PIK3CA/AKT/mTOR

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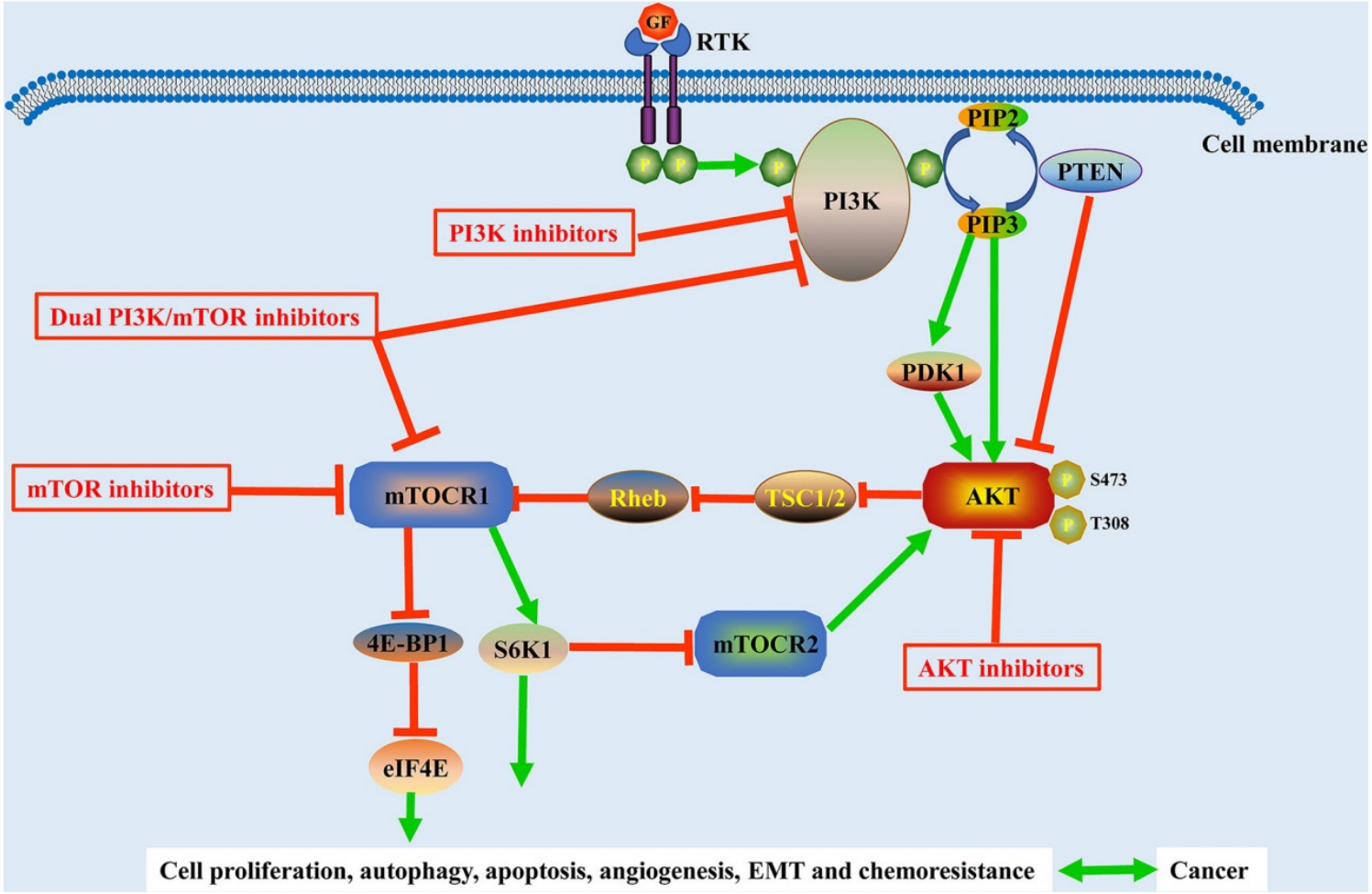
August 26, 2023

PI3K / AKT / mTOR pathway



Peng Y, Wang Y, Zhou C, Mei W and Zeng C (2022) PI3K/Akt/mTOR Pathway and Its Role in Cancer Therapeutics: Are We Making Headway? Front. Oncol. 12:819128

PI3K/AKT/mTOR Alterations in Cancer

Gene	Cancer Type	Mutation Frequency
PIK3CA	Endometrial Carcinoma	44.5%
	Cervical SCC	22.7%
	Breast Carcinoma	30.7%
	Head & Neck SCC	13.6%
	Colorectal Adenocarcinoma	24.8%
	Urothelial Carcinoma	20.4%
mTOR	Melanoma	11.9%
	Endometrial Carcinoma	10.6%
AKT	Endometrial Carcinoma	3-11%
	Ovarian Epithelial Tumor	4-9%
	Breast Carcinoma	~ 3%

