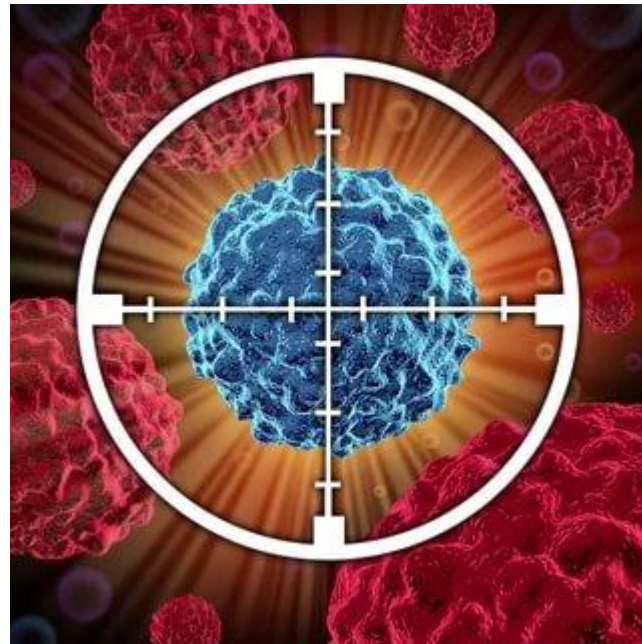




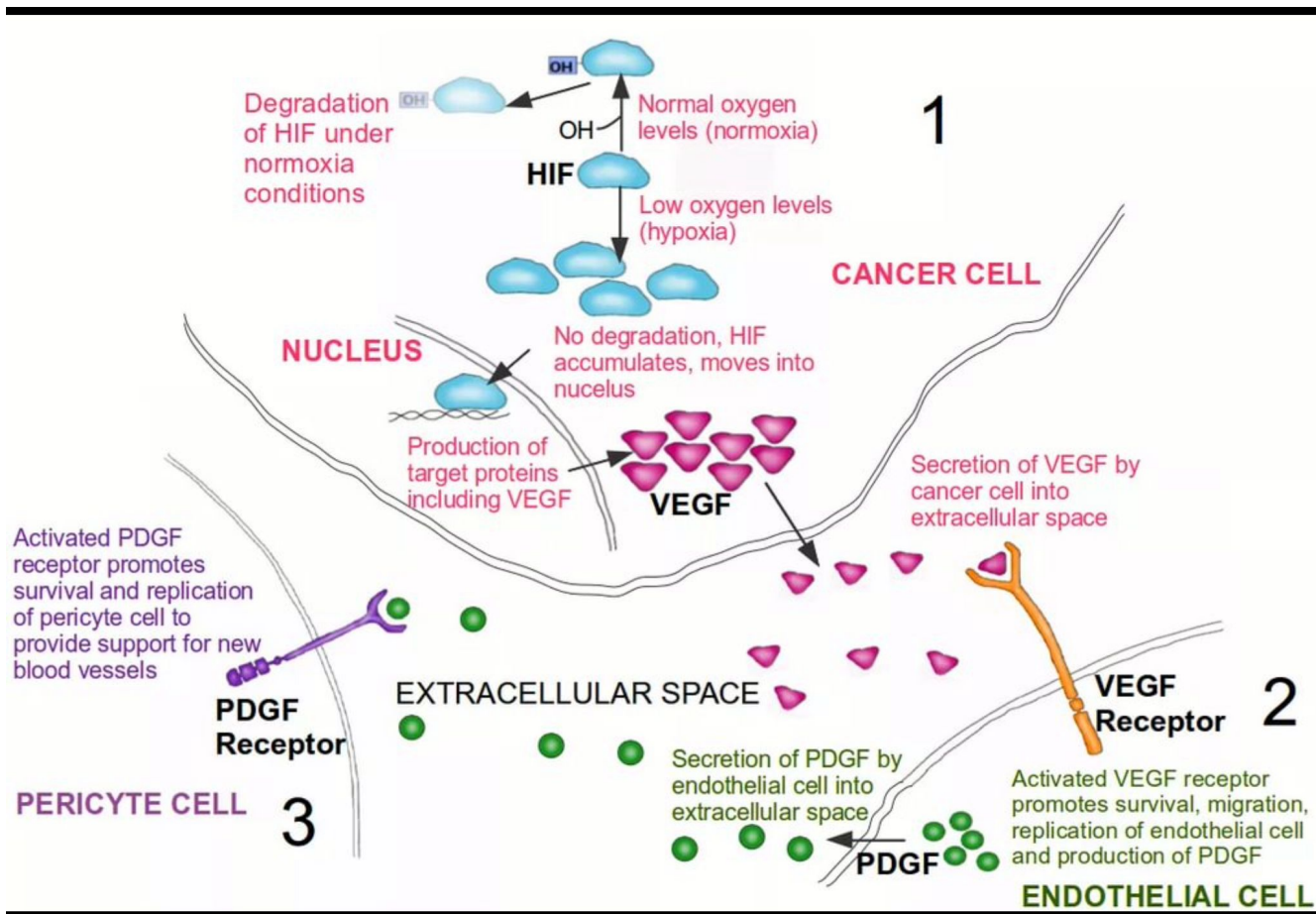
# ***Мультикиназные ингибиторы (VEGFRi, BRAFi, MEKi, mTORi, CDK 4/6 i)***

Подготовила студентка 5 курса  
Первого МГМУ им. И.М. Сеченова  
Пальчинская О.В.

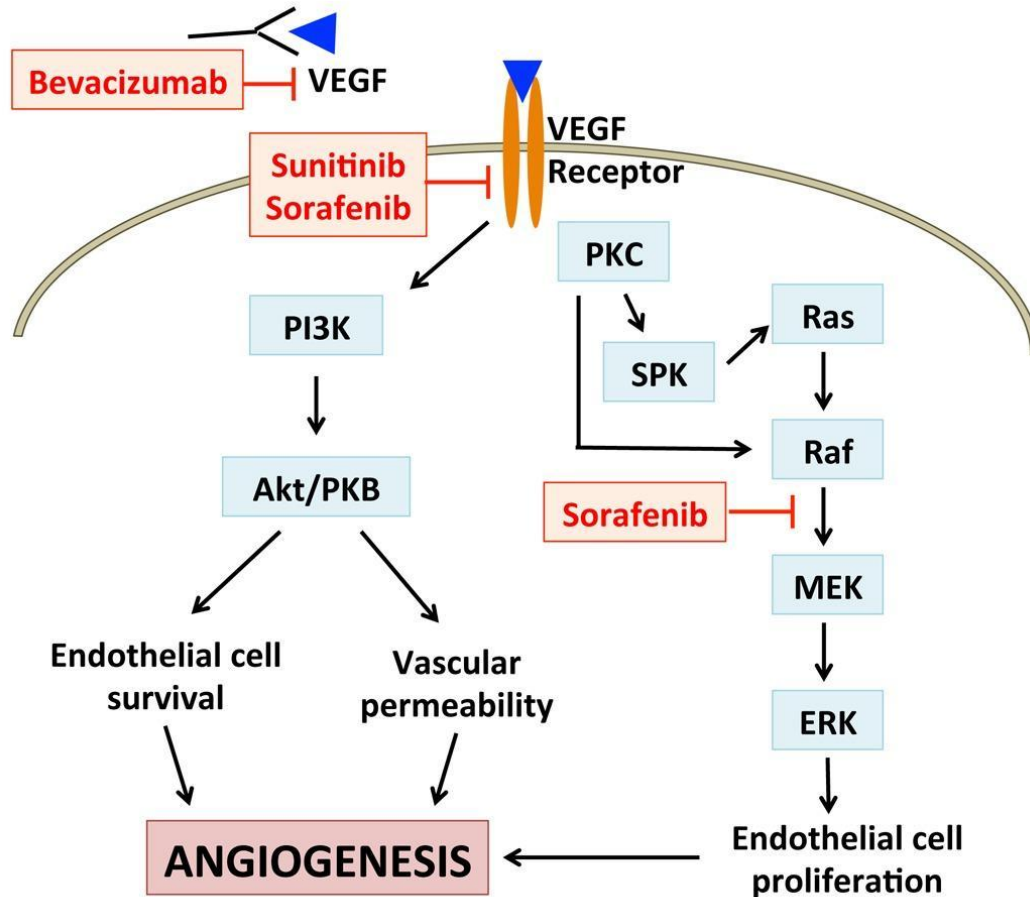
Таргетная терапия – терапия направленного действия, то есть воздействие на опухолевые «мишени» (белки, рецепторы, гены), имеющие важнейшее («критическое») значение для развития новообразований.



