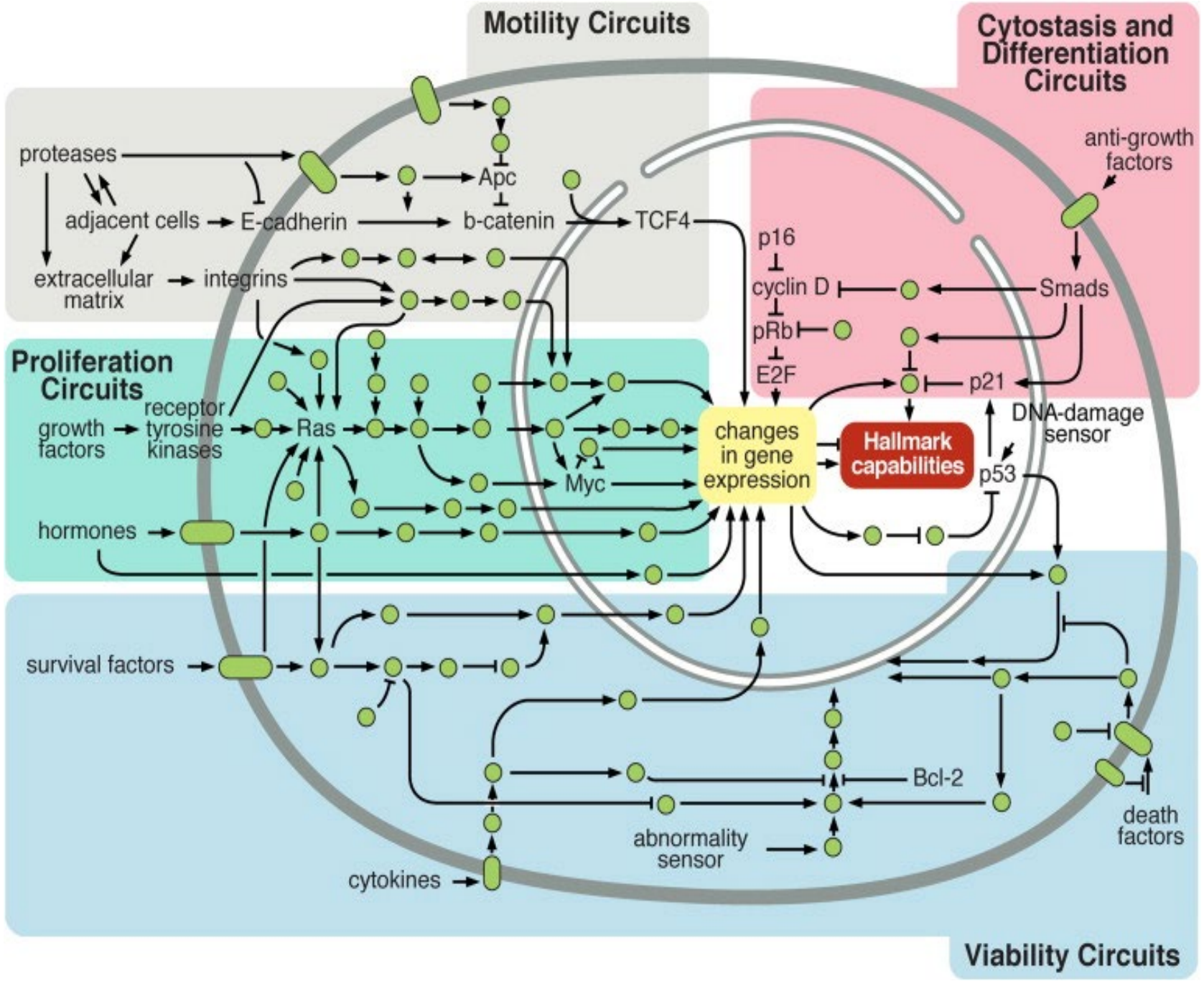
(Signal transduction in cytoplasma (Serine/threonine kinase inhibitors)

The PI3K-AKT-mTOR
Ras-Raf-Mek-ERK Pathway

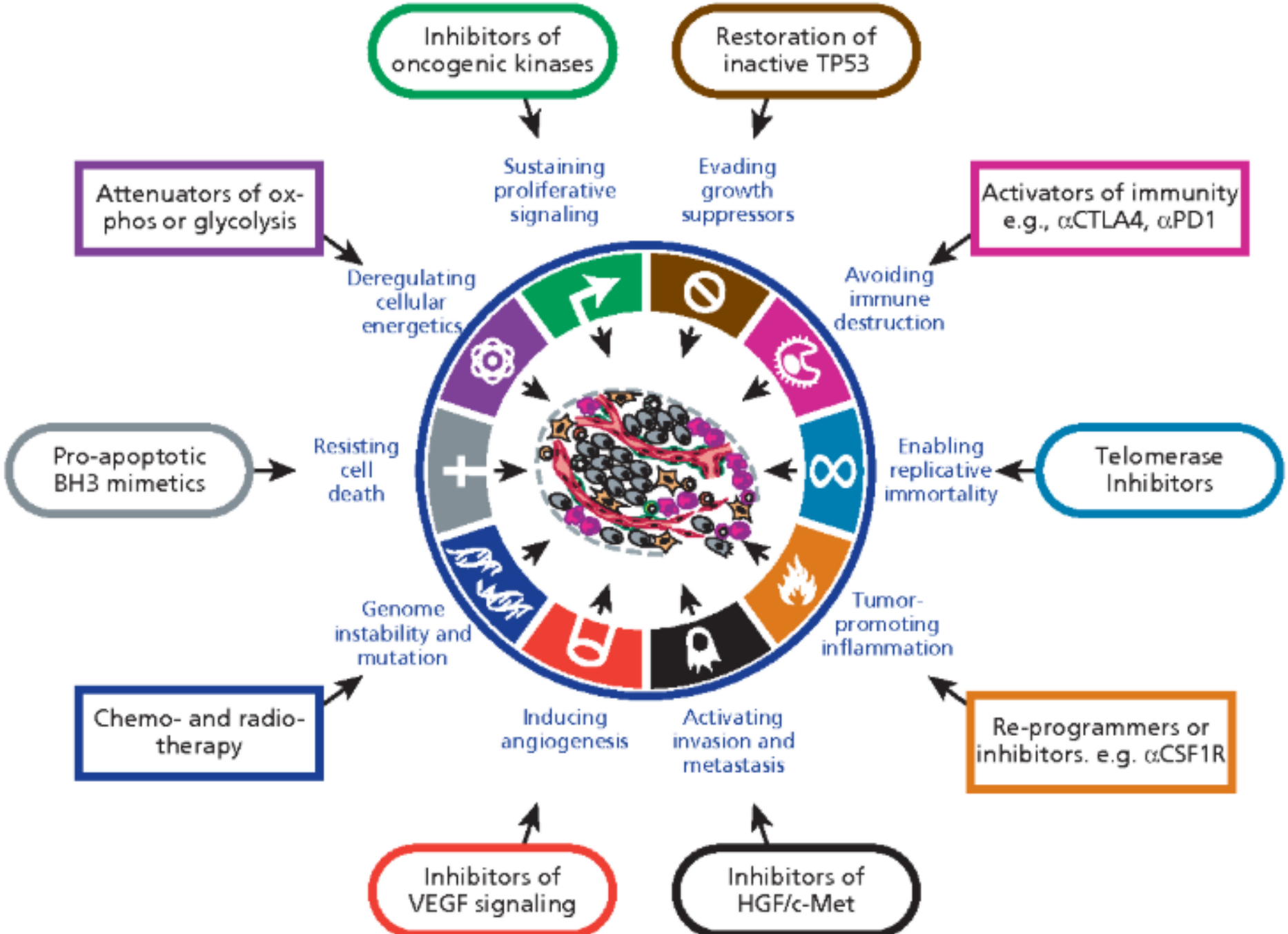
Clinical phatmacist : Li-hua Fang

2024/10/23



正常細胞內運行如同精細的集成電路，並經過重新編程以調節癌細胞內的標誌性功能。 單獨的子電路（此處在不同顏色的區域中進行了描述）專用於協調各種功能。 一方面，這種描述是簡單的，因為在這些子電路之間存在相當大的串擾(crosstalk)。 此外，由於每個癌細胞都暴露於來自其微環境的信號的複雜混合物，因此這些子電路中的每一個都與來自腫瘤微環境中其他細胞的信號相連。

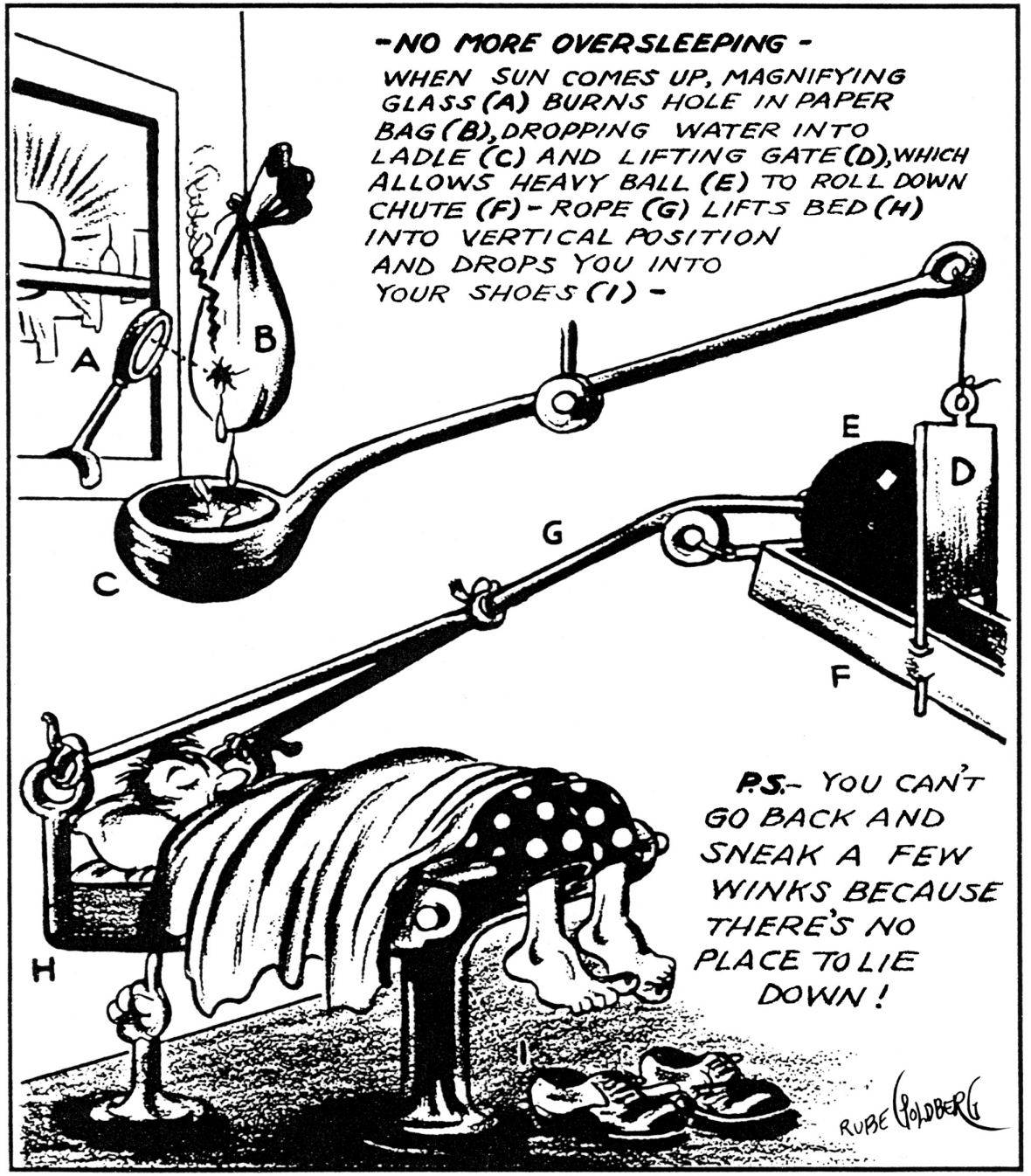
Cell 2011 Mar 4;144(5):646-74


Inhibitors of oncogenic kinases
Restoration of inactive TP53
Sustaining proliferative signaling
Evading growth suppressors
Attenuators of ox-phos or glycolysis
Activators of immunity e.g., αCTLA4, αPD1
Deregulating cellular energetics
Avoiding immune destruction
Pro-apoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability and mutation
Tumor-promoting inflammation
Chemo- and radio-therapy
Inducing angiogenesis
Activating invasion and metastasis
Re-programmers or inhibitors. e.g. αCSF1R
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met

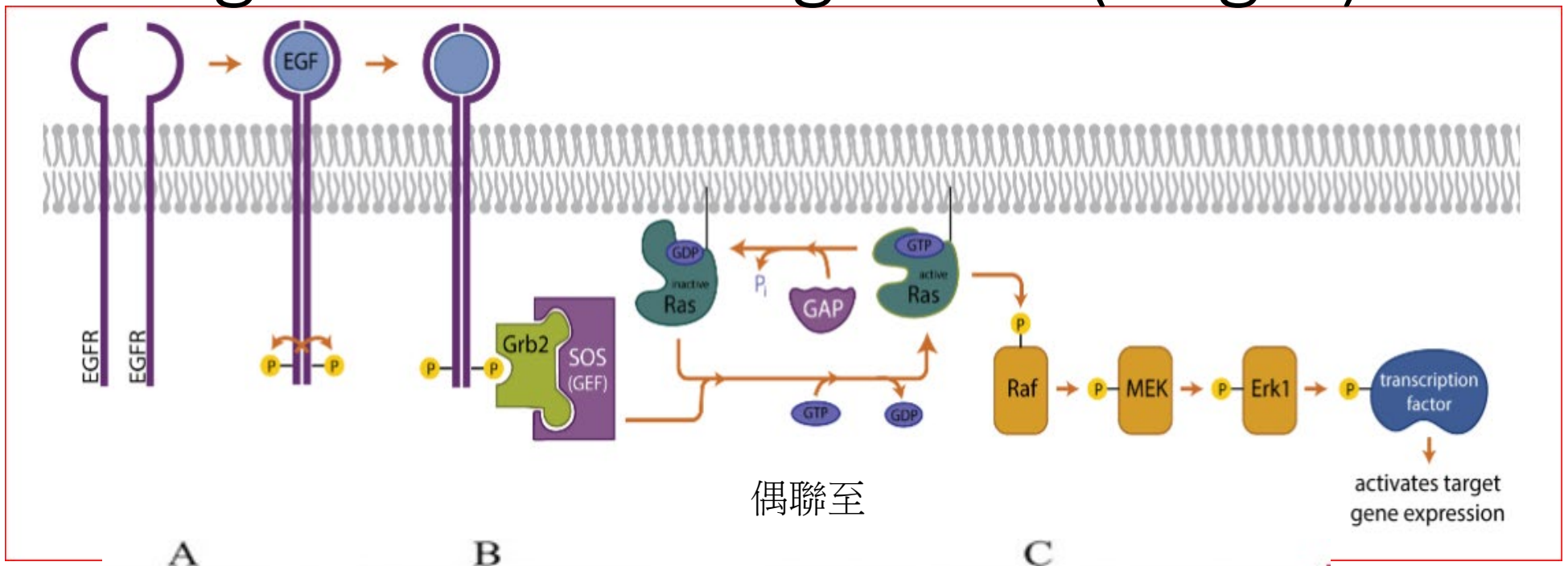
Cancer biology : Rube Goldberg model

The concept of targeted therapy

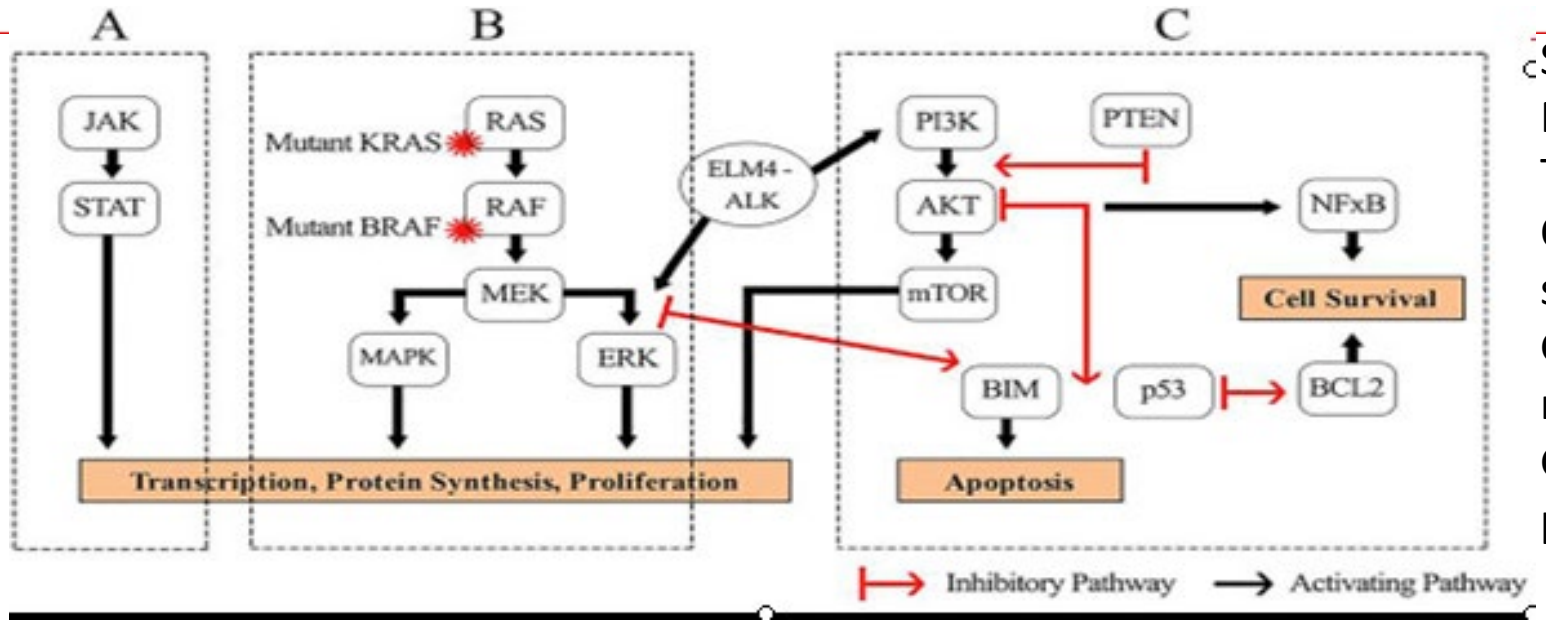
- Find out the message
- Cancer Driven gene
- Resistance is the destiny



Regulation of cell growth (target)



偶聯至



- SOS： "Son of Sevenless“
- PTEN（Phosphatase and Tensin Homolog Deleted on Chromosome Ten): tumor suppressor gene
- Grb2 : Growth factor receptor-bound protein 2
- GAP = GTPase activating proteins

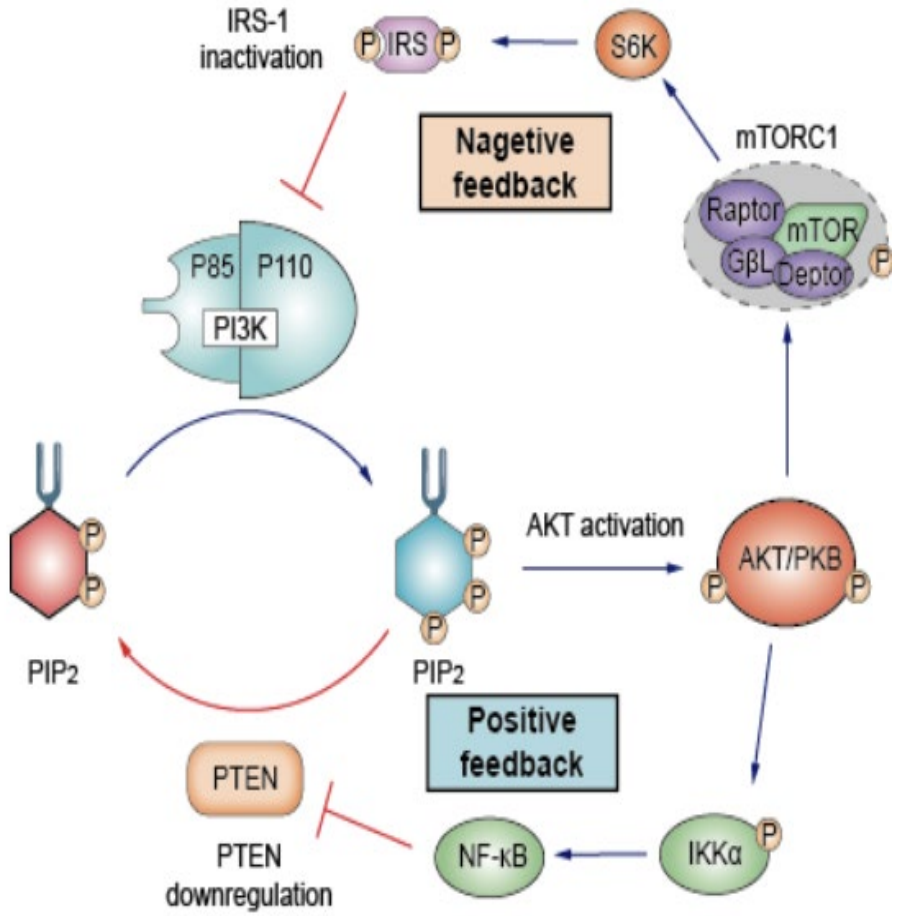
RAS Signaling Pathways

- The PI3K-AKT-mTOR
  - PI3K Inhibitors (-Lisib)
    - Alpelisib (PI3Kα)-breast
    - Copanlisib (Pan-PI3K) follicular lymphoma
    - Duvelisib (PI3Kγ/δ) :CLL, SLL, Follicular lymphoma
    - Idelalisib (PI3Kδ) : CLL, Follicular lymphoma
    - Umbralisib (PI3Kδ, CK1ε (casein kinase 1 epsilon) :MZL, FL
  - mTOR inhibitor (-Limus)
    - Everolimus, :RCC, breast cacner, Pancreatic cancer
    - Temsirolimus

