Клиническая и лабораторная генетика в онкологии

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Санкт-Петербургский государственный университет

С.-Петербург

Клиническая генетика

- Наследственные опухолевые синдромы

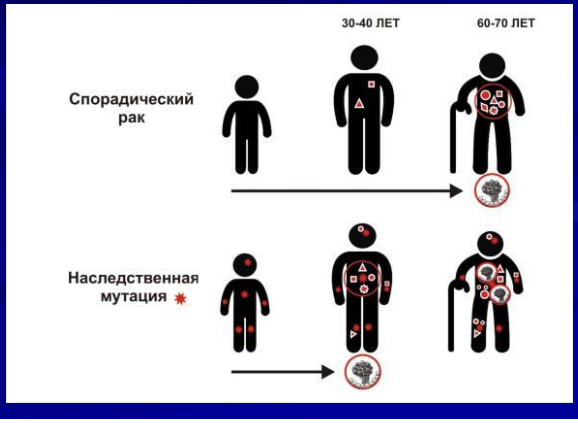
Лабораторная генетика

- Выбор терапии на основе молекулярных характеристик опухоли
  - Детекция диссеминированных (циркулирующих) опухолевых клеток
  - Дифференциальная диагностика опухолей с неизвестным первичным очагом

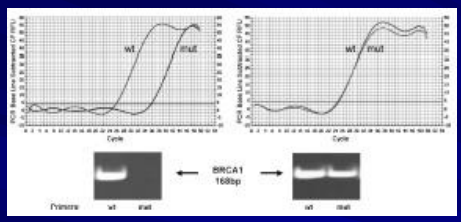
Наследственные опухолевые синдромы

Наследственные опухолевые синдромы

- Самое частое наследственное заболевание (1-2% популяции)
- 10% опухолей молочной железы, 20% карцином яичника, 3% новообразований толстой кишки и эндометрия



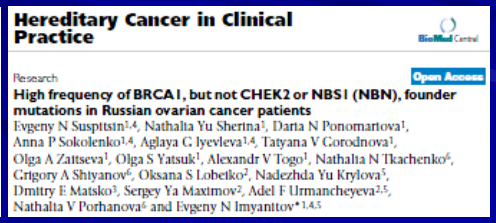
BRCA1 5382insC: эффект основателя



- 0.1% в популяции
- 3.7% у больных РМЖ
- 10% у пациенток с билатеральным и наследственным РМЖ
- 15-20% у больных раком яичника

High frequency of BRCA1 5382insC mutation in Russian breast cancer patients

Anna P. Sokolenko[a], Natalia V. Mitiushkina[a], Konstantin G. Buslov[a], Elena M. Bit-Sava[a], Aglaya G. Iyevleva[a], Elena V. Chekmariova[a], Ekaterina Sh. Kuligina[a], Yulia M. Ulibina[a], Maxim E. Rozanov[a], Evgeny N. Suspitsin[a], Dmitry E. Matsko[b], Oleg L. Chagunava[b], Dmitry Yu. Trofimov[c], Peter Devilee[d], Cees Cornelisse[d], Alexandr V. Togo[a], Vladimir F. Semiglazov[a], Evgeny N. Imyanitov[a,*]



Hereditary Cancer in Clinical Practice

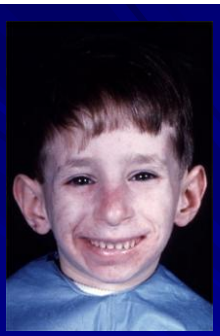
Research

Open Access

High frequency of BRCA1, but not CHEK2 or NBS1 (NBN), founder mutations in Russian ovarian cancer patients

Evgeny N Suspitsin[1,4], Nathalia Yu Sherina[1], Darta N Ponomartova[1], Anna P Sokolenko[1,4], Aglaya G Iyevleva[1,4], Tatyana V Gorodnova[1], Olga A Zaitseva[1], Olga S Yatsuk[1], Alexandr V Togo[1], Nathalia N Tkachenko[6], Grigory A Shityanov[6], Oksana S Lobeiko[2], Nadezhda Yu Krylova[5], Dmitry E Matsko[3], Sergey Ya Maximov[2], Adel F Urmancheyeva[2,5], Nathalia V Porhanova[6] and Evgeny N Imyanitov*[1,4,5]

BLM: новый ген наследственного рака молочной железы



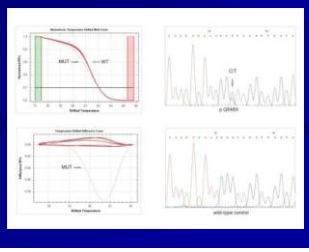
Синдром Блума

- Bloom syndrome
- Ген репарации ДНК
- Гомозиготы: низкий рост, гиперчувствительность кожи к УФ, нарушения фертильности, предрасположенность к раку
- Гетерозиготы: риск РМЖ

High prevalence and breast cancer predisposing role of the BLM c.1642 C>T (Q548X) mutation in Russia

Anna P. Sokolenko[1,2], Aglaya G. Iyevleva[1,2], Elena V. Preobrazhenskaya[1], Nathalia V. Mitiushkina[1], Svetlana N. Abysheva[1], Evgeny N. Suspitsin[1,2], Ekatherina Sh. Kuligina[1], Tatiana V. Gorodnova[1], Werner Pfeifer[1], Alexandr V. Togo[1], Elena A. Turkevich[1], Alexandr O. Ivantsov[1], Dmitry V. Voskresenskiy[2], Georgy D. Dolmatov[3], Elena M. Bit-Sava[1], Dmitry E. Matsko[1], Vladimir F. Semiglazov[1], Iduna Fichtner[4], Alexey A. Larionov[5], Sergey G. Kuznetsov[6], Antonis C. Antoniou[7] and Evgeny N. Imyanitov[1,2,8]

