In the Name
of
God

Emerging Treatment Modalities for Pheochromocytoma and Paraganglioma (PPGL)

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Introduction

- The clinical presentation is so variable that a PPGL has been described as "the great masquerader“
- PPGLs are uncommon tumors with malignant potential
  - Highly variable natural history
- Metastases
  - Pheochromocytoma = 10–15 %
  - Paraganglioma = up to 60 %
- Some patients achieve a cure through surgical resection
- Others experience an aggressive and protracted disease course characterized by recurrence and metastasis
  - Probability of developing metastases can appear even 20 years after the first diagnosis !

Introduction

- In 60% of patients, the tumor is discovered incidentally during CT Scan or MRI of the abdomen for unrelated symptoms
- Prevalence
  - ≈ 1% in hypertensive patients
  - <0.05% in the general population
- About 30-40% of PPGLs are hereditary(at least 20 genes associated)
- The tumor can be associated with genetic syndromes such as MEN-2 or VHL
- The measurement of plasma metanephrine, normetanephrine and 3-methoxy tyramine by LC-MS
  - ≈ 97% sensitivity
  - ≈ 95% specificity

Metastatic PPGL(mPPGL)

- Distinguishing between benign and malignant PPGLs are difficult on the basis of clinical, biochemical, or histopathologic characteristics
- Malignancy is rare in patients with MEN2 or VHL syndrome
- Malignancy is common in those with familial paraganglioma caused by pathogenic variants in SDHB
- Surgical debulking procedures continue to be the mainstay of palliative treatment

Multifocal and mPPGLs

- There are currently no effective cures for mPPGLs
- The natural course of mPPGLs are highly heterogeneous
- The most frequent metastatic locations are
  - Lymph nodes (80%)
  - Bones (72%)
  - Liver (50%)
  - Lungs (50%)
- Palliative relief may be achieved through therapeutic procedures that should be considered according to presentation

Molecular Phenotypes

- **Cluster 1**(pseudohypoxia signaling)
  - cluster1A
    - Mutations in SDHA-D
    - 10-15% of paragangliomas
  - Cluster1B
    - Mutations in VHL, HIF2A
    - 15-20% of paragangliomas
- **Cluster 2** (kinase signaling)
  - Mutations in RET, NF1
  - 50-60% of paragangliomas
- **Cluster 3** (Wnt signaling)
  - Mutations in MAML3
  - 5-10% of paragangliomas

Scoring systems for predicting metastatic risk

- PASS
  - Pheochromocytoma of the Adrenal Gland Scaled Score
- GAPP/mGAPP
  - Grading System for Adrenal Pheochromocytoma and Paraganglioma
- COPPS
  - COomposite Pheochromocytoma/paraganglioma Prognostic Score
- ASES
  - Age, Size, Extra-adrenal location, Secretion type
- SGAP
  - Size, Genetic, Age, and PASS model

PASS

PASS parameters	Points
Nuclear hyperchromasia	1
Profound nuclear pleomorphism	1
Capsular invasion	1
Vascular invasion	1
Extension into periadrenal adipose tissue	2
Atypical mitotic figures	2
>3 mitotic figures/10 HPF	2
Tumor cell spindling	2
Cellular monotony	2
High cellularity	2
Central or confluent tumor necrosis	2
Large nests or diffuse growth (>10% of tumor volume)	2
Total maximum score	20

Scores ≥4 are predictive of malignancy

GAPP

- Well differentiated (0–2)
- Moderately differentiated (3–6)
- Poorly differentiated (7–10)

GAPP parameters	Points
Histological pattern	
Zellballen	0
Large and irregular nest	1
Pseudorosette (even focal)	1
Comedo-type necrosis	
Absence	0
Presence	2
Cellularity	
Low (<150 cells/U)	0
Moderate (150–250 cells/U)	1
High (> 250 cells/U)	2
Ki67 labeling index (%)	
<1	0
1–3	1
>3	2
Vascular or capsular invasion	
Absence	0
Presence	2
Catecholamine type	
Non-functioning	0
Adrenergic type	0
Noradrenergic type	1
Total maximum score	10

M-GAPP

- Scores ≥3 are predictive of malignancy

M-GAPP parameters	Points
Histological pattern	
Zellballen	0
Large and irregular nest or pseudorosette	2
Comedo-type necrosis	
Absence	0
Presence	2
Ki67 labeling index (%)	
<1	0
≥1	2
Vascular or capsular invasion	
Absence	0
Presence	1
Catecholamine type	
Non-functioning	0
Adrenergic type	0
Noradrenergic type	1
SDHB immunochemistry	
Positive	0
Negative	2
Total maximum score	10

Treatment Modalities

- The choice of the therapy should include factors such as
  - Resectability of the tumor
  - Infiltration of adjacent structures
  - Presence of distant metastases
  - Amount of hormones secretion
  - Growth rate
  - Patient's comorbidities

Management of Pheochromocytoma

- Key Points
  - Surgical resection provides optimal treatment of pheochromocytoma in nearly all patients
    - Minimally invasive surgery by laparoscopic/robotic adrenalectomy
  - Perioperative Management
    - α-adrenoceptor blockers
    - β-adrenoceptor blockers
    - Calcium-channel blockers
  - Postoperative management
    - Follow-up biochemical testing
    - Confirm success of surgical intervention
    - Continual follow-up to screen for recurrent or metastatic disease

