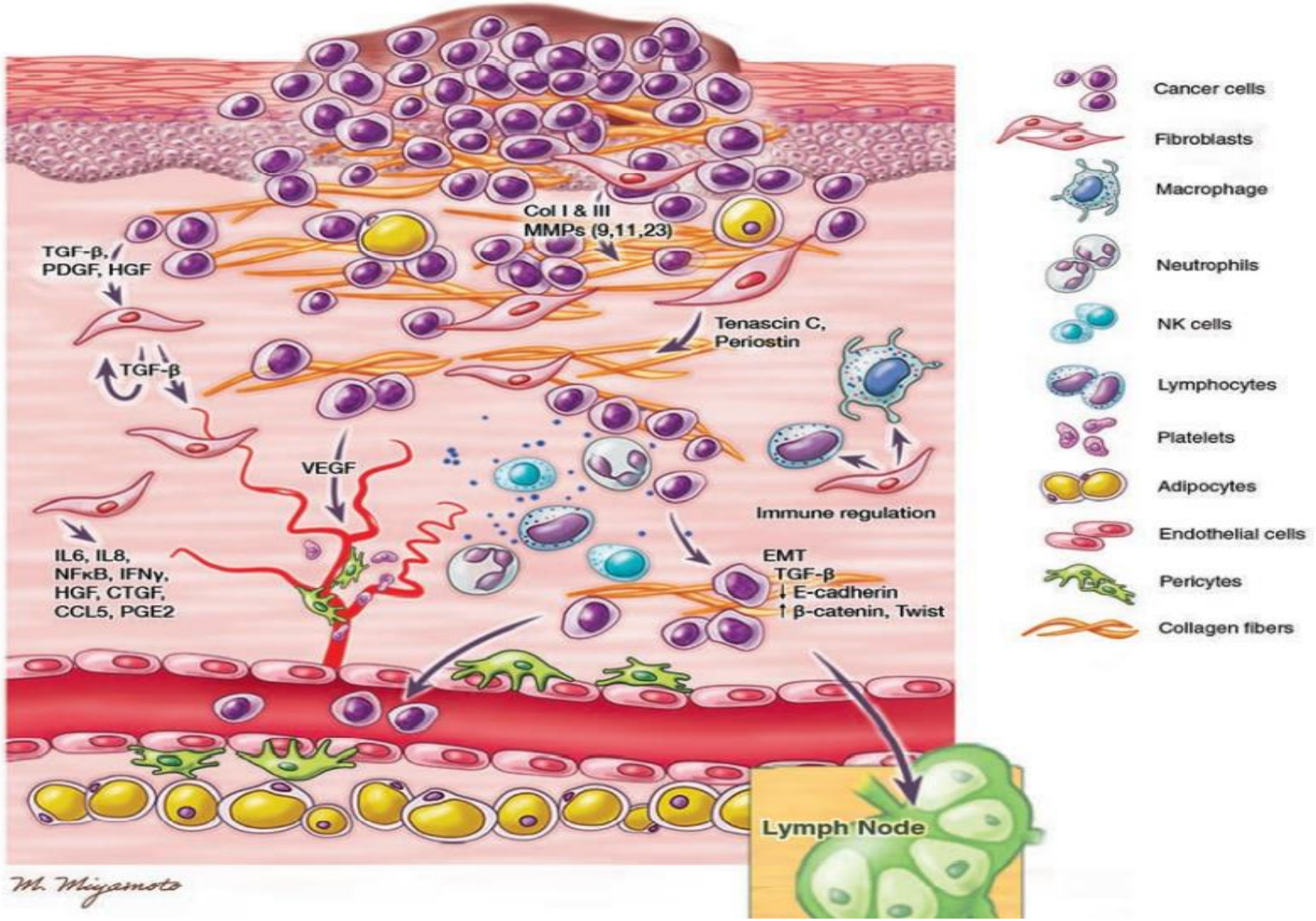
(Hanahan and Weinberg 2011, *Cell* **144**: 646–674)