# Ангиогенез



# Механизм действия ингибиторов тирозинкиназы VEGFR



Препарат	Мишень действия	Показания
Сорафениб (Нексавар)	Внутриклеточные киназы (с-CRAF, BRAF) и киназы, расположенные на поверхности клетки (KIT, FLT-3, RET, VEGFR-1, VEGFR-2, VEGFR-3 и PDGFR- $\beta$ )	<ul style="list-style-type: none"> <li>•печечно-клеточный рак;</li> <li>•местно-распространенный или метастатический дифференцированный рак щитовидной железы, резистентный к радиоактивному йоду</li> <li>•метастатический почечно-клеточный рак</li> </ul>
Сунитиниб (Сутент)	Ингибитор рецепторов тромбоцитарного фактора роста (PDGFR $\alpha$ и PDGFR $\beta$ ), рецепторов фактора роста сосудистого эндотелия (VEGRF1, VEGRF2 и VEGRF3); рецептора фактора стволовых клеток (KIT), рецептора Fms-подобной тирозинкиназы-3 (FLT), рецептора колониестимулирующего фактора и рецептора нейротрофического глиального фактора (RET)	<ul style="list-style-type: none"> <li>• гастроинтестинальные стромальные опухоли при отсутствии эффекта от терапии иматинибом вследствие резистентности или непереносимости;</li> <li>• распространенный и/или метастатический почечноклеточный рак у пациентов, не получавших ранее специфического лечения или при отсутствии эффекта от терапии цитокинами</li> </ul>
Пазопаниб (Вотриент)	Ингибитор тирозинкиназы VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- $\alpha$ и PDGFR- $\beta$ , рецептора фактора роста фибробластов-1 и -3 (FGFR-1, -3), рецептора цитокина (Kit), рецептора интерлейкина-2, индуцируемого киназой Т-клеток (Itk), лейкоцитспецифической протеин-тирозинкиназы (Lck) и трансмембранного гликопротеинового рецептора тирозинкиназы (с-Fms)	<ul style="list-style-type: none"> <li>• распространенный почечно-клеточный рак;</li> <li>• распространенная саркома мягких тканей (кроме гастроинтестинальных стромальных опухолей и липосаркомы) у пациентов, ранее получавших химиотерапию</li> </ul>

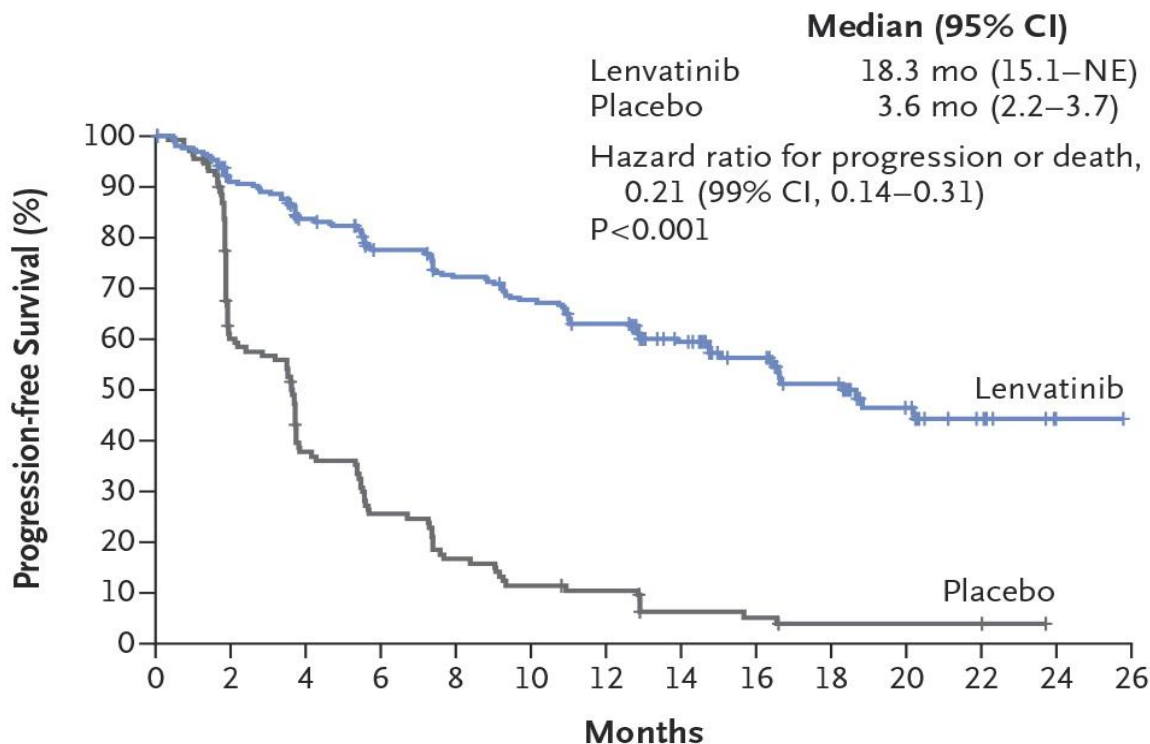
Препарат	Мишень действия	Показания
Вандетаниб(Зактима, Капрелса)	Ингибитор тирозинкиназы VEGFR-2, EGF	<ul style="list-style-type: none"> <li>• нерезектабельный местнораспространенный или метастатический медуллярный рак щитовидной железы</li> </ul>
Акситиниб (Инлита)	Ингибитор тирозинкиназы VEGFR-1, VEGFR-2, VEGFR-3	<ul style="list-style-type: none"> <li>• распространенный почечно-клеточный рак</li> </ul>
Ленватиниб (Ленвима)	Ингибитор киназ VEGFR, FGFR, RET, KIT и PDGFR	<ul style="list-style-type: none"> <li>• прогрессирующий дифференцированный рак щитовидной железы, рефрактерный к радиоактивному йоду</li> </ul>
Регорафениб (Стиварга)	Ингибитор тирозинкиназы VEGFR-1, VEGFR-2, VEGFR-3	<ul style="list-style-type: none"> <li>• колоректальный рак;</li> <li>• гастроинтестинальные стромальные опухоли</li> </ul>
Афлиберцепт (Залтрап)	Блокирует активацию рецепторов VEGF	<ul style="list-style-type: none"> <li>• метастатический КРР, резистентный к оксалиплатин-содержащей химиотерапии или при прогрессировании опухоли после применения такой терапии в сочетании с режимом, включающим иринотекан, фторурацил и калия фолинат (FOLFIRI)</li> </ul>



## Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer

Martin Schlumberger, M.D., Makoto Tahara, M.D., Ph.D., Lori J. Wirth, M.D., Bruce Robinson, M.D., Marcia S. Brose, M.D., Ph.D., Rossella Elisei, M.D., Mohammed Amir Habra, M.D., Kate Newbold, M.D., Manisha H. Shah, M.D., Ana O. Hoff, M.D., Andrew G. Gianoukakis, M.D., Naomi Kiyota, M.D., Ph.D., Matthew H. Taylor, M.D., Sung-Bae Kim, M.D., Ph.D., Monika K. Krzyzanowska, M.D., M.P.H., Corina E. Dutcus, M.D., Begoña de las Heras, M.D., Junming Zhu, Ph.D., and Steven I. Sherman, M.D.