Medical Therapy and Preparation for Surgery

- α-adrenoceptor blockers
  - Nonselective
    - Phenoxybenzamine
  - Selective
    - Prazosin
    - Terazosin
    - Doxazosin
- β-adrenoceptor blockers
  - Atenolol
  - Metoprolol
- α- and β-adrenoceptor blocker
  - Labetalol (α- to β-blocking ratio of 1:7)
- Calcium Channel Blockers
  - Amlodipine
  - Diltiazem
  - Nicardipine SR
  - Nifedipine SR
  - Verapamil SR
- Metyrosine

Locoregional treatments

- Surgery
  - Primary tumor
  - Resectable distant metastases
- Radiotherapy/Stereotactic radiosurgery (SRS)
- Cryoablation
- Radiofrequency ablation
- Percutaneous ethanol injection
- Arterial embolization
- Vertebroplasty

Robot-assisted adrenalectomy: state of the art

- Classic laparoscopic technique shortcomings
  - Rigid instruments
  - Loss of 3D vision
  - Unstable camera
- The robotic system(Da Vinci)
  - Stereoscopic 3D-magnified vision
  - Additional degree of freedom
  - Tremor-filtering technology
  - Stable camera
  - Finer dissection

Treatment modalities

- Systemic therapies
  - ^{131}IMIBG
  - Chemotherapy
  - Targeted therapies
    - Tyrosine kinase inhibitors
    - mTOR inhibitors
    - PI3K Inhibitor
    - Immunotherapy
    - Peptide-receptor radiotherapy: β and α radiation emitters

Systemic Chemotherapy

- CVD regimen
  - Cyclophosphamide
  - Vincristine
  - Dacarbazine
- Temozolomide

Targeted Therapies

- Tyrosine Kinase Inhibitors (TKIs)
  - Sunitinib
  - Cabozantinib
  - Pazopanib
  - Anlotinib
- mTOR Pathway Inhibitor
  - Everolimus
- Immunotherapy
  - Immune checkpoint inhibitors
- HIF2a Inhibitor
  - Belzutifan

Pseudohypoxia group (cluster I) targeted therapies

- Antiangiogenic therapy
- Hypoxia-inducible factor (HIF) inhibitors
- Immunotherapy
- Poly (ADP-ribose) polymerase (PARP) inhibition

Kinase signaling group (cluster II) targeted therapies

- mTOR inhibitor
  - Everolimus

Wnt signaling group (cluster III) targeted therapies

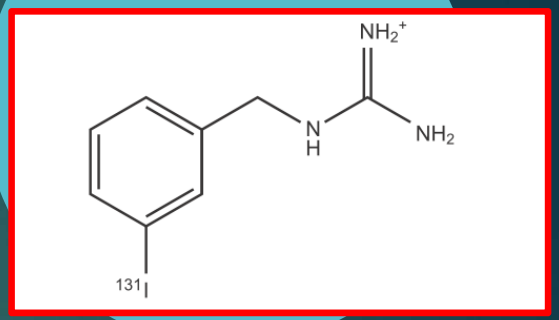
- Porcupine

Novel Radiopharmaceuticals

- High-Specific-Activity ^{131}IMIBG
- Peptide Receptor Radionuclide Therapy (PRRT)
  - ^{177}Lu DOTA-somatostatin analogs(T1/2 = 6.7 d)
    - Lutetium-177 DOTATATE/TOC
  - ^{90}Y DOTA-somatostatin analogs(T1/2 = 64 h)
    - Yttrium-90 DOTATATE/TOC
  - ^{213}Bi DOTA-somatostatin analogs(T1/2 = 46 min)
    - Bismuth-213 DOTATOC

High-Specific-Activity ^{131}I-MIBG(Azedra®)

- On July 30, 2018, the FDA approved AZEDRA for adult and pediatric patients (12 years and older) with MIBG scan-positive, unresectable, locally advanced or mPPGLs
- Clinical responses
  - Complete = 3%
  - Partial = 27%
  - Stable = 52%
- Biochemical responses
  - Complete =11%
  - Partial = 40%
  - Stable disease = 21%
- ^{131}IMIBG treatment is generally well-tolerated
- High-dose regimens may cause bone marrow toxicity
- On August 18, 2023 Azedra discontinued and retired June 6, 2024
  - Due to limited uses and the high costs



Peptide Receptor Radionuclide Therapy (PRRT)