- “Founder” мутация в России
- Частота в популяции: 0.2-0.3%
- РМЖ: >1%
- Увеличение риска РМЖ в ~6 раз



«Эффект основателя» в России

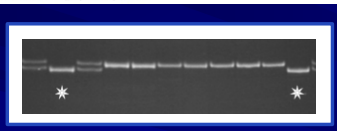
- Относительная генетическая гомогенность славянского населения России
- Подтверждается исследованиями мутаций в генах наследственного РМЖ (BRCA1, CHEK2, NBS1, BLM)
- Обоснование целесообразности полноэкзомного секвенирования для поиска новых генов наследственного рака

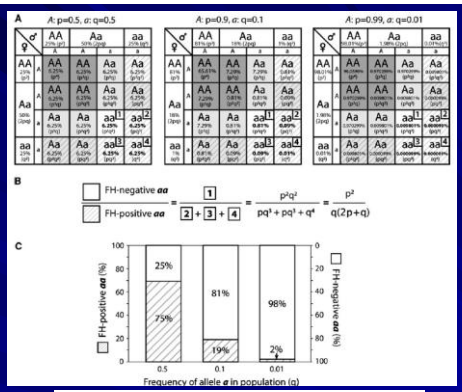
Familial Cancer (2013) 12:129–132
DOI 10.1007/s10689-012-9575-x

LETTER TO THE EDITOR

Value of bilateral breast cancer for identification of rare recessive at-risk alleles: evidence for the role of homozygous *GEN1* c.2515_2519delAAGTT mutation

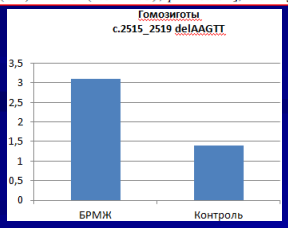
Ekatherina Sh. Kuligina · Anna P. Sokolenko · Nathalia V. Mitiushkina · Svetlana N. Abysheva · Elena V. Preobrazhenskaya · Tatiana V. Gorodnova · Grigoriy A. Yanus · Alexandr V. Togo · Nadezhda V. Cherdyntseva · Svetlana A. Bekhtereva · J. Michael Dixon · Alexey A. Larionov · Sergey G. Kuznetsov · Evgeny N. Imyanitov

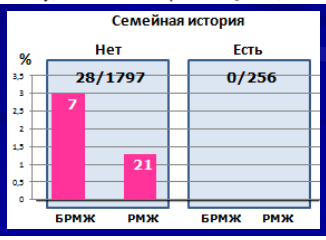




that the c.2515_2519delAAGTT homozygous mutation in a Holliday junction resolvase, GEN1, was overrepresented in women with bilateral breast cancer (BC) as compared to healthy controls [11/360 (3.1 %) vs. 18/1305 (1.4 %); odds ratio (OR) = 2.25 (1.02–4.75); $p = 0.031$], although this

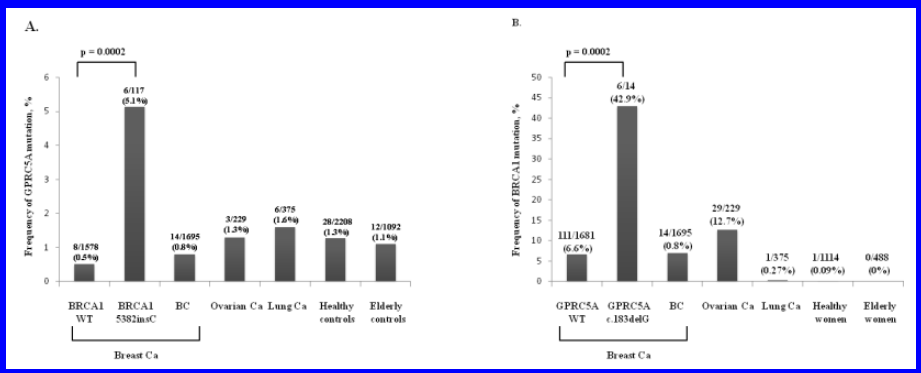
delAAGTT mutation was associated with the absence of BC in mother both in bilateral and unilateral BC cases [7/239 (3.0 %) vs. 0/41 (0 %) and 21/1,558 (1.3 %) vs. 0/215 (0 %), respectively; Mantel–Haenszel $p = 0.041$]. Thus, this study