- The RAS-RAF-MEK-ERK (Mitogen-activated protein kinase pathway)
  - RAS inhibitors : sotorasib, Adagrasib
  - RAF inhibitors (fenib):BRAF V600E mutation melanoma
    - Vemurafenib
    - Darafenib (BRAF/CRAF) : combination with trametinib (MEK inhibitor),
    - Encorafenib (BRAF) : combined with binimetinib (MEK inhibitor)
  - MEK inhibitor (metinib)
    - Binimetinib
    - Cobimetinib (MEK1/2)
    - Selumetinib (MEK1/2)
    - Trametinib (MEK1/2)
  - Neurofibromatosis type1 : Selumetinib
  - Plexiform neurofibroma
    - Trametinib (MEK1/2)

A brief history of AKT signaling

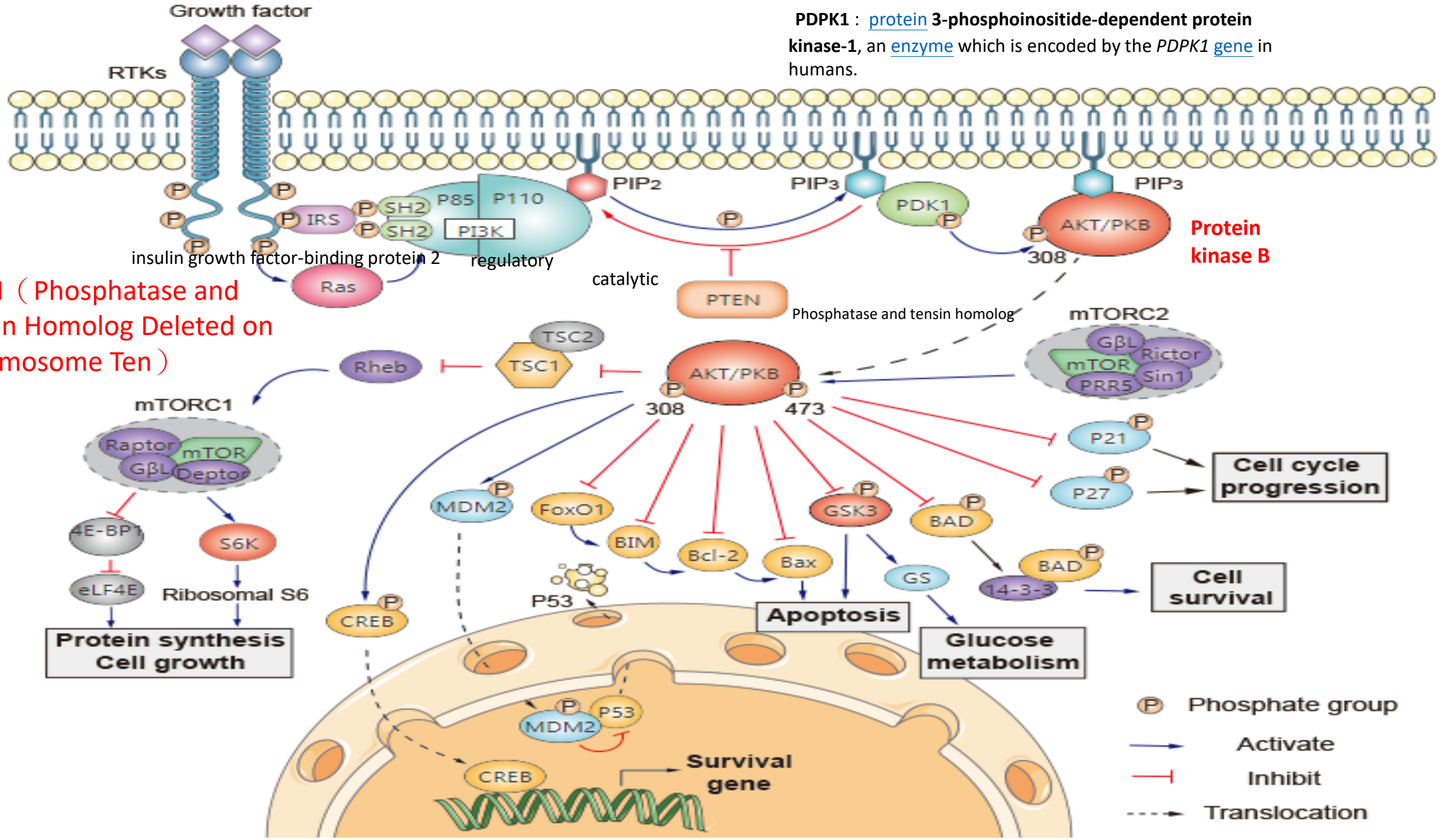
- PI3K-Akt途徑是一種細胞內信號轉導途徑，回應於細胞外信號來促進新陳代謝，增殖，細胞存活，生長和血管生成。
- 通過一系列絲氨酸(serine)和/或（threonine)酸磷酸化調解下游物質。
- 涉及的關鍵蛋白有磷脂酰肌醇3-激酶（PI3K）和Akt/PKB（蛋白激酶B)。PKB / Akt研究的起源可以追溯到1977年，由Staal和同事發現，這是以前未曾描述過的病毒癌基因ATK8。並分離出該細胞來源的致癌序列並命名為ATK。
- 1991年，三個獨立的研究小組鑑定了與PKB / Akt對應的基因(The serine/threonine kinase AKT, also known as protein kinase B (PKB)。這三篇論文確立了PKB / Akt作為一種廣泛表達的新型磷蛋白激酶，並奠定了PKB / Akt在多種細胞過程中的作用的方式。
- 一種叫做磷脂酰肌醇3激酶（The phosphoinositide 3' kinase, PI3K）的酶是1990年由Cantley小組分離出來的。PI3K產生的PIP3（膜磷脂)是激活PKB/Akt所必需的組成部分。

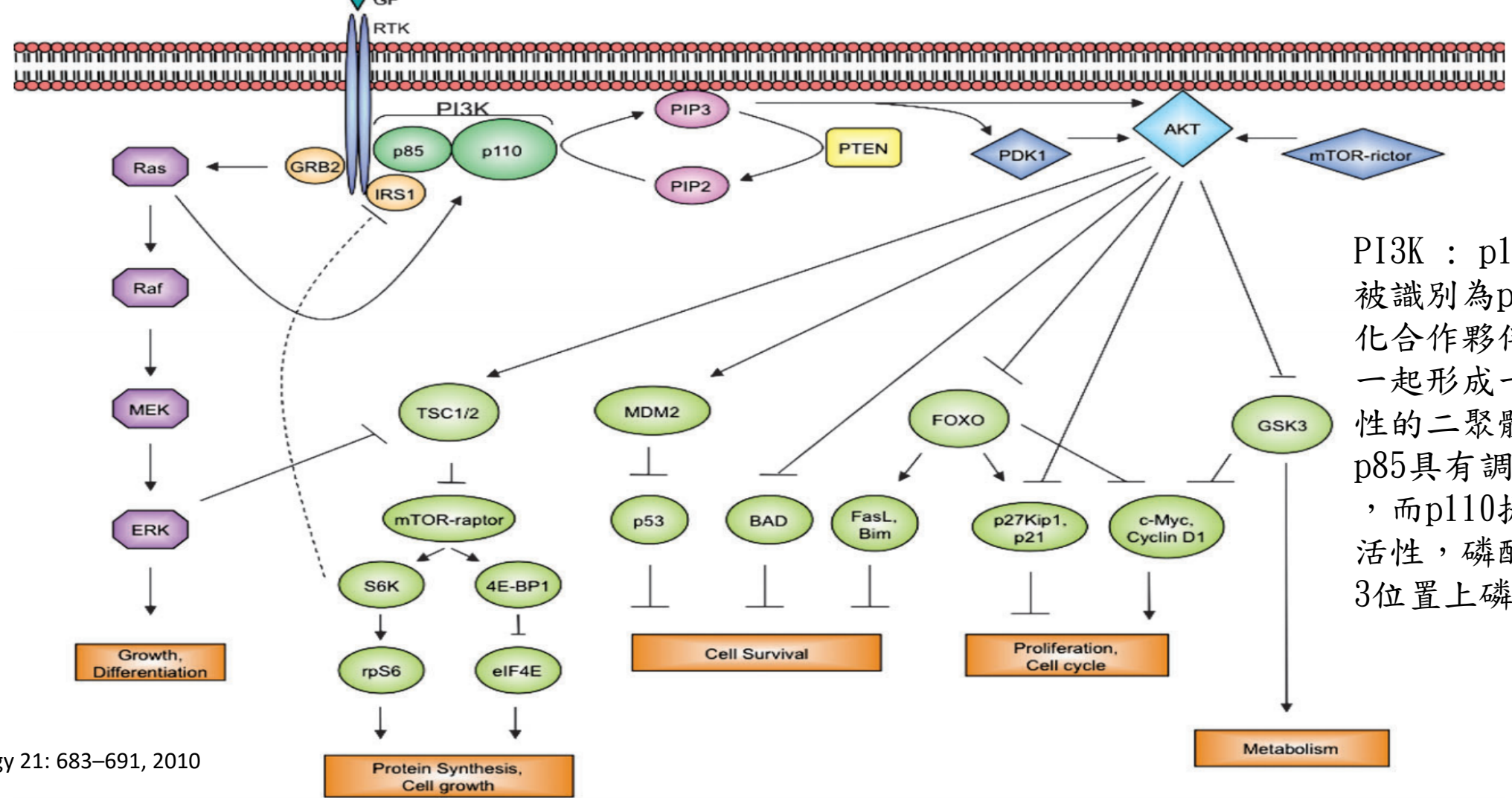


Akt: protein kinase-B

PDPK1： protein **3-phosphoinositide-dependent protein kinase-1**, an enzyme which is encoded by the *PDPK1* gene in humans.

PTEN（Phosphatase and Tensin Homolog Deleted on Chromosome Ten）

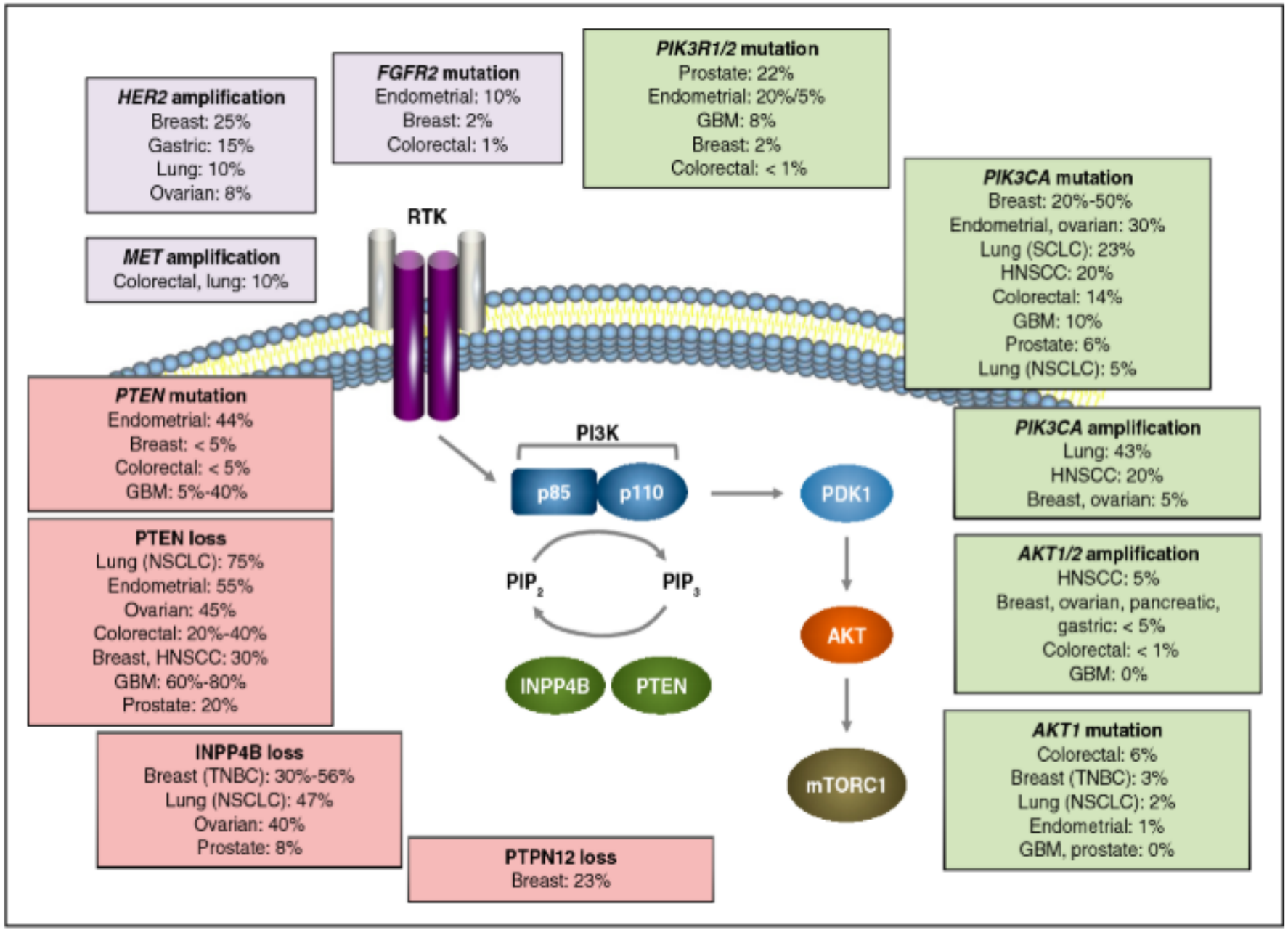




PI3K ： p110亞基被識別為p85的催化合作夥伴。它們一起形成一個功能性的二聚體，其中p85具有調節作用，而p110提供激酶活性，磷酸肌醇在3位置上磷酸化

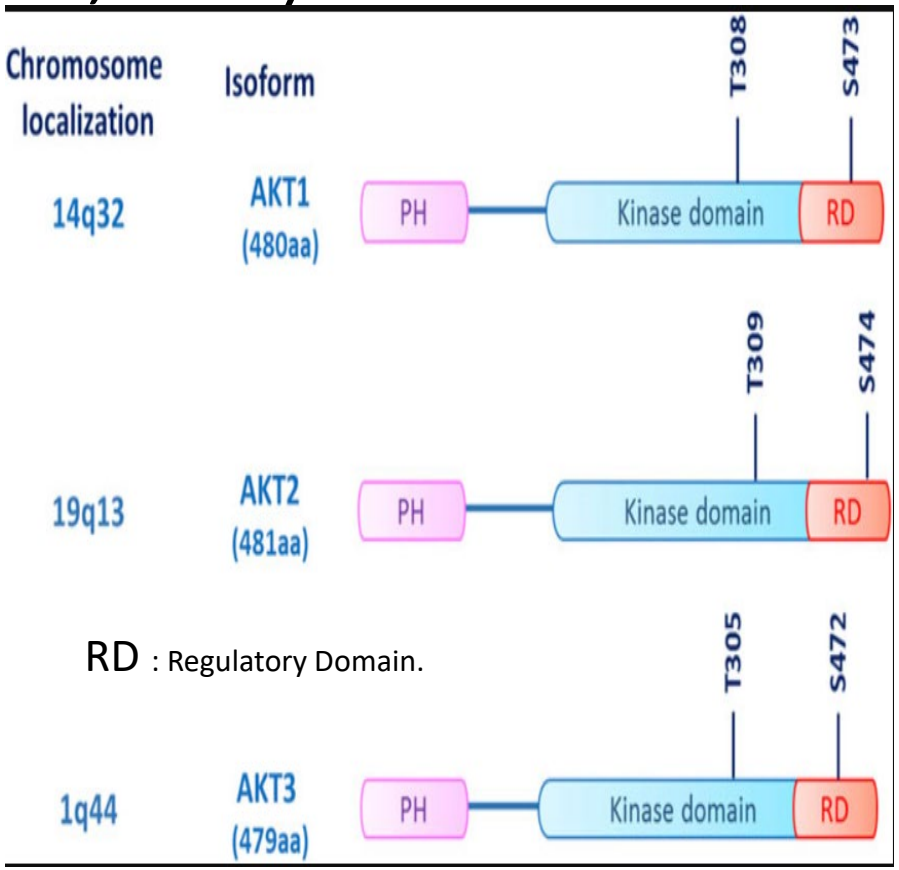
Annals of Oncology 21: 683–691, 2010

Figure 1. Signalling through class I phosphatidylinositol 3-kinases (PI3Ks): a ligand engaged receptor tyrosine kinase binds PI3K, either directly or indirectly via adapter molecules such as insulin receptor substrate 1 (IRS1), removing the inhibitory action of p85 subunit on the catalytic p110 subunit. The active kinase generates PIP3 at the lipid membrane. PIP3 facilitates the phosphorylation of Akt by phosphoinositide-dependent kinase 1, while the mTOR-rictor complex contributes a second phosphate residue to Akt. As the central effector of the PI3K pathway, Akt transmits signal to a host of downstream substrates, thus orchestrating a variety of key cellular functions, including growth, metabolism, proliferation and survival. Pathway activity is negatively regulated by phosphate and tensin homologue deleted from chromosome 10, opposing the action of PI3K by converting PIP3 back into PIP2, and the S6 kinase (S6K)-IRS1 feedback loop. The Ras/Raf/mitogen-activated protein kinase cascade also influences signalling through PI3K at various levels, with the small guanosine triphosphatase RAS able to activate the p110 subunit directly, while downstream extracellular signal-regulated kinase negatively affects tuberous sclerosis 2.


HER2 amplification
Breast: 25%
Gastric: 15%
Lung: 10%
Ovarian: 8%
FGFR2 mutation
Endometrial: 10%
Breast: 2%
Colorectal: 1%
PIK3R1/2 mutation
Prostate: 22%
Endometrial: 20%/5%
GBM: 8%
Breast: 2%
Colorectal: < 1%
MET amplification
Colorectal, lung: 10%
RTK
PIK3CA mutation
Breast: 20%-50%
Endometrial, ovarian: 30%
Lung (SCLC): 23%
HNSCC: 20%
Colorectal: 14%
GBM: 10%
Prostate: 6%
Lung (NSCLC): 5%
PTEN mutation
Endometrial: 44%
Breast: < 5%
Colorectal: < 5%
GBM: 5%-40%
PI3K
p85
p110
PDK1
PIK3CA amplification
Lung: 43%
HNSCC: 20%
Breast, ovarian: 5%
PTEN loss
Lung (NSCLC): 75%
Endometrial: 55%
Ovarian: 45%
Colorectal: 20%-40%
Breast, HNSCC: 30%
GBM: 60%-80%
Prostate: 20%
PIP2
PIP3
AKT
AKT1/2 amplification
HNSCC: 5%
Breast, ovarian, pancreatic, gastric: < 5%
Colorectal: < 1%
GBM: 0%
INPP4B
PTEN
INPP4B loss
Breast (TNBC): 30%-56%
Lung (NSCLC): 47%
Ovarian: 40%
Prostate: 8%
mTORC1
AKT1 mutation
Colorectal: 6%
Breast (TNBC): 3%
Lung (NSCLC): 2%
Endometrial: 1%
GBM, prostate: 0%
PTPN12 loss
Breast: 23%

Targeted drugs (breast cancer, FL,CLL)

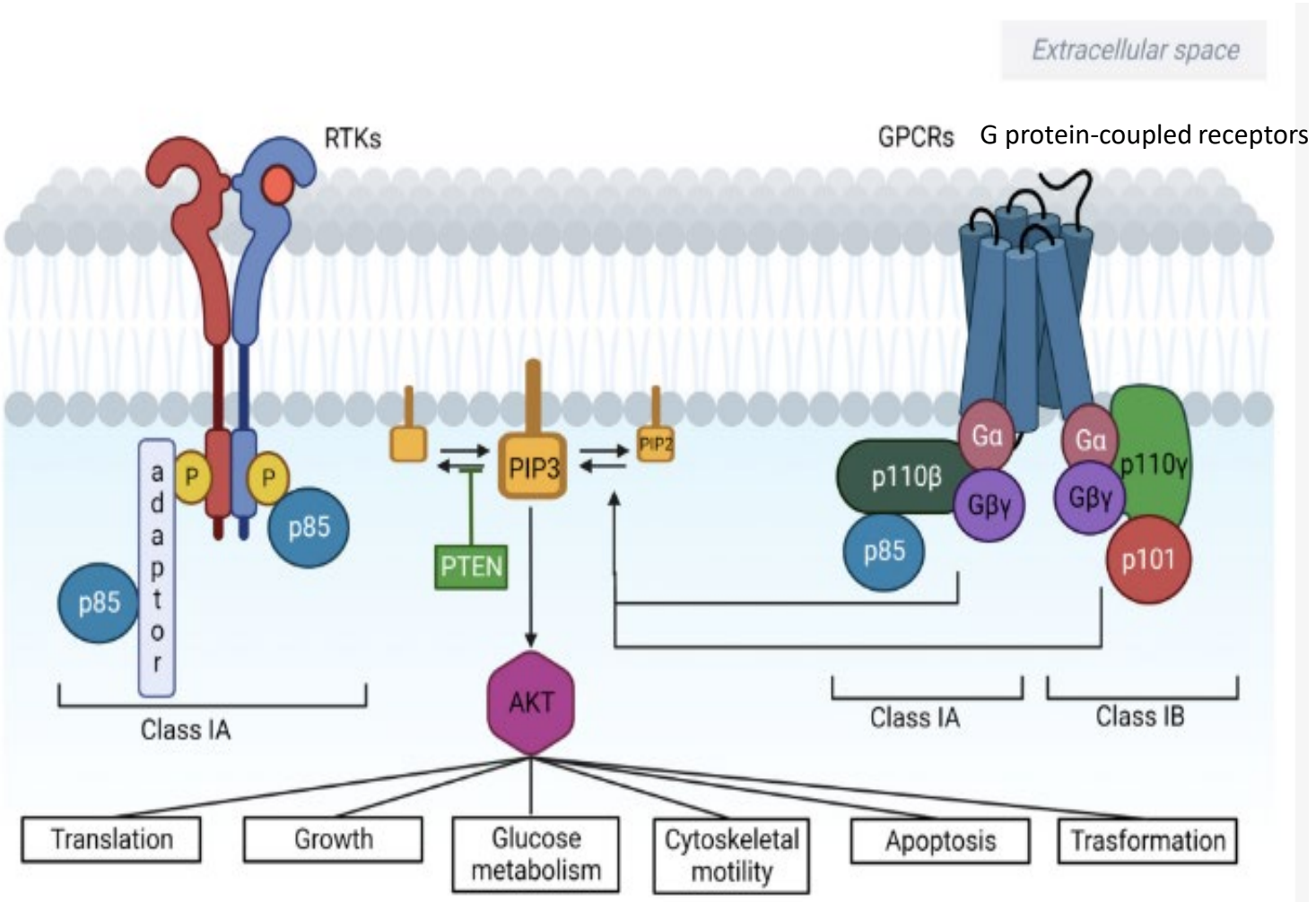
- PI3K-AKT-mTOR Signaling Pathway
  - PI3K inhibitor
    - Alpelisib, Copanlisib, Duvelisib, Idelalisib
  - mTOR inhibitor (mammalian target of rapamycin)
    - Everolimus , Temsirolimus
  - AKT inhibitor
    - capivasertib (selective ATP-competitive pan-AKT kinase inhibitor)
- AKT target protein
  - FoxO1, **GSK-3 (**Glycogen synthase kinase-3), PTEN
  - **Mtor (a** serine/threonine protein kinase)
- Three AKT isoforms (AKT1, AKT2, and AKT3)
- AKT1 and AKT2 present a ubiquitous distribution, AKT3 : in neural cells
- Enhanced activation in breast, ovarian, pancreatic, and prostate cancers among others.
- AKT1 is involved in proliferation and growth, promoting tumor initiation and suppressing apoptosis, whereas AKT2 regulates cytoskeleton dynamics, favoring invasiveness and metastatization.
- AKT3 hyperactivation : controversial



RD : Regulatory Domain.