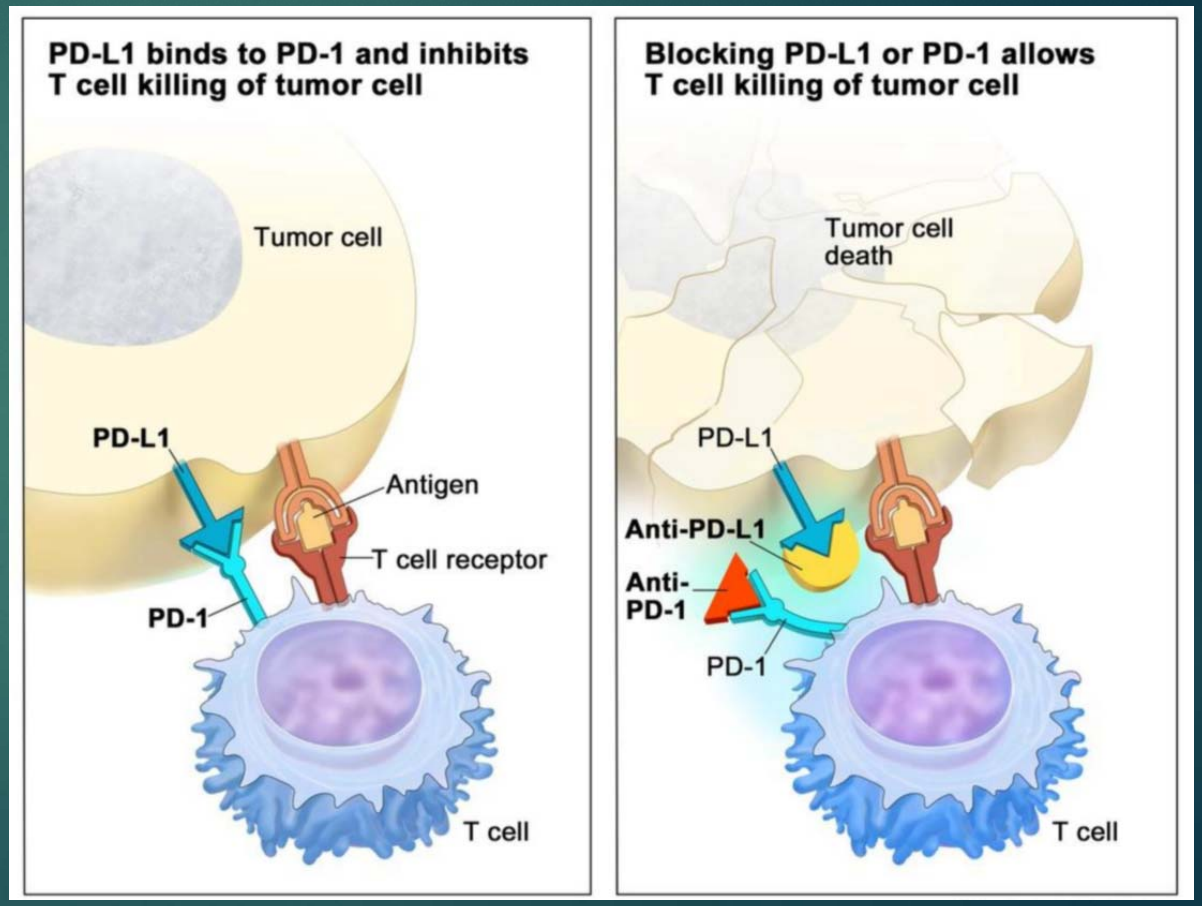
- ^{90}Y-yttrium and ^{177}Lu-lutetium-based PRRT regimens
  - Adverse effects
    - Bone marrow toxicity
    - Nephrotoxicity
- Success rates
  - Objective response = 25%
  - Disease control = 84%
  - Clinical response = 61%
  - Biochemical responses = 64%

Targeted Alpha emitter Therapy (TAT)
"Theranostic Radiopharmaceuticals"

- Advantages
  - Shorter path length in tissue
    - Low level of irradiation to the surrounding healthy tissues
  - High linear energy transfer
  - ^{203}Pb VMT-a-NET(T½ 52 hours)SPECT/CT imaging agent
  - ^{212}Pb VMT-a-NET(T½10 hours)
  - ^{212}Bi DOTATOC(T½1hour) → ^{208}Tl
    → ^{212}Po → ^{208}Pb