N Engl J Med 2015; 372:621-630 | February 12, 2015 | DOI: 10.1056/NEJMoa1406470



**No. at Risk**

Lenvatinib	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

**Table 2. Efficacy Measures.\***

Outcome	Lenvatinib (N = 261)	Placebo (N = 131)	Hazard Ratio†	Odds Ratio (95% CI)
<b>Progression-free survival</b>				
Primary analysis, IRR and ITT populations‡				
Median (95% CI) — mo	18.3 (15.1–NE)	3.6 (2.2–3.7)	0.21 (0.14–0.31)§	
Rate — % (95% CI)				
6 mo	77.5 (71.7–82.3)	25.4 (18.0–33.6)		
12 mo	63.0 (56.5–68.9)	10.5 (5.7–16.9)		
18 mo	51.1 (43.3–58.3)	3.8 (1.1–9.2)		
24 mo	44.3 (35.1–53.1)	NE		
Prespecified sensitivity analyses				
Investigator assessment, ITT population — mo			0.24 (0.16–0.35)§	
Median	16.6	3.7		
95% CI	14.8–NE	3.5–5.4		
IRR population — mo¶			0.22 (0.15–0.32)§	
Median	16.6	3.6		
95% CI	14.8–20.3	2.2–3.7		
<b>Secondary efficacy end points</b>				
Overall survival, RPSFT adjusted, ITT population			0.62 (0.40–1.00)¶	
Median (95% CI) — mo	NE (22.0–NE)	NE (14.3–NE)		
Rate, RPSFT adjusted — % (95% CI)				
6 mo	90.7 (86.4–93.7)	85.3 (78.0–90.4)		
12 mo	81.6 (76.2–85.8)	70.0 (57.1–79.7)		
18 mo	72.3 (65.7–77.9)	63.0 (44.3–76.9)		
24 mo	58.2 (46.0–68.6)	NE		
Response rate — no. (%)**	169 (64.8)	2 (1.5)		28.87 (12.46–66.86)§
Complete response	4 (1.5)	0		
Partial response	165 (63.2)	2 (1.5)		
Stable disease	60 (23.0)	71 (54.2)		
Durable stable disease ≥23 wk	40 (15.3)	39 (29.8)		
Progressive disease	18 (6.9)	52 (39.7)		
Could not be evaluated	14 (5.4)	6 (4.6)		
<b>Exploratory efficacy end points</b>				
Disease-control rate — no. (%)††	229 (87.7)	73 (55.7)		5.05 (2.98–8.54)§
Clinical-benefit rate — no. (%)§§	209 (80.1)	41 (31.3)		7.63 (4.55–12.79)§
Time to first objective response — mo				
Median	2.0	5.6		
95% CI	1.9–3.5	1.8–9.4		



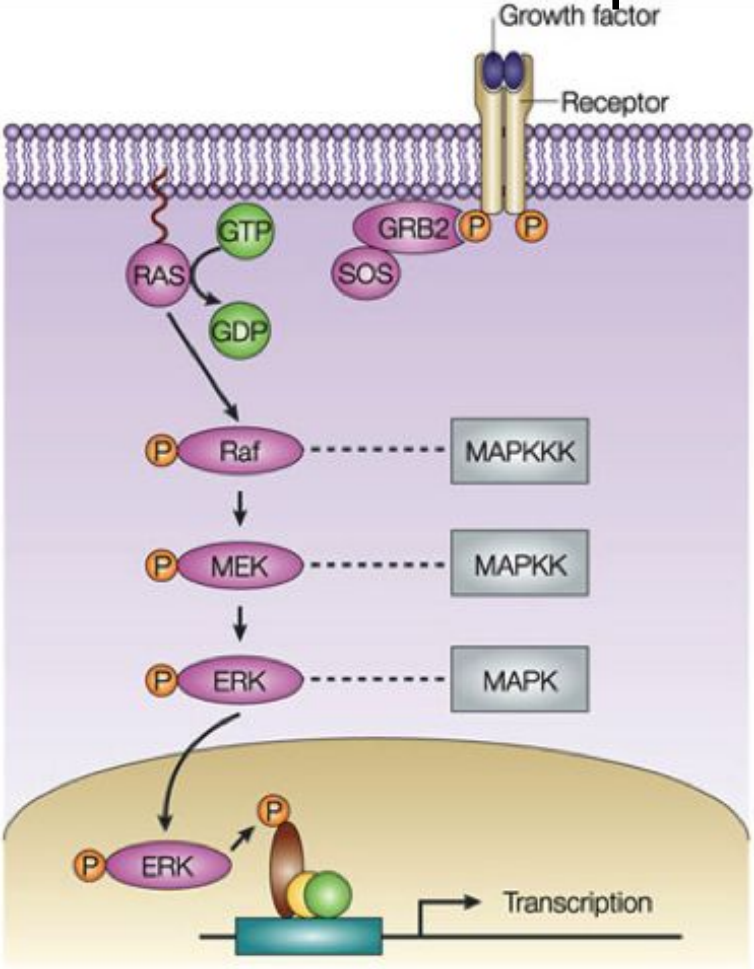
**Table 3. Adverse Effects.**

Effect	Lenvatinib (N = 261)		Placebo (N = 131)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any treatment-related adverse effect — no. of patients (%)	254 (97.3)	198 (75.9)	78 (59.5)	13 (9.9)
Adverse effect developing during treatment — no. of patients (%)				
Serious*				
Total	130 (49.8)		30 (22.9)	
Treatment-related	79 (30.3)		8 (6.1)	
Fatal				
Total†	20 (7.7)		6 (4.6)	
Treatment-related	6 (2.3)		0	
Treatment-related adverse effect of any grade in ≥10% of patients, of grade ≥3 in ≥2%, or both — %				
Hypertension	67.8	41.8	9.2	2.3
Diarrhea	59.4	8.0	8.4	0
Fatigue or asthenia	59.0	9.2	27.5	2.3
Decreased appetite	50.2	5.4	11.5	0
Decreased weight	46.4	9.6	9.2	0
Nausea	41.0	2.3	13.7	0.8
Stomatitis	35.6	4.2	3.8	0
Palmar–plantar erythrodysesthesia syndrome	31.8	3.4	0.8	0
Proteinuria	31.0	10.0	1.5	0
Vomiting	28.4	1.9	6.1	0
Headache	27.6	2.7	6.1	0
Dysphonia	24.1	1.1	3.1	0
Arthralgia	18.0	0	0.8	0
Dysgeusia	16.9	0	1.5	0
Rash	16.1	0.4	1.5	0
Constipation	14.6	0.4	8.4	0
Myalgia	14.6	1.5	2.3	0
Dry mouth	13.8	0.4	3.8	0
Upper abdominal pain	13.0	0	3.8	0
Abdominal pain	11.5	0.4	0.8	0.8
Peripheral edema	11.1	0.4	0	0
Alopecia	11.1	0	3.8	0
Dyspepsia	10.0	0	0	0
Oropharyngeal pain	10.0	0.4	0.8	0
Hypocalcemia	6.9	2.7	0	0
Pulmonary embolism	2.7	2.7	1.5	1.5

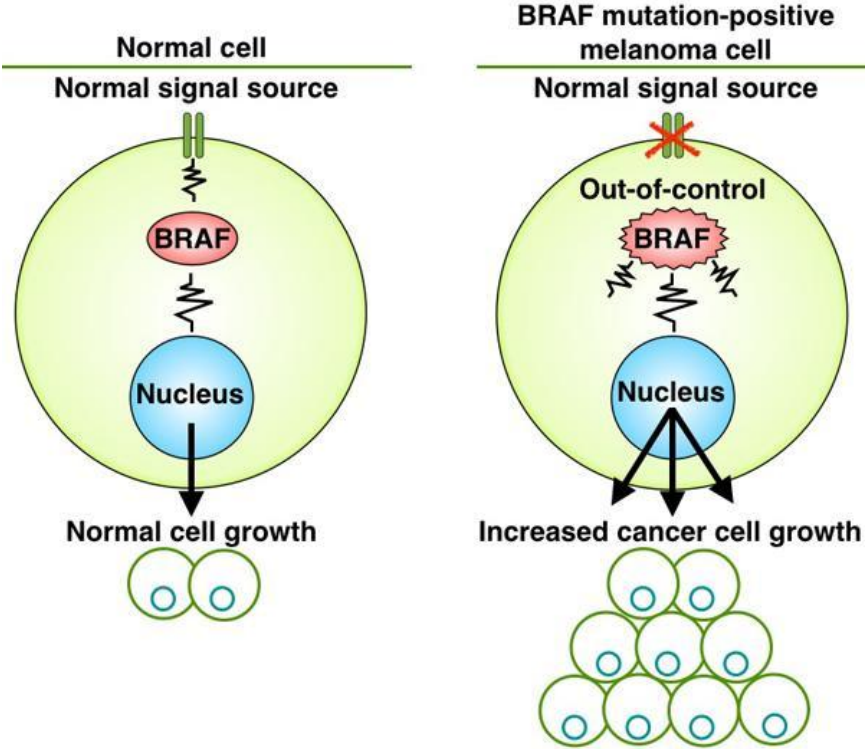
\* A complete list of serious adverse effects is provided in Table S2 in the Supplementary Appendix.

† A complete list of fatal adverse effects that developed during treatment is provided in Table S3 in the Supplementary Appendix.