Cancer cell signalling

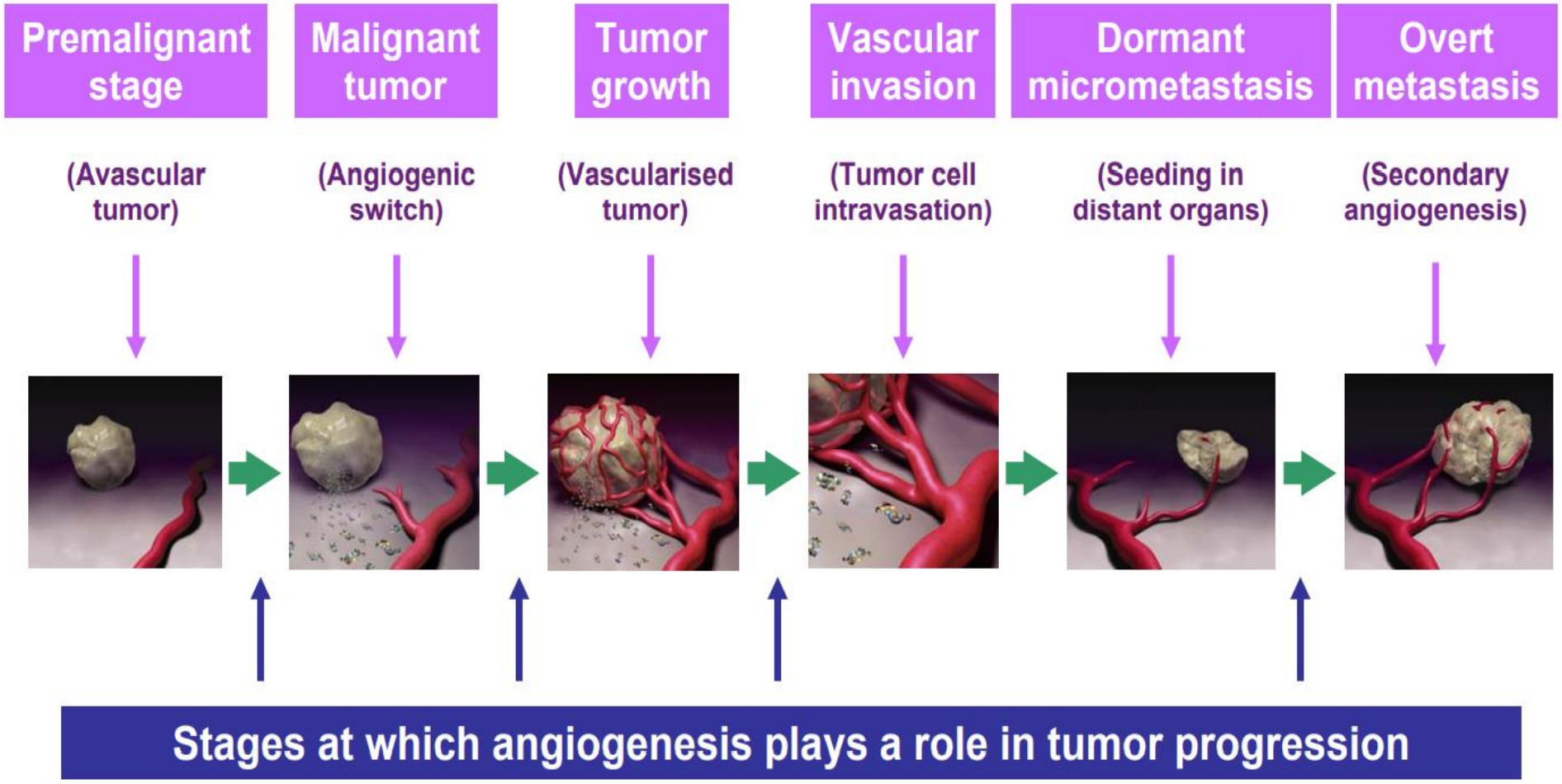


Tumour microenvironment



Foster et al JCI Insight. 2018;3(18)