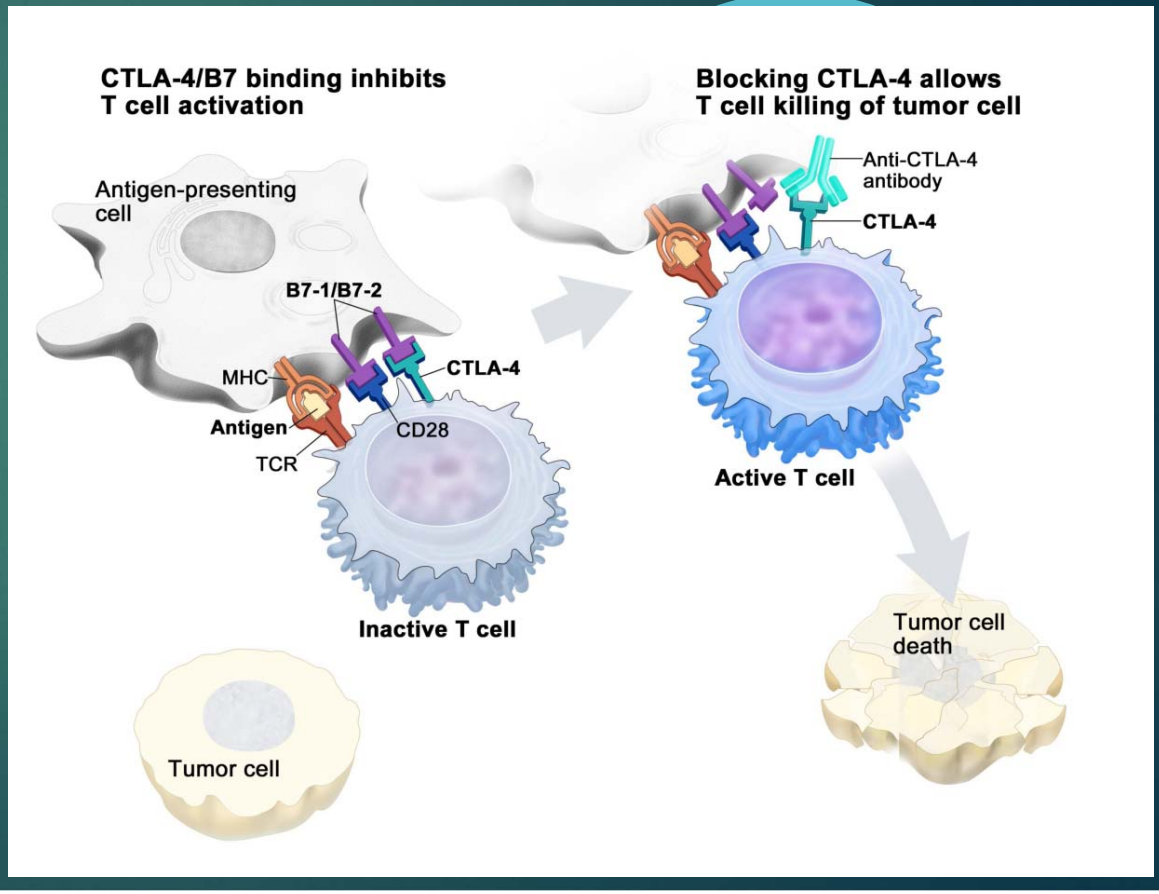
Immune Checkpoint Inhibitors(ICIs)

- PD-1inhibitors
  - Nivolumab
  - Pembrolizumab
  - Cemiplimab
  - Spartalizumab
- PD-L1inhibitors
  - Avelumab
  - Atezolizumab
  - Durvalumab



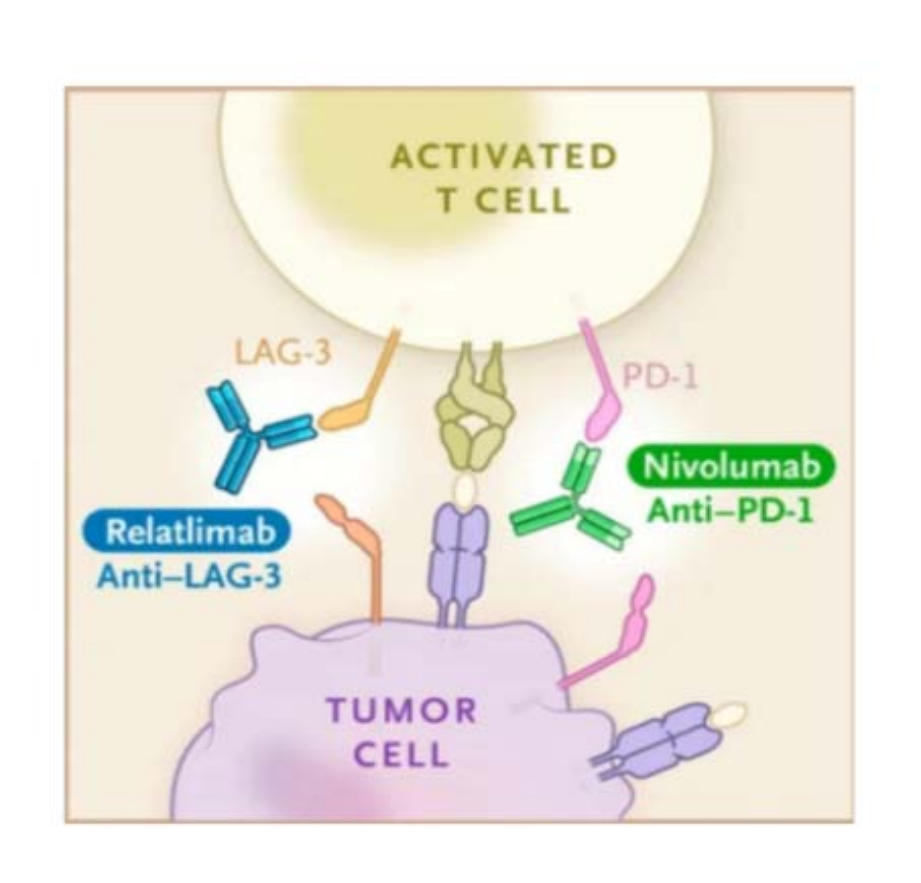
Cytotoxic T-Lymphocyte Associated protein 4, (CTLA-4)Inhibitors