# Сигнальный путь MAPK (mitogen-activated proteinkinase)



Nature Reviews | Molecular Cell Biology



# Ингибиторы BRAF

- **Вемурафениб (Зелбораф)** – лечение неоперабельной или метастатической меланомы с BRAF V600 мутацией у взрослых пациентов в виде монотерапии.
- **Дабрафениб (Тафинлар)** – лечение неоперабельной или метастатической меланомы у пациентов с мутацией гена BRAF V600, лечение метастатического НМРЛ с мутацией гена BRAF V600.

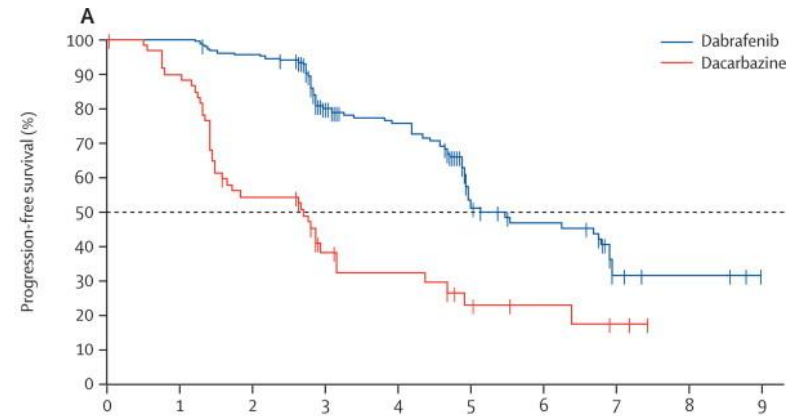


## Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial

Prof Axel Hauschild, MD, Prof Jean-Jacques Grob, MD, Prof Lev V Demidov, MD, Thomas Jouary, MD, Ralf Gutzmer, MD, Michael Millward, MD, Piotr Rutkowski, PhD, Christian U Blank, PhD, Wilson H Miller Jr, PhD, Eckhart Kaempgen, PhD, Salvador Martin-Algarra, PhD, Boguslawa Karaszewska, MD, Prof Cornelia Mauch, PhD, Vanna Chiarion-Sileni, MD, Anne-Marie Martin, PhD, Suzanne Swann, PhD, Patricia Haney, BSN, Beloo Mirakhur, PhD, Mary E Guckert, MSN, Vicki Goodman, MD, Paul B Chapman, MD

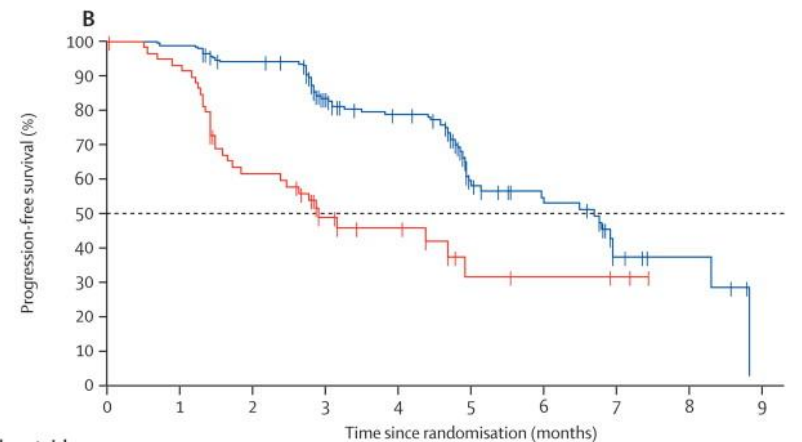
Published: 25 June 2012

	Dabrafenib (n=187)	Dacarbazine (n=63)
Complete response	6 (3%)	1 (2%)
Partial response	87 (47%)	3 (5%)
Stable disease*	78 (42%)	30 (48%)
Progressive disease	10 (5%)	23 (37%)
Not evaluable†	6 (3%)	6 (10%)
Response rate (complete+partial response, n [%], 95% CI)	93 (50%, 42.4–57.1)	4 (6%, 1.8–15.5)



Number at risk

Dabrafenib	187	184	173	113	100	41	31	5	3	0
Dacarbazine	63	53	31	14	11	6	4	2	0	0



Number at risk

Dabrafenib	187	182	167	112	98	39	28	7	4	0
Dacarbazine	63	53	32	16	12	5	4	2	0	0

	Dabrafenib	Dacarbazine
Any event	100 (53%)	26 (44%)
Skin		
Hyperkeratosis*		
Grade 2	23 (12%)	0
Grade 3	1 (<1%)	0
Grade 4	1 (<1%)	0
PPE/palmar-plantar hyperkeratosis†		
Grade 2	12 (6%)	0
Grade 3	4 (2%)	0
Squamous cell carcinoma/keratoacanthoma‡		
Grade 2	4 (2%)	0
Grade 3	8 (4%)	0
Gastrointestinal		
Nausea		
Grade 2	2 (1%)	8 (14%)
Grade 3	0	0
Vomiting		
Grade 2	2 (1%)	3 (5%)
Grade 3	0	0
Haematological		
Neutropenia		
Grade 2	0	2 (3%)
Grade 3	1 (<1%)	3 (5%)
Grade 4	0	4 (7%)
Thrombocytopenia		
Grade 2	0	0
Grade 3	1 (<1%)	1 (2%)
Grade 4	0	2 (3%)
Leukopenia		
Grade 2	0	2 (3%)
Grade 3	0	1 (2%)

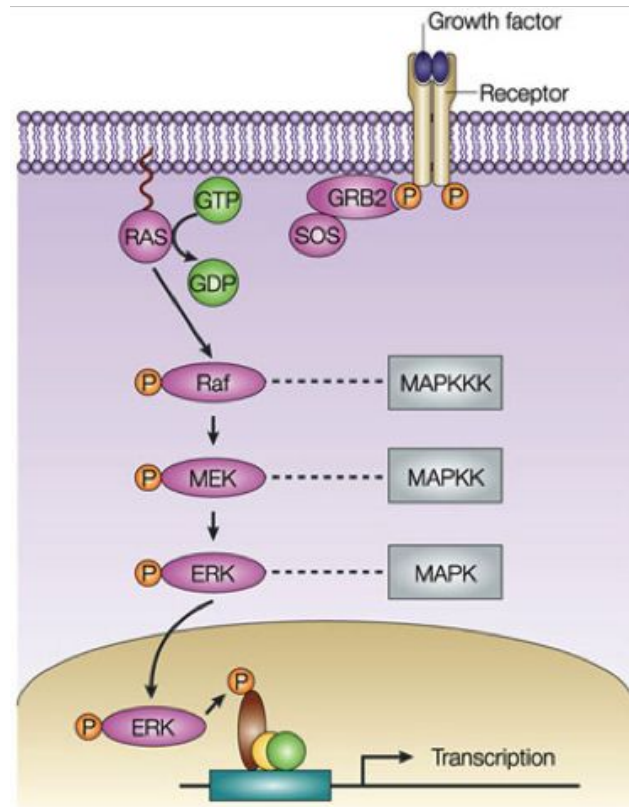
(Continues in next column)

	Dabrafenib	Dacarbazine
(Continued from previous column)		
Other		
Arthralgia		
Grade 2	9 (5%)	0
Grade 3	1 (<1%)	0
Asthenia		
Grade 2	6 (3%)	3 (5%)
Grade 3	0	0
Fatigue		
Grade 2	10 (5%)	3 (5%)
Grade 3	2 (1%)	0
Headache		
Grade 2	9 (5%)	0
Grade 3	0	0
Pyrexia		
Grade 2	15 (8%)	0
Grade 3	5 (3%)	0

Data are number of patients (%). PPE=palmar-plantar erythrodysesthesia. \*Hyperkeratosis includes acanthoma, acrochordon, actinic keratosis, hyperkeratosis, keratosis pilaris, lichenoid keratosis, papilloma, seborrheic keratosis and skin papilloma. †PPE/palmar-plantar hyperkeratosis includes hyperkeratosis palmaris and plantaris, and palmar-plantar erythrodysesthesia syndrome. ‡Includes squamous cell carcinoma of skin, squamous cell carcinoma, and keratoacanthoma (grade 2).