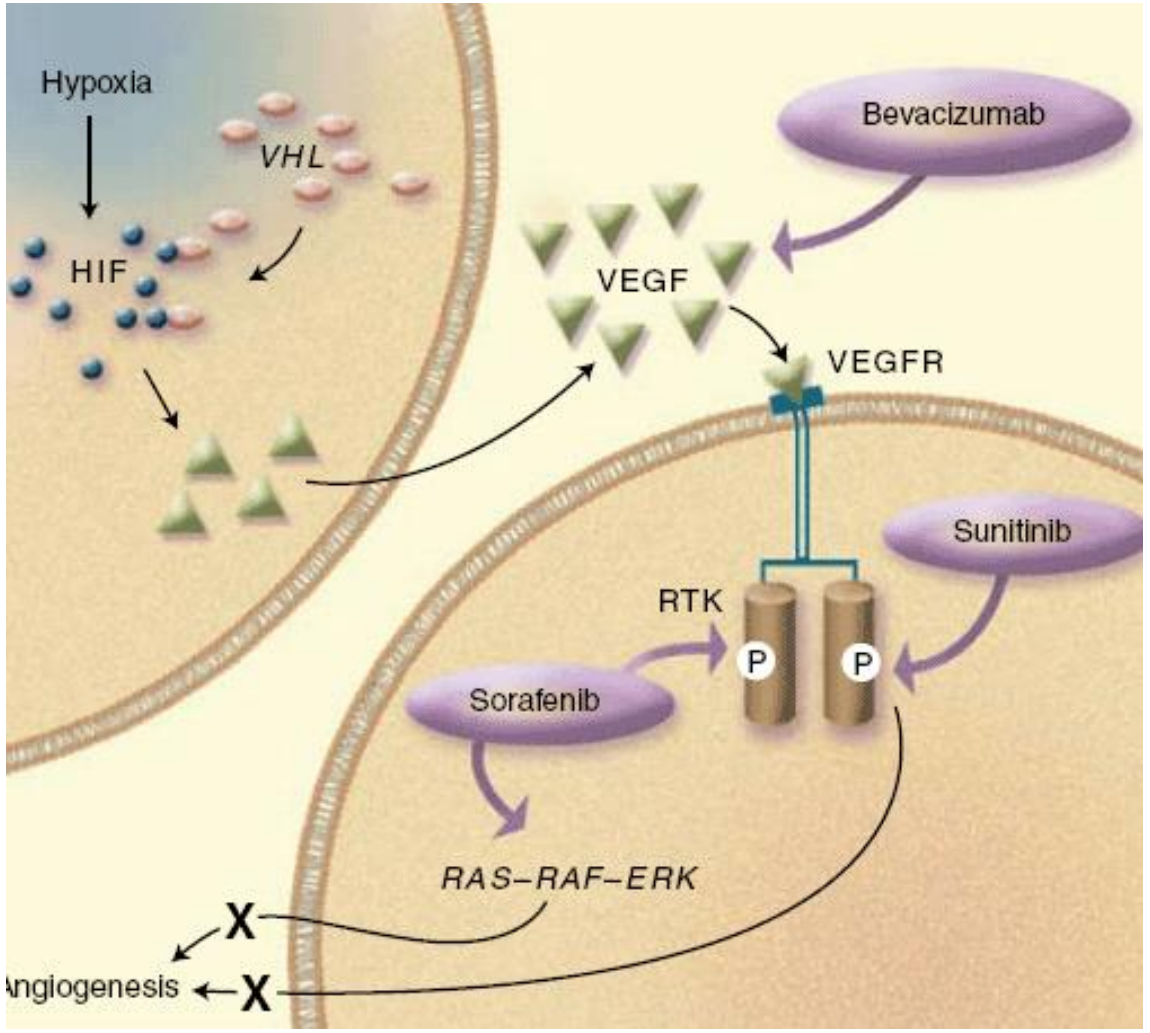
Cancer Angiogenesis



Poon et al J Clin Oncol 2001;19:1207–25

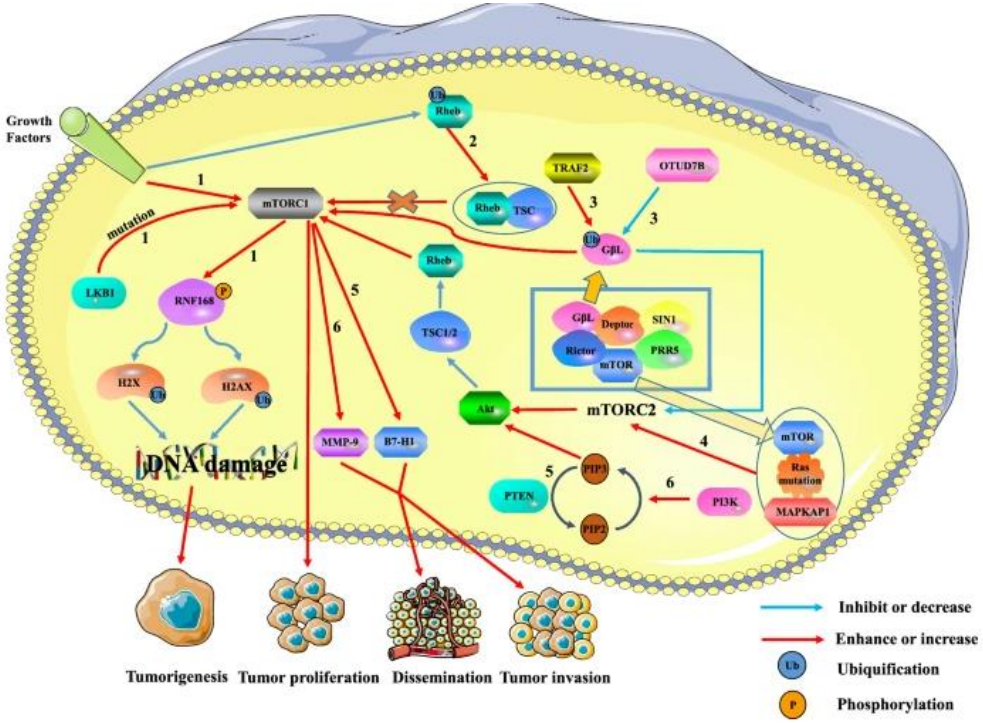
Angiogenesis inhibitors – Sorafenib and Sunitinib

- Sunitinib and Sorafenib target the VEGF/VEGFR signaling pathway
- They inhibit the tyrosine kinase activity of VEGFR on endothelial cells (ATP binding site competitive inhibitors)
- They prevent phosphorylation of the receptor and block signalling
- Sorafenib also inhibits the activity of Raf-1 kinase that functions in the signaling pathway, which is initiated after VEGFR binds its ligand.
- Approved for the treatment of metastatic renal cell carcinomas