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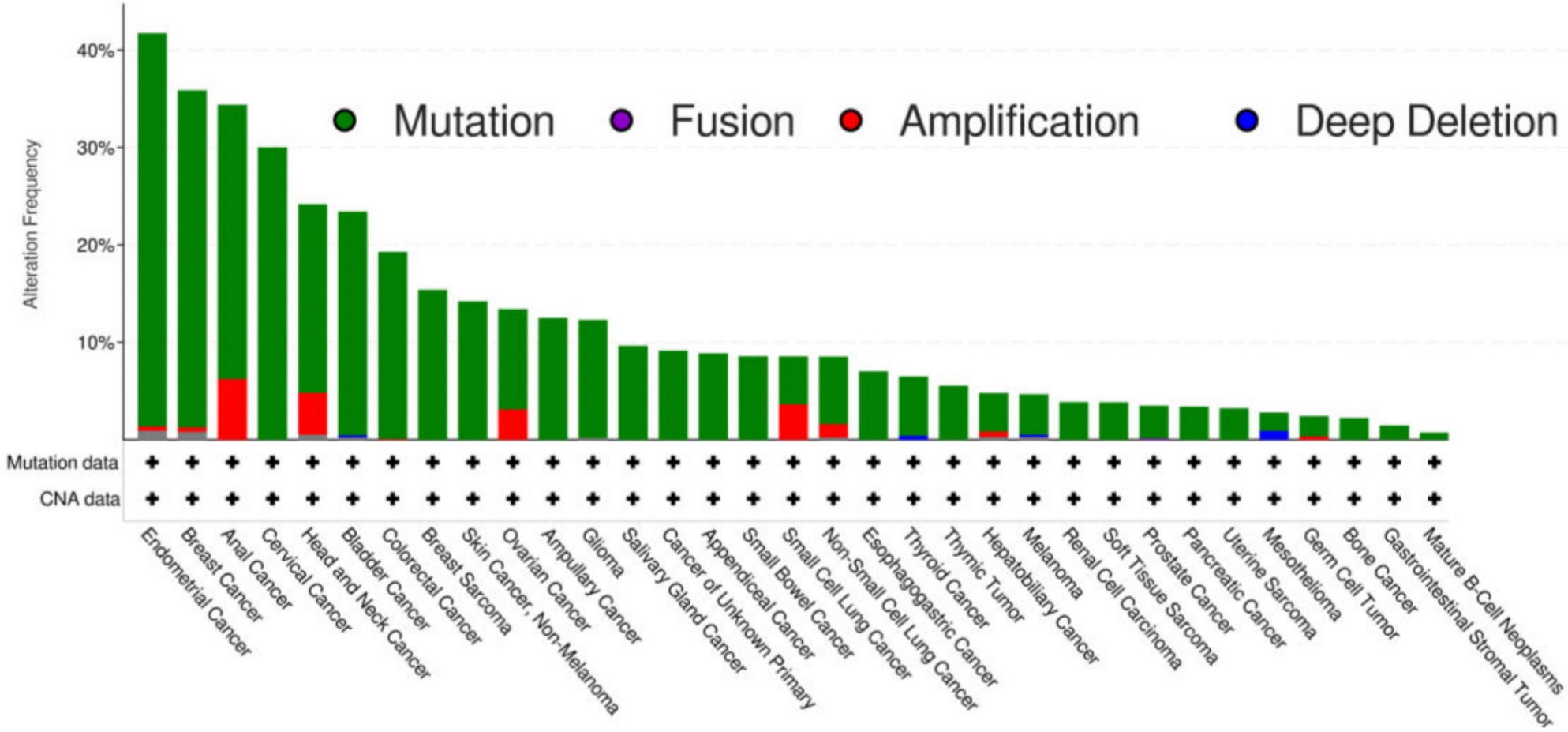
PI3K Alterations



Nat Cancer. 2021 June ; 2(6): 587–597.

PI3K Inhibitors

- PI3K – Multiple sub-units and isoforms
- Pan-PI3K inhibitors may have more off-target AEs
  - Copanlisib
- Isoform-selective PI3K inhibitors – decreased AEs

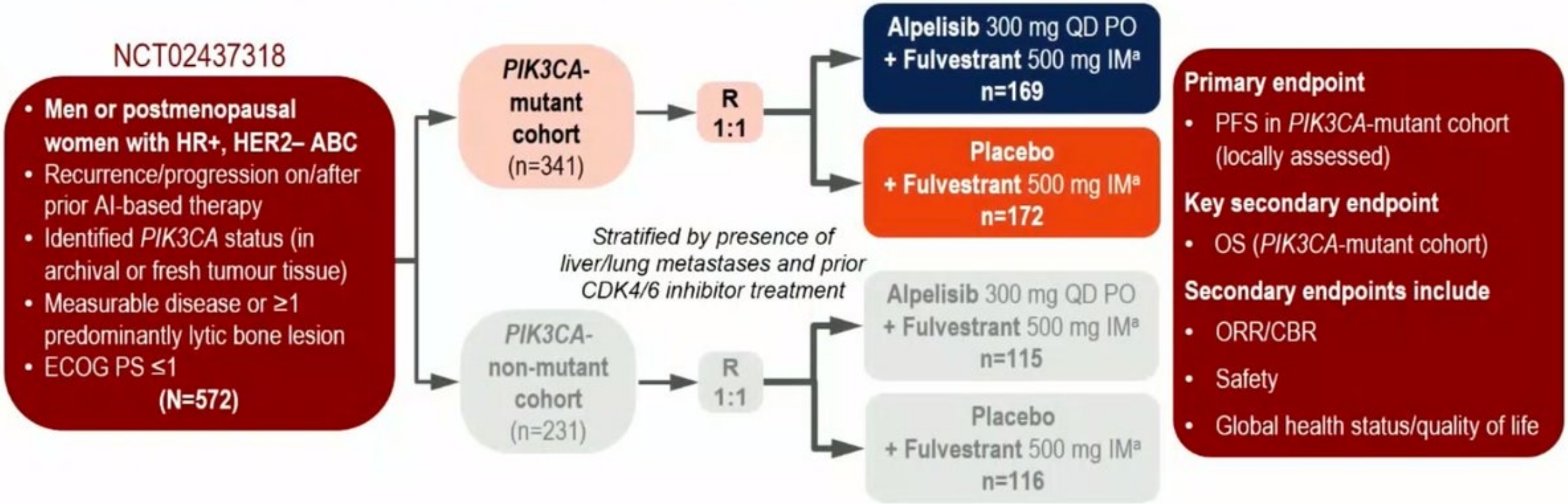
Nat Cancer. 2021 June ; 2(6): 587–597.