**Table 3: Treatment-related adverse events grade 2 or higher, experienced by at least 5% of patients on either group**

# Сигнальный путь MAPK



# МЕК ингибиторы

- **Траметиниб (Мекинист)** в комбинации с дабрафенибом: лечение пациентов с нерезектабельной или метастатической меланомой с мутацией гена BRAF V600; в виде монотерапии: лечение пациентов с нерезектабельной или метастатической меланомой с мутацией гена BRAF V600.
- **Кобиметиниб (Котеллик)** в комбинации с вемурафенибом: лечение пациентов с неоперабельной или метастатической меланомой с BRAF V600 мутацией.

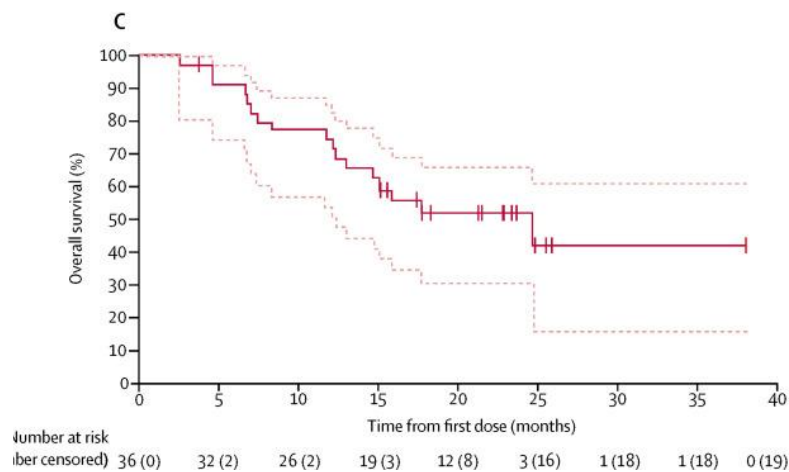
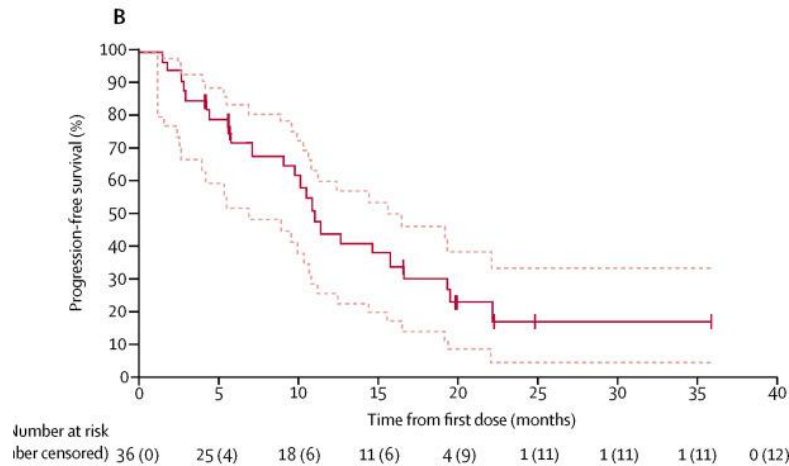


# THE LANCET Oncology

## Dabrafenib plus trametinib in patients with previously untreated *BRAF*<sup>V600E</sup>-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial

David Planchard, MD, Prof Egbert F Smit, MD, Prof Harry J M Groen, MD, Prof Julien Mazieres, MD, Benjamin Besse, MD, Åslaug Helland, MD, Vanessa Giannone, MPA, Anthony M D'Amelio Jr, PhD, Pingkuan Zhang, MD, Bijoyesh Mookerjee, MD, Prof Bruce E Johnson, MD

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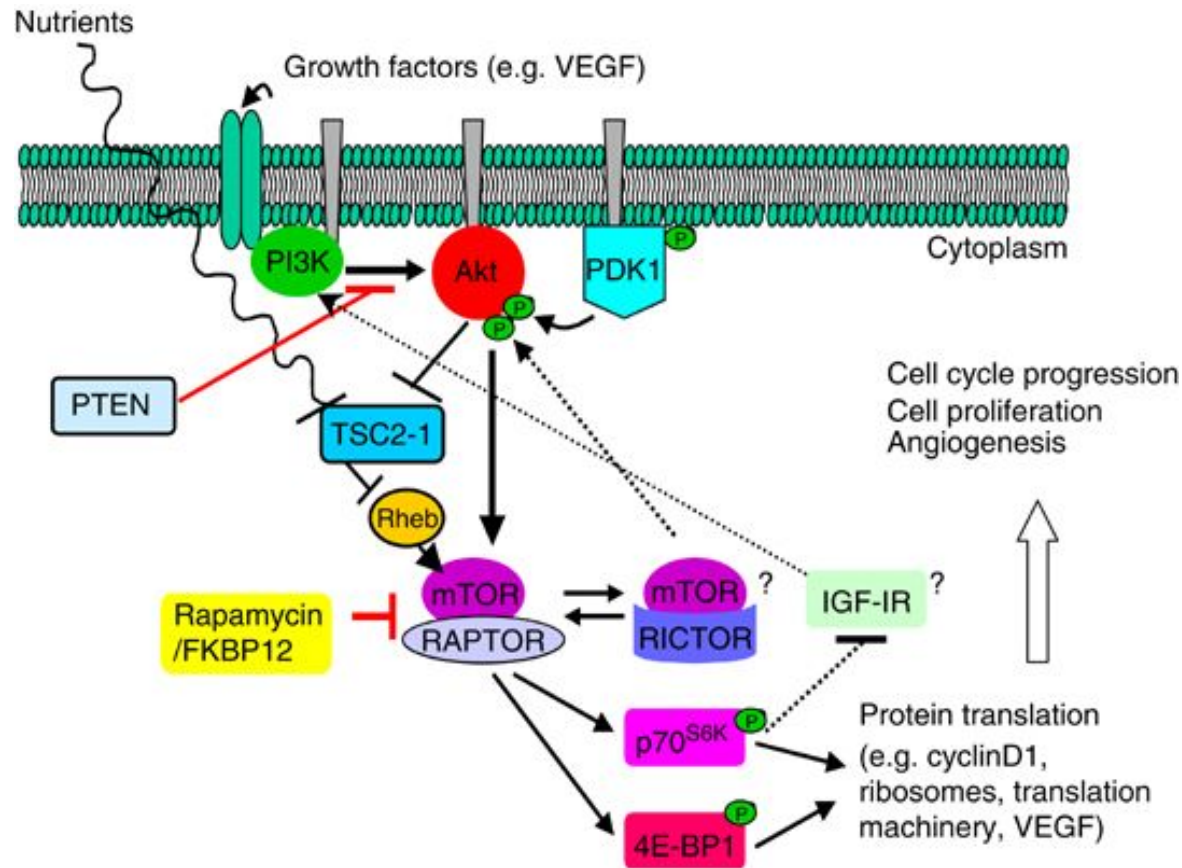


	Investigator assessed (n=36)	Independent review committee assessed (n=36)
Overall response (complete and partial responses)	23 (64%; 46-79)	23 (64%; 46-79)
Disease control (complete responses, partial responses, and stable disease)	27 (75%; 58-88)	26 (72%; 55-86)
Complete response	2 (6%)	2 (6%)
Partial response	21 (58%)	21 (58%)
Stable disease	4 (11%)	3 (8%)
Progressive disease	5 (14%)	7 (19%)
Not evaluable	4 (11%)	3 (8%)



	Grade 1-2	Grade 3	Grade 4	Grade 5
Total	10 (28%)	23 (64%)	2 (6%)	1 (3%)
Pyrexia	19 (53%)	4 (11%)	0	0
Nausea	20 (56%)	0	0	0
Diarrhoea	12 (33%)	1 (3%)	0	0
Fatigue	13 (36%)	0	0	0
Peripheral oedema	13 (36%)	0	0	0
Vomiting	9 (25%)	3 (8%)	0	0
Dry skin	12 (33%)	0	0	0
Decreased appetite	12 (33%)	0	0	0
Chills	9 (25%)	0	0	0
Headache	9 (25%)	0	0	0
Rash	7 (19%)	1 (3%)	0	0
Dizziness	8 (22%)	0	0	0
Cough	8 (22%)	0	0	0
Alanine aminotransferase increase	2 (6%)	4 (11%)	0	0
Dyspnoea	4 (11%)	2 (6%)	0	0
Hypotension	4 (11%)	2 (6%)	0	0
Back pain	6 (17%)	0	0	0
Weight decrease	6 (17%)	0	0	0
Abdominal pain	4 (11%)	1 (3%)	0	0
Anaemia	4 (11%)	1 (3%)	0	0
Arthralgia	4 (11%)	1 (3%)	0	0
Constipation	5 (14%)	0	0	0
Insomnia	5 (14%)	0	0	0
Myalgia	5 (14%)	0	0	0
Hypertension	0	4 (11%)	0	0
Hyponatraemia	2 (6%)	2 (6%)	0	0
Aspartate aminotransferase increase	3 (8%)	1 (3%)	0	0
Asthenia	3 (8%)	1 (3%)	0	0
Pruritus	3 (8%)	1 (3%)	0	0
Pain in extremity	3 (8%)	1 (3%)	0	0
Erythema	4 (11%)	0	0	0
Dysphonia	3 (8%)	0	0	0
Malaise	4 (11%)	0	0	0
Musculoskeletal chest pain	4 (11%)	0	0	0
Urinary tract infection	4 (11%)	0	0	0
Dehydration	2 (6%)	1 (3%)	0	0
Ejection fraction decrease	1 (3%)	2 (6%)	0	0
Pulmonary embolism	1 (3%)	2 (6%)	0	0
Weight increase	2 (6%)	1 (3%)	0	0