PI3K/AKT (The phosphoinositide 3' kinase/ protein kinase-B)

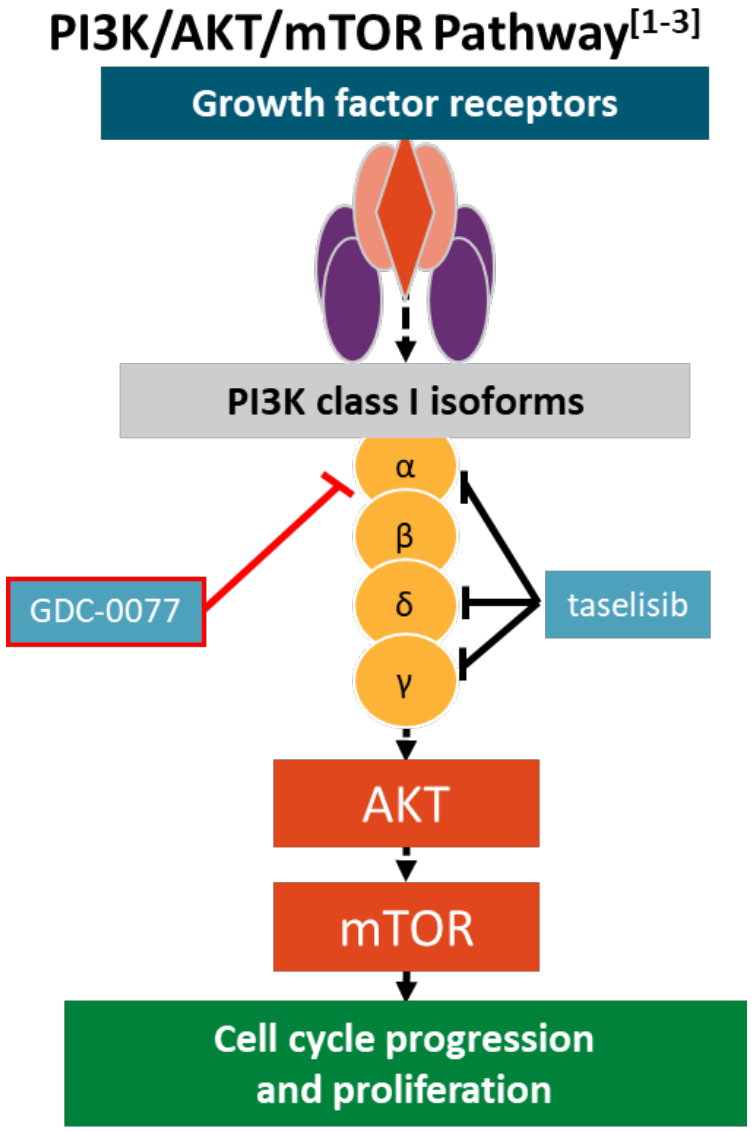
- **PI3Ks are grouped into three classes based on their structures and substrate specificities**
- The phosphoinositide 3' kinase (PI3K) family consists of 3 classes of lipid kinases that have a regulatory subunit (p85) and a catalytic subunit (p110) that phosphor catylate the 3'OH group of phosphoinositols.
- Class IA PI3Ks : somatic mutations in the catalytic subunit p110a (*PIK3CA*)
  - 30% of epithelial cancers (breast, colon, prostate, endometrial).
- Class I PI3Ks, which are further divided into four isoforms: α (alpha), β (beta), γ (gamma), and δ (delta).



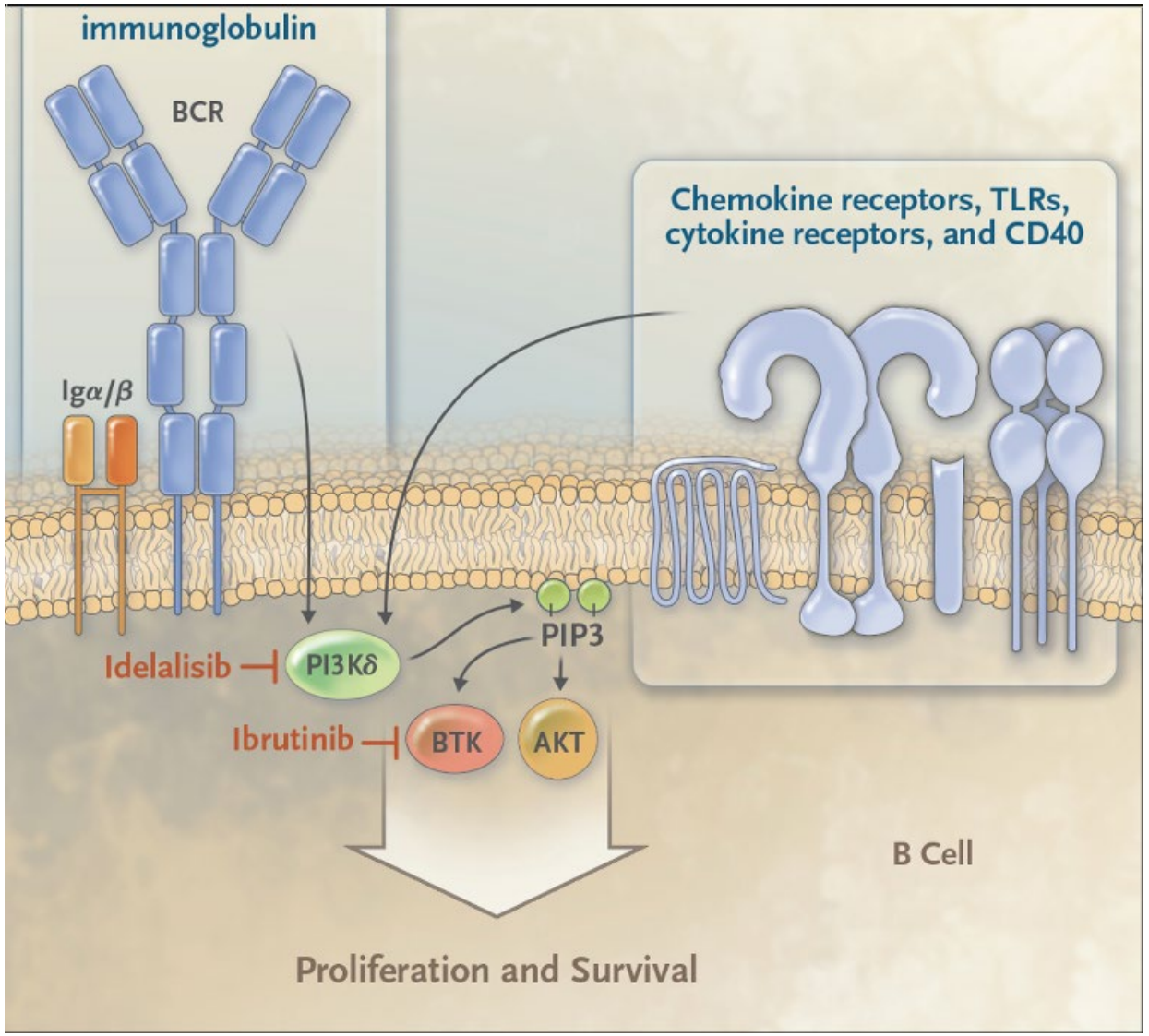
Cancers 2023, 15(3), 703; https://doi.org/10.3390/cancers15030703

Phosphoinositide 3-kinase (PI3K)inhibitors

- PI3Kα (alpha): Widely expressed in tissues, with a notable presence in the insulin-responsive tissues.
- PI3Kβ (beta): Ubiquitously expressed, but plays a unique role in platelets.
- PI3Kγ (gamma): Primarily expressed in leukocytes.
  - hematological malignancies and has roles in certain immune-mediated disorders.
- PI3Kδ (delta) : Predominantly found in lymphoid (CLL, Indolent Non-Hodgkin Lymphoma)



A PI3Kδ Inhibitor for B-Cell Cancers Idelalisib



B 細胞受體 (BCR) 訊號傳導會活化磷酸肌醇 3- 激酶 (PI3K)，產生第二信使磷酸肌醇 3,4,5- 三磷酸酯 (PIP3)，進而活化布魯頓酪氨酸激酶 (BTK) 和 AKT，AKT 是一種可結合 PIP3 的促生存激酶，在許多實體腫瘤中扮演關鍵角色。
Idelalisib 是 PI3K δ 異構型的選擇性抑制劑，針對惡性 B 細胞中 BCR 下游的信號轉導，而 ibrutinib 則針對 BTK。PI3K 和 BTK 也會在 B 細胞上許多其他受體的下游被活化，包括 CD40、細胞激素受體、化學因子受體和 toll-like 受體 (TLR)。BCR 由與 Igα 和 Igβ 兩種訊號鏈相關的抗體重鏈和輕鏈組成。

N Engl J Med 2014;370:1061-1062

PI3K Inhibitors in FL

All patients (patients with FL)	Duvelisib (PI3K-γ,δ)[12]	Idelalisib (PI3K-δ)[13]	Copanlisib (PI3K-α,δ)[14]
	129 (83)	125 (72)	142 (104)
Median prior therapies	3 (1-10)	4 (2-12)*	3 (2-9)*
Median time since progression	3.2	NA	8.3 (1-73)*
ORR, % - CR - PR - SD	42 1 41 34.9	57* 6 50	59 14 44 34
PFS, months	9.5	11*	11.2
Discontinued due to adverse events, %	31*	20*	25*
Key grade ≥3 adverse events with frequency >10%	Neutropenia, diarrhea, anemia, thrombocytopenia	Neutropenia, diarrhea, ALT elevation	Hyperglycemia, hypertension, neutropenia, pneumonia

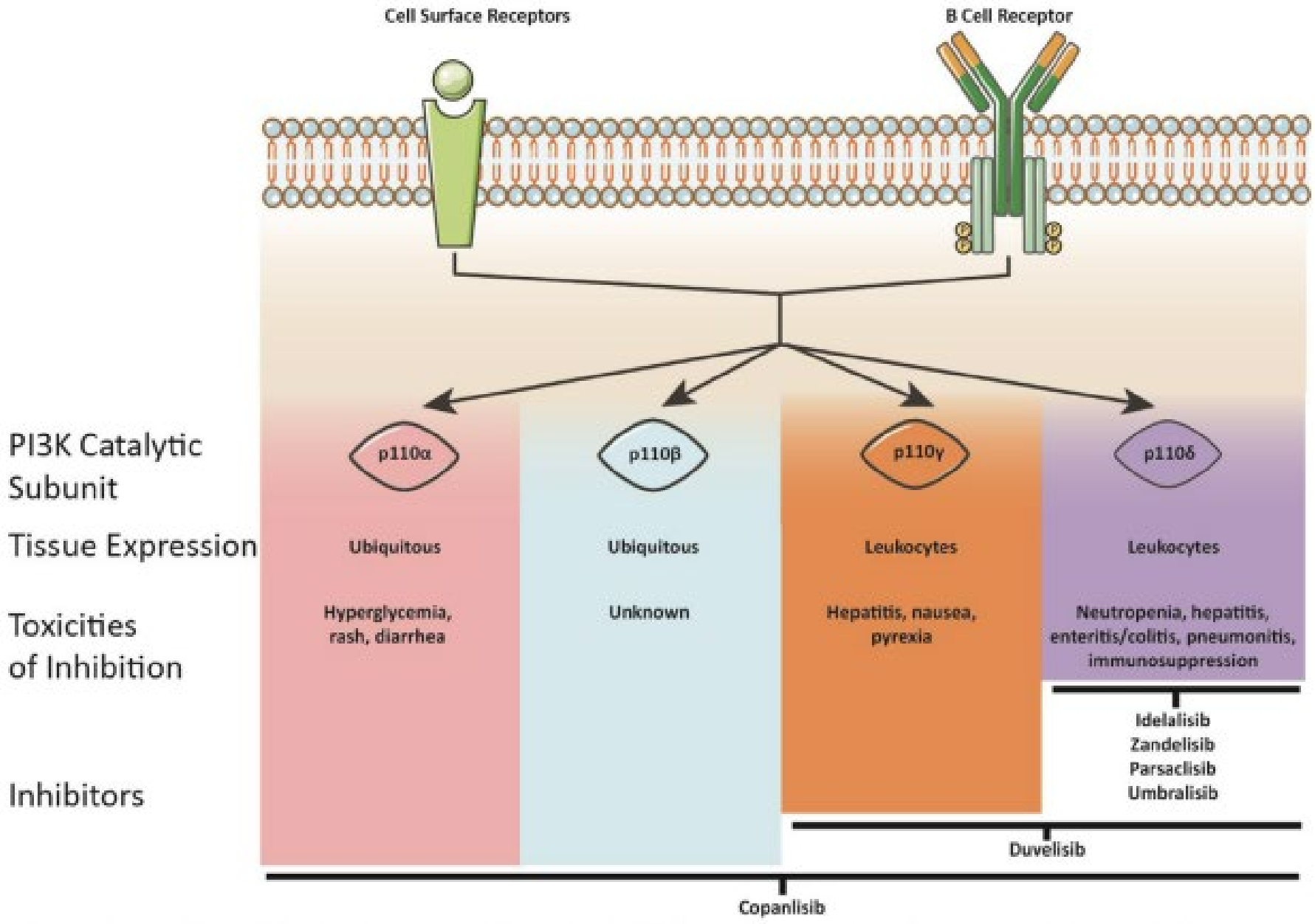
12 Journal of Clinical Oncology. 2019;37(11):912-922. 13. N Engl J Med. 2014;370(11):1008-1018. 14. . J Clin Oncol. 2017;35(35):3898-3905.

PI3K Inhibitors in CLL

	Phase I: Duvelisib Monotherapy[9]	Phase III DUO: Duvelisib vs Ofatumomab[10]	Phase III: Idelalisib-Rituximab vs Rituximab[22]
N	55 (R/R CLL)	160 (Duvelisib), 159 (Ofatumumab)	110 (Idelalisib-Rituximab), 110 (Rituximab)
Median prior therapies	4 (1-11)	2 (1-10) vs 2 (1-8)	3 (1-12) vs 3 (1-9)
Median years since diagnosis	8.5 (0.7-20.9)	7.5 vs 6.7	8.6 vs 9.0
ORR, %	56.4	73.8 vs 45.3*	83.6 vs 15.5*
- CR	1.8	0.6 vs 0.6	0 vs 0
- PR	54.5	72.5 vs 44.7	83.6 vs 15.5*
- SD	34.5	21.3 vs 39.6	11.8 vs 64.5
PFS, months	15.7	13.3 vs 9.9	19.4 vs 6.5
Discontinued due to adverse events, %	36.4	35.0 vs 4	20 vs 10.9
Key Grade ≥3 adverse events with frequency ≥10%	Neutropenia, anemia, thrombocytopenia, pneumonia, transaminitis	Neutropenia, Anemia, Diarrhea/Colitis, Pneumonia	Neutropenia, Pneumonia

NR = not reached, *p<0.0001

Blood . 2019 Nov 7;134(19):1573-1577



Hematol Oncol Clin N Am 35 (2021) 807–826

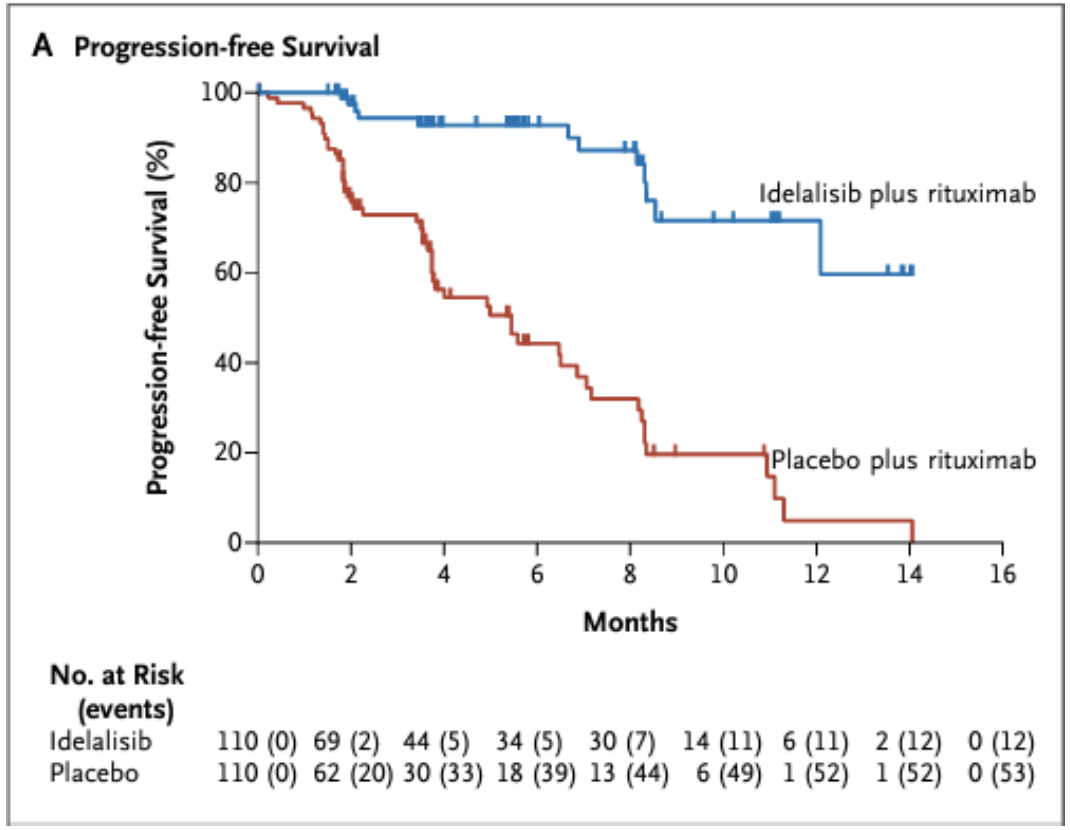
Phosphoinositide 3-kinase (PI3K)inhibitors

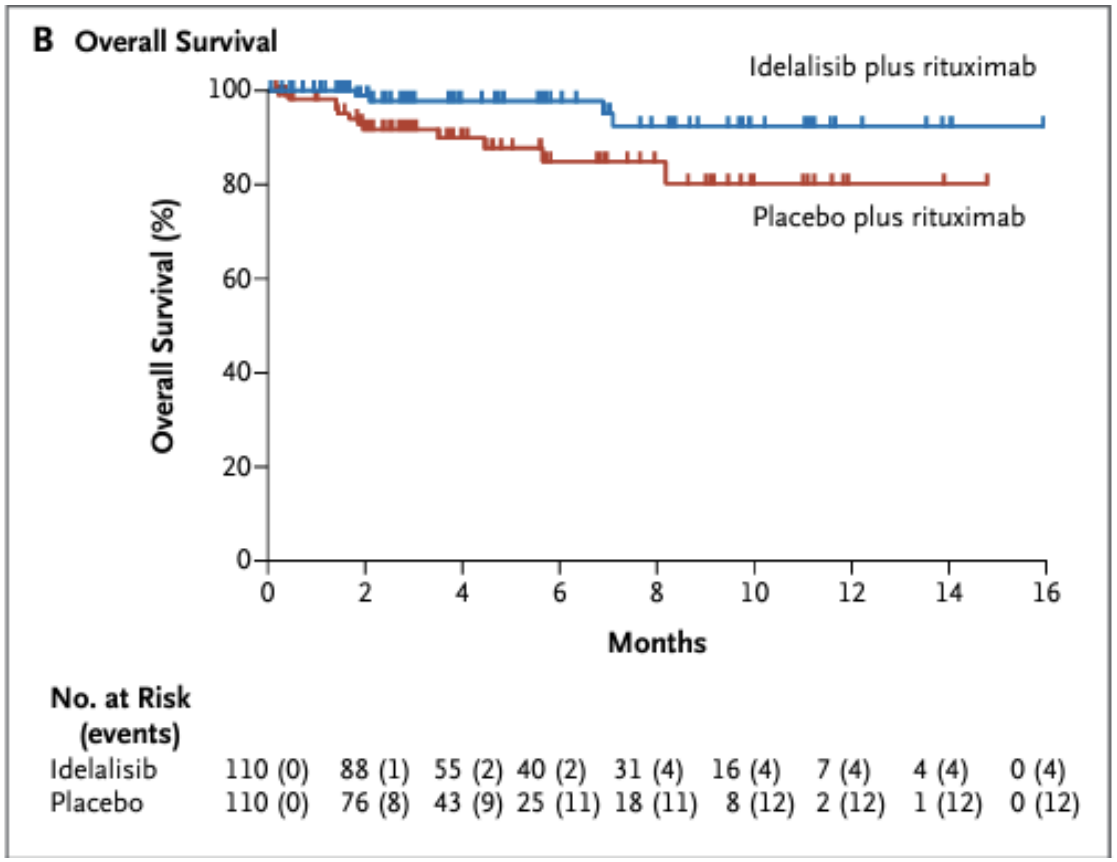
- Idelalisib (PI3K Delta inhibitor) :FDA approved July 2014
  - relapsed or refractory chronic lymphocytic leukemia (CLL) in combination with rituximab
  - relapsed small lymphocytic lymphoma in patients who have received at least two prior systemic therapies,
  - 3rd line follicular lymphoma in patients who have received at least two prior systemic therapies. 
- Copanlisib (Inhibitor of PI3K, PI3K-α and PI3K-δ) :Approved in 2017 
  - Relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.
- Duvelisib (an oral dual inhibitor of PI3K-delta and PI3K-gamma) Approved in 2018
  - Adult patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) after at least two prior therapies
  - Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. 
- Alpelisib (alpha-specific PI3K inhibitor) : Approved in 2019
  - combination with fulvestrant for treatment of HR-positive and HER2/neu-(-) breast cancer