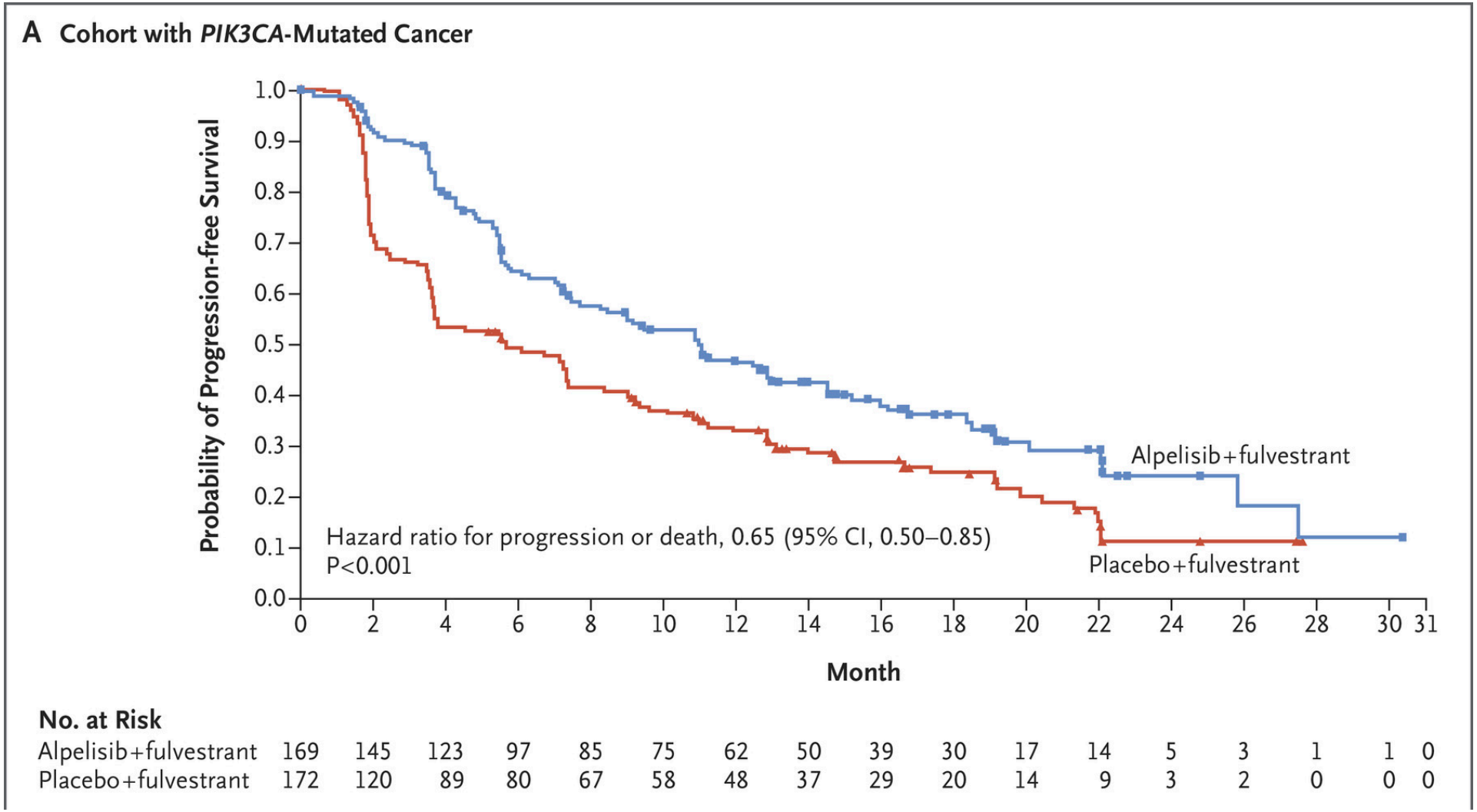
PI3Ki Adverse events

	Indication	Adverse Events (> 20%)
Copanlisib (Pan-PI3K)	Follicular Lymphoma (2017)	Hyperglycemia, diarrhea, fatigue, hypertension, neutropenia, nausea, pneumonia, thrombocytopenia
Idelalisib (PI3Kδ)	CLL, Follicular Lymphoma (2014)	Diarrhea, pyrexia, fatigue, nausea, cough, pneumonia, chills, rash, neutropenia, hypertriglyceridemia, hyperglycemia, AST / ALT elevation
Duvelisib (PI3K-δ and PI3K-γ)	CLL, Follicular Lymphoma (2018)	Diarrhea, neutropenia, rash, fatigue, pyrexia, cough, nausea, URI, anemia, musculoskeletal pain
Alpelisib (PI3Kα)	PIK3CA-mutated metastatic breast cancer (combo with fulvestrant 2019)	Hyperglycemia, increased creatinine, diarrhea, rash, nausea, stomatitis, ALT elevation