# mTOR (mammalian target of rapamycin)




# Ингибиторы mTOR

- **Темсиролимус** – терапия 1-й линии распространенного рака почки у пациентов с неблагоприятным прогнозом течения заболевания.
- **Эверолимус** – лечение распространенного рака почки после неудачи антиангиогенной терапии, лечение местнораспространенного HER2-положительного рака молочной железы.

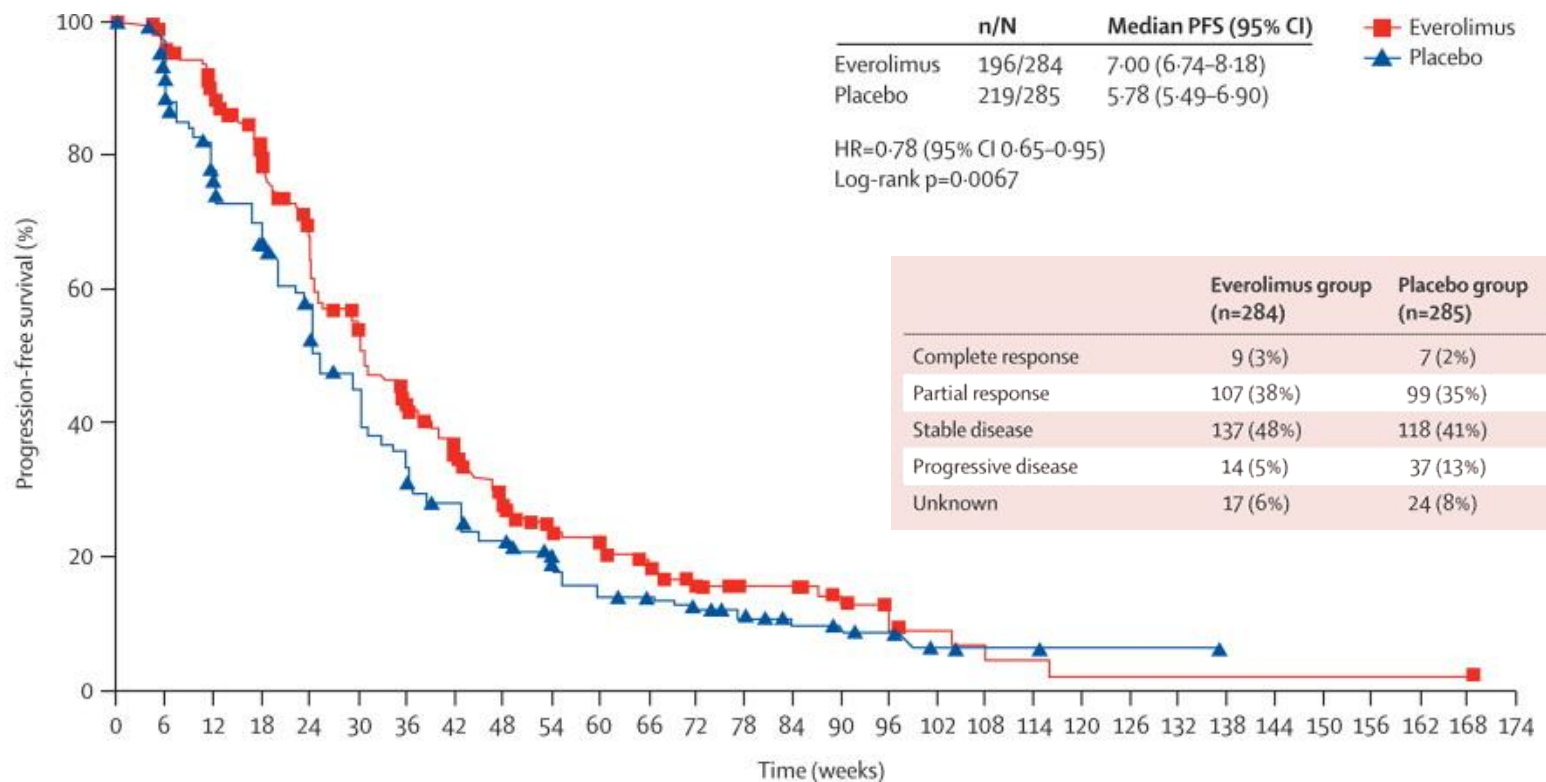


# THE LANCET Oncology

## Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial

Prof Fabrice André, MD, Prof Ruth O'Regan, MD, Prof Mustafa Ozguroglu, MD, Prof Masakazu Toi, MD, Prof Binghe Xu, MD, Prof Guy Jerusalem, MD, Norikazu Masuda, MD, Sharon Wilks, MD, Francis Arena, MD, Prof Claudine Isaacs, MD, Yoon-Sim Yap, MD, Zsuzsanna Papai, MD, Prof Istvan Lang, MD, Anne Armstrong, MD, Guillermo Lerzo, MD, Michelle White, MD, Prof Kunwei Shen, MD, Jennifer Litton, MD, David Chen, PhD, Yufen Zhang, PhD, Shyanne Ali, Tetiana Taran, MD, Dr Luca Gianni, MD 

Published: 14 April 2014

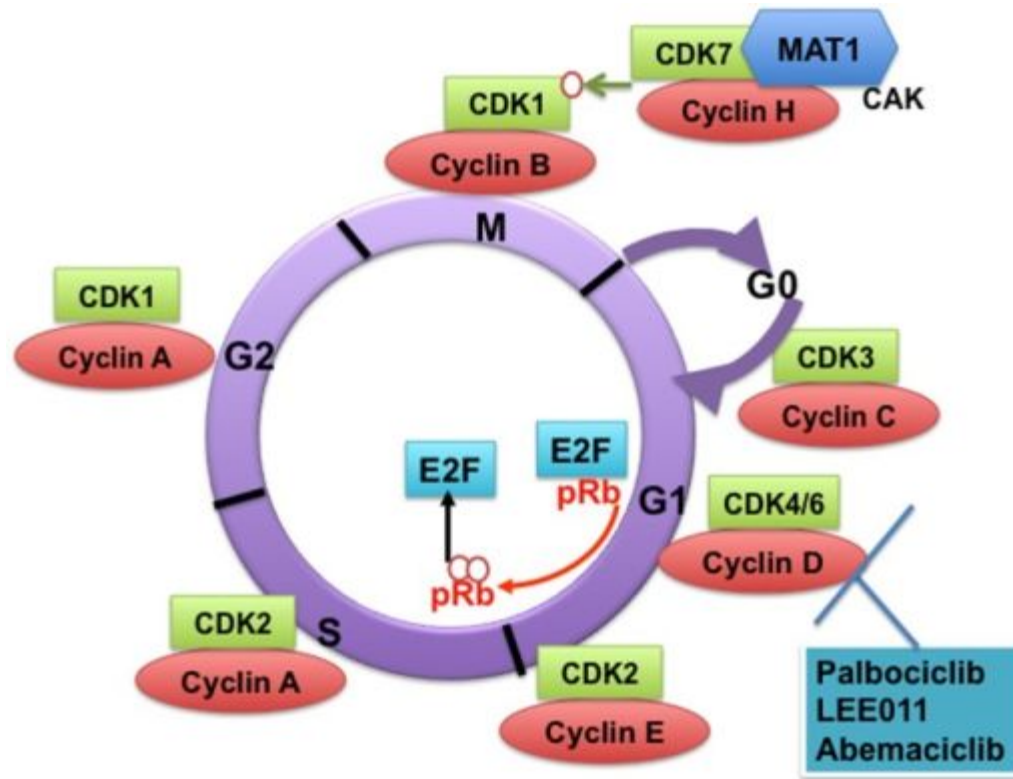


### Number at risk

Everolimus	284	259	233	200	161	126	98	78	54	40	35	26	18	14	14	9	5	4	2	2	1	1	1	1	1	1	1	0
Placebo	285	253	202	177	138	109	85	64	49	38	26	23	19	16	12	10	7	4	3	3	1	1	1	1	0	0	0	0