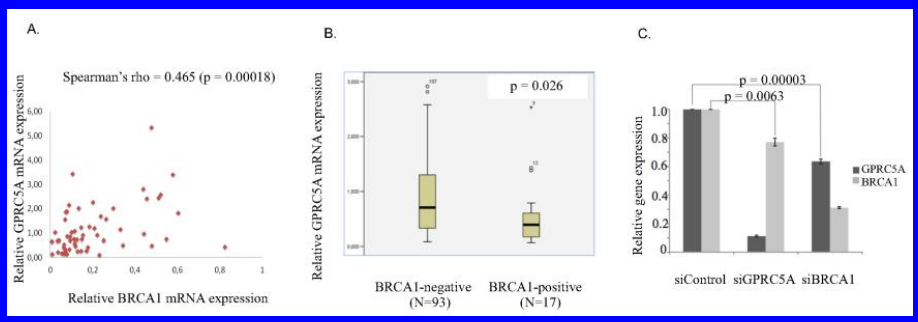


GPRC5A c.183delG [p.Arg61fs]: модификатор пенетрантности BRCA1

- *GPRC5A:* orphan G protein-coupled receptor

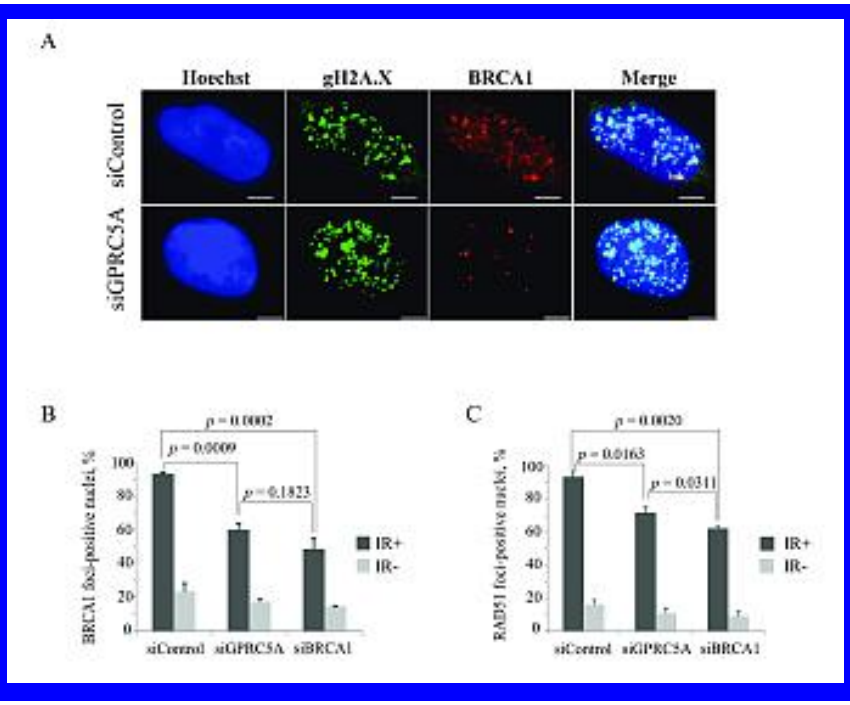


Координированная экспрессия *GPRC5A* и *BRCA1*



High prevalence of *GPRC5A* germline mutations in *BRCA1*-mutant breast cancer patients

Anna P. Sokolenko[1,2*], Daria R. Bulanova[3*], Aglaya G. Iyevleva[1,2], Svetlana N. Aleksakhina[1], Elena V. Preobrazhenskaya[1], Alexandr O. Ivantsov[1], Ekatherina Sh. Kuligina[1], Natalia V. Mitiushkina[1], Evgeny N. Suspitsin[1], Grigoriy A. Yanus[1,2], Olga A. Zaitseva[1], Olga S. Yatsuk[1], Alexandr V. Togo[1], Poojitha Kota[3], J. Michael Dixon[4], Alexey A. Larionov[4,5], Sergey G. Kuznetsov[3] and Evgeny N. Imyanitov[1,2,6]



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Выбор терапии на основе молекулярных характеристик опухоли

Рак молочной железы
Рак яичника

BRCA1-ассоциированные опухоли

- В организме: инактивация одного аллеля BRCA1
- В опухоли: инактивация обоих аллелей BRCA1
- Чувствительность к препаратам платины
- Резистентность к «золотому стандарту» лечения РМЖ – таксанам
- PARP-ингибиторы

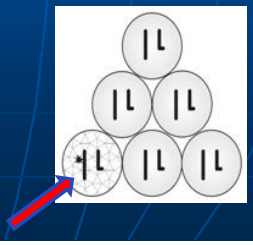


Table 2 Neoadjuvant cisplatin in BC patients carrying BRCA1 mutation

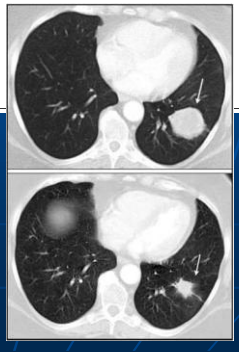
Study	Number of patients	Mode of patient recruitment	Baseline disease characteristics	Cisplatin dose	Clinical response	Complete pathologic response
Silver et al. [6]	2	Patients included in neoadjuvant cisplatin trial for triple-negative BC	T2N + and T3N+	75 mg/m^2, every 3 weeks, 4 cycles	2/2 (100 %)	2/2 (100 %)
Kolacinska et al. [5]	1	Retrospective analysis of various groups of BC patients treated by neoadjuvant therapy	T2N2	75 mg/m^2, every 3 weeks, number of cycles not specified (between 4 and 6)	nd	1/1 (100 %)
Byrski et al. [4]	107	Prospective study	T1: 49 (46 %) T2: 33 (31 %) T3: 17 (16 %) T4: 8 (7 %) N0: 69 (65 %) N1: 24 (22 %) N2: 2 (11 %) N3: 2 (2 %)	75 mg/m^2, every 3 weeks, 4 cycles	nd	pCR in 65/107 (61 %) patients
Present study	6	Prospective study	T1: 0 (0 %) T2: 2 (33 %) T3: 1 (17 %) T4: 3 (50 %) N0: 2 (33 %) N1: 1 (17 %) N2: 3 (50 %) N3: 0 (0 %)	75–100 mg/m^2, every 3–4 weeks, 4–6 cycles	6/6 (100 %)	3/5 (60 %)

Med Oncol (2015) 32:89
DOI 10.1007/s12032-015-0514-1

SHORT COMMUNICATION

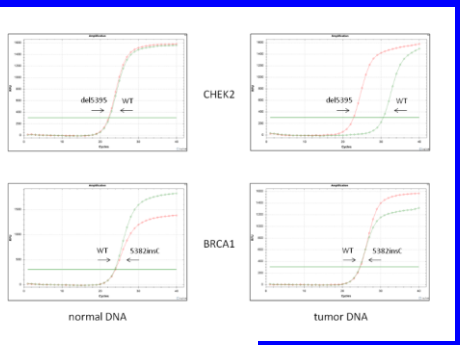
High efficacy of cisplatin neoadjuvant therapy in a prospective series of patients carrying BRCA1 germ-line mutation