SOLAR-1: OS Is a Key Secondary Endpoint

Prospective evaluation of an α-selective PI3K inhibitor in HR+, HER2– ABC





N Engl J Med 2019; 380:1929-1940

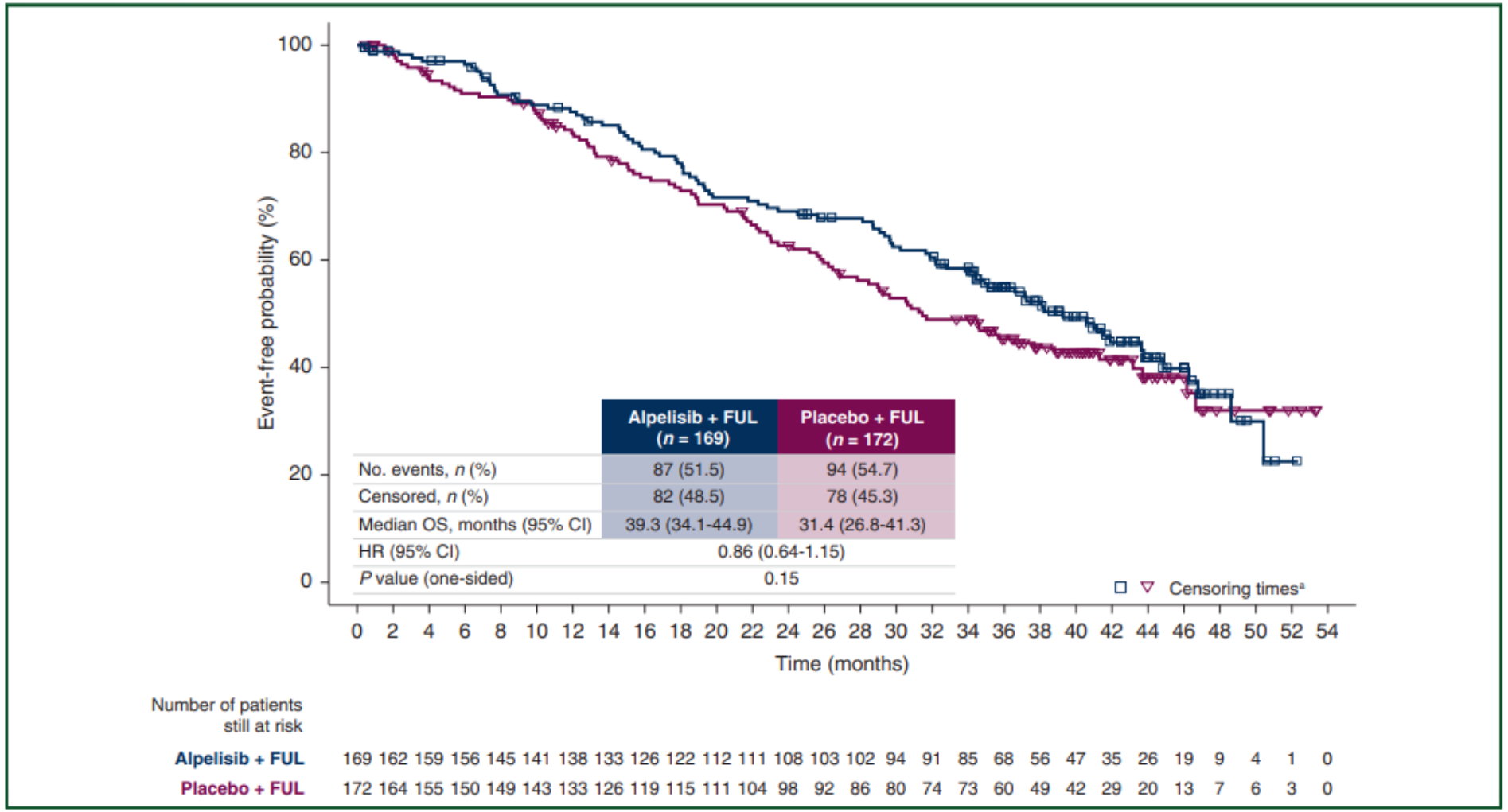


Figure 1. Overall survival in *PIK3CA*-mutant cohort of patients comparing alpelisib plus fulvestrant and placebo plus fulvestrant treatment arms using one-sided stratified log-rank test.

CI, confidence interval; FUL, fulvestrant; HR, hazard ratio; OS, overall survival.

[a] Date of censoring is defined as the last contact date.

Table 3. Most Frequent Adverse Events, According to Single Preferred Term and Regardless of Relationship to Intervention, in the Overall Patient Population.*

Adverse Event	Alpelisib–Fulvestrant Group (N=284)			Placebo–Fulvestrant Group (N=287)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia†	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea‡	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea‡	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash§	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0
Vomiting‡	77 (27.1)	2 (0.7)	0	28 (9.8)	1 (0.3)	0
Weight loss	76 (26.8)	11 (3.9)	0	6 (2.1)	0	0
Stomatitis	70 (24.6)	7 (2.5)	0	18 (6.3)	0	0
Fatigue	69 (24.3)	10 (3.5)	0	49 (17.1)	3 (1.0)	0
Asthenia	58 (20.4)	5 (1.8)	0	37 (12.9)	0	0
Alopecia	56 (19.7)	0	0	7 (2.4)	0	0
Mucosal inflammation	52 (18.3)	6 (2.1)	0	3 (1.0)	0	0
Pruritus	51 (18.0)	2 (0.7)	0	16 (5.6)	0	0
Headache	50 (17.6)	2 (0.7)	0	38 (13.2)	0	0
Dysgeusia	47 (16.5)	0	0	10 (3.5)	0	0
Arthralgia	32 (11.3)	1 (0.4)	0	47 (16.4)	3 (1.0)	0

PI3Ki - Efficacy

Hematologic Malignancies		Solid Tumor Malignancies	
Copanlisib (Pan-PI3K)	Follicular Lymphoma	Alpelisib (+ Fulvestrant)	Breast cancer (PIK3CA mutant)
Duvelisib (PI3K-δ and PI3K-γ)	Follicular Lymphoma, CLL		
Idelalisib (PI3Kδ)	Follicular Lymphoma, CLL		
Umbrasilib (PI3Kδ + CK1ε) (Approval withdrawn 2022 for safety concern)	Follicular Lympoma, Marginal zone lymphoma		