	Everolimus group (n=280)			Placebo group (n=282)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Neutropenia	24 (9%)	98 (35%)	106 (38%)	22 (8%)	90 (32%)	85 (30%)
Stomatitis	138 (49%)	37 (13%)	0	74 (26%)	4 (1%)	0
Anaemia	85 (30%)	47 (17%)	6 (2%)	66 (23%)	16 (6%)	1 (<1%)
Leucopenia	22 (8%)	85 (30%)	21 (8%)	23 (8%)	71 (25%)	11 (4%)
Fatigue	87 (31%)	33 (12%)	1 (<1%)	107 (38%)	11 (4%)	0
Pyrexia	101 (36%)	7 (3%)	0	62 (22%)	3 (1%)	0
Diarrhoea	96 (34%)	11 (4%)	0	84 (30%)	2 (<1%)	0
Nausea	91 (33%)	7 (3%)	0	100 (35%)	3 (1%)	0
Decreased appetite	88 (31%)	4 (1%)	0	46 (16%)	3 (1%)	0
Constipation	82 (29%)	1 (<1%)	0	87 (31%)	1 (<1%)	0
Weight decreased	81 (29%)	2 (<1%)	0	43 (15%)	1 (<1%)	0
Cough	80 (29%)	1 (<1%)	0	53 (19%)	1 (<1%)	0
Asthenia	60 (21%)	14 (5%)	0	44 (16%)	10 (4%)	2 (<1%)
Headache	70 (25%)	2 (<1%)	0	56 (20%)	2 (<1%)	1 (<1%)
Rash	69 (25%)	0	0	49 (17%)	2 (<1%)	0
Epistaxis	60 (21%)	3 (1%)	0	38 (13%)	0	0
Vomiting	58 (21%)	2 (<1%)	0	57 (20%)	2 (<1%)	0
Dyspnoea	47 (17%)	4 (1%)	1 (<1%)	32 (11%)	9 (3%)	0
Arthralgia	46 (16%)	1 (<1%)	0	33 (12%)	2 (<1%)	0
Febrile neutropenia	3 (1%)	30 (11%)	14 (5%)	1 (<1%)	7 (2%)	3 (1%)
Abdominal pain	45 (16%)	0	0	48 (17%)	1 (<1%)	0
Peripheral oedema	42 (15%)	0	0	24 (9%)	2 (<1%)	0
Pain in extremity	39 (14%)	2 (<1%)	0	40 (14%)	2 (<1%)	0
Thrombocytopenia	30 (11%)	7 (3%)	3 (1%)	5 (2%)	1 (<1%)	0
Myalgia	36 (13%)	2 (<1%)	0	31 (11%)	0	0
Nasopharyngitis	38 (14%)	0	0	28 (10%)	0	0
Back pain	37 (13%)	0	0	41 (15%)	2 (<1%)	0
Upper respiratory tract infection	37 (13%)	0	0	26 (9%)	0	0
Increased alanine aminotransferase	26 (9%)	8 (3%)	1 (<1%)	17 (6%)	8 (3%)	0
Upper abdominal pain	32 (11%)	2 (<1%)	0	36 (13%)	3 (1%)	0
Insomnia	34 (12%)	0	0	25 (9%)	0	0
Hypokalaemia	21 (8%)	11 (4%)	1 (<1%)	16 (6%)	2 (<1%)	0
Increased aspartate aminotransferase	24 (9%)	6 (2%)	1 (<1%)	14 (5%)	7 (2%)	0
Mouth ulceration	28 (10%)	3 (1%)	0	6 (2%)	0	0
Muscle spasms	29 (10%)	2 (<1%)	0	45 (16%)	1 (<1%)	0
Increased gamma-glutamyltransferase	11 (4%)	13 (5%)	5 (2%)	7 (2%)	14 (5%)	2 (<1%)
Bone pain	24 (9%)	2 (<1%)	1 (<1%)	20 (7%)	2 (<1%)	0
Peripheral neuropathy	26 (9%)	1 (<1%)	0	33 (12%)	6 (2%)	0
Hyperglycaemia	19 (7%)	6 (2%)	0	10 (4%)	4 (1%)	0
Peripheral sensory neuropathy	23 (8%)	2 (<1%)	0	15 (5%)	1 (<1%)	0
Decreased haemoglobin	8 (3%)	14 (5%)	0	14 (5%)	3 (1%)	0
Hypertension	20 (7%)	2 (<1%)	0	8 (3%)	1 (<1%)	0
Hypertriglyceridaemia	20 (7%)	2 (<1%)	0	7 (2%)	1 (<1%)	0
Pneumonitis	13 (5%)	1 (<1%)	2 (<1%)	4 (1%)	4 (1%)	1 (<1%)

# CDK (cyclin-dependent kinases)



# Ингибиторы CDK 4/6

- **Палбоциклиб** – лечение местнораспространенного или метастатического HR-положительного и HER2-отрицательного рака молочной железы (в сочетании с фулвестрантом), после предшествующей гормональной терапии.
- ESMO 2017: в рандомизированном исследовании MONARCH 3 **абемациклиб** продемонстрировал эффективность в качестве терапии первой линии у пациенток с HR+/HER2-распространенным раком молочной железы.