Drug Name	Trial Name (Study Pts N)	Target Subtype	Indication	Comparative Protocol	Comparative ORR	Comparative PFS (months)	Comparative OS months	Adverse Events	Source Journal
Idelalisib	Study 116 (220)	PI3Kδ	Relapsed Chronic Lymphocytic Leukemia (CLL)	Idelalisib + Rituximab vs. Placebo + Rituximab	81% vs. 13%	not reached vs. 5.5 months	overall survival at 12 months (92% vs. 80%; P = 0.02).	Diarrhea, hepatotoxicity, pneumonitis, neutropenia	NEJM. 2014 370(11): 997–1007.
Duvelisib	DUO Trial (319)	PI3Kδ/γ	Relapsed/Refractory CLL/SLL	Duvelisib vs. Ofatumumab	74% vs. 45%	13.3 vs. 9.9 months	38.4 months vs. 31.6 months	Diarrhea, neutropenia, infections, transaminase elevation	Blood (2018) 132 (23): 2446–2455.
Copanlisib IV	CHRONOS-3 (458)	PI3Kα/δ	Relapsed Indolent Non-Hodgkin Lymphoma	Copanlisib + Rituximab vs. Placebo + Rituximab	81% vs. 48%	21.5 vs. 13.8 months (p<0·0001))	Not Reached vs. Not Reached	Hypertension, hyperglycemia, neutropenia, infections	Lancet Oncol. 2021 Jun;22(6):e23
Umbralisib	UNITY-CLL (421)	PI3Kδ/CK1ε	Relapsed/Refractory CLL/SLL	Umbralisib + Ublituximab vs. Obinutuzumab + Chlorambucil	83% vs. 68%	31.9 vs. 17.9 months	Not Reached vs. Not Reached	Diarrhea, neutropenia, nausea, hepatotoxicity	Lancet Haematology, 2021
Alpelisib	SOLAR-1 (572)	PI3Kα	HR+/HER2- Advanced Breast Cancer	Alpelisib + Fulvestrant vs. Placebo + Fulvestrant	36% vs. 16%	11.0 vs. 5.7 months	39.3 months vs. 31.4 months	Hyperglycemia, rash, diarrhea, fatigue	NEJM, 2019

Idelalisib + Rituximab vs Idelasib

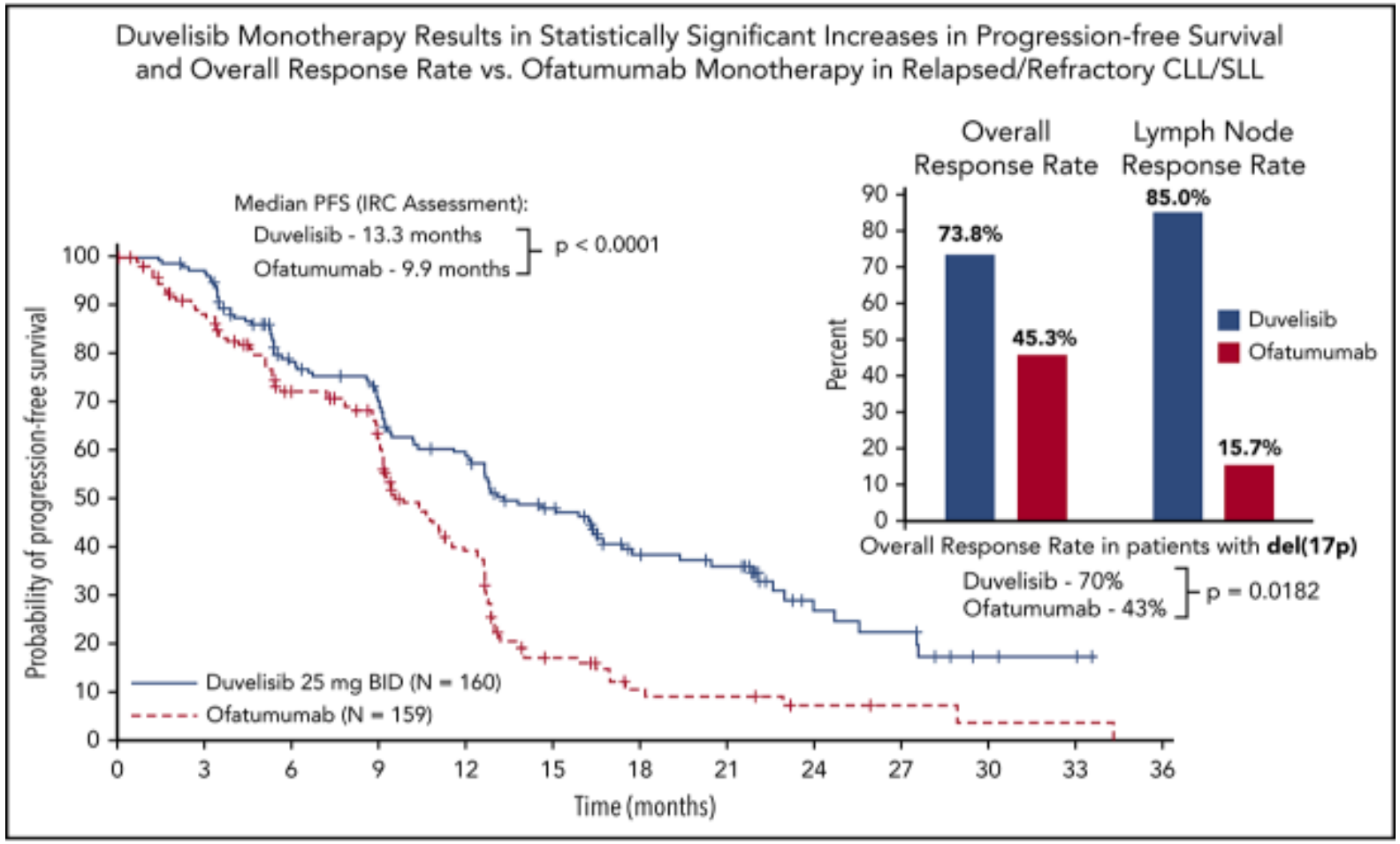
- Duration of progression-free survival : idelalisib and rituximab : not reached; placebo and rituximab : 5.5 months (P<0.001) (Panel A)
- The median duration of overall survival in the two study groups had also not been reached; the overall survival rate was 92% in the idelalisib group versus 80% in the placebo group at 12 months (P = 0.02)





NEJM. 2014 370(11): 997–1007.

The phase 3 DUO trial: duvelisib vs ofatumumab (CD20) in relapsed and refractory CLL/SLL



The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL, Blood, 2018,

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

PI3K Inhibitor Toxicities

	Idelalisib N= 146	Copanlisib N= 244	Duvelisib N= 442	Umbralisib N= 371
Grade ≥ 3 AE	71%	85%	84%	51%
SAEs	50%	51%	65%	26%
Discontinuations due to AE	23%	24%	35%	15%
Dose Reduction due to AE	41%	24%	23%	10%
Grade ≥ 3 Infection	23%	23%	27%	20%
Grade ≥ 3 Neutropenia	28%	29%	43%	17%
Grade ≥ 3 Diarrhea/Colitis	14%	5%	23%	7%
Grade ≥ 3 AST/ALT increase	18%	2%	8%	7%
Grade ≥ 3 Rash	4%	2%	9%	3%
Grade ≥ 3 Pneumonitis	5%	7%	7%	1%
Grade ≥ 3 Hyperglycemia	-	34%	-	-
Grade ≥ 3 Hypertension	-	29%	-	-

Abbreviations: AE- Adverse Event; SAE- Serious Adverse Event

The saga of PI3K inhibitors in haematological malignancies: survival is the ultimate safety endpoint

The Lancet Oncology, Volume 23, Issue 5, 563 – 566

	Initial approval information*	Post-approval trials	Outcome
Idelalisib (PI3Kδ inhibitor)			
Regular approval	2014: in combination with R + idelalisib vs placebo + R in relapsed CLL : progression-free survival HR 0·18 (95% CI 0·10–0·31), OS : immature	2016: three RCTs halted in CLL or indolent non-Hodgkin lymphoma for increased deaths and serious toxic side-effects: ●idelalisib + bendamustine + R vs placebo plus bendamustine plus R in untreated CLL ●idelalisib + R vs placebo + R in relapsed or refractory indolent non-Hodgkin lymphoma ●idelalisib with bendamustine + R vs placebo with Bendamustine + R in relapsed or refractory indolent non-Hodgkin lymphoma. Pooled analysis : idelalisib groups vs control: deaths 7·4% vs 3·5%; overall survival HR 2·29 (95% CI 1·26–4·18)[1]	Warning and limitations of use added to prescribing information (2016, 2018)
Accelerated approval	2014: relapsed FL and SLL after ≥2 systemic therapies on single-arm trial: FL : ORR 54% , MRD : not reached; SLL : ORR 58% (95% CI 37–77), MDR : 11·9 months	Required post-marketing trial: slow accrual to trial evaluating idelalisib dosage in relapsed or refractory follicular lymphoma	Voluntary withdrawal of FL and SLL indications (2022)
Copanlisib (PI3Kα and PI3Kδ inhibitor)			
Accelerated approval	2017: relapsed FL after ≥2 systemic therapies based on single-arm trial: ORR 59% (95% CI 49–68), MDR: 12.2 months	CHRONOS-3: RCT of copanlisib + rituximab vs placebo + rituximab in relapsed indolent non-Hodgkin lymphoma:[2] progression-free survival HR 0·52 (95% CI 0·39–0·69), interim OS HR 1·07 (95% CI 0·63–1·82)	Voluntary withdrawal of NDA based on CHRONOS-3

	Initial approval information*	Post-approval trials	Outcome
Duvelisib (PI3Kδ and PI3Kγ inhibitor)			
Regular approval	2018: relapsed or refractory CLL or SLL after ≥2 therapies based on a RCT of duvelisib vs ofatumumab in relapsed or refractory CLL or SLL: PFS HR 0·52 , OS : immature	Final analysis, duvelisib vs ofatumumab: overall survival HR 1·11 (95% CI 0·80–1·53)	Under FDA review: Not indicated for initial or 2nd line treatment in CLL or SLL
Accelerated approval	2018: relapsed or refractory FL after ≥2 systemic therapies based on single-arm trial: ORR 42% (95% CI 31–54), 43% of responses were ongoing at ≥6 months and 17% at ≥12 months	Required post-marketing trial: RCT was not initiated for commercial reasons	Voluntary withdrawal of follicular lymphoma indication (2021)
Umbralisib (PI3Kδ and CK1ε inhibitor)			
Accelerated approval	2021: relapsed or refractory FL after ≥3 systemic therapies and relapsed or refractory MZL after ≥1 anti-CD20-based regimen on single-arm trial: FL : ORR 43%, MDR 11·1 months; MZL : ORR 49% , MDR : not reached	UNITY-CLL: RCT of umbralisib + ublituximab vs obinutuzumab + chlorambucil in untreated and relapsed or refractory CLL : PFS HR 0·55 (95% CI 0·41–0·72); interim OS : HR 1·23[5‡]	 Withdrawal in CLL , June, 2022

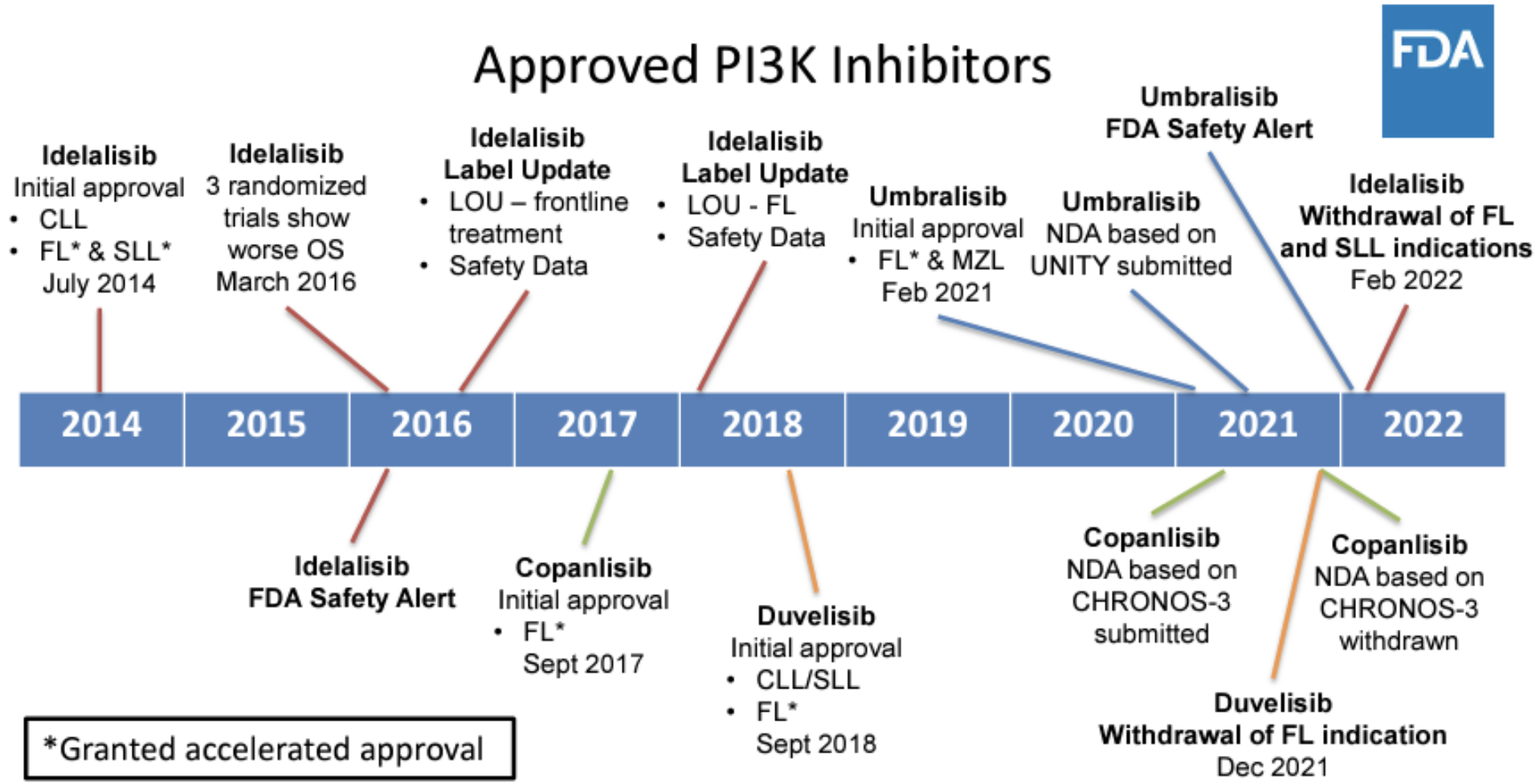
FDA=US Food and Drug Administration. HR=hazard ratio. NDA=new drug application. ODAC=Oncologic Drugs Advisory Committee. RCT=randomised controlled trial. chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), follicular lymphoma (FL) MZL: marginal zone lymphoma, Median of response duration (MRD)

Multiple Randomized Trials with Concerning Overall Survival

Study	Population & Treatment	Deaths PI3Ki arm	Deaths Control arm	Hazard Ratio (95% CI)
312-0123	• Untreated CLL • Bendamustine and rituximab ± idelalisib	8% (12/157)	3% (4/154)	3.34 (1.08, 10.39)
313-0124	• Previously treated indolent NHL • Rituximab ± idelalisib	5% (10/191)	1% (1/95)	4.74 (0.6, 37.12)
313-0125	• Previously treated indolent NHL • Bendamustine and rituximab ± idelalisib	8% (27/320)	6% (9/155)	1.51 (0.71, 3.23)
DUO	• Previously treated CLL • Duvelisib vs ofatumumab	50% (80/160)	44% (70/159)	1.09 (0.79, 1.51)
CHRONOS-3	• Previously treated indolent NHL • Rituximab ± copanlisib	18% (56/307)	21% (32/151)	0.87 (0.57, 1.35)
UNITY-CLL	•Untreated and previously treated CLL •Umbralisib + ublituximab vs GC	-	-	1.23

Abbreviations: CI, confidence interval, CLL, chronic lymphocytic leukemia, GC, Obinutuzumab + Chlorambucil, NHL, non-Hodgkin lymphoma, PI3Ki, phosphatidylinositol 3-kinase inhibitor

Approved PI3K Inhibitors



www.fda.gov

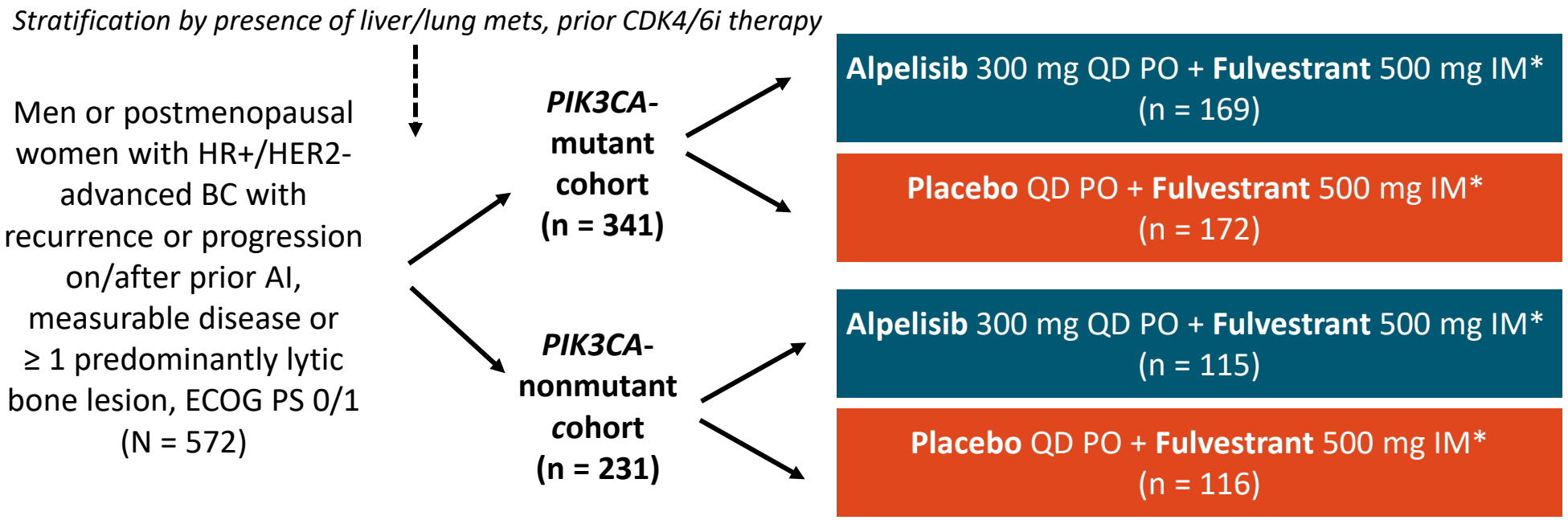
Abbreviations: CLL, chronic lymphocytic leukemia, FL, follicular lymphoma, LOU, limitation of use, MZL, marginal zone lymphoma, NDA, new drug application, OS, overall survival, SLL, small lymphocytic lymphoma

The status of PI3K inhibitors (忘了吧)

- **Toxicity and Safety Concerns**
  - **Infections:** Higher risk of opportunistic infections (PJP, CMV), **Diarrhea and Colitis:** Significant gastrointestinal toxicities, including severe diarrhea and colitis, **Hepatotoxicity, Pneumonitis**
  - **Higher Mortality:** trials revealed a higher mortality rate in patients taking PI3K inhibitors, even though the drugs were effective in shrinking tumors.
- **Disappointing Long-Term Efficacy:**
  - **Shorter PFS:** showed promising progression-free survival (PFS) data, the benefits often did not translate into prolonged overall survival (OS)
  - **Relapse and Resistance:** Resistance mechanisms often emerged, leading to early relapse or disease progression .
- **Regulatory Scrutiny (監管審查) Specific Withdrawals:**
  - **Umbralisib** (withdrawn in 2022): An interim analysis of the UNITY-CLL trial showed increased risks of death and severe adverse events.
  - **Duvelisib**: While still approved, it has faced restrictions and negative recommendations
  - **Idelalisib**: Associated with high rates of serious infections and liver toxicity, leading to several clinical trial halts and decreased usage in practice.