Vladimir M. Moiseyenko · Georgiy D. Dolmatov · Fedor V. Moiseyenko · Alexandr O. Ivantsov · Nikita M. Volkov · Vyacheslav A. Chubenko · Nuriniso Kh. Abduloeva · Alexey A. Bogdanov · Anna P. Sokolenko · Evgeny N. Imyanitov



Утрата оставшегося аллеля

- CHEK2: 3/18 (17%)
- BLM: 0/10 (0%)
- NBS1: 1/4 (25%)

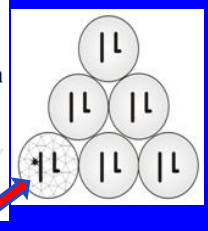


Med Oncol (2014) 31:828
DOI 10.1007/s12032-013-0828-9

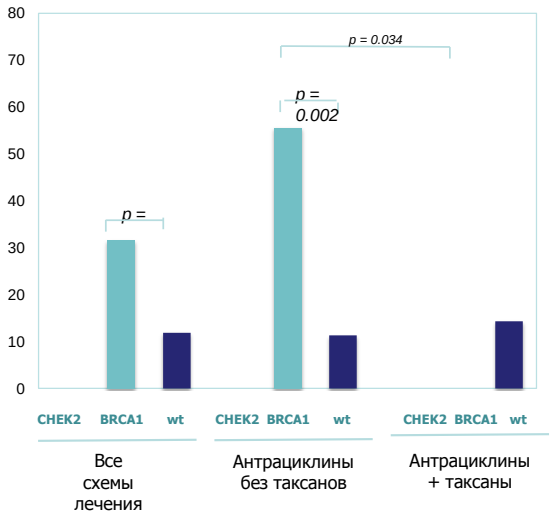
ORIGINAL PAPER

Development of breast tumors in CHEK2, NBN/NBS1 and BLM mutation carriers does not commonly involve somatic inactivation of the wild-type allele

Evgeny N. Suspitsin · Grigory A. Yanus · Anna P. Sokolenko · Olga A. Yatsuk · Olga A. Zaitseva · Alexandr A. Bessonov · Alexandr O. Ivantsov · Valeria A. Heinstein · Valery F. Klimashevskiy · Alexandr V. Togo · Evgeny N. Imyanitov