- Ipilimumab
- Tremelimumab



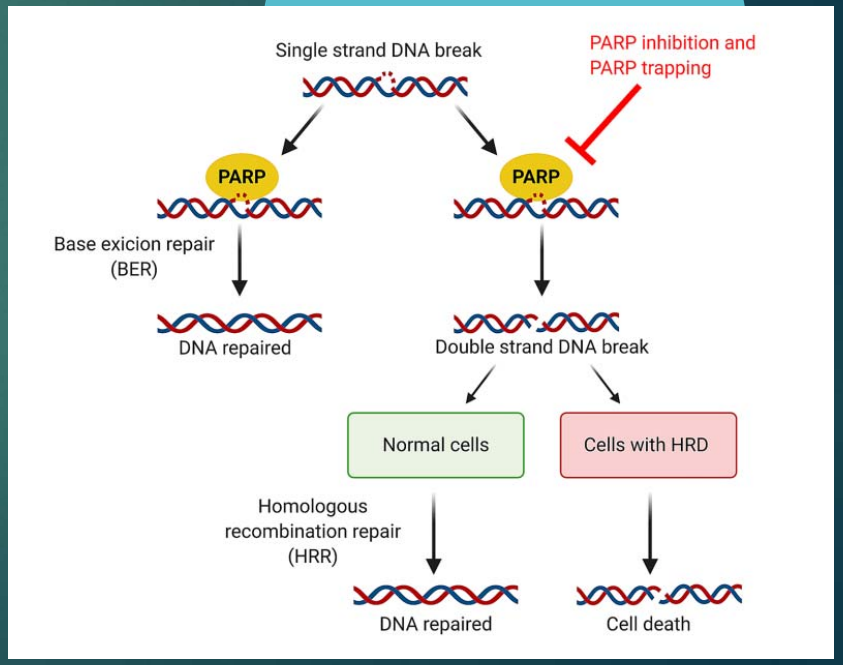
Lymphocyte-Activation Gene-3 (LAG-3) Inhibitor

- Relatlimab



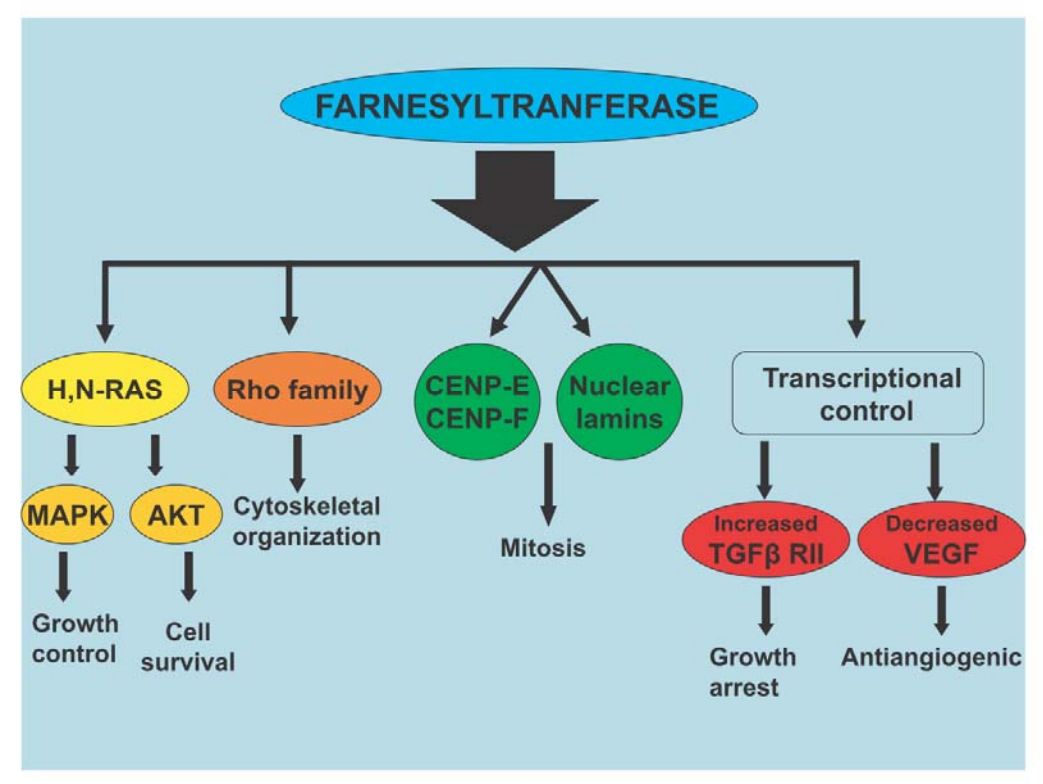
Poly ADP-Ribose)Polymerase(PARP)Inhibitors