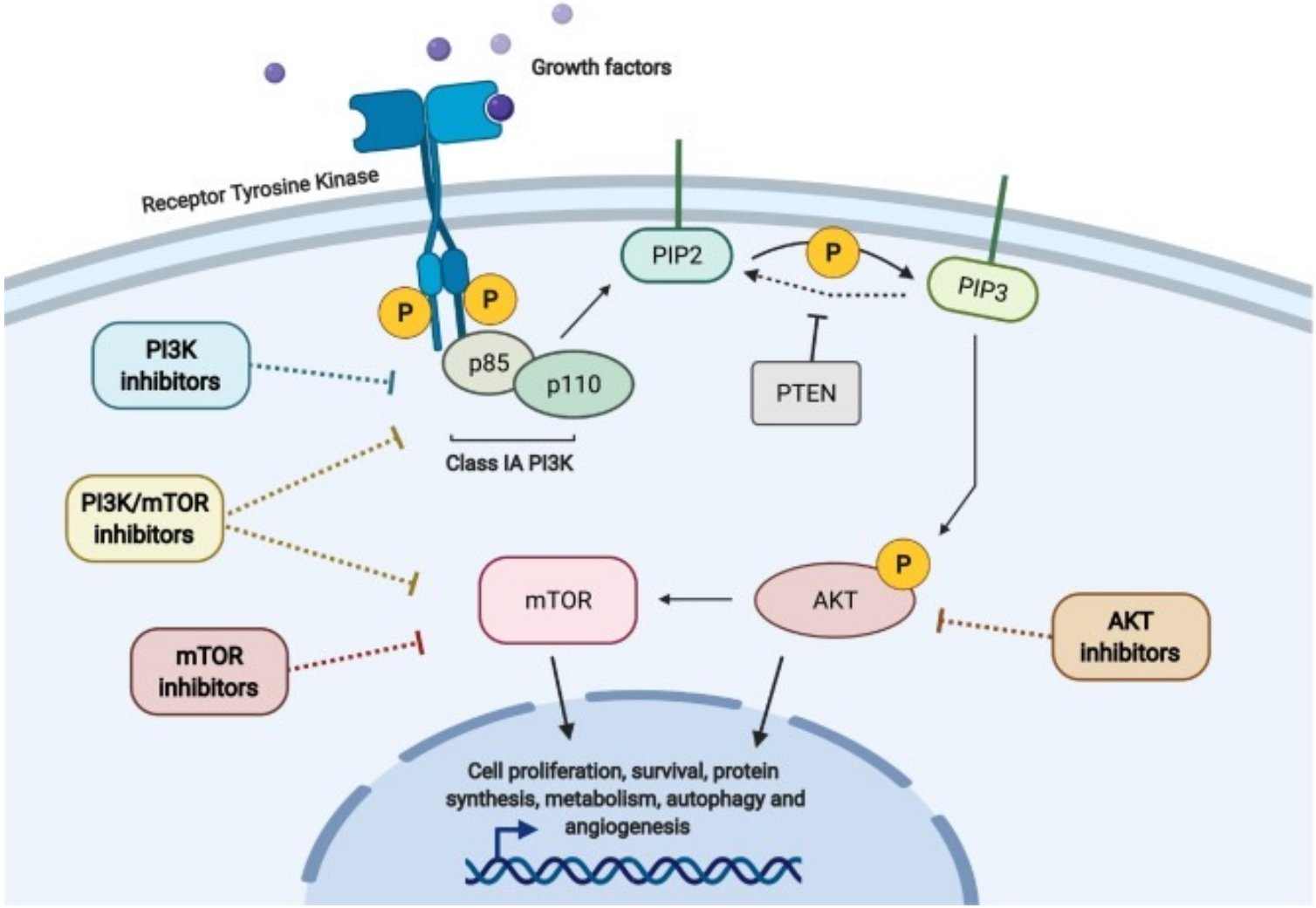
Future of PI3Ki

- Novel Combinations
  - Palbociclib + Gedatolisib (PI3K / mTOR dual inhibitor) (NCT03065062)
  - Tipifarnib + Alpelisib in HNSCC (NCT04997902)
  - Alpelisib + Sacituzumab Govitecan in breast cancer (NCT05143229)
  - Copanlisib + EPOCH-R in high grade B-cell lymphomas (NCT04933617)
- Immunotherapy combinations

PI3Ki – Immunomodulatory effects

- PI3Kδ - Inhibition of MDSC, Regulatory T-cells
- PI3K-δ and PI3K-γ – Inhibit M2 macrophage polarization
- Immunotherapy clinical trials
  - NCT03131908 – PI3Ki + pembrolizumab in melanoma
  - NCT04317105 – Copanlisib + Nivolumab +/- Ipilimumab in solid tumors
  - NCT03961698 - PI3K- γ inhibitor + I/O in RCC / TNBC

mTOR

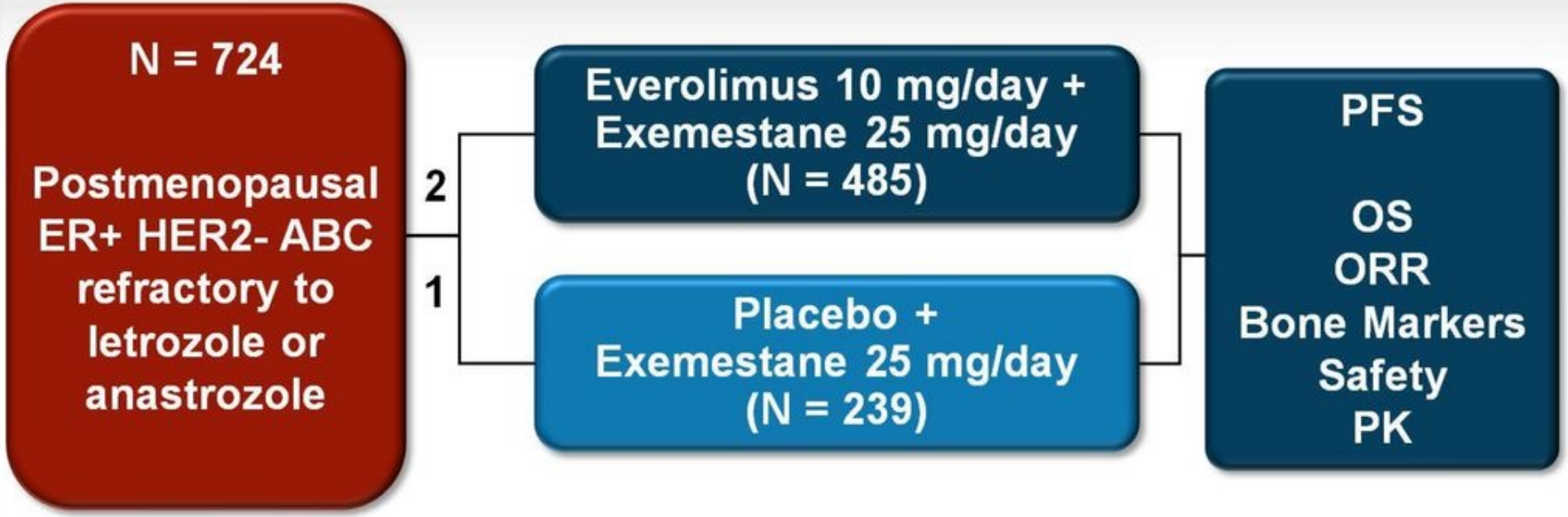


Gynecologic Oncology 163 (2021) 433–444

mTOR – Approved agents

- Everolimus
- Temsirolimus
- Nab-sirolimus

BOLERO-2: Trial Design



Stratification:

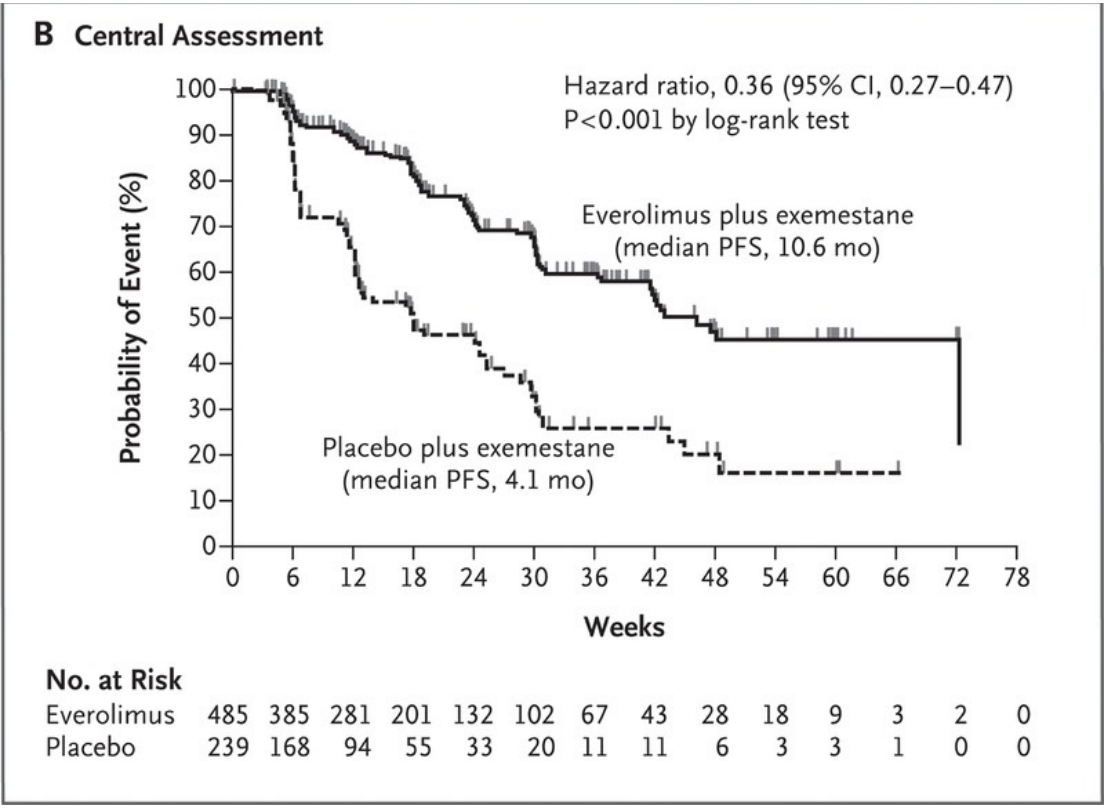
1. Sensitivity to prior hormonal therapy
2. Presence of visceral disease

No cross-over

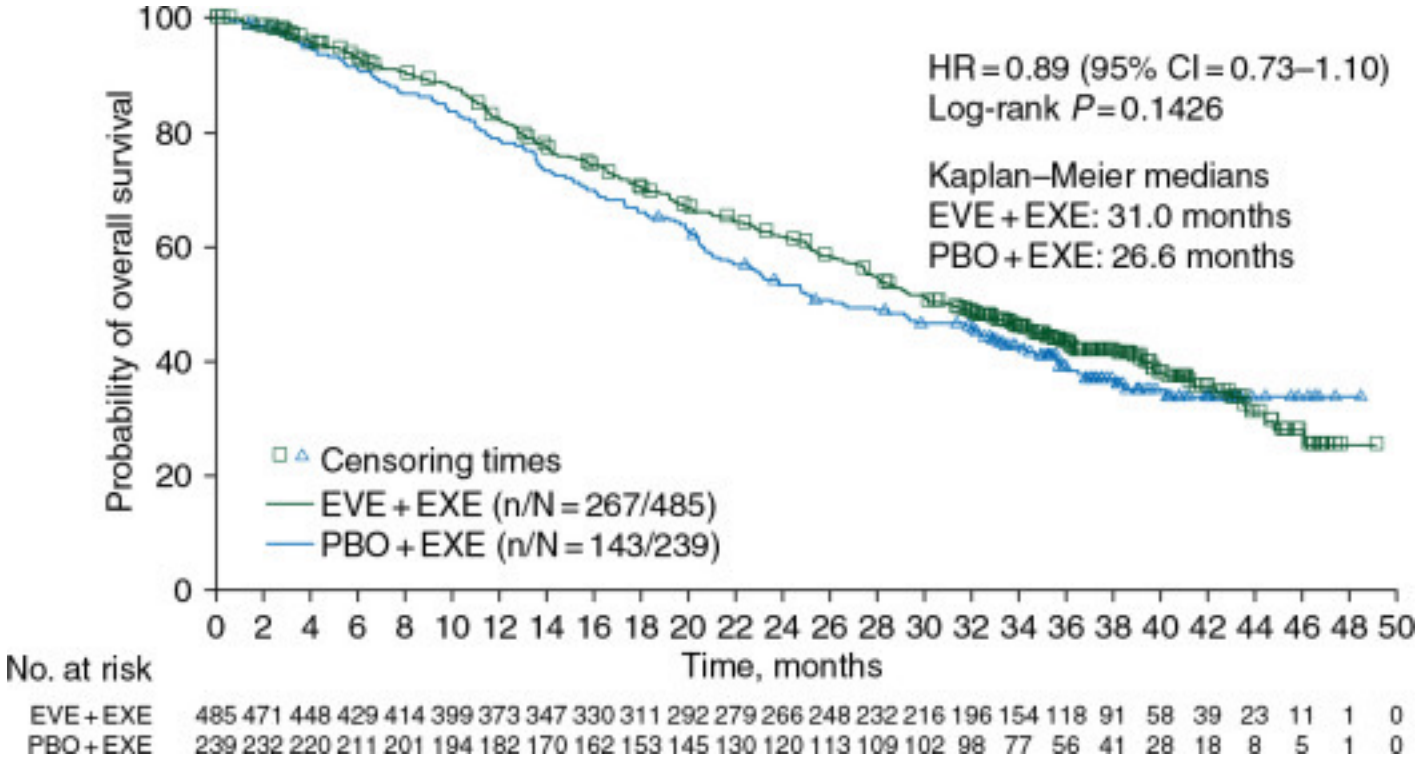
ABC = advanced breast cancer, NSAI = non steroidal aromatase inhibitors, HER2- = human epidermal growth factor receptor 2 – negative; PFS = progression-free survival; PK = pharmacokinetics

a. Baselga J et al. *N Engl J Med*. 2012;366:520-529.[17]