SOLAR-1: Alpelisib + Fulvestrant vs Placebo + Fulvestrant in HR+/HER2- Advanced Breast Cancer

- Randomized, double-blind, placebo-controlled phase III trial



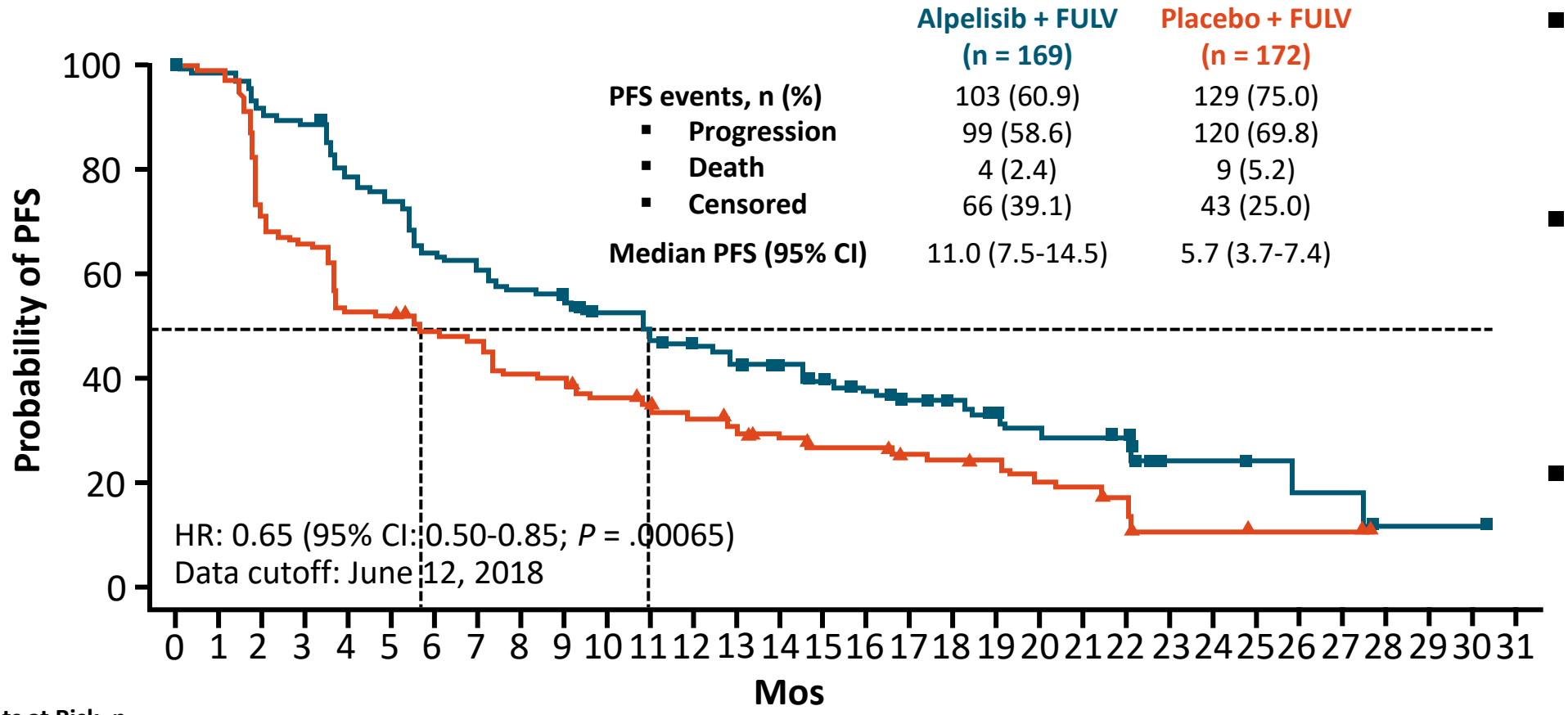
*Fulvestrant given on Days 1,15 of 28 in cycle 1, then Day 1 thereafter.

- **Primary endpoint:** PFS (locally assessed) in all patients randomized to *PIK3CA*-mutant cohort
- **Secondary endpoints:** OS in *PIK3CA*-mutant cohort; PFS in *PIK3CA*-nonmutant cohort (proof of concept); PFS in ctDNA and ORR/CBR for both cohorts; safety for patients with ≥ 1 dose study drug

André. NEJM. 2019;380:1929. Juric. SABCS 2018. Abstr GS3-08.

Slide credit: clinicaloptions.com

SOLAR-1: Locally Assessed PFS in *PIK3CA*-Mutant Cohort (Primary Endpoint)



Patients at Risk, n

Alpelisib + FULV	169	158	145	141	123	113	97	95	85	82	75	71	62	54	50	43	39	32	30	27	17	16	14	5	5	4	3	3	1	1	1	0
Placebo + FULV	172	167	120	111	89	88	80	77	67	66	58	54	48	41	37	29	29	21	20	19	14	13	9	3	3	2	2	2	0	0	0	0

- Mutation status from tissue
- Similar results when mutation status from ctDNA
- Only 6% of patients with prior CD4/6i exposure

André. NEJM. 2019;380:1929. Andre. ESMO 2018. Abstr LBA3_PR.

Slide credit: clinicaloptions.com

Before Initiating Alpelisib: Considerations

All Patients[1]

Verify pregnancy status in women of reproductive potential prior to initiating alpelisib

Consider an antihistamine when initiating alpelisib

- Prophylactic antihistamines administered prior to rash onset on SOLAR-1 decreased incidence and severity of rash

Baseline glucose

Assess **FPG and A1C** before initiating treatment with alpelisib

- **Optimize blood glucose** before initiating alpelisib

Plan for glucose monitoring after treatment initiation

Monitor fasting glucose:

- At least weekly during the first 2 wks
- Then at least every 4 wks and as clinically indicated

Monitor A1C:

- Every 3 mos and as clinically indicated

Hyperglycemia Monitoring Schedule[1,2]

Additional monitoring as clinically indicated

Prediabetic/Diabetic Patients*[1]

Closely monitor glucose, may require intensified antihyperglycemic treatment

Counsel patients on lifestyle changes related to exercise and dietary intake, as appropriate

*SOLAR-1 excluded patients with type 1 diabetes or uncontrolled type 2 diabetes. At baseline in alpelisib arm, 56% of patients were prediabetic (FPG 5.6 to < 7.0 mmol/L and A1C 5.7% to < 6.5%) and 4% were diabetic (FPG ≥ 7.0 mmol/L or A1C ≥ 6.5%).[2,3]

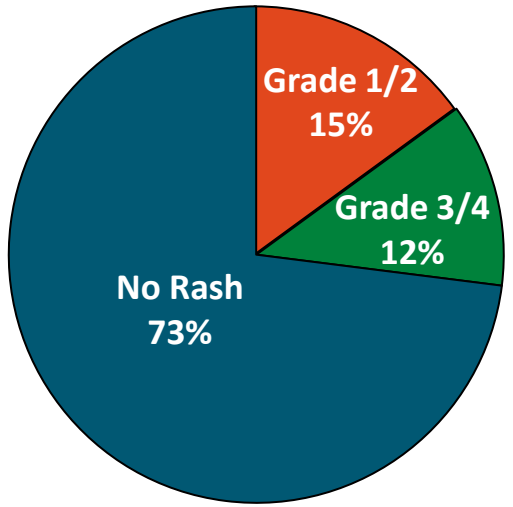
1. Alpelisib PI. 2. Rugo. Ann Oncol. 2020;[Epub]. 3. André. NEJM. 2019;380:1929.

Slide credit: clinicaloptions.com

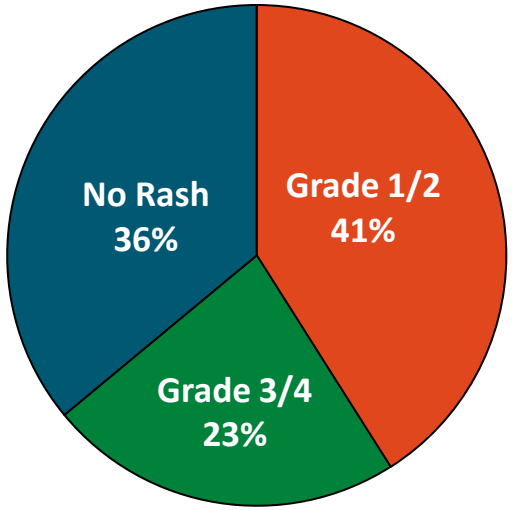
Understanding and Modifying Toxicity Associated With Alpelisib

- For patients who received alpelisib + FULV, antihistamine prophylaxis markedly reduced rash
  - Of patients who received anti-rash prophylaxis
    - 69.8% received antihistamines
    - Rash occurred in 26.7% with prophylaxis and 64.1% without
    - Grade 3/4 reduced by 50%

Alpelisib + FULV
Prophylactic Anti-rash Medication
(n = 86)



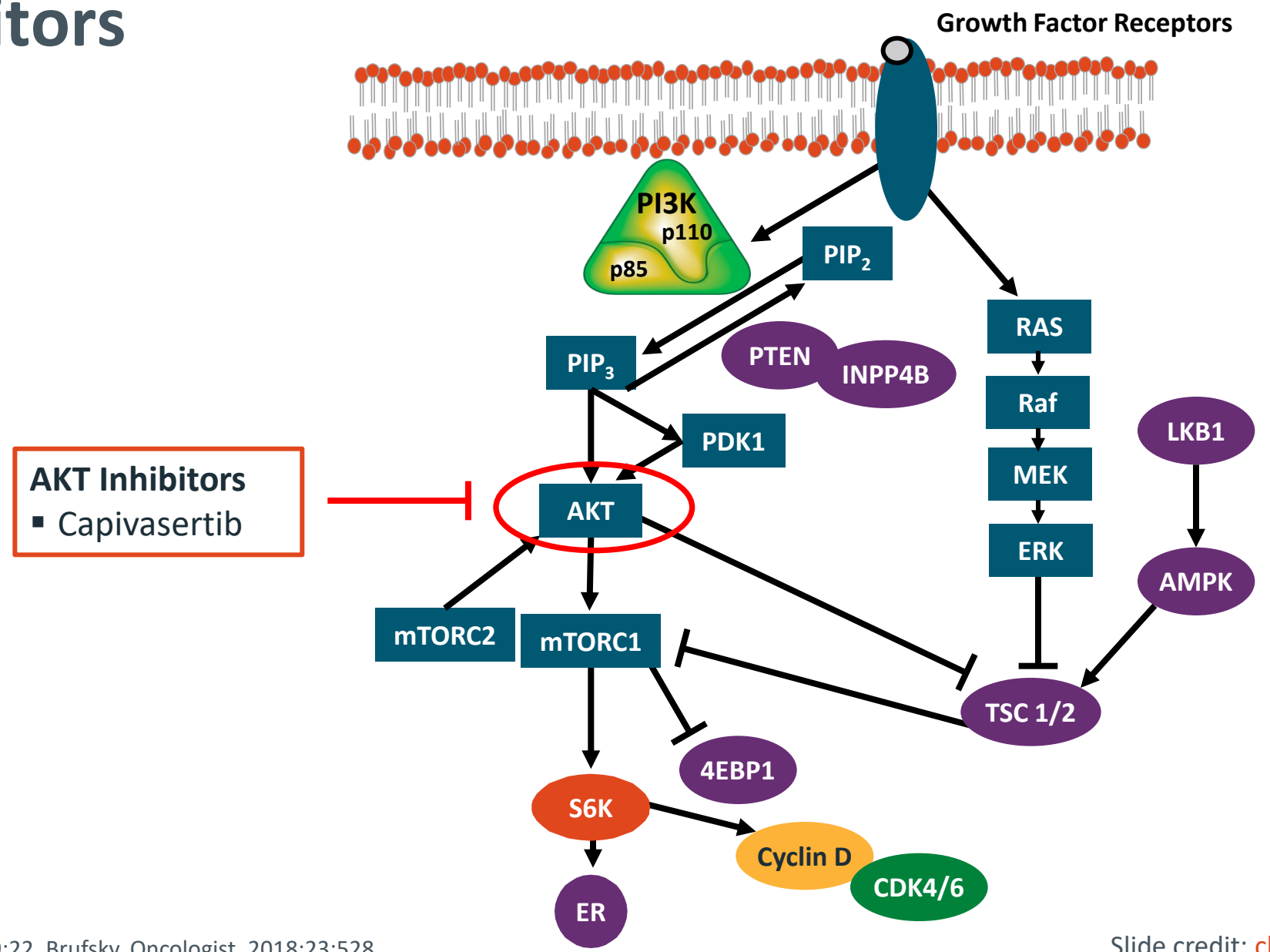
Alpelisib + FULV
No Prophylactic Anti-rash Medication
(n = 198)



Rugo. ESMO 2019. Abstr 324P.

Slide credit: clinicaloptions.com

AKT Inhibitors

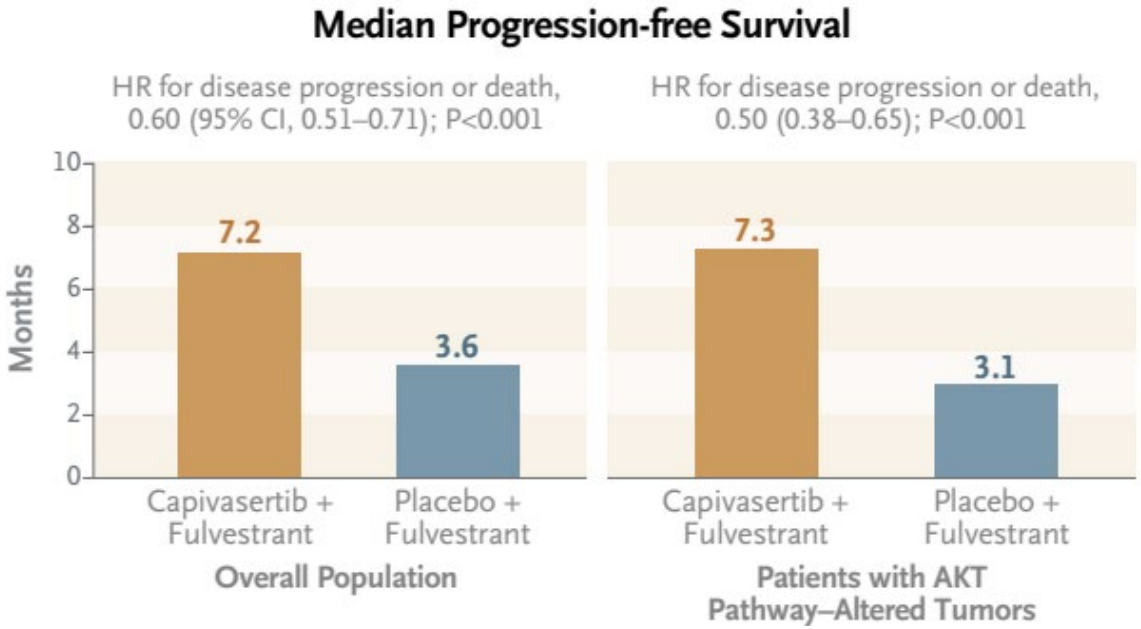


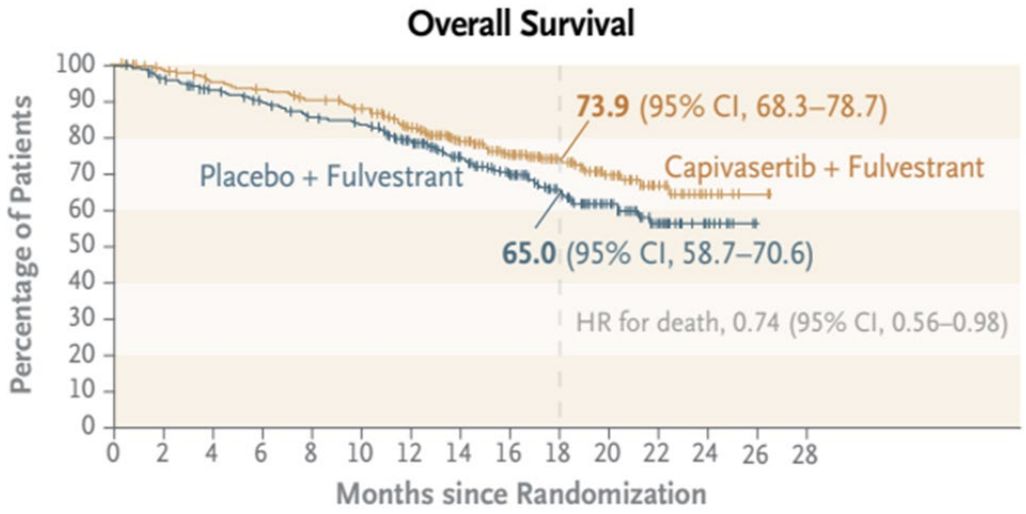
Brufsky. Cancer Treat Rev. 2017;59:22. Brufsky. Oncologist. 2018;23:528.

Slide credit: clinicaloptions.com

Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer

- HR(+), HER2(-), disease progression after first-line treatment with endocrine therapy, with or without CDK4/6 inhibitors.
- Intervention: 708 women or men
  - oral capivasertib (400 mg bid for 4 days, followed by 3 days off) plus IM fulvestrant (500 mg q 14 days for the first three injections and every 28 days thereafter) VS matching placebo plus fulvestrant.
- PFS, AKT pathway–altered tumors, overall survival.