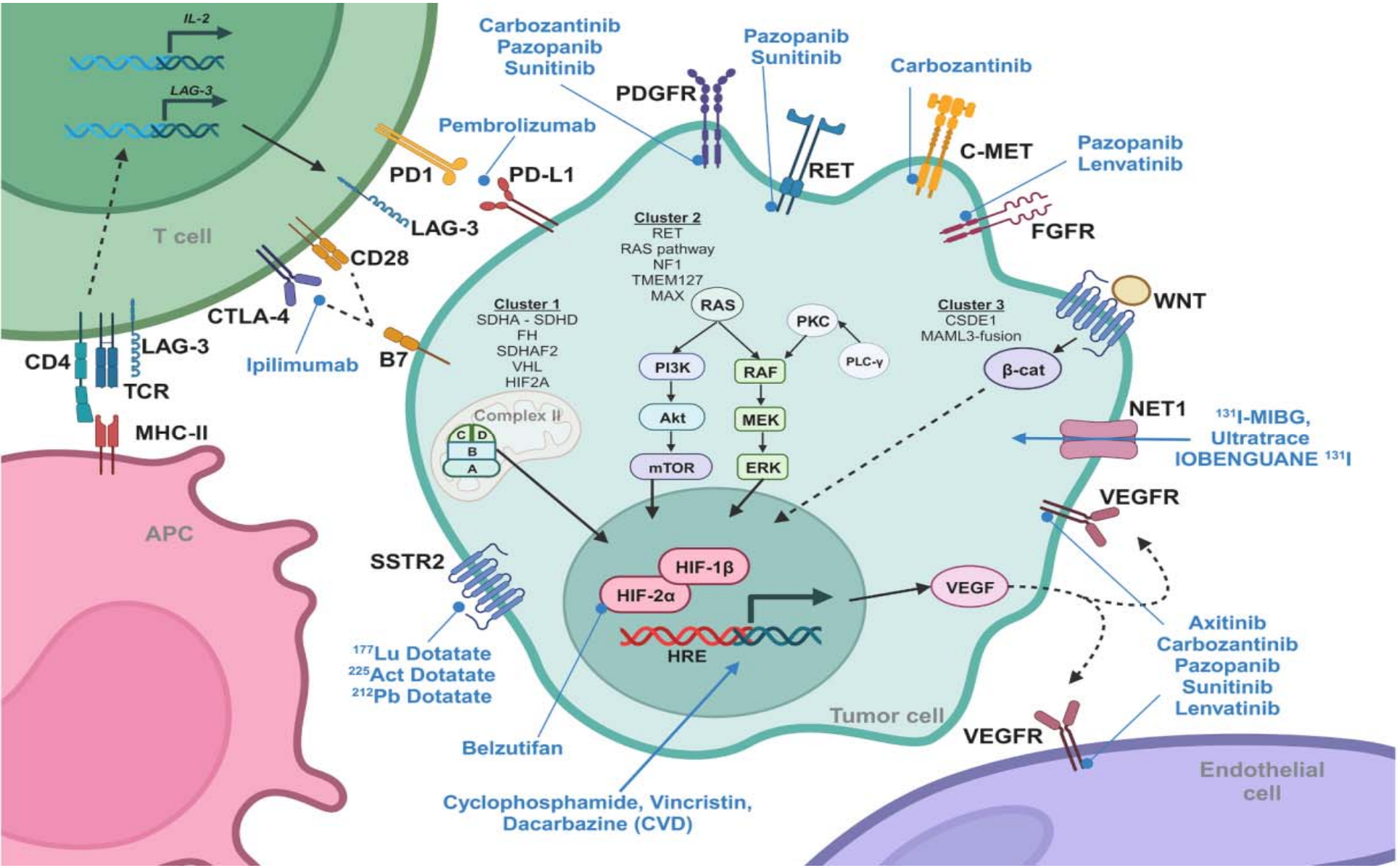
- Accumulation of single-strand breaks, ultimately resulting in double-strand breaks
  - Olaparib
  - Niraparib
  - Rucaparib
  - Talazoparib