BOLERO-2



N Engl J Med 2012; 366:520-529



Annals of Oncology 25: 2357–2362, 2014

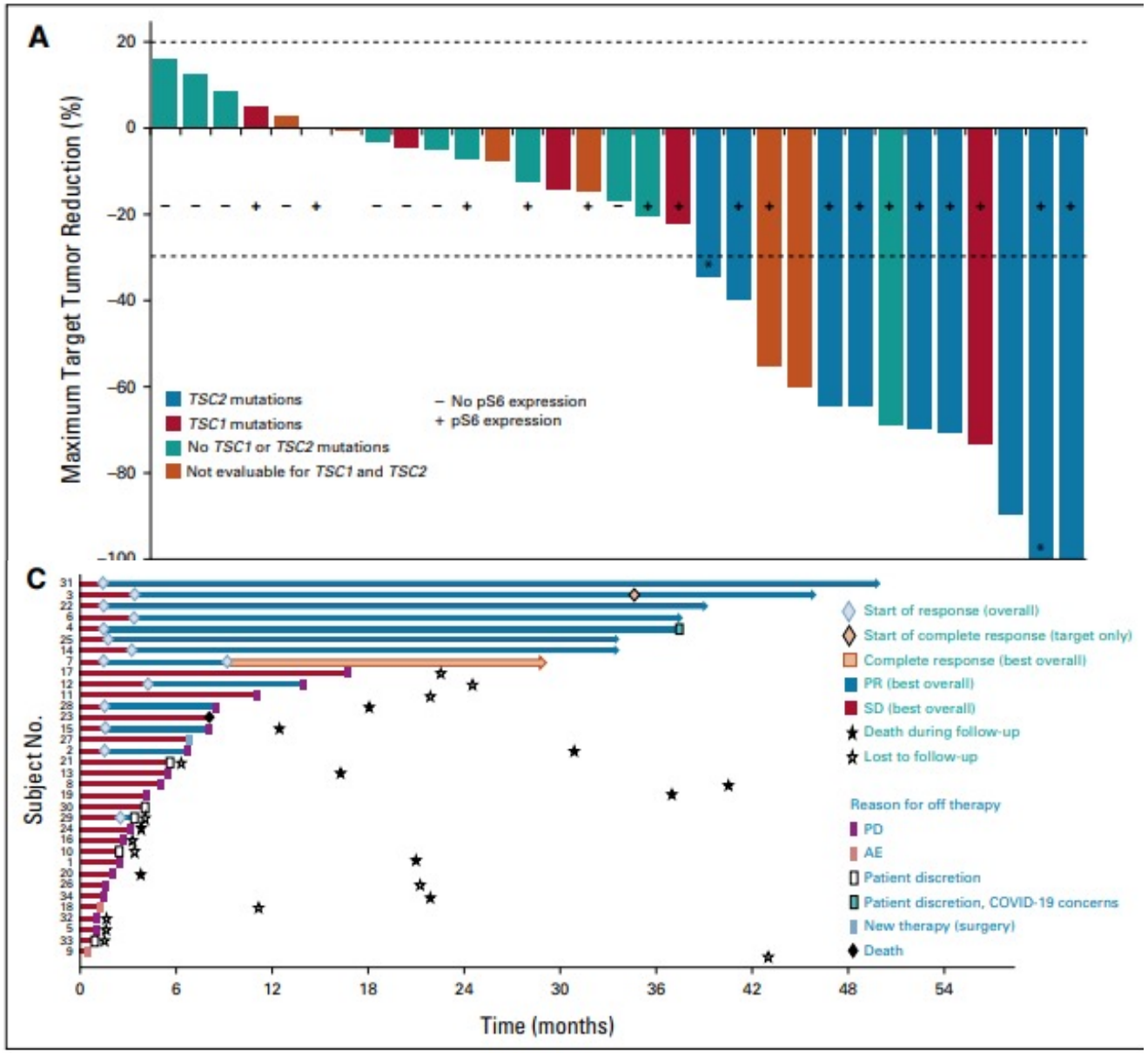
Table 2. Adverse Events Irrespective of Relationship to Study Treatment (with at Least 10% Incidence in the Everolimus–Exemestane Group).

Adverse Event	Everolimus and Exemestane (N=482)			Placebo and Exemestane (N=238)		
	Any Event	Grade 3 Event	Grade 4 Event	Any Event	Grade 3 Event	Grade 4 Event
	percent					
Stomatitis	56	8	0	11	1	0
Rash	36	1	0	6	0	0
Fatigue	33	3	<1	26	1	0
Diarrhea	30	2	<1	16	1	0
Decreased appetite	29	1	0	10	0	0
Nausea	27	<1	<1	27	1	0
Cough	22	1	0	11	0	0
Dysgeusia	21	<1	0	5	0	0
Headache	19	<1	0	13	0	0
Decreased weight	19	1	0	5	0	0
Dyspnea	18	4	0	9	1	<1
Arthralgia	16	1	0	16	0	0
Anemia	16	5	1	4	<1	<1
Epistaxis	15	0	0	1	0	0
Vomiting	14	<1	<1	11	<1	0
Peripheral edema	14	1	0	6	<1	0
Pyrexia	14	<1	0	6	<1	0
Aspartate aminotransferase level increased	13	3	<1	6	1	0
Constipation	13	<1	0	11	<1	0
Hyperglycemia	13	4	<1	2	<1	0
Pneumonitis	12	3	0	0	0	0
Thrombocytopenia	12	2	1	<1	0	<1
Asthenia	12	2	0	3	0	0
Alanine aminotransferase level increased	11	3	<1	3	2	0
Pruritus	11	<1	0	3	0	0
Insomnia	11	<1	0	8	0	0
Back pain	11	0	0	8	1	0

N Engl J Med 2012; 366:520-529

Nab-Sirolimus

- Novel IV mTOR inhibitor
  - 100mg/m2 IV infusion D1,D8 of 21 day cycle
- AMPECT trial led to FDA approval for advanced malignant PEComa (11/2021)