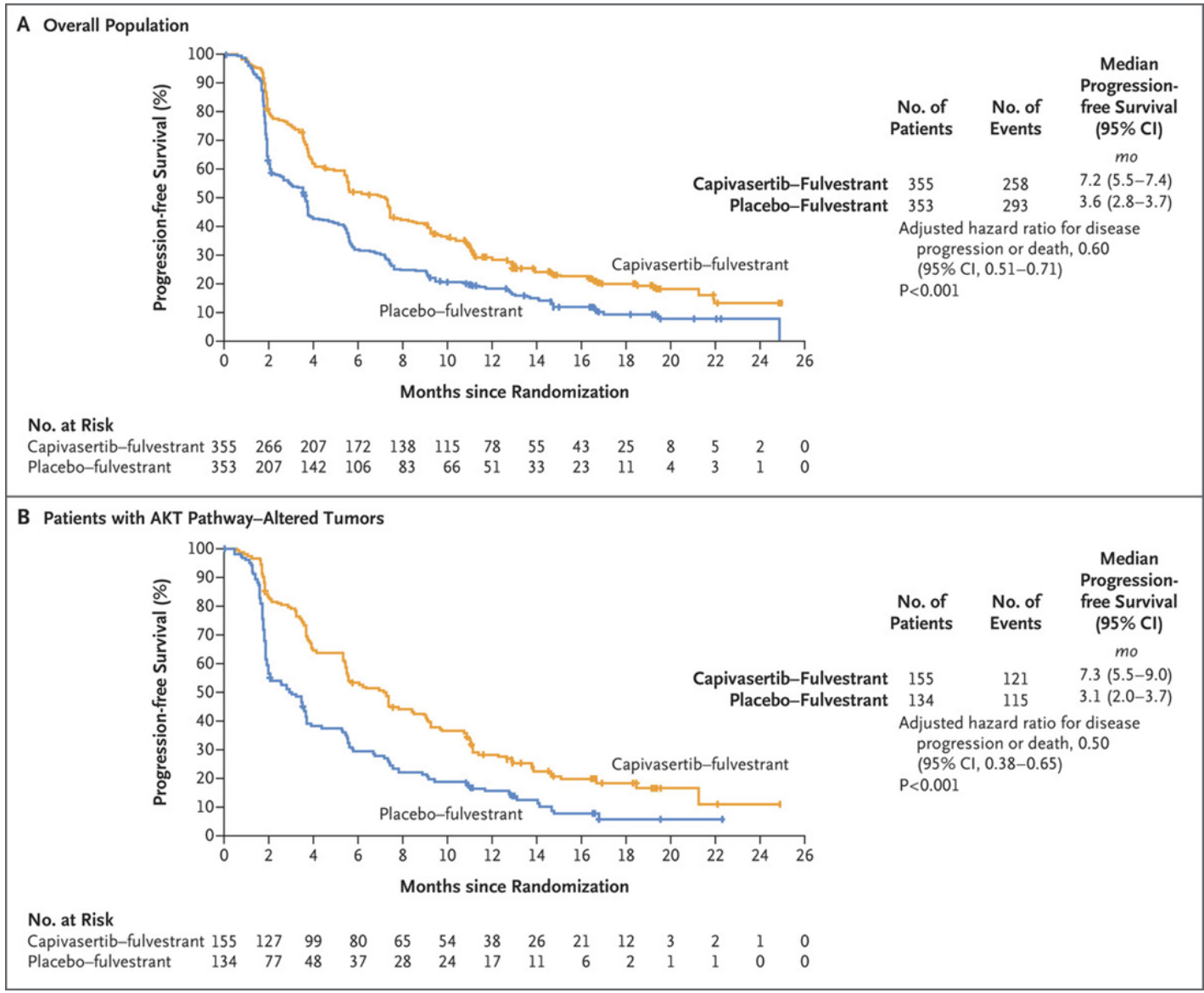




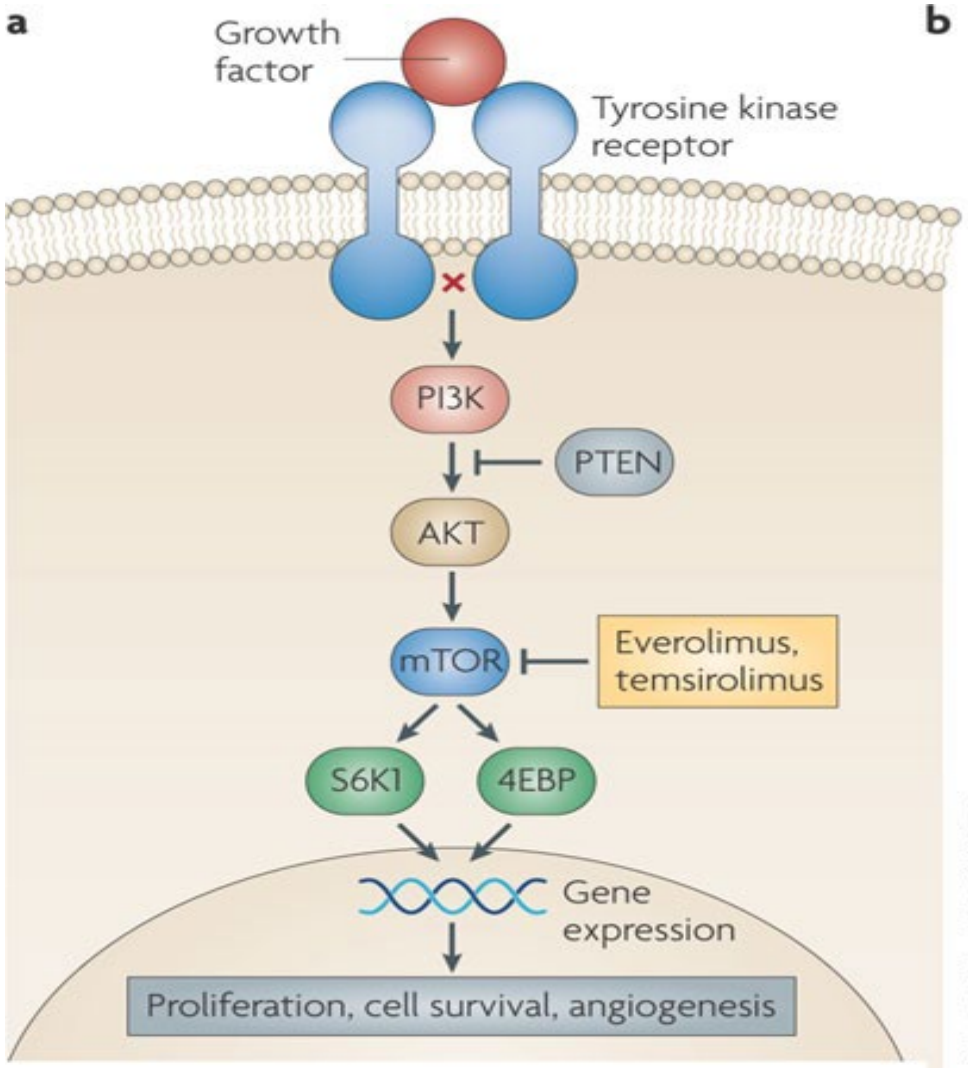
N Engl J Med 2023; 388:2058-2070

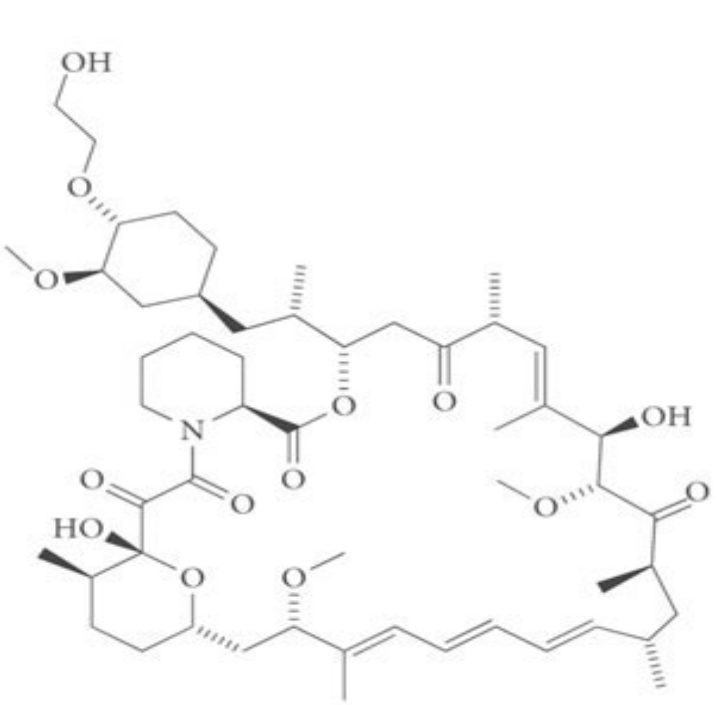
Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer

- Efficacy: PFS was significantly longer with capivasertib plus fulvestrant than with placebo plus fulvestrant, both in the overall population and among patients with AKT pathway–altered tumors.
- Safety: capivasertib, diarrhea hyperglycemia, and rash were the most common adverse events, occurring in 72.4% and 38.0% of patients, respectively



mTOR： is a serine/threonine-specific protein kinase that belongs to the family of phosphatidylinositol-3 kinase (PI3K) related kinases (PIKKs).





Everolimus

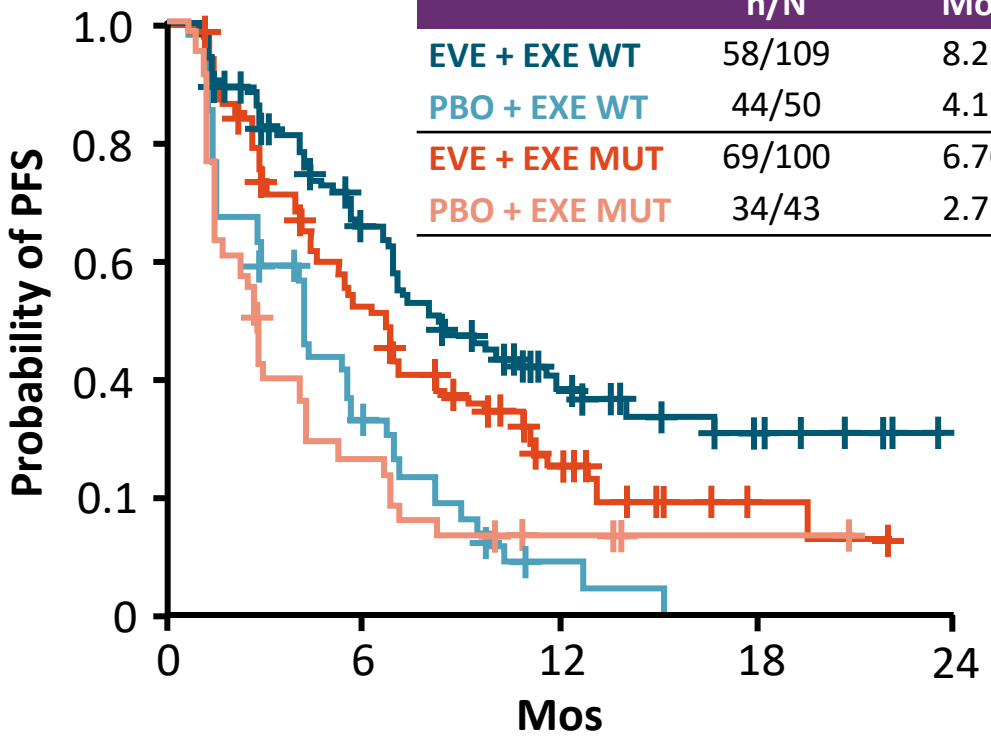
(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*, 32*S*,35*R*)-1,18- dihydroxy-12-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3methoxycyclohexyl]-1 -methylethyl}-19,30-dimethoxy-15,17,21,23,29, 35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$] hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone; $C_{53}H_{83}NO_{14}$; M_r = 958.2

Nature Reviews | Drug Discovery

BOLERO-2: PFS by *PIK3CA* Mutational Status

PFS by *PIK3CA* Mutation Status in Tumor Tissue[1]

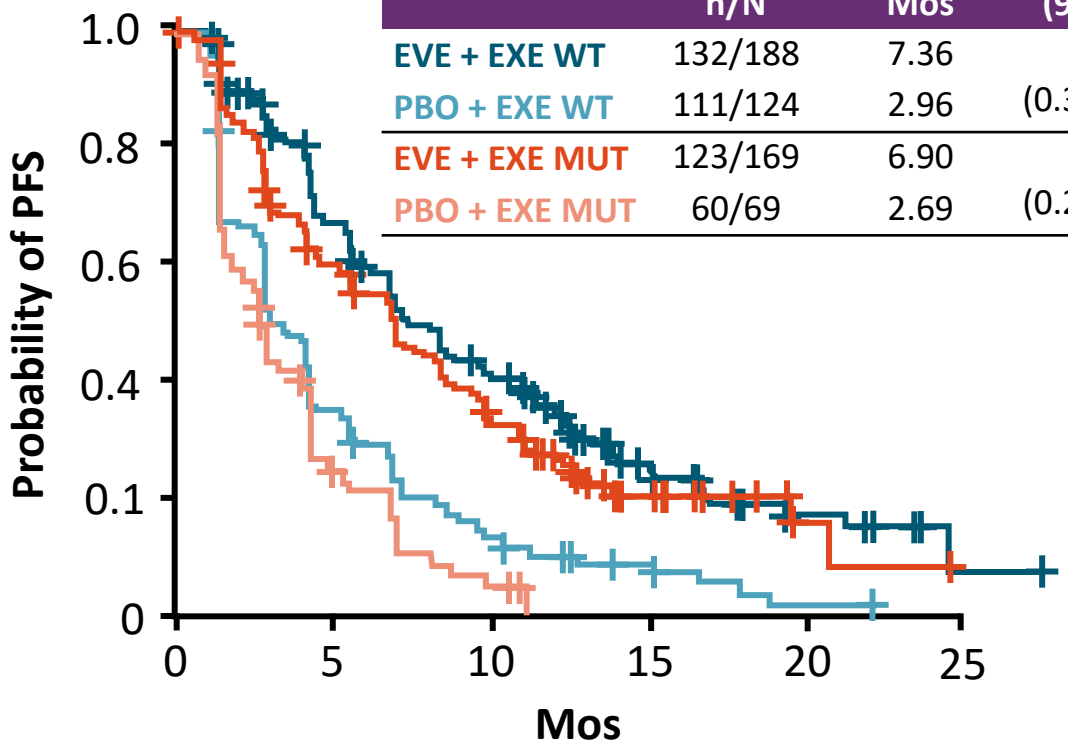
	Events, n/N	Median PFS, Mos	HR (95% CI)
EVE + EXE WT	58/109	8.25	0.37 (0.25-0.55)
PBO + EXE WT	44/50	4.17	
EVE + EXE MUT	69/100	6.70	0.51 (0.34-0.77)
PBO + EXE MUT	34/43	2.76	



- Tumor samples (all archival) from 302 (42%) patients had NGS data available for evaluation

PFS by *PIK3CA* Mutation Status in cfDNA[2]

	Events, n/N	Median PFS, Mos	HR (95% CI)
EVE + EXE WT	132/188	7.36	0.43 (0.34-0.56)
PBO + EXE WT	111/124	2.96	
EVE + EXE MUT	123/169	6.90	0.37 (0.27-0.51)
PBO + EXE MUT	60/69	2.69	



- 550 patients (76%) underwent *PIK3CA* cfDNA analysis

No prior CDK4/6i exposure

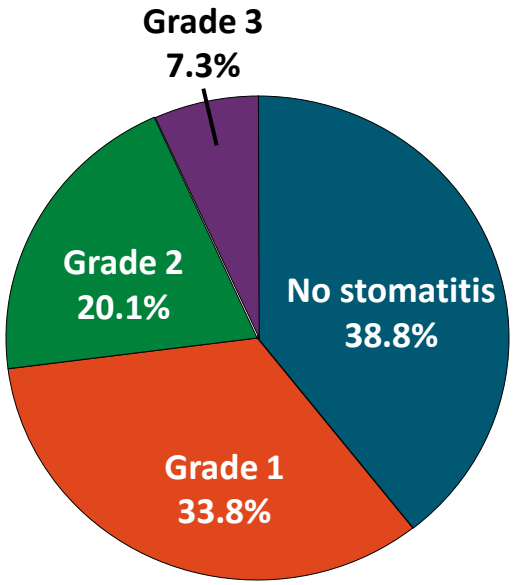
1. Hortobagyi. J Clin Oncol. 2016;34:419. 2. Moynahan. Br J Cancer. 2017;116:726.

Slide credit: clinicaloptions.com

Understanding and Modifying Toxicity Associated With Everolimus

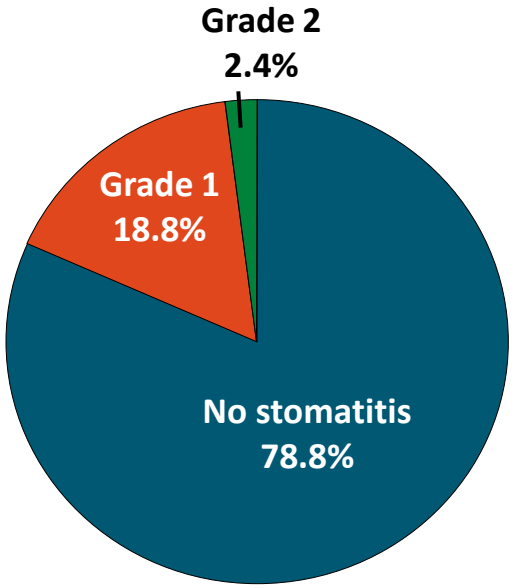
- Understanding timelines and mechanism (to some degree) helps develop effective prophylactic and management strategies for toxicity
- Phase II SWISH trial: steroid mouthwash‡ essentially eliminated stomatitis in postmenopausal patients with HR+/HER2- MBC receiving everolimus + exemestane
  - Grade ≥ 2 stomatitis was 2.4% (n = 2) by 8 wks in SWISH vs 27.4% by 8 wks in BOLERO-2 (primary endpoint) and 33% over total study duration

BOLERO-2:
Wk 8 Stomatitis* (N = 482)



*No grade 4 stomatitis.

SWISH:
Wk 8 Stomatitis† (N = 85)



†No grade 3/4 stomatitis.

‡Dosing: 10 mL alcohol-free dexamethasone 0.5 mg per 5 mL oral solution. Swish for 2 min then spit. Repeat 4x per day for 8 wks.

Rugo. Lancet Oncol. 2017;18:654.

Slide credit: clinicaloptions.com

The PI3K-AKT-mTOR Inhibition: Summary

- α-specific inhibitor, alpelisib, suggests significant improvements in ORR and PFS and now FDA approved for *PIK3CA*m ER+ breast cancer
- Activity of AKT inhibitors with endocrine therapy appears promising from phase 3 data, PFS was significantly longer with capivasertib plus fulvestrant than with fulvestrant alone.
- The addition of everolimus to fulvestrant or exemestane results in a significant improvement in PFS and can be a standard option in patients who progress on CDK4/6 inhibition
- The saga of PI3K inhibitors in haematological malignancies: survival is the ultimate safety endpoint.

Ras-Raf-Mek-ERK Pathway

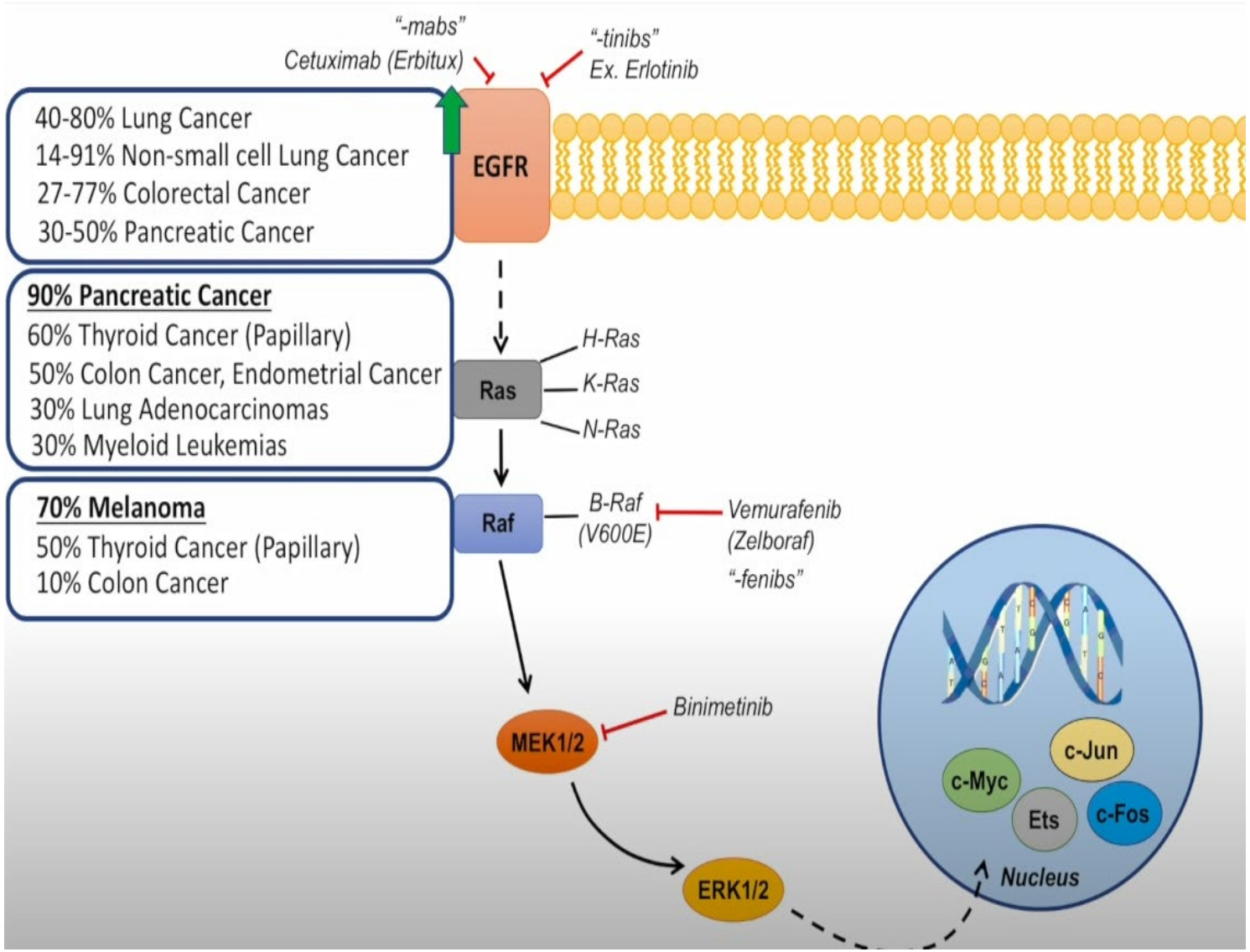
As a critical target in cancer research, particularly because mutations in components of this pathway, especially Ras and Raf (such as BRAF mutations), are commonly found in a variety of cancers.

Development of targeted therapies, such as BRAF and MEK inhibitors, which are now used in the treatment of cancers like melanoma, colorectal cancer, and non-small cell lung cancer (NSCLC).

History of The Ras-Raf-MEK-ERK pathway (MAPK pathway)

- Cell signaling pathway (cell division, differentiation, and survival)
- Mutations in this pathway, particularly in the BRAF gene, are implicated in various cancers
- Discovery of Ras proteins (Late 1970s and 1980s): The oncogenes of several retroviruses were identified as homologs of human genes.
  - The Harvey (H-Ras) and Kirsten (K-Ras) rat sarcoma viral oncogenes were discovered.
  - These genes were later found to encode small GTPases, which are central components of the Ras signaling pathway.
- Raf was identified as a cellular protein that associates with Ras (1980). Subsequent work showed that Ras can activate Raf, a kinase that phosphorylates and activates MEK.
- Discovery of MEK and ERK (1990s)
  - MEK as an upstream activator of ERK (extracellular signal-regulated kinase)
  - Three-tiered kinase cascade: Ras activates Raf, which activates MEK, which in turn activates ERK.
- 1990s and 2000s: the regulation of cell proliferation, differentiation, survival, and angiogenesis – all critical processes in cancer development and progression. Followed by Drug Development (Late 1990s onwards)

The RAS-RAF-MEK-ERK (Mitogen-activated protein kinase pathway)



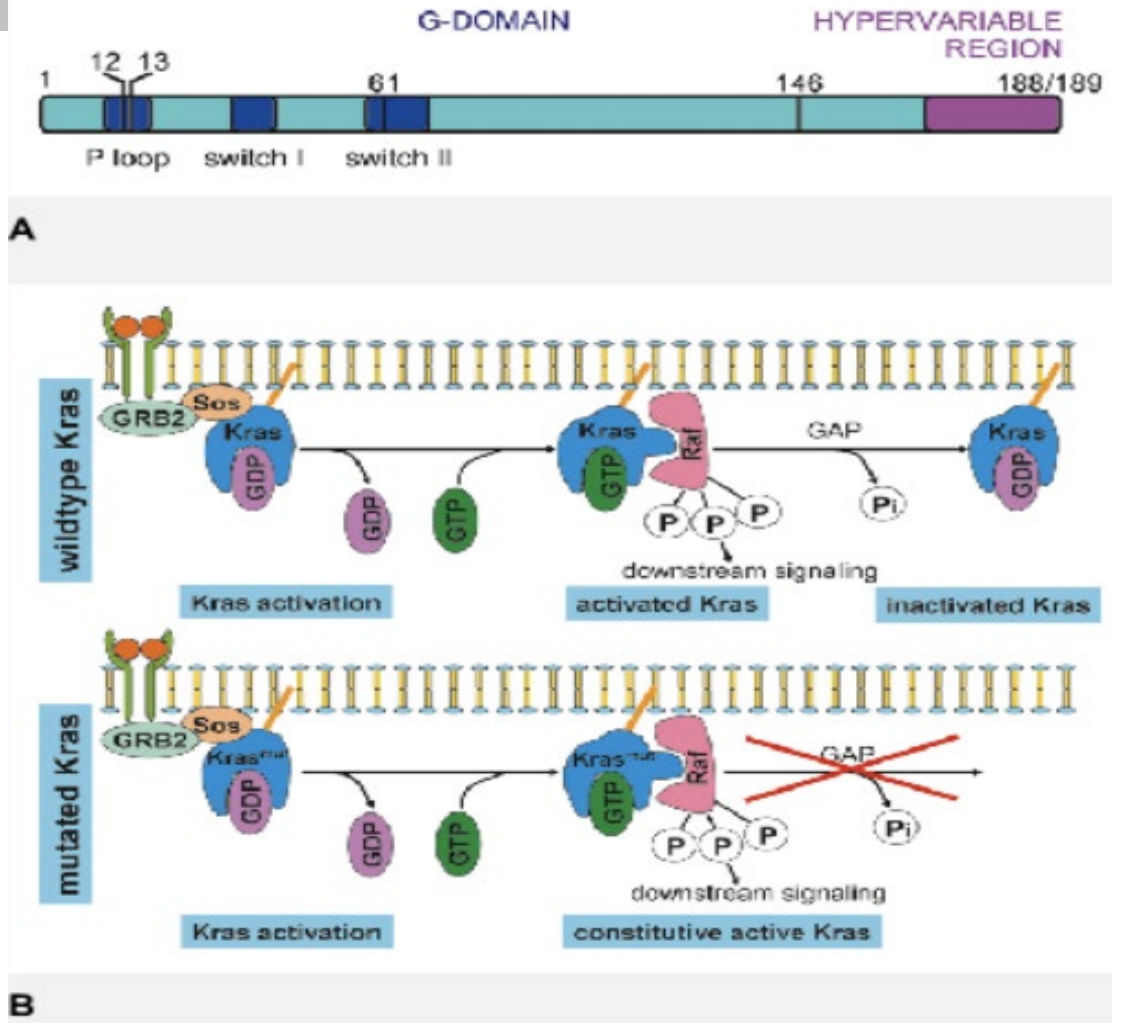
H-Ras : 膀胱癌
K-Ras : 大腸、胰臟癌。
N-Ras : 血液腫瘤

Oncogene 26, 3291–3310 (2007).