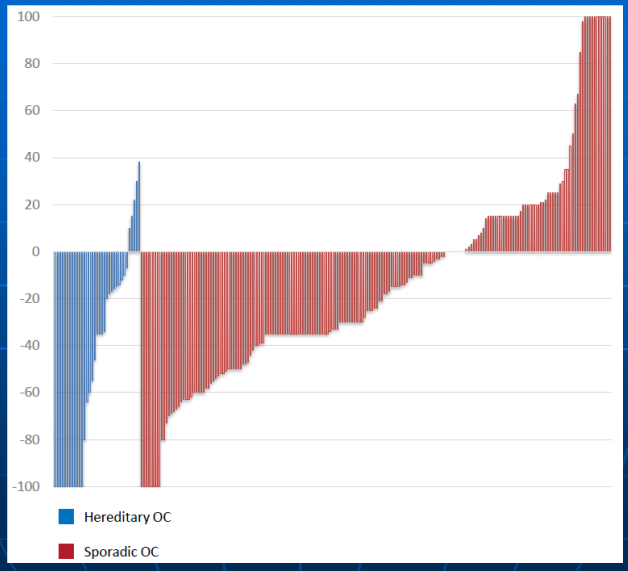


Неоадъювантная терапия спорадических и наследственных РМЖ



Pfeifer et al., 2014

Неоадъювантная терапия рака яичника



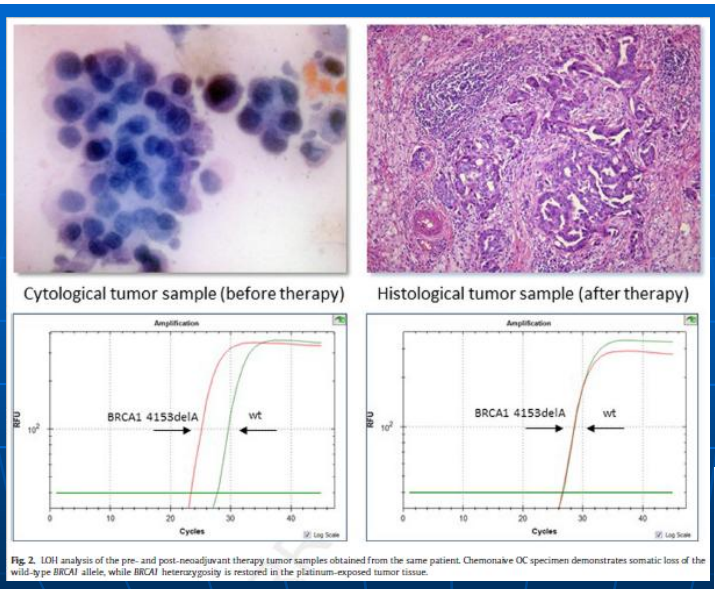
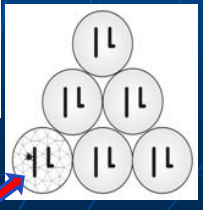
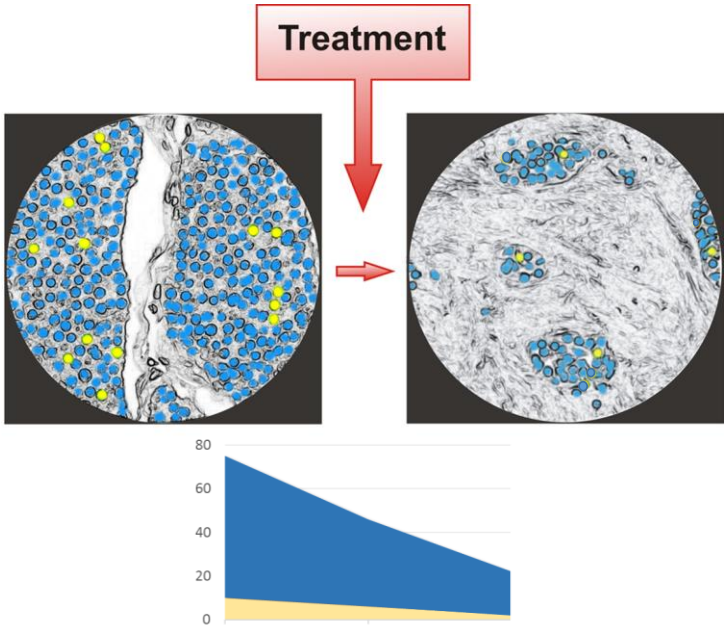
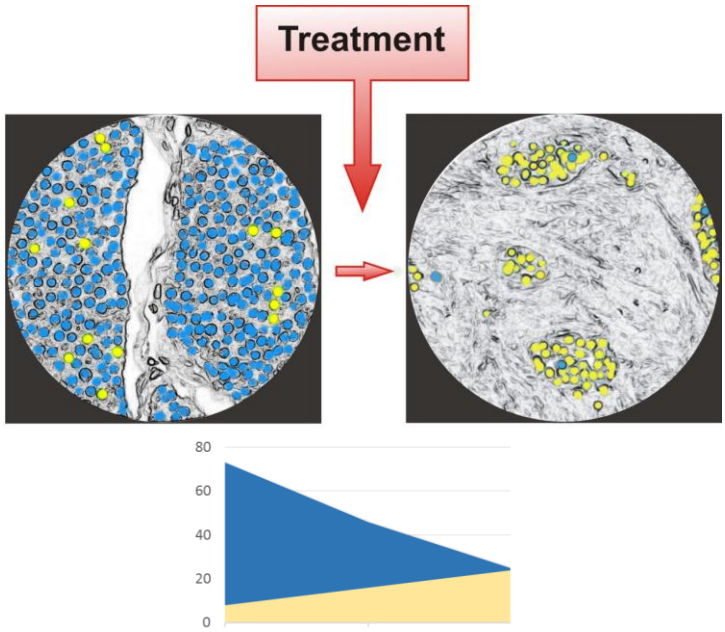
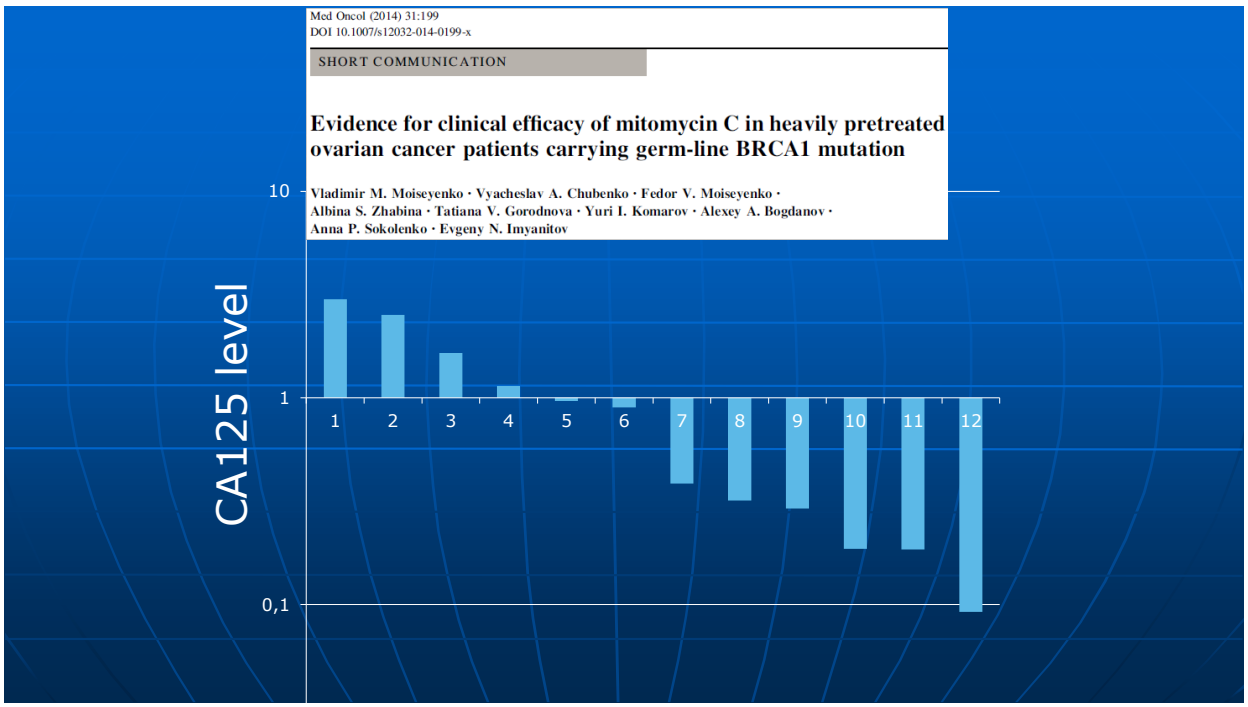


Fig. 2. LOH analysis of the pre- and post-neoadjuvant therapy tumor samples obtained from the same patient. Chemonaive OC specimen demonstrates somatic loss of the wild-type *BRCA1* allele, while *BRCA1* heterozygosity is restored in the platinum-exposed tumor tissue.