Everolimus

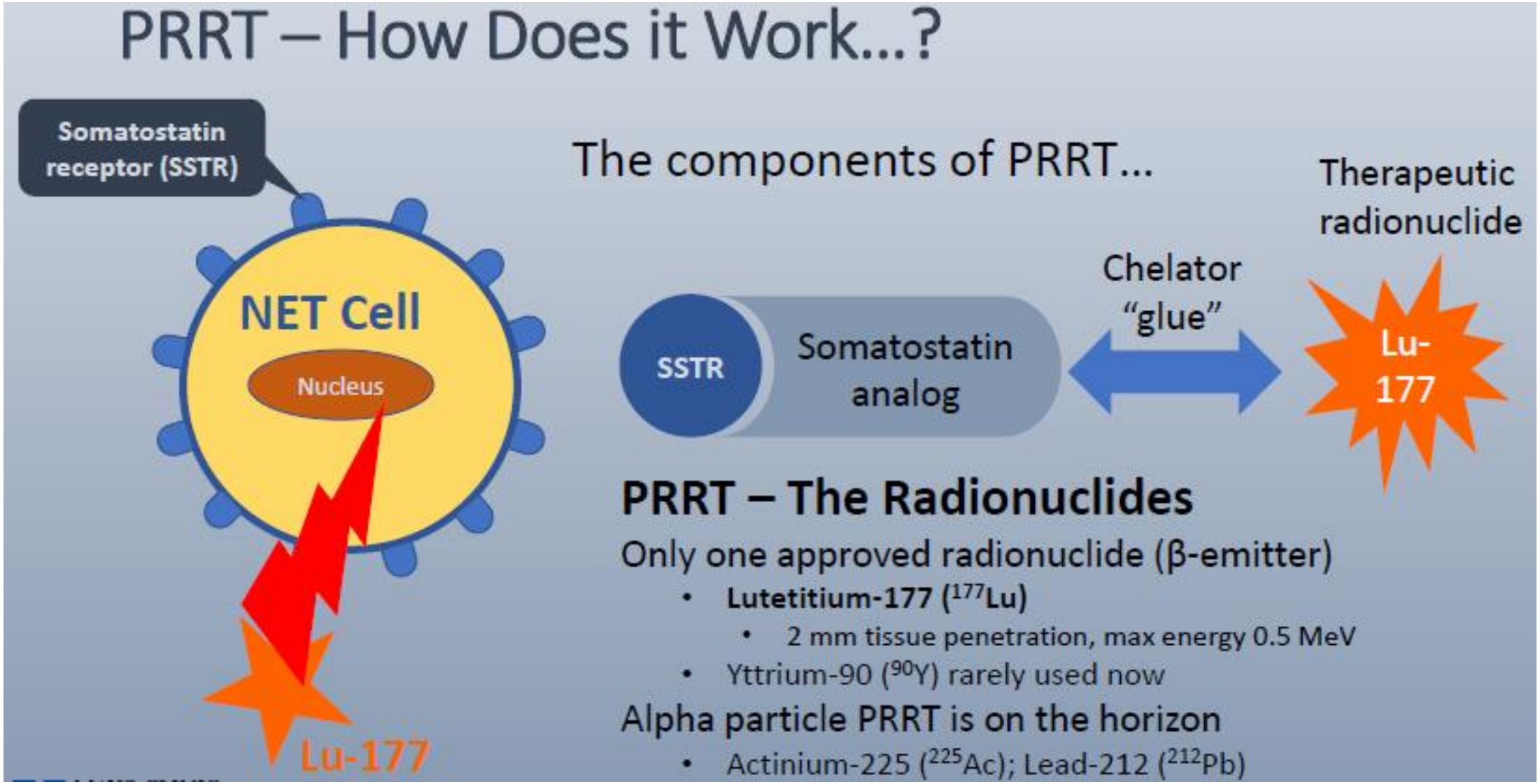
Georges Nogrady 1964



mTOR inhibition by EVEROLIMUS

Radionuclide Treatment

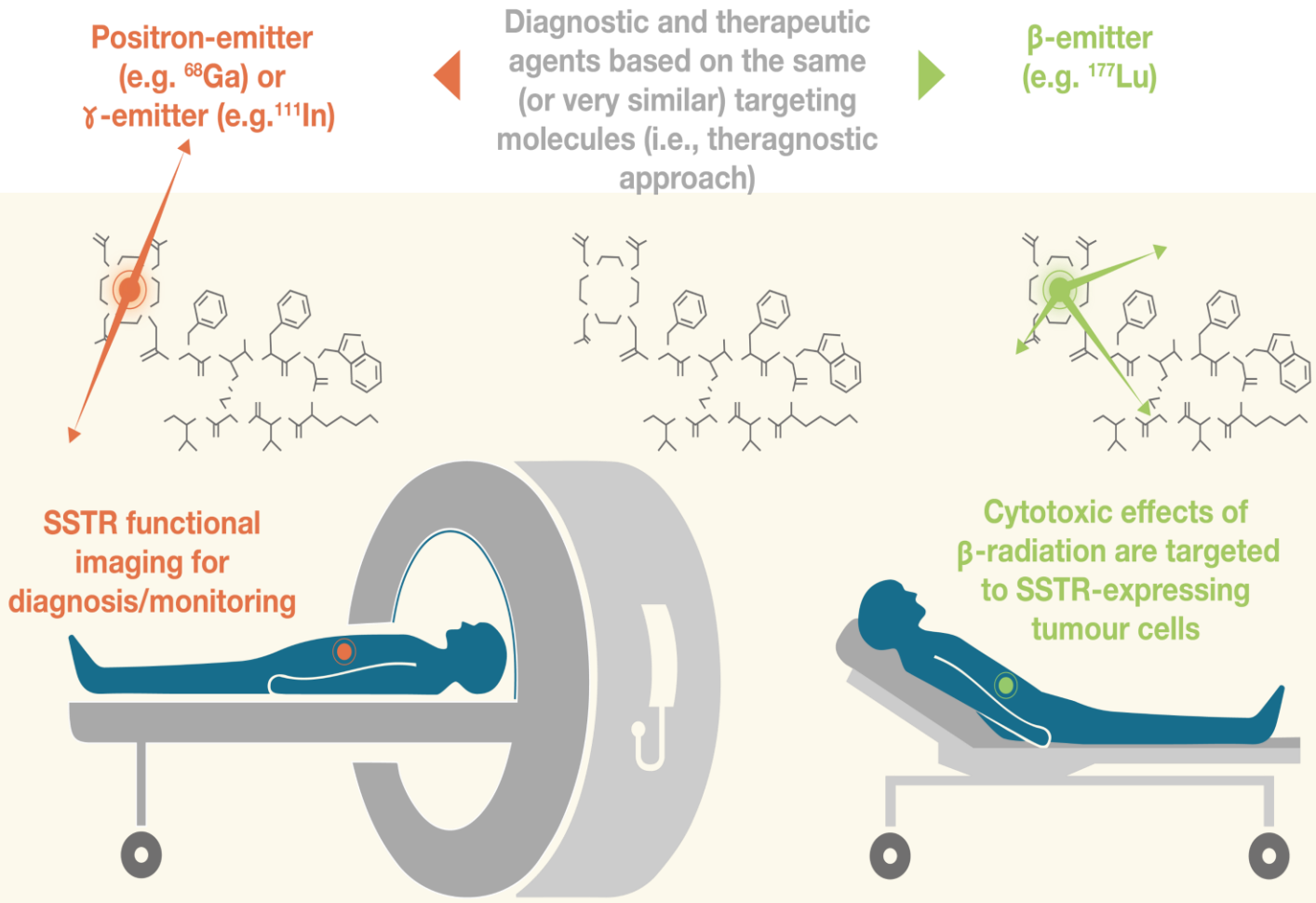
TREATMENT OF NETs – PRRT



TREATMENT OF NETs – PRRT

PRRT is a molecular radiotherapeutic modality in which ligands for peptide hormone receptors (namely SSTRs) are attached to therapeutic radionuclides to target NET cells.[52]

- Eligibility for PRRT is dependent on demonstration of adequate tumoral uptake of an imaging radiotracer that also binds SSTRs.[52]
- The coupling of SSTR imaging with delivery of PRRT to patients with SSTR-positive tumours is an example of what is known as a theragnostic approach.[52]