- **RAS (Rat Sarcoma)**
  - **Function**: RAS proteins are small GTPases that act as molecular switches.
  - Type of mutation : **KRAS, NRAS, and HRAS Mutations**: common in various cancers, including pancreatic, colorectal, and lung cancers.
  - **RAS Inhibitors**: KRAS G12C inhibitors sotorasib and adagrasib
- **RAF (Rapidly Accelerated Fibrosarcoma)**
  - **Function**: RAF kinases (ARAF, BRAF, CRAF) are serine/threonine-specific protein kinases.
  - Type of mutation : **BRAF Mutations**: Particularly the V600E mutation, in melanomas, thyroid and colorectal cancer.
  - **RAF Inhibitors**: Vemurafenib, dabrafenib, and encorafenib are BRAF inhibitors used in cancers with BRAF V600E mutations.
- **MEK (Mitogen-Activated Protein Kinase)**
  - **Function**: MEK1 and MEK2 are dual-specificity kinases that phosphorylate ERK on both threonine and tyrosine residues.
  - MEK **Inhibitors**: Trametinib, Cobimetinib, and Binimetinib are used in combination BRAF inhibitors to target the pathway more effectively.
- **ERK (Extracellular Signal-Regulated Kinase)**
  - **Function**: ERK1 and ERK2 (serine/threonine kinases) that regulate various cellular processes. ERK translocates to the nucleus to activate transcription factors that promote gene expression.
  - Type of mutation : various cancers, making it a target for therapy.
  - Inhibitors : under development

Protein Mutations in the Ras-Raf Pathway

- **EGFR**
  - *Overexpression* of EGFR
  - Increased activation of Ras-Raf-MEK-ERK pathway
- **Ras**
  - *Mutated Ras unable to hydrolyze GTP ("On") back to GDP ("Off")*
    - *Permanently Active*
  - 3 Ras Proteins (H, K, N)
    - *Mutations in Codons 12, 13, 59, 61*
  - *H-Ras* → *Bladder Tumors*
  - *K-Ras* → *Colon & Pancreas Tumors*
  - *N-Ras* → *Hematopoeitic Tumors*
- **Raf**
  - 3 Raf Proteins (A, B, C)
  - *B-Raf* (V600E)
    - Constitutively Active



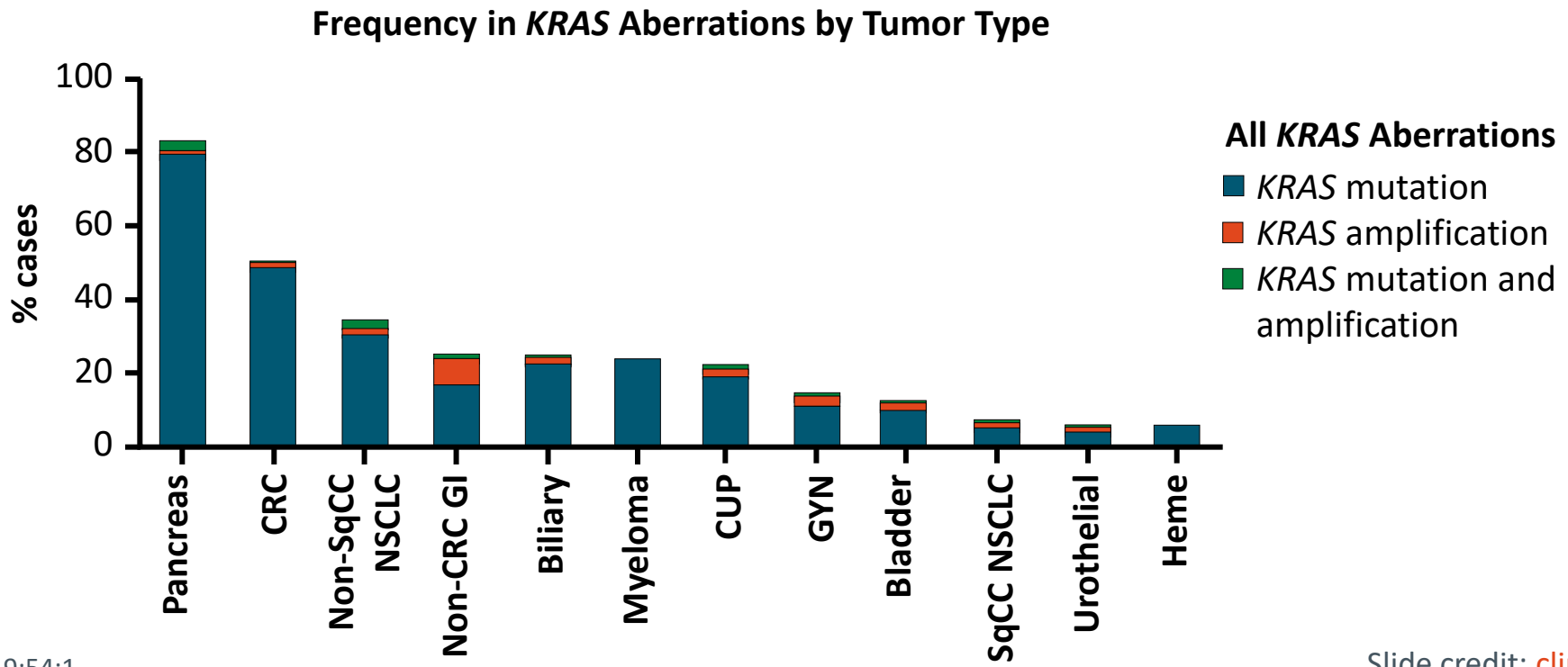
GTPases通過在活性（GTP結合）和非活性（GDP結合）狀態之間進行循環，充當細胞功能調控的計時器或開關。

KRAS in medical history development

- RAS gene family : KRAS, NRAS, and HRAS encode a group of related proteins
  - play a critical role in signal transduction, control cell growth, differentiation, and survival.
- KRAS is located on chromosome 12 in humans.
  - RAF/MEK/ERK and PI3K/AKT/mTOR.
  - Mutations : pancreatic, colorectal, and lung cancers.
- NRAS: is located on chromosome 1 in humans.
  - Like KRAS
  - Mutations: NRAS are common in certain types of leukemia, melanoma, and thyroid cancer.
- HRAS: is located on chromosome 11 in humans.
  - same as KRAS and NRAS.
  - Mutations: HRAS mutations rare. In bladder cancer, head and neck tumors, and some types of skin cancers.

KRAS Mutations in Cancer

- Approximately 30% of all cancers are associated with a *RAS* mutation, suggesting that a mutation in *RAS* oncogenes may be a leading cause of carcinogenesis
  - Of the *RAS* oncogenes, mutation in *KRAS* is the most frequent, followed by *NRAS* and *HRAS*

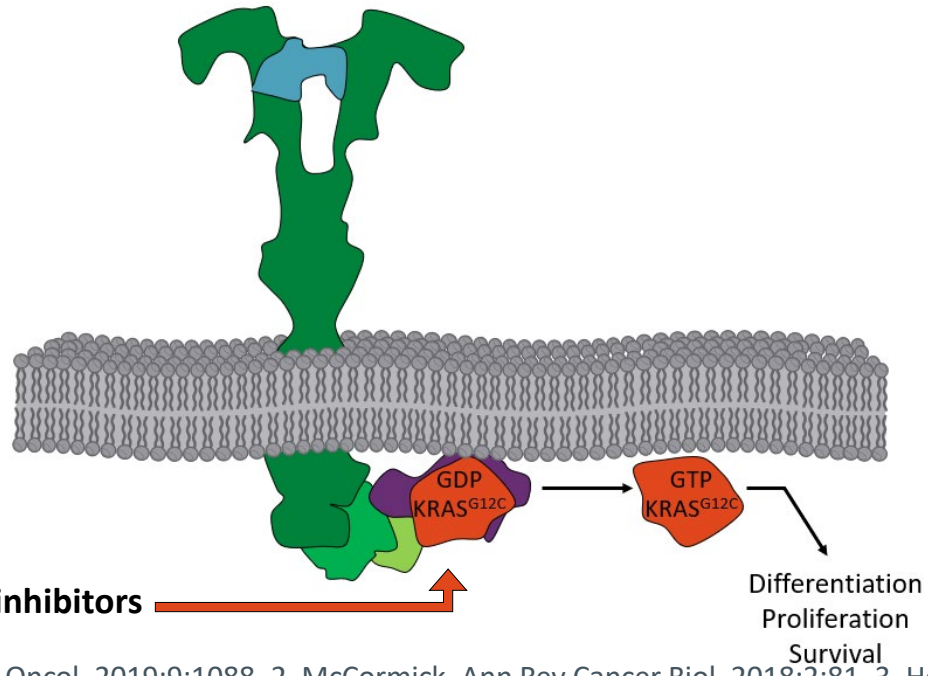


Khan. Semin Cancer Biol. 2019;54:1.

Slide credit: clinicaloptions.com

KRAS p.G12C Mutation: Background

- GTP-bound KRAS^{G12C} enhances downstream signaling and drives tumor growth[1,2]
- *KRAS* p.G12C mutation in 13% of NSCLC, and 1% to 3% of CRC and other solid tumors[3]
- To date, sotorasib (AMG 510) and MRTX849 are the only small molecule inhibitors with known clinical efficacy inhibiting this pathway[3,4]



1. Muñoz-Maldonado. Front Oncol. 2019;9:1088. 2. McCormick. Ann Rev Cancer Biol. 2018;2:81. 3. Hong. NEJM. 2020;383:1207. 4.Jänne. AACR-NCI-EORTC 2019. Abstr CS5.

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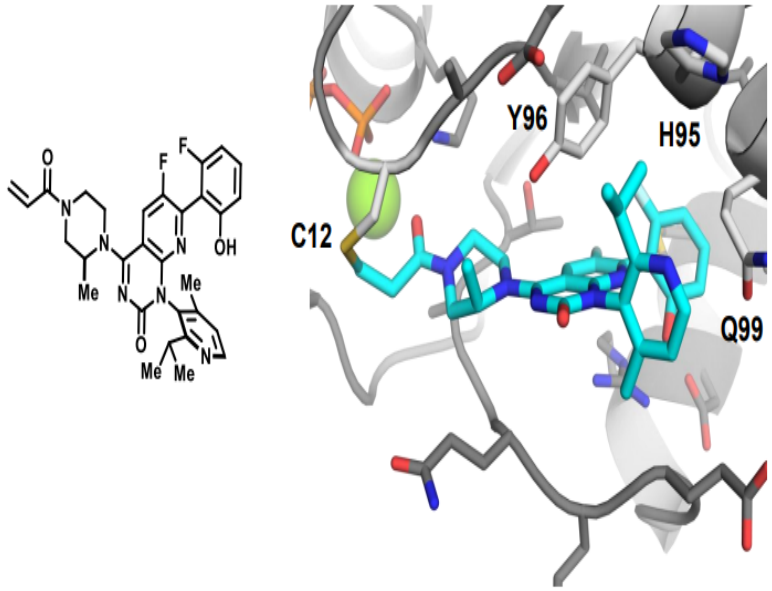
One Step at a Time — Clinical Evidence That KRAS Is Indeed Druggable

- Survival among patients with advanced-stage *KRAS*G12C non–small-cell lung cancer (NSCLC) or colorectal cancer is approximately 1 to 2 years nearly four decades
- RAS has picomolar affinity for guanosine triphosphate (GTP) and intracellular GTP concentrations are exceedingly high, early strategies to find compounds that preferentially bind to the RAS–GTP pocket failed.
- Other strategies have attempted to interfere with RAS activation by preventing its membrane localization or by inhibiting downstream kinase signaling, but these also failed because of resistance stemming from compensatory signaling.
- Shokat and colleagues designed covalent small-molecule inhibitors that irreversibly targeted the cysteine residue at codon 12 of KRAS, locking the protein into an inactive state. This major advance opened the door for a precision-medicine approach to targeting *KRAS*G12C-mutant tumors.
- Sotorasib (AMG510)
- Adagrasib (MRTX849) : a long half-life (23 hours), dose-dependent pharmacokinetics, and central nervous system (CNS) penetration.

Supplementary Figures

Figure S1. Co-crystal Structure of GDP-KRAS^{G12C} Bound by Sotorasib

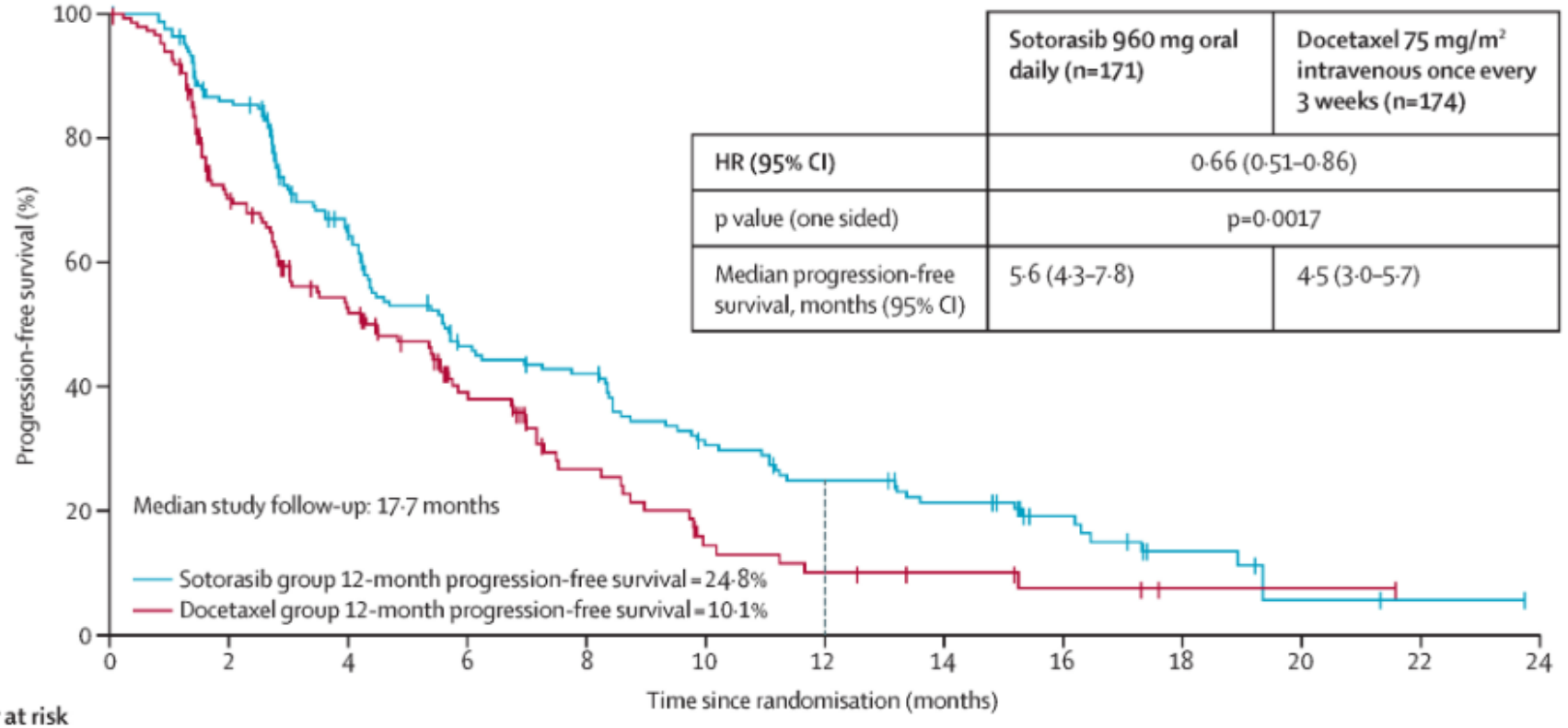
Co-crystal structure of sotorasib bound to GDP-KRAS^{G12C}, confirming covalent bond formation between the acrylamide warhead and C12 and illustrating non-covalent contacts between the isopropylpyridine substituent and the H95/Y96/Q99 cryptic pocket. H95 denotes amino acid of histidine at position 95 of KRAS^{G12C}. Y96 denotes amino acid of tyrosine at position 96 of KRAS^{G12C}. Q99 denotes amino acid of glutamine at position 99 of KRAS^{G12C}. C12 denotes mutated cysteine at position 12.



NEJM 2020; 383:1277-1278

Drug	Trial Name	Indication	Comparative Protocol	ORR	PFS (months)	OS	Adverse Events	Source Journal
Sotorasib (CodeBreaK 100)	Pts : 127	KRAS G12C-mutated advanced NSCLC	Single-arm	41%	Mdr: 12.3 PFS : 6.3	12.5 months 2-year OS : 33%.	Diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, cough	J Clin Oncol. 2023 Jun 20; 41(18): 3311–3317
Sotorasib (CodeBreaK 200)	Pts : 616 KRAS G12C-mutated NSCLC (2nd line)	mutated advanced NSCLC, after previous platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor.	Sotorasib 960mg qd Vs Docetaxel (75 mg/m2 q 3 weeks)	28·1% VS 37·1%)	5.6 vs 4.5 months	10.6 vs 11.3 months (P: 0.53)	Gastrointestinal AEs : diarrhea, hepatic toxicity, musculoskeletal pain, metabolic changes, pneumonia, rash	Lancet . 2023 Mar 4; 401 (10378):733-746
Adagrasib	KRYSTAL-1 Pts : 116	KRAS G12C-mutated NSCLC	600mg q12 (Single-arm)	48%	6.5 months	12.6 months	Nausea, diarrhea, fatigue, vomiting, hepatotoxicity, rash, abdominal pain	**NEJM 2022;387:120-131**
Adagrasib	KRYSTAL-1 (Pts: 76)	KRAS G12C-mutated heavily pretreated patients with metastatic colorectal cancer	Cetuximab +Agagrasib vs Agagrasib	46% vs 19%	6.9 vs 5.6 months	13.4 vs 19.8 months	Rash, nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, headache, dry skin, abdominal pain, decreased appetite, edema	NEJM 2023;388:44-54

A



	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
HR (95% CI)	0·66 (0·51–0·86)	
p value (one sided)	p=0·0017	
Median progression-free survival, months (95% CI)	5·6 (4·3–7·8)	4·5 (3·0–5·7)

Number at risk (number censored)													
Sotorasib group	171 (0)	139 (9)	93 (14)	63 (4)	56 (1)	38 (3)	30 (1)	24 (2)	14 (8)	6 (4)	2 (1)	1 (1)	0 (1)
Docetaxel group	174 (0)	93 (39)	62 (9)	36 (12)	20 (6)	10 (1)	7 (0)	5 (2)	3 (1)	1 (2)	1 (0)	0 (1)	..

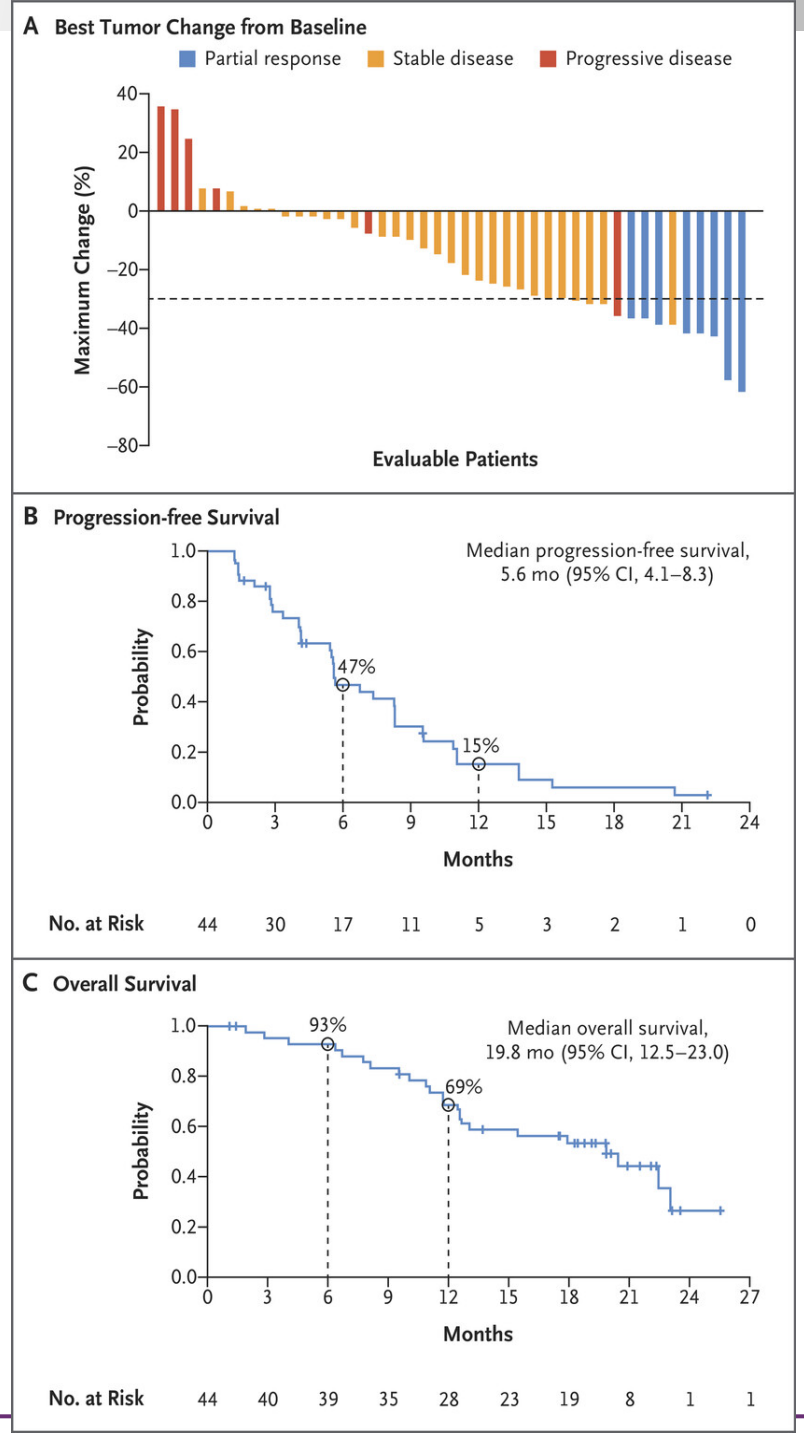
Lancet . 2023 Mar 4;401(10378):733-746

Adagrasib Monotherapy.