Treatment
80
60
40
20
0


Med Oncol (2014) 31:199
DOI 10.1007/s12032-014-0199-x
SHORT COMMUNICATION
Evidence for clinical efficacy of mitomycin C in heavily pretreated ovarian cancer patients carrying germ-line BRCA1 mutation
Vladimir M. Moiseyenko · Vyacheslav A. Chubenko · Fedor V. Moiseyenko · Albina S. Zhabina · Tatiana V. Gorodnova · Yuri I. Komarov · Alexey A. Bogdanov · Anna P. Sokolenko · Evgeny N. Imyanitov
CA125 level
10
1
0,1
1
2
3
4
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6
7
8
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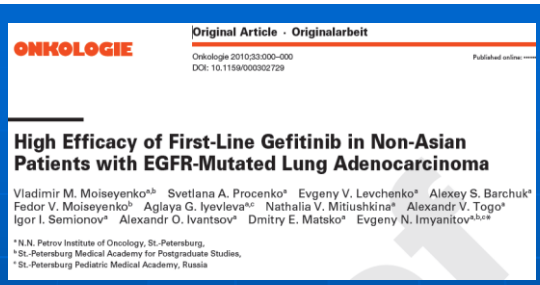
10
11
12

Рак лёгкого



ONKOLOGIE

Original Article · Originalarbeit

Onkologie 2010;33:000–000
DOI: 10.1159/000302729

High Efficacy of First-Line Gefitinib in Non-Asian Patients with EGFR-Mutated Lung Adenocarcinoma

Vladimir M. Moiseyenko[a,b] Svetlana A. Procenko[a] Evgeny V. Levchenko[a] Alexey S. Barchuk[a] Fedor V. Moiseyenko[b] Aglaya G. Iyevleva[a,c] Nathalia V. Mitiushkina[a] Alexandr V. Togo[a] Igor I. Semionov[a] Alexandr O. Ivantsov[a] Dmitry E. Matsko[a] Evgeny N. Imyanitov[a,b,c]

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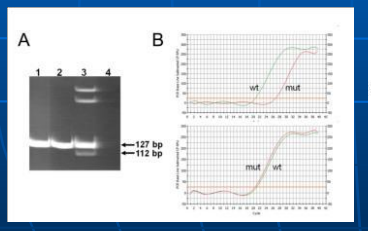
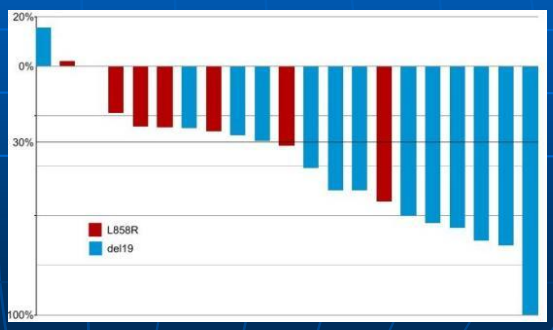
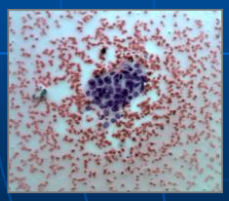




Detection of *EGFR* Mutations and *EML4-ALK* Rearrangements in Lung Adenocarcinomas Using Archived Cytological Slides

Natalia V. Mitiushkina, PhD[1]; Aglaya G. Iyevleva, MD, PhD[1,2]; Artiom N. Poltoratskiy, MD[3]; Alexandr O. Ivantsov, MD, PhD[4]; Alexandr V. Togo, PhD[1]; Igor S. Polyakov, MD, PhD[5]; Sergey V. Orlov, MD, PhD[3]; Dmitry E. Matsko, MD, PhD[4]; Viktor I. Novik, MD, PhD[6]; and Evgeny N. Imyanitov, MD, PhD[2,7,8]



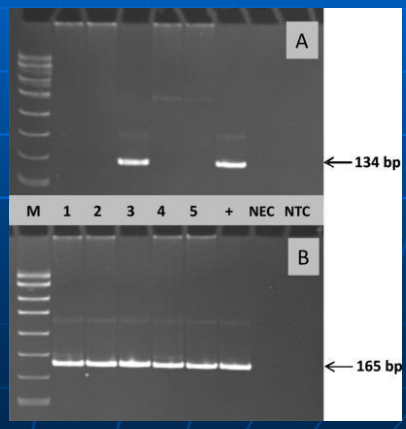


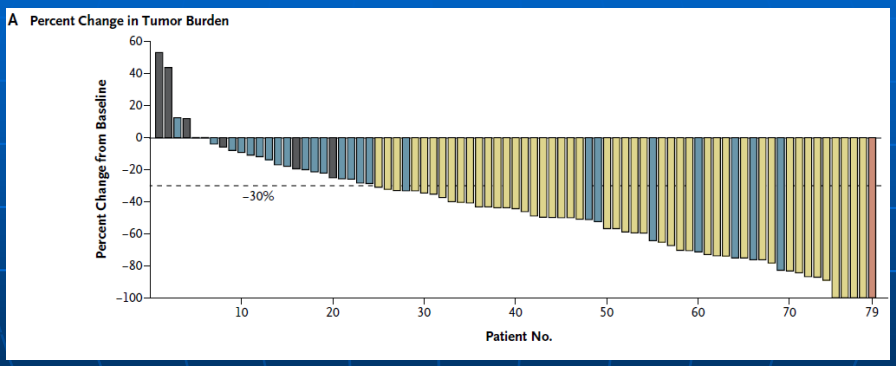
TABLE 1. Success Rate for DNA and RNA Isolation From Cytological and Histological Lung Cancer Samples[a]

DNA/RNA	Cytological Samples	Histological Samples	No of Informative Sample Pairs
DNA isolation (n=75)	73 (97%)	74 (99%)	72 (96%)
RNA isolation (n=44)	42 (95%)	38 (86%)	36 (82%)

TABLE 3. *EGFR* and *EML4-ALK* Testing in Cytological and Histological Lung Cancer Samples