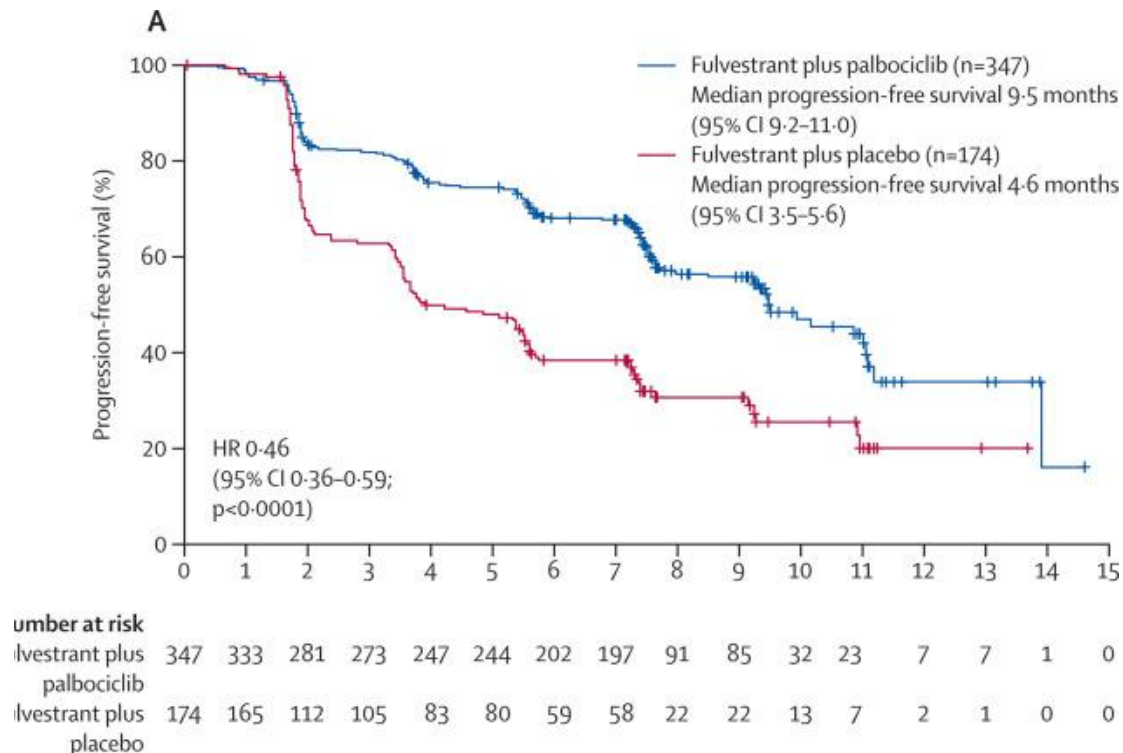


## Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial

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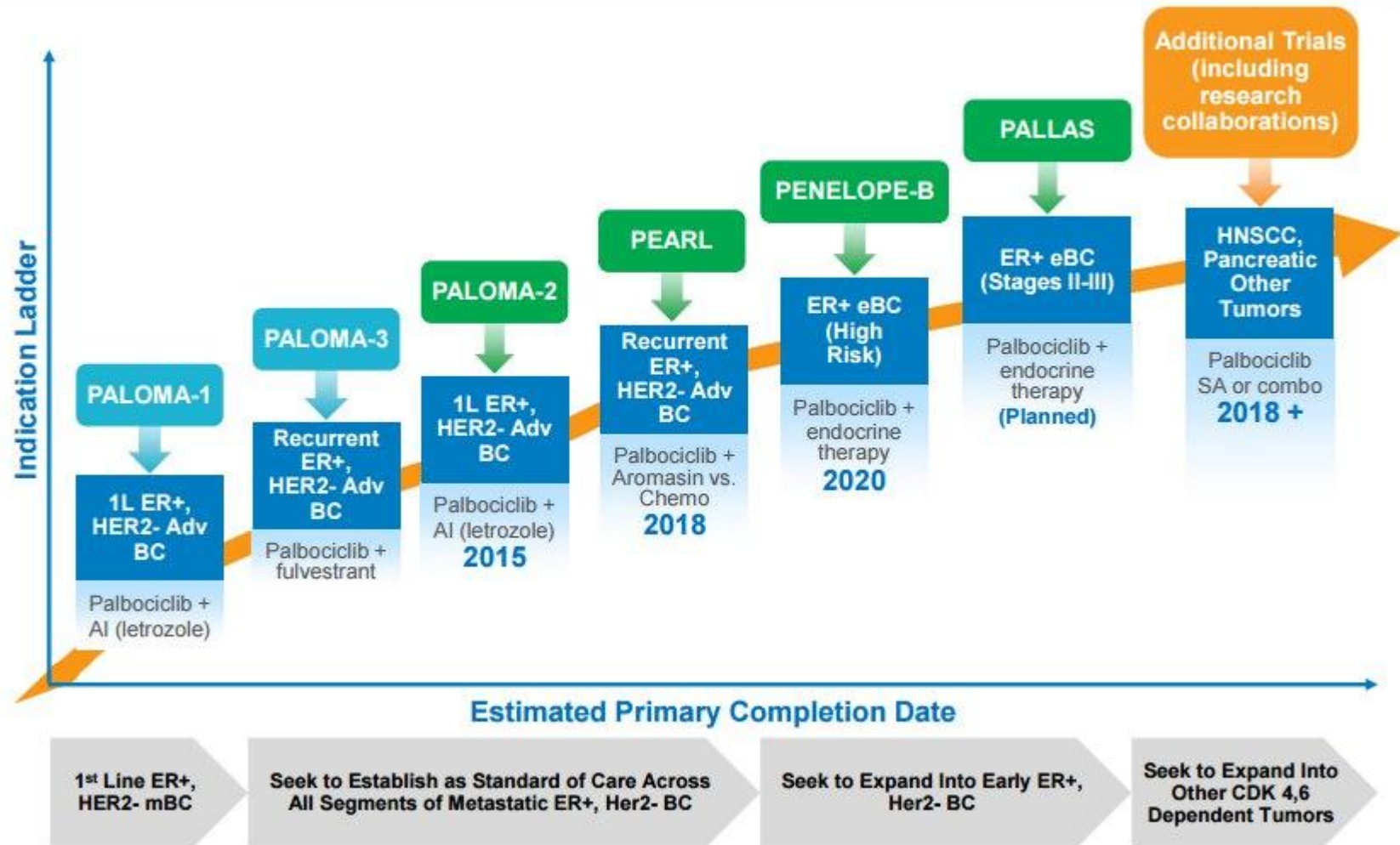




	Fulvestrant plus palbociclib (n=345)				Fulvestrant plus placebo (n=172)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
<b>Haematological</b>								
Neutropenia	56 (16%)	189 (55%)	34 (10%)	0	5 (3%)	0	1 (1%)	0
Anaemia	86 (25%)	10 (3%)	0	0	16 (9%)	3 (2%)	0	0
Leucopenia	76 (22%)	93 (27%)	2 (1%)	0	5 (3%)	1 (1%)	1 (1%)	0
Thrombocytopenia	65 (19%)	6 (2%)	2 (1%)	0	0	0	0	0
Lymphopenia	4 (1%)	1 (<1%)	1 (<1%)	0	1 (1%)	1 (1%)	0	0
<b>Non-haematological</b>								
Infections	137 (40%)	6 (2%)	1 (<1%)	0	47 (27%)	5 (3%)	0	0
Fatigue	127 (37%)	8 (2%)	0	0	47 (27%)	2 (1%)	0	0
Nausea	112 (32%)	0	0	0	46 (27%)	1 (1%)	0	0
Headache	78 (23%)	2 (1%)	0	0	33 (19%)	0	0	0
Diarrhoea	74 (21%)	0	0	0	31 (18%)	1 (1%)	0	0
Constipation	66 (19%)	0	0	0	27 (16%)	0	0	0
Alopecia	58 (17%)	0	0	0	11 (6%)	0	0	0
Vomiting	57 (17%)	1 (<1%)	0	0	24 (14%)	1 (1%)	0	0
Hot flush	53 (15%)	0	0	0	28 (16%)	1 (1%)	0	0
Decreased appetite	49 (14%)	3 (1%)	0	0	13 (8%)	1 (1%)	0	0
Rash	50 (14%)	2 (1%)	0	0	9 (5%)	0	0	0
Back pain	47 (14%)	4 (1%)	0	0	26 (15%)	3 (2%)	0	0
Cough	51 (15%)	0	0	0	22 (13%)	0	0	0
Arthralgia	48 (14%)	1 (<1%)	0	0	27 (16%)	0	0	0
Pain in extremity	43 (12%)	0	0	0	18 (10%)	3 (2%)	0	0
Stomatitis	41 (12%)	2 (1%)	0	0	4 (2%)	0	0	0
Dizziness	40 (12%)	1 (<1%)	0	0	16 (9%)	0	0	0
Dyspnoea	39 (11%)	0	1 (<1%)	0	12 (7%)	2 (1%)	0	0
Pyrexia	37 (11%)	1 (<1%)	0	0	9 (5%)	0	0	0
Insomnia	32 (9%)	1 (<1%)	0	0	12 (7%)	0	0	0
Abdominal pain	25 (7%)	2 (1%)	0	0	9 (5%)	1 (1%)	0	0
Upper-respiratory-tract infection	25 (7%)	2 (1%)	0	0	12 (7%)	0	0	0
Musculoskeletal pain	25 (7%)	1 (<1%)	0	0	11 (6%)	1 (1%)	0	0
Increased aspartate aminotransferase	15 (4%)	9 (3%)	0	0	5 (3%)	3 (2%)	0	0
Injection-site pain	21 (6%)	1 (<1%)	0	0	17 (10%)	0	0	0
Depression	19 (6%)	2 (1%)	0	0	9 (5%)	1 (1%)	0	0
Hypertension	14 (4%)	7 (2%)	0	0	3 (2%)	1 (1%)	0	0
Increased alanine aminotransferase	13 (4%)	6 (2%)	0	0	6 (3%)	0	0	0
Bone pain	15 (4%)	2 (1%)	0	0	5 (3%)	2 (1%)	0	0
Pain	16 (5%)	1 (<1%)	0	0	12 (7%)	2 (1%)	0	0
Abdominal distension	15 (4%)	1 (<1%)	0	0	8 (5%)	0	0	0
Gastro-oesophageal reflux disease	14 (4%)	2 (1%)	0	0	3 (2%)	0	0	0
Upper abdominal pain	13 (4%)	1 (<1%)	0	0	13 (8%)	0	0	0
Malaise	9 (3%)	3 (1%)	0	0	7 (4%)	0	0	0
Neck pain	10 (3%)	1 (<1%)	0	0	6 (3%)	0	0	0

# Ibrance Brand Vision:

*Breakthrough Therapy That Has Potential to Revolutionize Treatment Outcomes in Breast Cancer and Other CDK 4,6 Dependent Tumors*



Source: Pfizer Oncology ASCO Analyst Call 2015