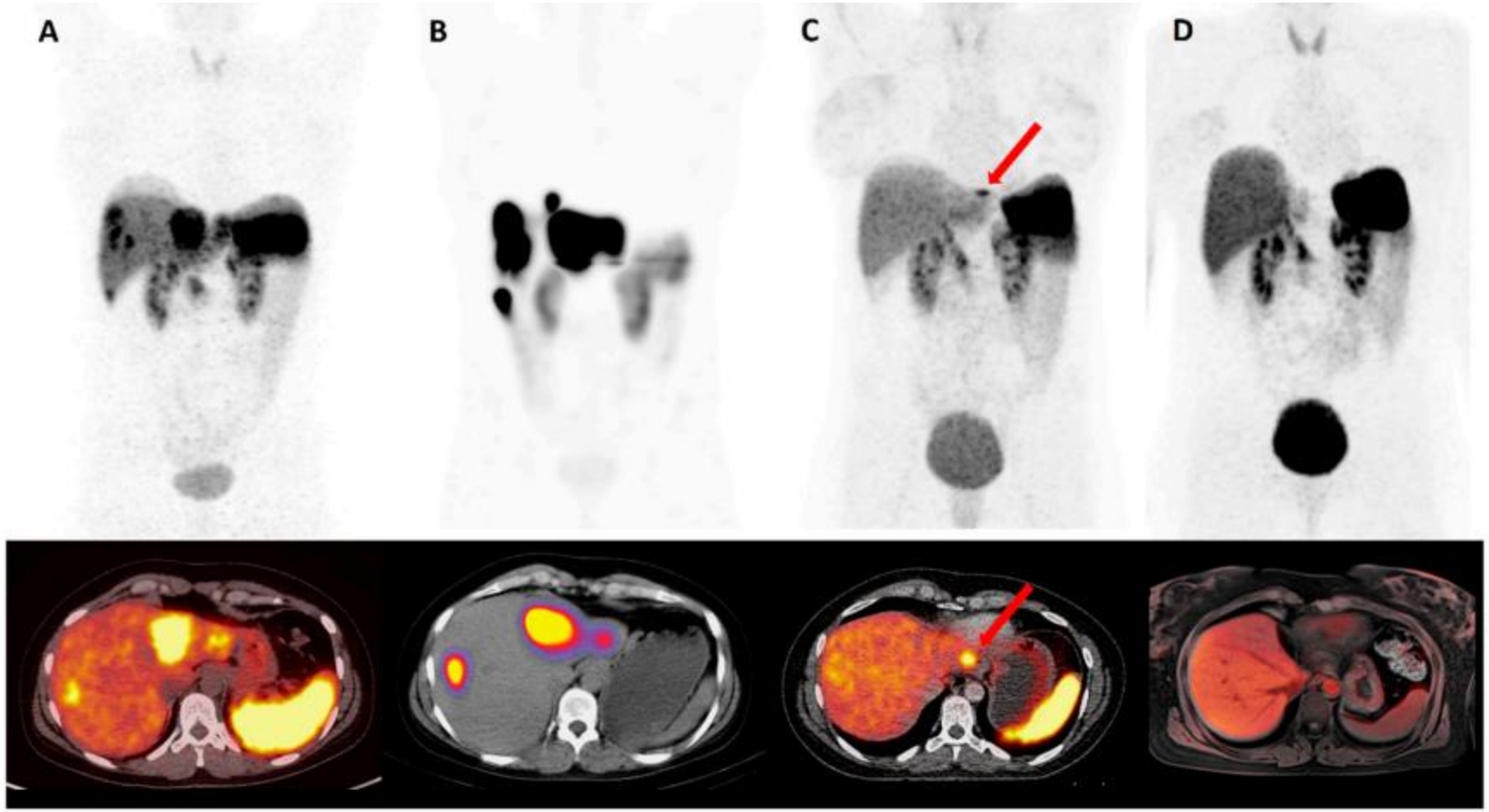
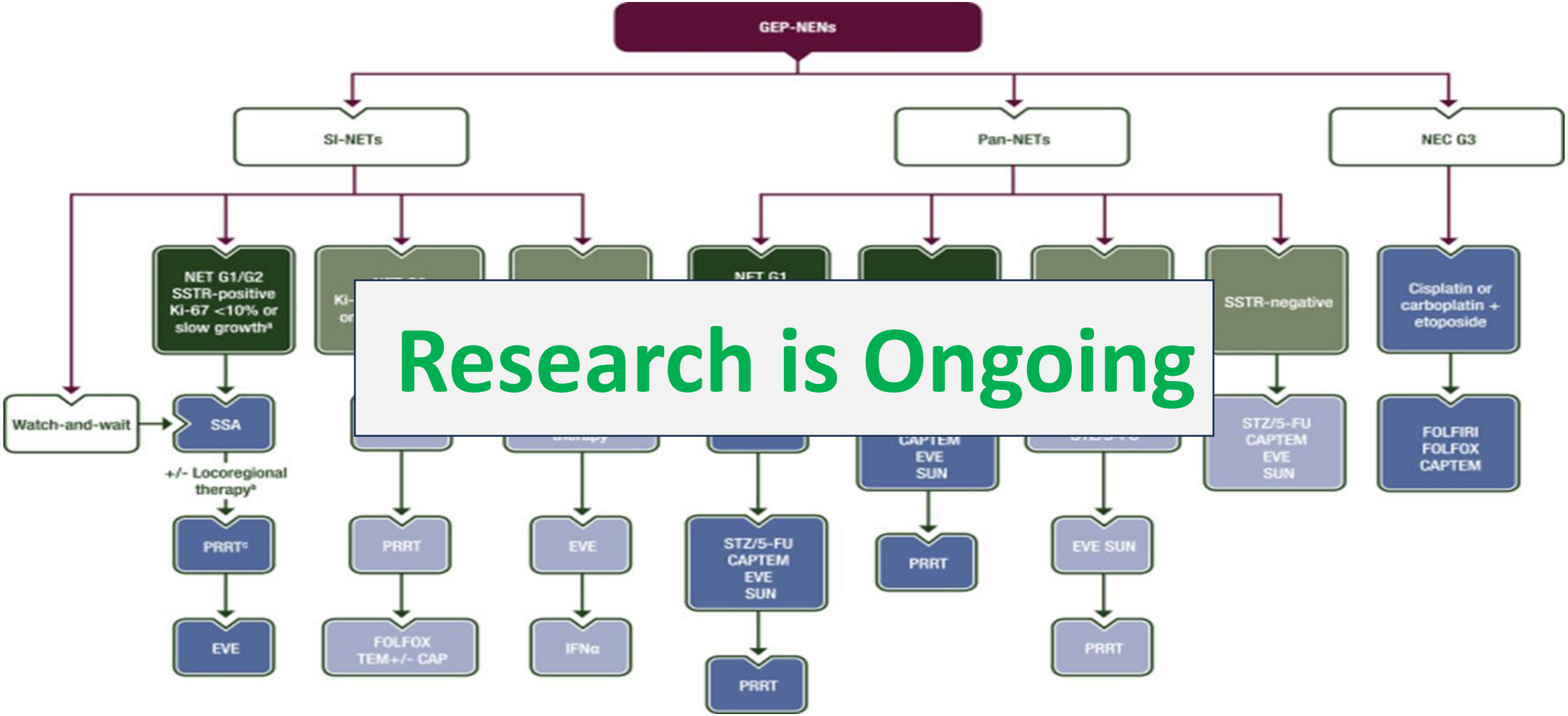


Figure 1. A 38-year-old woman with NET of the rectum G3 (Ki-67 in hotspots up to 25%) with hepatic and locoregional lymph node metastases. Pretherapeutic (**A**) and post-therapeutic (**C**) ^{68}Ga-DOTATAOC-PET/CT. After interdisciplinary tumor board decision, 1st cycle PRRT with 7.4 GBq ^{177}Lu-DOTATOC (**B**). After three cycles of PRRT, only one remaining hepatic lesion in segment II (**C**, red arrow head) is left. Following a curative approach, the patient underwent a laparoscopic left-lateral liver resection. The patient is currently undergoing semi-annual screening at complete response (CR) ^{68}Ga-DOTATAOC-PET/MR (**D**).

Int. J. Mol. Sci. 2019, 20, 3049

Summary



Research is Ongoing

Questions