Метастатическая форма базальноклеточного рака – клинические, гистологические и молекулярно-генетические предикторы

И.Л. Плакса

Москва
2019

Определение

1. Первичная опухоль и метастаз должны иметь сходное гистологическое строение, преимущественно не плоскоклеточного строения

2. Первичная опухоль должна располагаться в коже и не в слюнной железе или слизистых

3. Должно быть исключено прямое распространение

METASTASIZING BASAL-CELL EPITHELIOMA OF THE SKIN

Report of Two Cases

RAFFAELE LATTES, M.D., and RICHARD W. KESSLER, M.D.

THE object of this article is to report, and to comment upon, two cases of skin epitheliomas of the basal-cell type that exhibited a quite unusual clinical behavior. In fact, both of them, over a period of many years, metastasized first to the regional lymph nodes and then presumably to internal viscera, thus causing the death of the patients.

The subject is not entirely new, and indeed several cases are reported in the literature—only very few of these, however, have seemed acceptable to us.

Without pretending to present a complete analysis of the available literature, we will list here the case reports that came to our attention, divided into three groups, namely: acceptable, questionable, and nonacceptable. We have considered as nonacceptable: (1) those cases in which either the primary tumor or the metastases were frankly squamous in type; (2) cases in which the presumed metastatic nodule or nodules were not proved to have occurred in lymph nodes, and could be interpreted as new primary growths or direct extensions from the original tumor; and (3) cases that, although classified by the authors as basal-cell carcinomas or epitheliomas, could not be included among those studied here because of their origin in salivary and other glands or mucous membranes.

REVIEW OF THE LITERATURE

Reports of Well-Documented Cases of Basal-Cell Epithelioma with Regional or Distant Metastases. Beadles reported a case of extensive rodent ulcer of the face with postmortem finding of a metastasis to a submaxillary lymph node in a 46-year-old man. The description of the histological findings is satisfactory. Fordyce described a "rodent ulcer" behind the ear in a 60-year-old patient, followed by local recurrence after excision and by a metastasis into a lymph node in the mastoid region. His histological description makes it probable that this is an authentic case of basal-cell epithelioma with metastasis to a regional lymph node, even though the illustration of the metastasis shows no lymphoid tissue. Körbl, in a paper dealing with the radiation therapy of epithelioma of skin in general, lists a long series of personal cases. Among these, case 61 of a rodent ulcer in the temporal region of a 66-year-old woman, apparently controlled by radiation but followed after seventeen months by a submaxillary metastasis, seems acceptable. His cases 26 and 53 are not acceptable because the metastases were of the squamous type.

Acceptable, also, are the four cases of Hazen, the two cases of Finnerud, the cases of Juon, and those of Mulzer. One of the three cases of Spies is acceptable, namely that of a rodent ulcer of the nasolabial region followed by widespread visceral metastases. His other two cases are obviously carcinomas of the cylindromatous type, one arising in the submaxillary gland, the other, in the mucous membrane of the nose.

Other well-documented basal-cell epitheliomas with metastases are those of De Navasquez, Streitmann, Foot, Amersbach, and the two cases of Small et al. In addition, we have learned of four other cases of metastasizing basal-cell epitheliomas observed by Ackerman. These have not yet been published, and we have not examined the sections.

Questionable Cases. The following cases, published as metastatic basal-cell epitheliomas, in our opinion are questionable or not sufficiently proved: Montgomery;[22] Dubreuilh and Auché; Willis, considered by him as "intermediate" in type; Warren et al., considered by them as questionable.

Unacceptable Cases. In one case of Niles, the original lesion was in the proximal pha-

From the Department of Surgery, Laboratory of Surgical Pathology, College of Physicians and Surgeons, Columbia University, and the Tumor Service of University Hospital of New York University Bellevue Medical Center, New York, New York.

Received for publication, March 23, 1951.