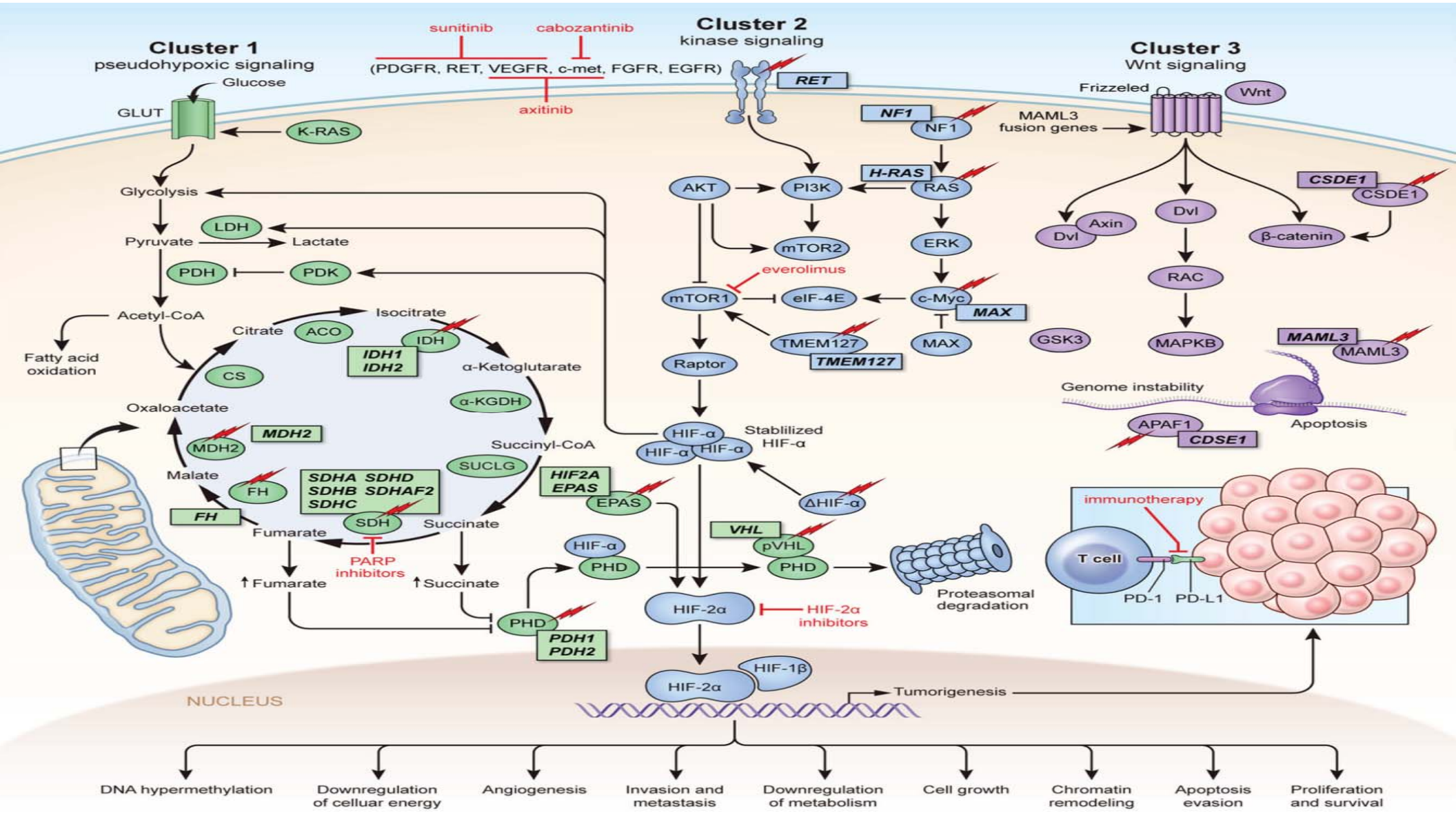


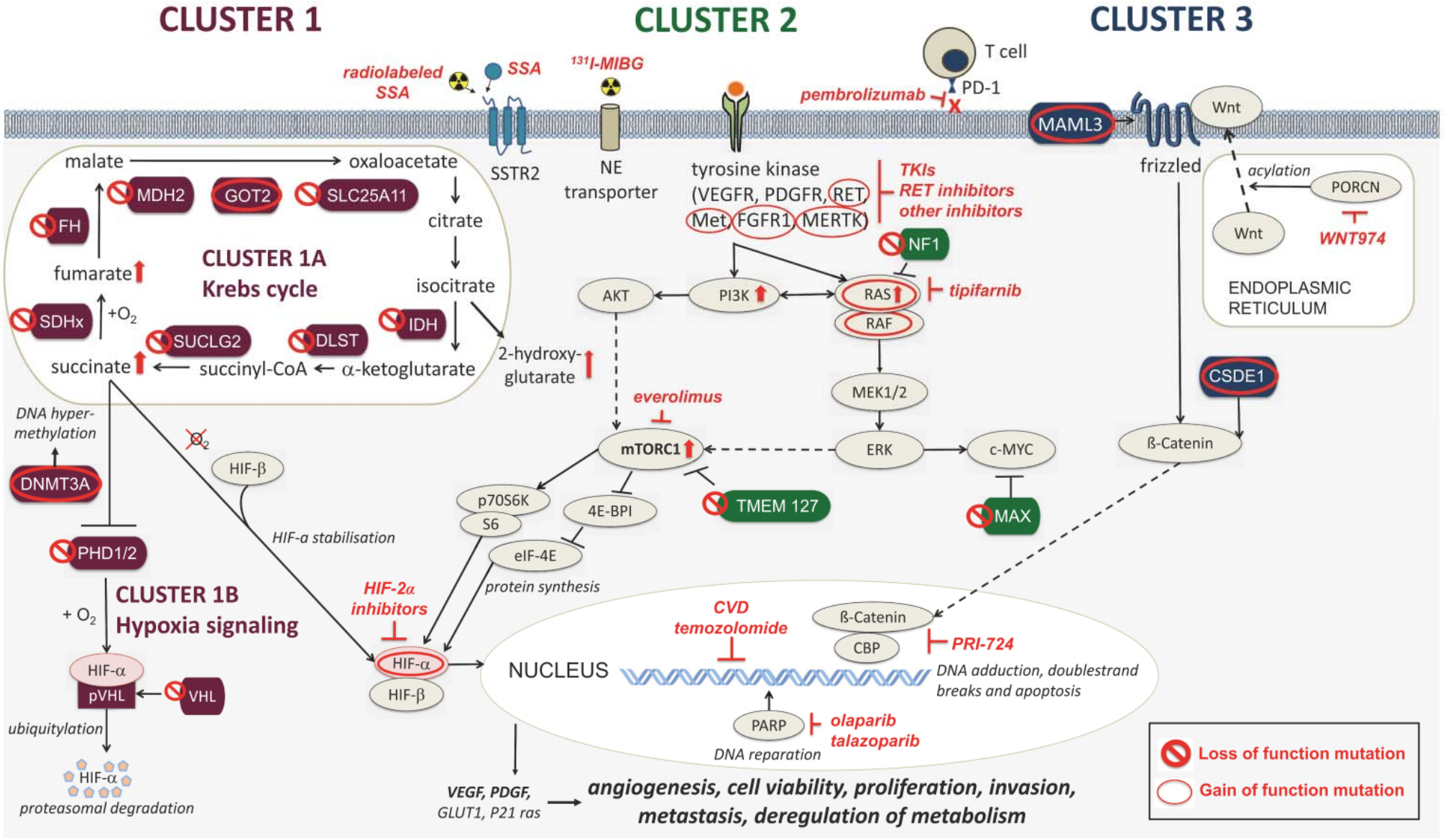
Farnesyl Transferase Inhibitors(FTIs)