ORR = 42%

*Majority of responses associated with TSC1 or TSC2 mutation

Median DOR not reached

12-month DOR 75%

J Clin Oncol. 2021 Nov 20;39(33):3660-3670

TABLE 3. Common TRAEs Occurring in ≥ 25% of Patients

TRAE	Any Grade ≥ 25%	Grade 3
Patients with any TRAEs, No. (%)	34 (100)	
Hematologic TRAEs		
Anemia[a]	16 (47)	4 (12)
Thrombocytopenia[a]	11 (32)	1 (3)
Nonhematologic TRAEs, No. (%)		
Mucositis[a]	27 (79)	6 (18)
Rash[a]	19 (56)	—
Fatigue	20 (59)	1 (3)
Nausea	16 (47)	—
Diarrhea	13 (38)	—
Weight decreased	13 (38)	—
Hyperglycemia[a]	12 (35)	3 (9)
Hypertriglyceridemia[a]	11 (32)	1 (3)
Hypercholesterolemia[a]	11 (32)	—
Decreased appetite	11 (32)	—
Dermatitis[a]	10 (29)	—
Dysgeusia	10 (29)	—
Headache	10 (29)	—
Peripheral edema	9 (26)	—

Abbreviation: TRAE, treatment-related adverse event.

[a]Reported on the basis of groupings of preferred terms defined by standardized queries in the Medical Dictionary for Regulatory Activities.

J Clin Oncol. 2021 Nov 20;39(33):3660-3670

Future of mTOR

- Nab-Sirolimus in tumors with TSC1/TSC2 mutations
  - NCT05103358

AKT

- Three isoforms (AKT1, AKT2, AKT3)
- Three types of inhibitors:
  - ATP-competitive (Ipatasertib, Capivasertib)
  - Allosteric (MK-2206)
  - Irreversible
- No FDA approved therapies

Capivasertib

- EAY131-Y trial (NCI-MATCH)
  - AKT1 E17K mutant tumors
  - ORR 28.6%
  - One CR for nearly 36 months
- ProCAID trial – Add capivasertib to docetaxel
  - No improvement in PFS
- FAKTION trial – Capivasertib + Fulvestrant
  - Improved PFS
- PAKT trial – Capivasertib + paclitaxel in TNBC
  - Improved PFS and OS

Future of Capivasertib

- Capivasertib + Abiraterone in hormone-sensitive prostate cancer with PTEN deficiency (NCT04493853)
- Capivasertib + CDK4/6i + Fulvestrant in HR+ breast cancer (NCT04862663)

Ipatasertib

- IPATential150 trial
  - Ipatasertib + ADT improves mPFS
- LOTUS trial
  - Ipatasertib + paclitaxel increases PFS in TNBC

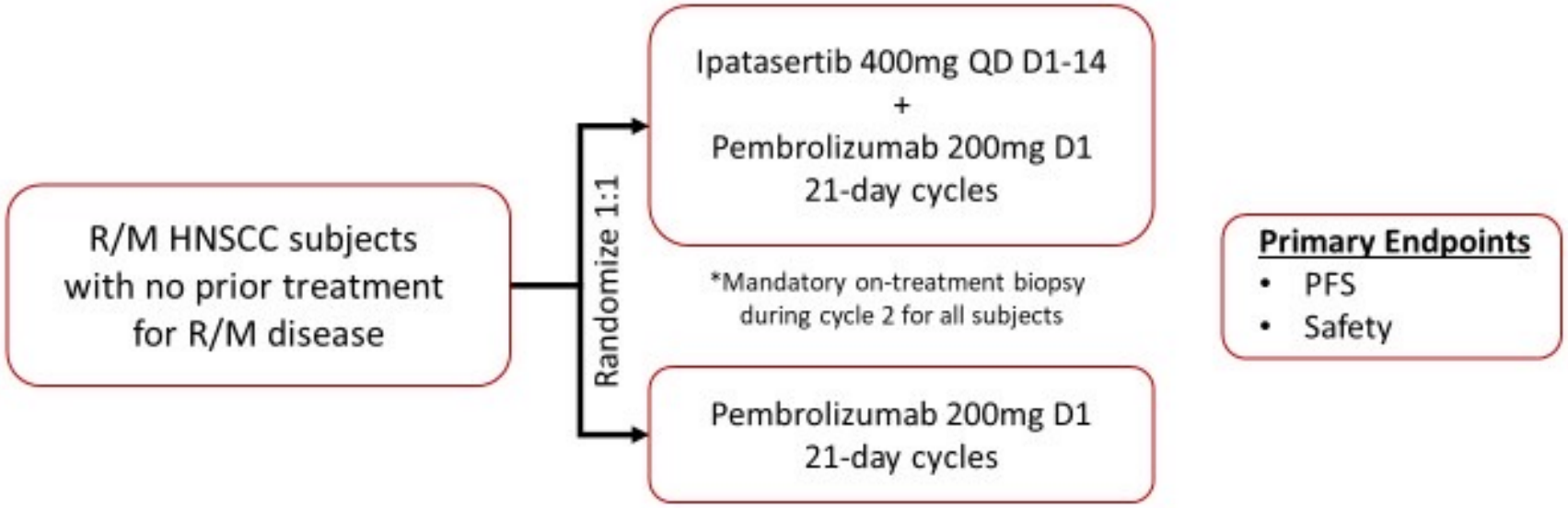
AKT Inhibitors Immunomodulatory Effects

- ICE-CAP trial
  - Ipatasertib 400mg D1-14 + Atezolizumab
  - Shown to deplete FOXP3+ Tregs in solid tumors (Lopez 2020, AACR)
  - Expansion in Glioblastoma shows preliminary efficacy (Tiu 2023, AACR)
    - One exceptional responder with pathologic CR and > 70% depletion of Tregs with increased CD8+ lymphocytes

Future development of Ipatasertib

A Phase 2 Study of Ipatasertib in Combination with Pembrolizumab for First Line Treatment of Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck

NCI Study #10496



Stratification Factor: PD-L1 CPS score (1-19 *vs.* 20+)
Expected enrollment: 48 patients over 2 years, 24 in each arm

Currently enrolling patients throughout the CCC and ETCTN (NCT05172258)

Conclusions

- FDA approvals of PI3K inhibitors, mTOR inhibitors
- No approved AKT inhibitors, but some preliminary evidence of efficacy
- Future directions include further patient selection and immunomodulatory use