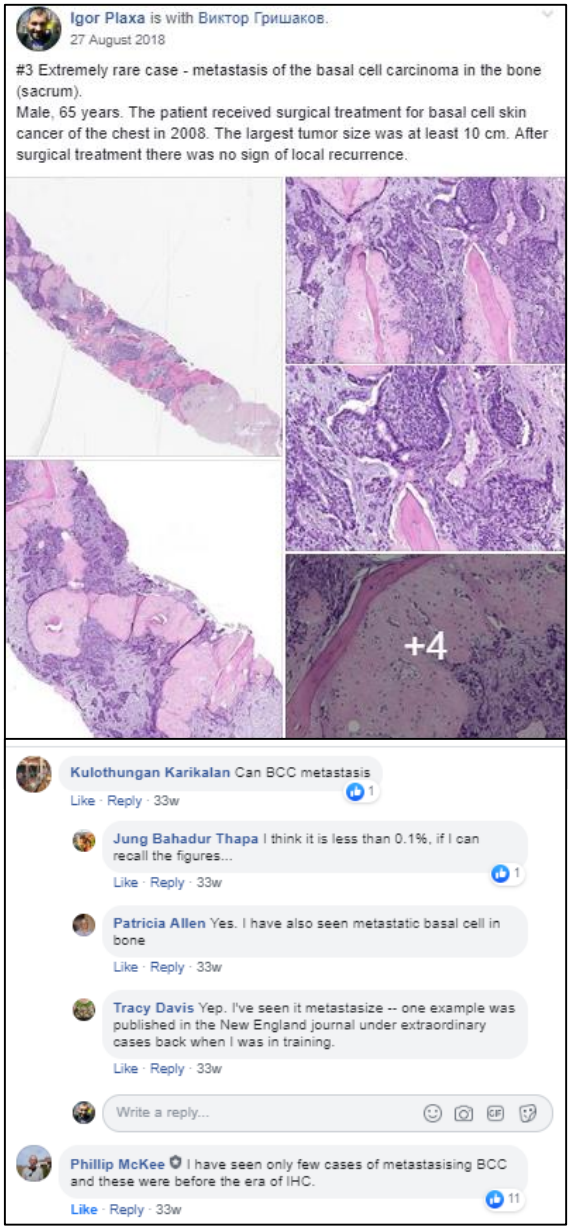
Встречается редко

– Набор 33 пациентов с метастатической формой в клиническое исследование Висмодегиба в 31 центре США, Европы и Австралии продолжался в течение **13 месяцев**;

- С момента первой публикации (1832 год) было описано чуть более **400 случаев**;

27/08/2018
Dr. Phillip H. McKee: I have seen only few cases of metastatic basal cell carcinoma and these were before the era of IHC

27/08/2018
Проф. Филипп МакКи: Мне довелось увидеть только несколько случаев метастатической формы базальноклеточного рака и все они были до эры иммуногистохимии



Биологическая характеристика *

- Средний возраст постановки диагноза базальноклеточный рак – **57,1 лет**;
- Средний возраст при обнаружении метастазов – **62,1 лет;**
- Средний интервал появления отдалённых метастазов после верификации первичного очага – **7,4 лет**;
- Самая частая область метастазирования – **лимфатические узлы (54%)**; лёгкие (28%); кости (24%) и т.д.