Test	*EGFR* Mutations (n=72)	*EML4-ALK* Translocations (n=36)
Concordant pairs		
Wild-type/wild-type	54 (75%)	32 (89%)
Mutation/mutation	14 (19%)	4 (11%)
Total	68/72 (94%)	36 (100%)
Discordant pairs		
Cytology: mutation/ histology: wild-type	3 (4%)	0
Cytology: wild-type/ histology: mutation	1 (1%)	0
Total	4 (6%)	0

Кризотиниб у больных с транслокацией EML4-ALK



Kwak et al., 2010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Original Articles

Novel *ALK* fusion partners in lung cancer

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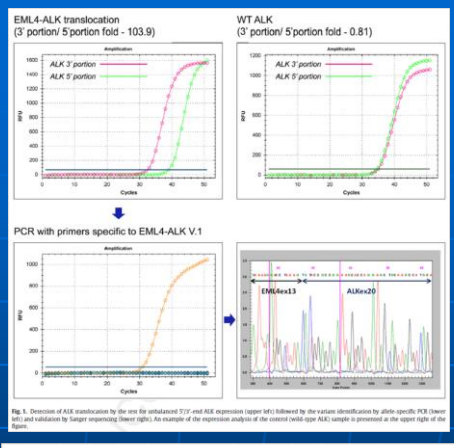


Fig. 1. Detection of ALK translocation by the test for unbalanced 5'/3'-end ALK expression (upper left) followed by the variant identification by allele-specific PCR (lower left) and validation by Sanger sequencing (lower right). An example of the expression analysis of the control (wild-type ALK) sample is presented at the upper right of the figure.

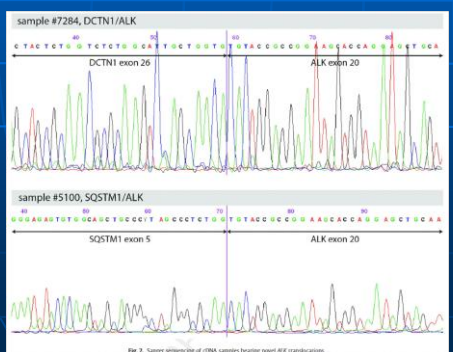


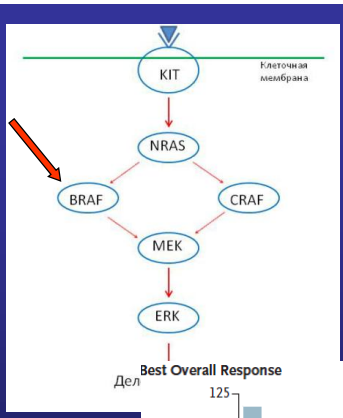
Fig. 2. Sanger sequencing of cDNA samples bearing novel ALK translocations.

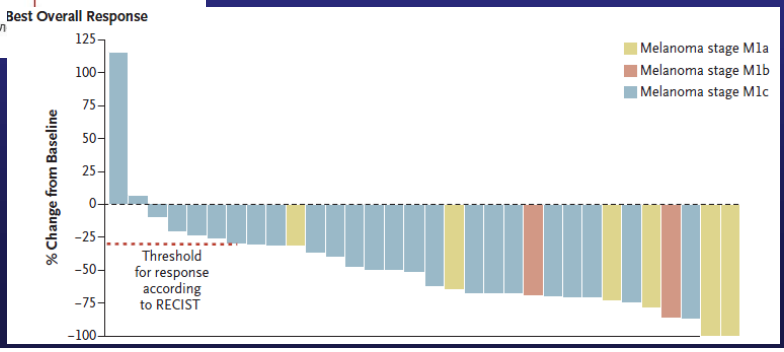
Table 2
Comparison of break-apart FISH and PCR assays.

Sample groups	FISH+	FISH−
Unbalanced ALK+ and variant-specific RT-PCR+ (n = 6)	6 (100%)	0 (0%)
Unbalanced ALK+ and variant-specific RT-PCR− (n = 5)	2* (40%)	3 (60%)
Unbalanced ALK− and variant-specific RT-PCR+ (n = 1)	1 (100%)	0 (0%)
Unbalanced ALK− and variant-specific RT-PCR− (n = 43)	0 (0%)	43 (100%)

* NGS analysis revealed novel translocations in both these samples.

Меланома





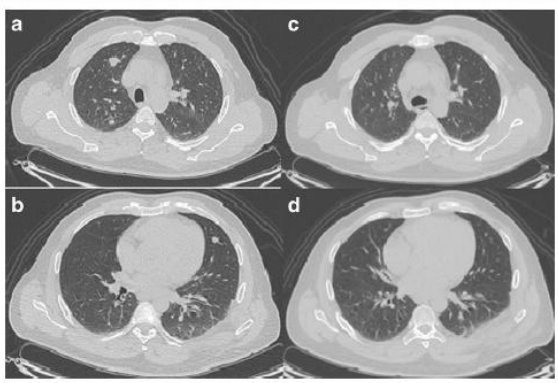
Invest New Drugs
DOI 10.1007/s10637-015-0280-0

SHORT REPORT

BRAF-mutated clear cell sarcoma is sensitive to vemurafenib treatment

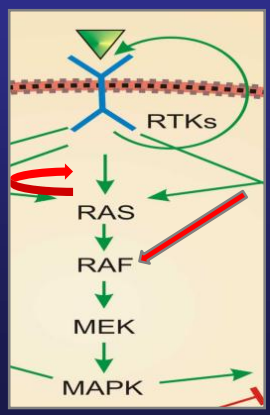
Svetlana A. Protsenko[1] · Anna I. Semionova[1] · Yuri I. Komarov[1] · Svetlana N. Aleksakhina[1] · Alexandr O. Ivantsov[1] · Aglaya G. Iyevleva[2] · Evgeny N. Imyanitov[1,2,3,4]