- Tipifarnib




IL-2
LAG-3
T cell
CD4
LAG-3
TCR
MHC-II
APC
CTLA-4
Ipilimumab
CD28
B7
PD1
Pembrolizumab
PD-L1
LAG-3
Carbozantinib
Pazopanib
Sunitinib
PDGFR
Pazopanib
Sunitinib
RET
Carbozantinib
C-MET
Pazopanib
Lenvatinib
FGFR
WNT
Cluster 1
SDHA - SDHD
FH
SDHAF2
VHL
HIF2A
Complex II
C
D
B
A
Cluster 2
RET
RAS pathway
NF1
TMEM127
MAX
RAS
PI3K
Akt
mTOR
PKC
PLC-γ
RAF
MEK
ERK
Cluster 3
CSDE1
MAML3-fusion
β-cat
NET1
131I-MIBG,
Ultratrace
IOBENGUANE 131I
VEGFR
SSTR2
HIF-1β
HIF-2α
HRE
VEGF
177Lu Dotatate
225Act Dotatate
212Pb Dotatate
Belzutifan
Cyclophosphamide, Vincristin,
Dacarbazine (CVD)
Tumor cell
Axitinib
Carbozantinib
Pazopanib
Sunitinib
Lenvatinib
VEGFR
Endothelial
cell


Cluster 1
pseudohypoxic signaling
Glucose
GLUT
K-RAS
Glycolysis
Pyruvate
LDH
Lactate
PDH
PDK
Acetyl-CoA
Fatty acid oxidation
Citrate
ACO
Isocitrate
IDH
IDH1
IDH2
α-Ketoglutarate
CS
α-KGDH
Oxaloacetate
MDH2
MDH2
Malate
FH
FH
SDHA SDHD
SDHB SDHAF2
SDHC
SDH
Succinate
Fumarate
PARP inhibitors
↑Fumarate
↑Succinate
Succinyl-CoA
SUCLG
HIF2A
EPAS
EPAS
PHD
PDH1
PDH2
sunitinib
cabozantinib
(PDGFR, RET, VEGFR, c-met, FGFR, EGFR)
axitinib
Cluster 2
kinase signaling
RET
NF1
NF1
H-RAS
RAS
AKT
PI3K
mTOR2
ERK
everolimus
mTOR1
eIF-4E
c-Myc
MAX
MAX
TMEM127
TMEM127
Raptor
HIF-α
HIF-α
HIF-α
HIF-α
Stablilized HIF-α
ΔHIF-α
VHL
pVHL
PHD
HIF-α
PHD
Proteasomal degradation
HIF-2α
HIF-2α inhibitors
HIF-2α
HIF-1β
NUCLEUS
Tumorigenesis
Cluster 3
Wnt signaling
Frizzeled
Wnt
MAML3 fusion genes
CSDE1
CSDE1
Dvl
Axin
Dvl
β-catenin
RAC
GSK3
MAPKB
MAML3
MAML3
Genome instability
Apoptosis
APAF1
CDSE1
immunotherapy
T cell
PD-1
PD-L1
DNA hypermethylation
Downregulation of cellular energy
Angiogenesis
Invasion and metastasis
Downregulation of metabolism
Cell growth
Chromatin remodeling
Apoptosis evasion
Proliferation and survival


CLUSTER 1
CLUSTER 2
CLUSTER 3
radiolabeled SSA
SSA
SSTR2
131I-MIBG
NE transporter
T cell
PD-1
pembrolizumab
MAML3
Wnt
frizzled
acylation
PORCN
WNT974
ENDOPLASMIC RETICULUM
tyrosine kinase (VEGFR, PDGFR, RET, Met, FGFR1, MERTK)
TKIs
RET inhibitors
other inhibitors
NF1
malate
oxaloacetate
MDH2
GOT2
SLC25A11
citrate
FH
fumarate
CLUSTER 1A
Krebs cycle
isocitrate
SDHx
+O2
SUCLG2
DLST
IDH
succinate
succinyl-CoA
α-ketoglutarate
2-hydroxy-glutarate
AKT
PI3K
RAS
RAF
tipifarnib
MEK1/2
everolimus
mTORC1
ERK
c-MYC
CSDE1
ß-Catenin
DNA hyper-methylation
DNMT3A
HIF-β
HIF-a stabilisation
p70S6K
S6
4E-BPI
eIF-4E
protein synthesis
TMEM 127
MAX
PHD1/2
CLUSTER 1B
Hypoxia signaling
+ O2
HIF-2α inhibitors
HIF-α
pVHL
VHL
ubiquitylation
HIF-α
proteasomal degradation
HIF-α
HIF-β
CVD
temozolomide
ß-Catenin
CBP
PRI-724
NUCLEUS
DNA adduction, doublestrand breaks and apoptosis
PARP
olaparib
talazoparib
DNA reparation
VEGF, PDGF, GLUT1, P21 ras
angiogenesis, cell viability, proliferation, invasion, metastasis, deregulation of metabolism
Loss of function mutation
Gain of function mutation


Thank you for your attention