43 patients in the population that could be evaluated for clinical activity.

hatch marks indicate data censoring. The data-cutoff date for clinical activity was June 16, 2022; the median follow-up was 20.1 months.

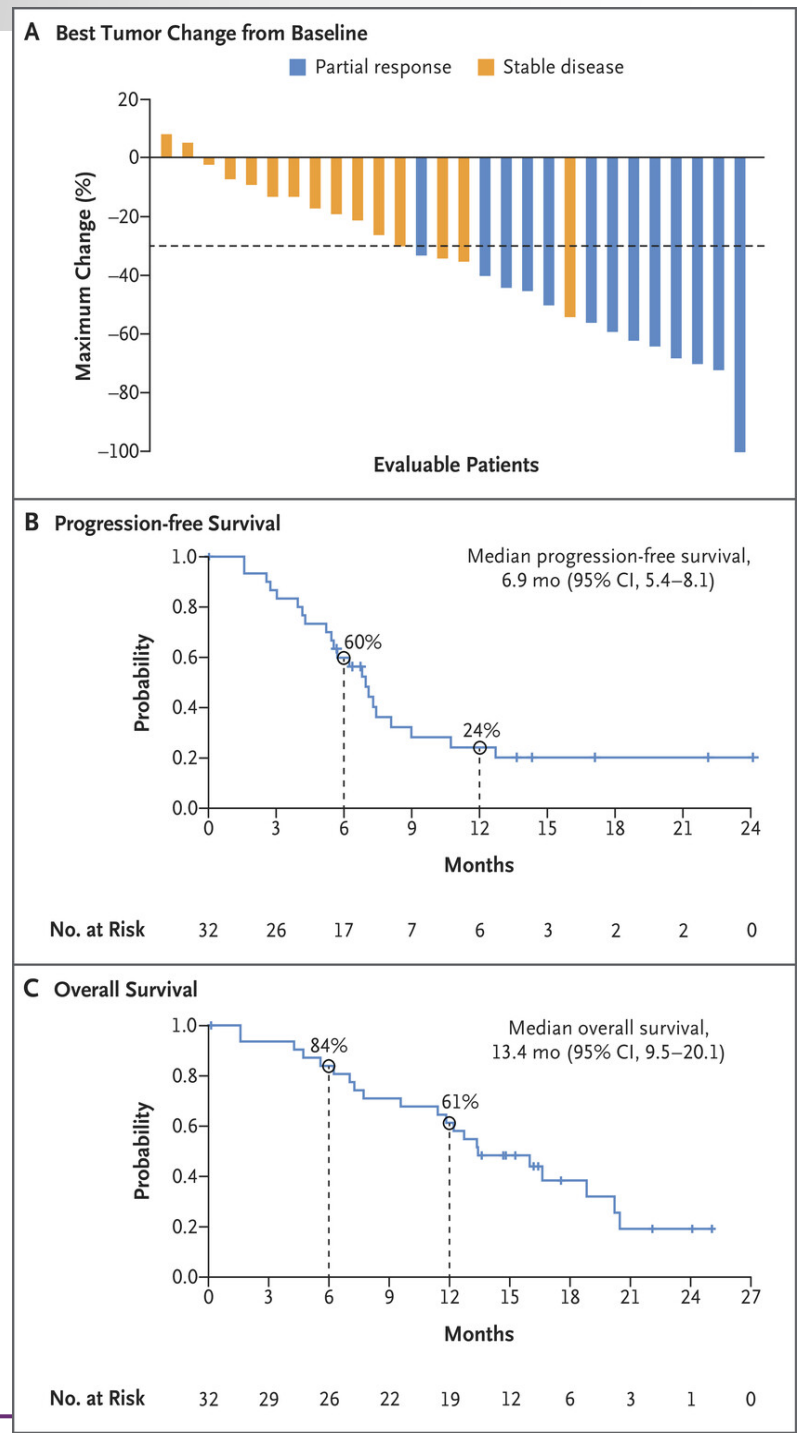
NEJM 2023;388:44-54



Adagrasib plus Cetuximab.

The best tumor change from baseline (Panel A) is shown for 28 patients in the population that could be evaluated for clinical activity.

Progression-free survival (Panel B) and overall survival (Panel C) are shown for 32 patients in the full analysis set. The median follow-up was 17.5 months.

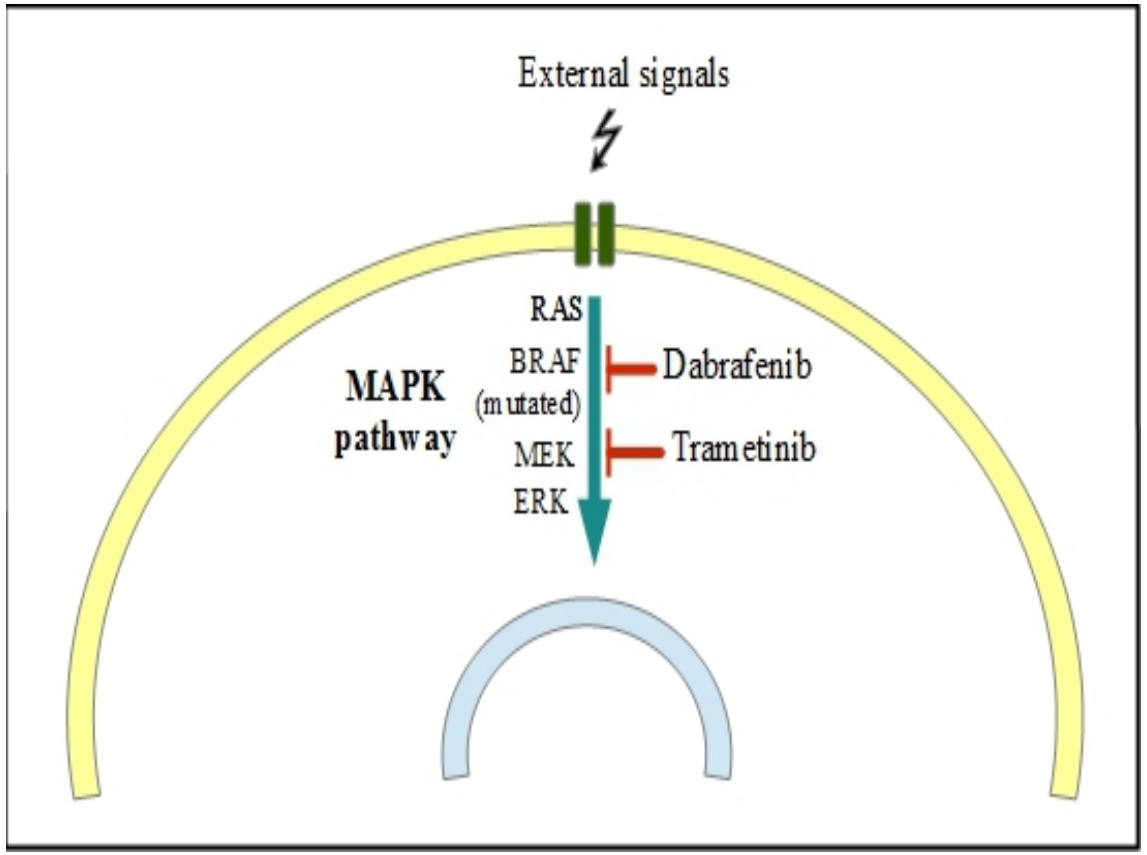


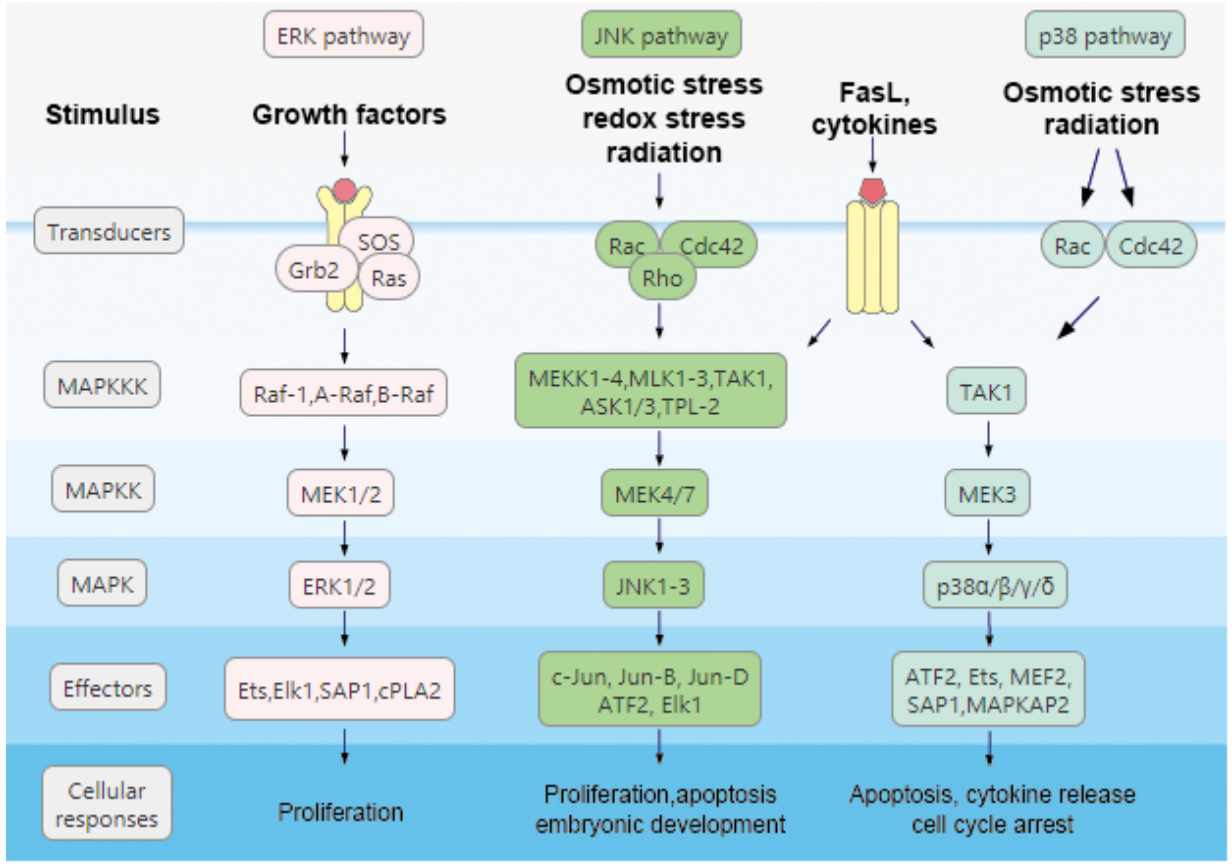
Targeted drugs

- Ras-Raf-MEK-ERK
  - Raf inhibitors : Vemurafenib, Dabrafenib, Ecorafenib
    - for BRAF-mutated melanomas.
  - MEK inhibitors : Trametinib, Binimetinib, Cobimetinib
    - clinical use in conjunction with Raf inhibitors or other therapies.
  - ERK inhibitors : under investigation in clinical trials.
- Issues with Resistance
  - Resistance mechanisms often emerged, limiting their long-term efficacy.
  - Strategies combining multiple inhibitors to overcome resistance.

MAPK pathway

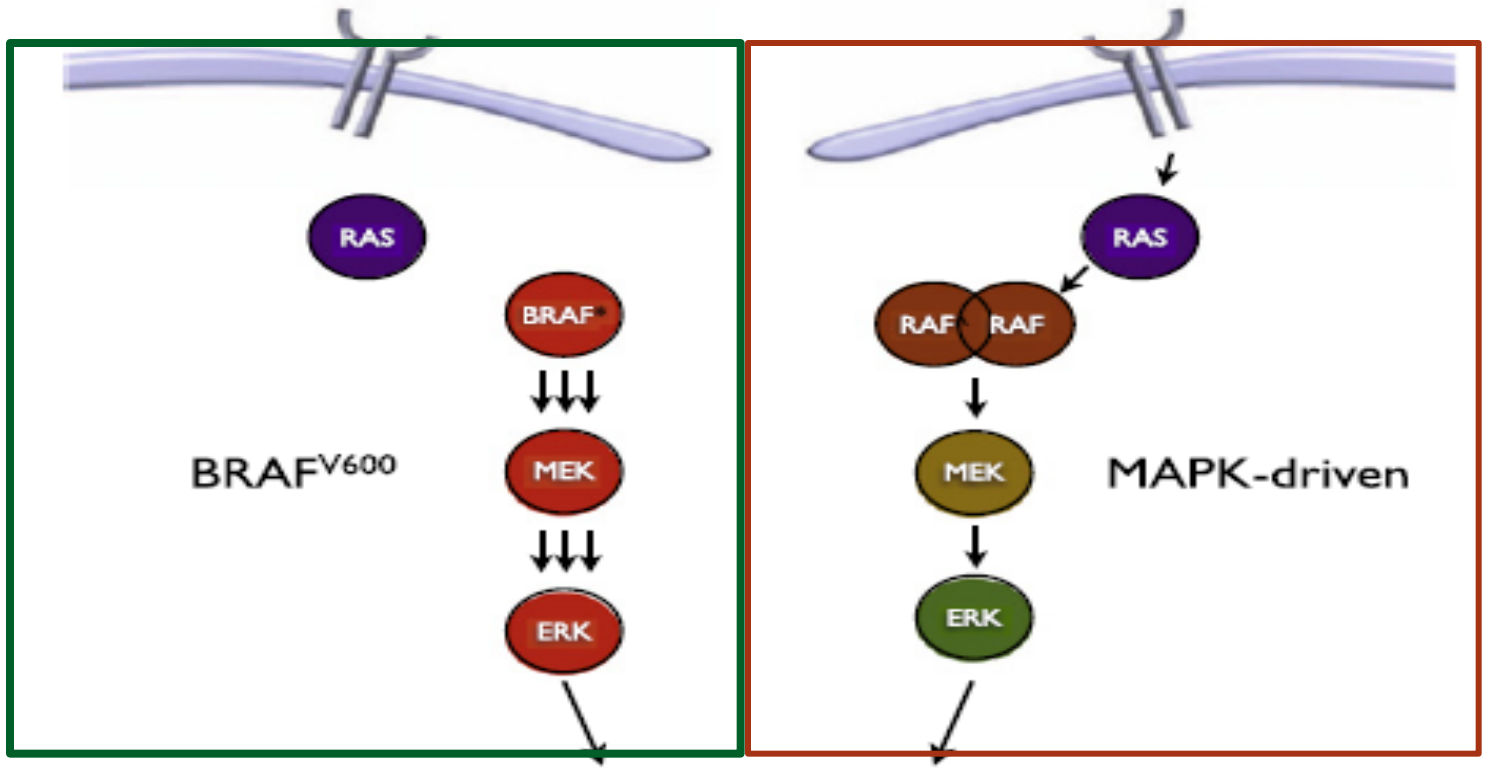
(Mitogen-activated protein kinase ,絲裂原活化蛋白激酶)





Oncogene 26, 3291–3310 (2007).

Mitogen-activated protein kinase (MAPK,絲裂原活化蛋白激酶) pathway



Growth, cell cycle upregulation, anti-apoptosis,
angiogenesis, metabolic regulation, immune suppression

Fig. 1. Differential Signalling: Oncogenic (left) versus Canonical (right)

BRAF inhibitors

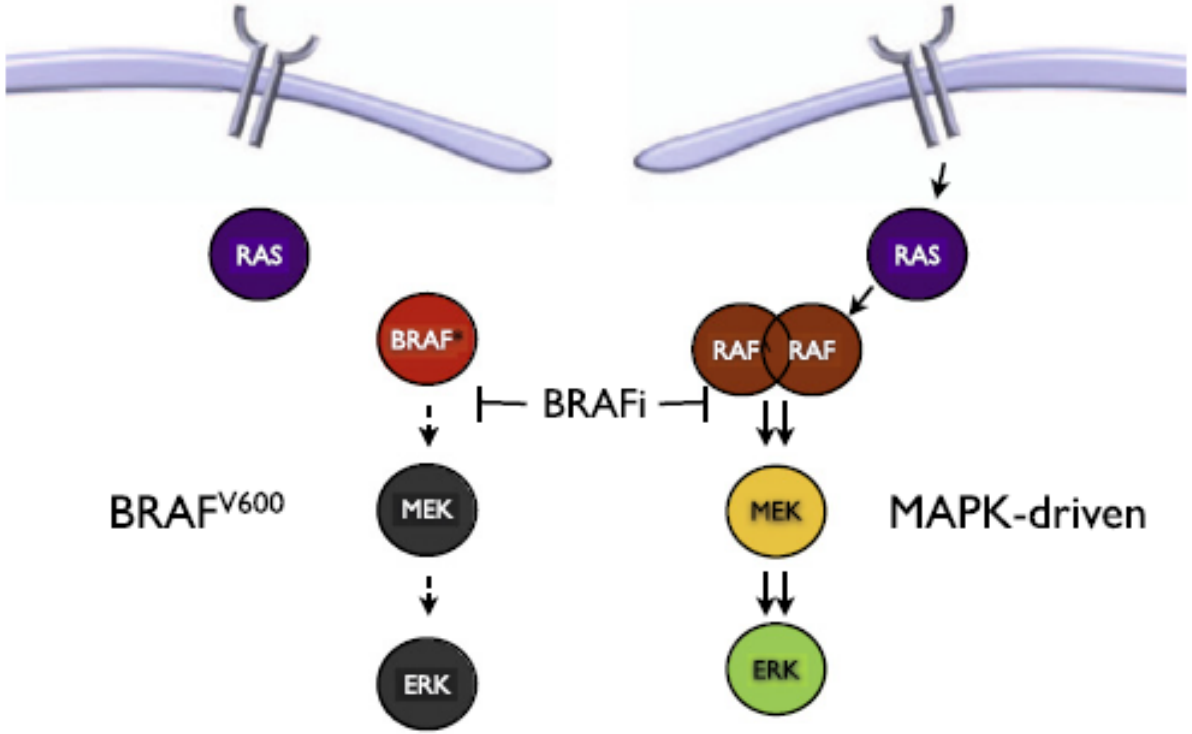


Fig. 2. The BRAF inhibitor paradox - BRAF inhibitors inhibit the MAPK pathway in BRAF mutant cells but activate the pathway in cells driven by the MAPK pathway other than through oncogenic BRAF mutation.

- Vemurafenib
- Dabrafenib
- Encorafenib

Trial Name (Pts Number)	Indication	Comparative Protocol	ORR	PFS (months)	OS (months)	Adverse Events	Source of Journal
COMBI-v (N=704)	Unresectable or metastatic melanoma with BRAF V600E or V600K mutations	Dabrafenib + Trametinib vs. Vemurafenib	64% vs. 51%	11.4 vs. 7.3 months	25.6 vs. 18.0 months	Fever, fatigue, nausea, vomiting, rash	N Engl J Med, 2015
COLUMBUS (N=577)	Unresectable or metastatic melanoma with BRAF V600E or V600K mutations	Encorafenib + Binimetinib vs. Vemurafenib	63% vs. 40%	14.9 vs. 7.3 months	33.6 vs. 16.9 months	Fatigue, nausea, diarrhea, vomiting, rash	Lancet Oncol, 2018
BEACON CRC (N=665)	Metastatic colorectal cancer with BRAF V600E mutation	Encorafenib + Cetuximab vs. Standard of Care	26% vs. 2%	4.3 vs. 1.5 months	9.3 vs. 5.9 months	Fatigue, nausea, diarrhea, abdominal pain	N Engl J Med, 2019
SPRINT (N=50)	Neurofibromatosis type 1 (NF1) with symptomatic, inoperable plexiform neurofibromas	Selumetinib vs. placebo	68% vs. 0%	Not applicable (due to durable responses and stable disease in majority)	Not reported (ongoing trial	Nausea, vomiting, diarrhea, fatigue, acneiform rash	N Engl J Med, 2020

)

MEK inhibitor (BRAF V600E, BRA V600K mutation)

- Trametinib : melanoma, Non-small cell lung cancer, thyroid)
- Bininmetinib : colorectal, melanoma
- Cobimetinib :melanoma
- Selumetinib : Neurofibromatosis type 1
  - can reduce the size of plexiform neurofibromas (叢 狀神經纖維瘤), improving quality of life for patients, especially in cases where surgery is not feasible.

MEK inhibitor :Selumetinib
Neurofibromatosis type 1

Trial Name	Study Patient Number	Indication	Comparative ORR	Comparative Overall Survival	Adverse Events	Source of Journal
SPRINT (NCT01362803)	50 pediatric patients	Inoperable plexiform neurofibromas in Neurofibromatosis Type 1 (NF1)	70% (PR)	OS not mature (long-term follow-up ongoing)	Most common: diarrhea, rash, nausea, vomiting, and fatigue. Serious: Cardiac dysfunction	Gross AM, et al. New England Journal of Medicine, 2020

Thank you for listening

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