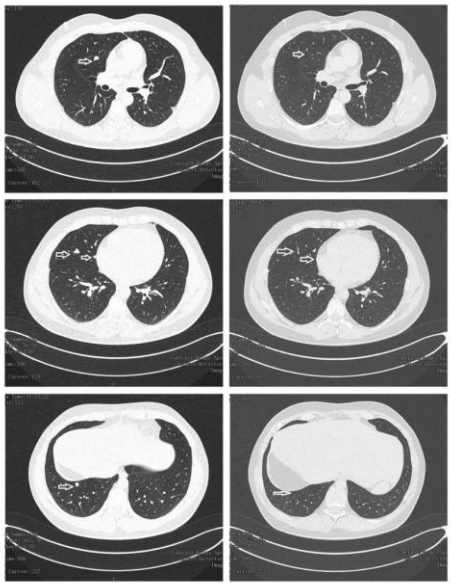
Fig 2 Multiple lung metastases (from 1.2 to 2.5 cm in diameter) before vemurafenib treatment (a, b); complete response of all lung metastases at 8 weeks of vemurafenib treatment (c, d)



Complete Clinical Response of BRAF-Mutated Cholangiocarcinoma to Vemurafenib, Panitumumab, and Irinotecan

Sergey V. Silkin [1] · Sergey S. Startsev [1] · Marina E. Krasn
Natalia V. Mitiushkina [3] · Aglaya G. Iyevleva [3,4] · Anna P.
Evgeny N. Imyanitov [3,4,5,6]





Targ Oncol
DOI 10.1007/s11523-015-0384-7

THERAPY IN PRACTICE

Vemurafenib-induced progression of breast cancer: a case report and review of the literature

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Aleksander O. Ivantsov [1] · Tatyana L. Nekhaeva [1,2] · Zinaida Y. Akhaeva [1] ·
Grigoriy A. Yanus [1,2] · Aglaya G. Iyevleva [1,2] · Evgeny N. Imyanitov [1,3,3,4]

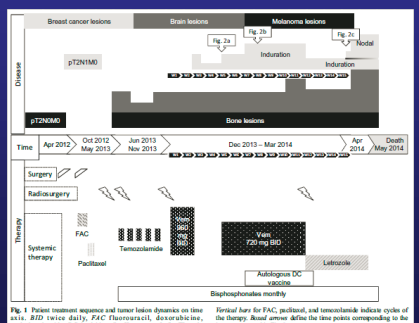

Fig. 1 Patient treatment sequence and tumor lesion dynamics on time axis. *BID* twice daily, *FAC* fluorouracil, doxorubicine, cyclophosphamide, *DC* dendritic cells, *Vem* vemurafenib, *W* week. *Vertical bars* for FAC, paclitaxel, and temozolamide indicate cycles of the therapy. *Round arrows* define the time points corresponding to the images presented in Fig. 2

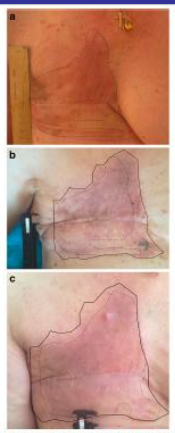

Fig. 2 a Breast cancer skin lesions on vemurafenib therapy at the time of their initial detection, i.e., at 4 weeks since the onset of vemurafenib therapy. *Dotted line* indicates the margins of skin elevation and infiltration. b Rapid progression of breast cancer skin metastases upon continuation of vemurafenib treatment. *Dotted line* indicates the border of the lesion at initial diagnosis (see Fig. 2a). *Solid line* demonstrates the enlargement of the infiltrate at 8 weeks of vemurafenib therapy. c Regression of breast cancer skin metastases upon vemurafenib discontinuation. *Solid line* marks the lesions at the time of cessation of vemurafenib treatment. *Dotted line* shows borders of the affected skin at 4 weeks after vemurafenib withdrawal. The changes in the size of the tumor lesions were assessed independently by two physicians (AVN, SAP). Photographs were prepared by AVN; *lines* were drawn by AVN right after taking a picture

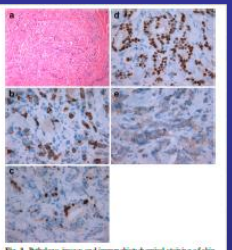

Fig. 3 Pathology images and immunohistochemical staining of skin lesions confirming breast cancer. a Hematoxylin and eosin, ×100; b mammaglobin, ×400; c progesterone receptor, ×400; d estrogen receptor, ×400; e HER2, ×400

Interestingly, a distinct tumor lesion appeared instead near the right mammillary line at the level of the 3rd rib, while the described above breast cancer relapse had clearly diffuse pattern of growth, this new metastasis presented as an isolated nodule. This lump was also biopsied, and its histological analysis detected no differences as compared to previously excised breast cancer lesions (data not shown). The patient died due to progression of brain metastatic lesions in May 2014.

3 Discussion

We attempted to systematically assess data on carcinogenic effect of BRAF inhibitors in humans, using PubMed search by the phrase "Vemurafenib [title] OR dabrafenib [title] OR BRAF [title] OR RAF [title]) AND (cancer* OR tumor* OR tumour* OR malign* OR leukemia) AND (progression OR induction) AND English [lang]." Callahan et al. [4] described accelerated progression of a previously unsuspected NRAS-mutated leukemia in a patient receiving vemurafenib for the treatment of melanoma; importantly, the growth of leukemic cells was ceased after the withdrawal of BRAF inhibitor [4]. Later, the same group demonstrated successful control of con-

- **Наследственные опухолевые синдромы**
- **Выбор терапии на основе молекулярных характеристик опухоли**
  - **Детекция диссеминированных (циркулирующих) опухолевых клеток**
  - **Дифференциальная диагностика опухолей с неизвестным первичным очагом**