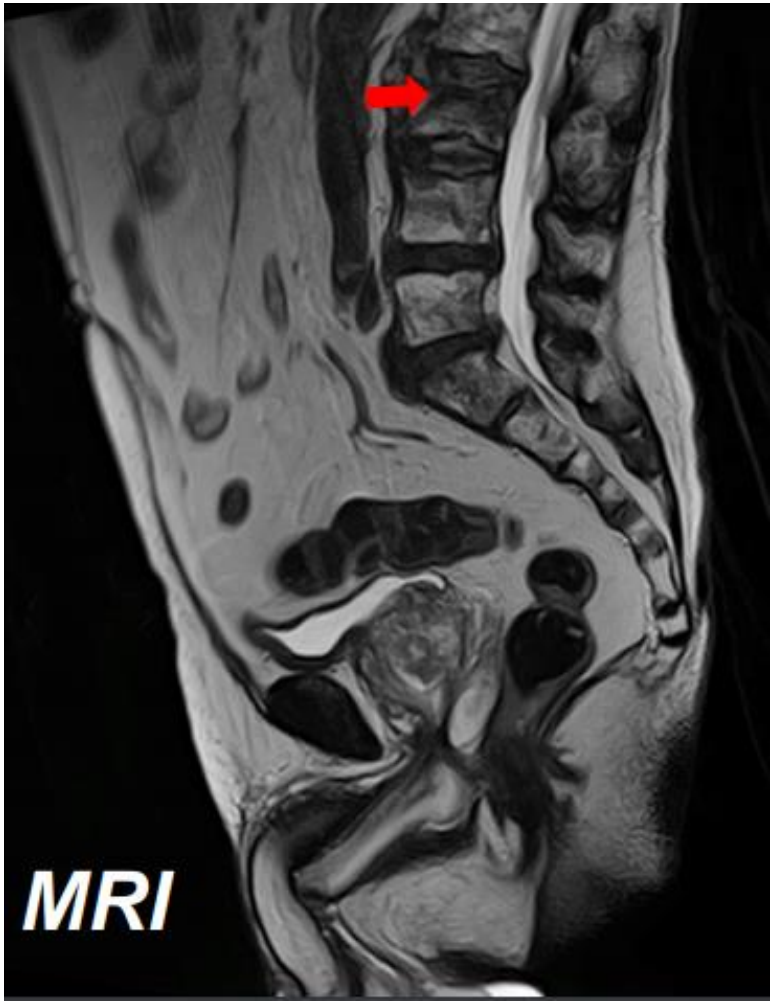
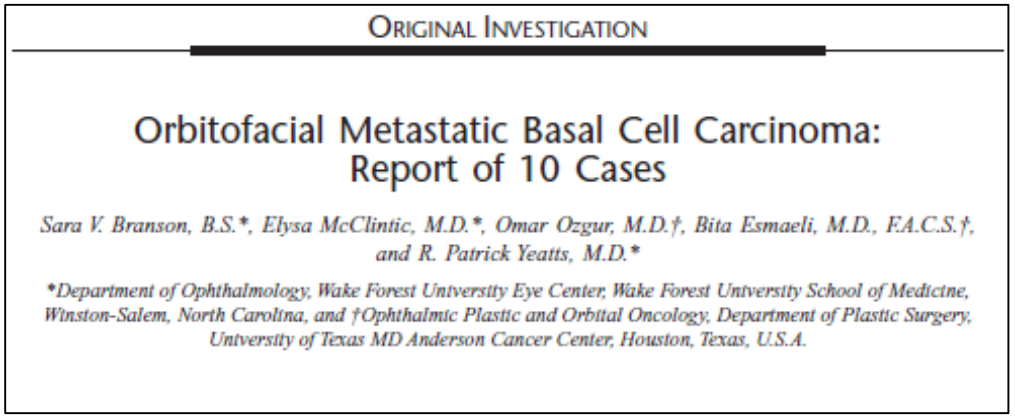


Фото из архива

*** по результатам мета-анализа более 100 пациентов –** ***M. McCusker et al. European Journal of Cancer 50 (2014) 774-783***

Клиническая предикторы *

- Размеры: средний размер очага при метастатической форме – 7,5 см;
- Локализация: чаще всего лицо и шея (56%); туловище – 26%; конечности – 5%; половые органы – 7%; множественные очаги – 6%



ORIGINAL INVESTIGATION

Orbitofacial Metastatic Basal Cell Carcinoma: Report of 10 Cases

Sara V. Branson, B.S., Elysa McClintic, M.D.*, Omar Ozgur, M.D.†, Bita Esmaeli, M.D., F.A.C.S.†, and R. Patrick Yeatts, M.D.**

**Department of Ophthalmology, Wake Forest University Eye Center, Wake Forest University School of Medicine, Winston-Salem, North Carolina, and †Ophthalmic Plastic and Orbital Oncology, Department of Plastic Surgery, University of Texas MD Anderson Cancer Center, Houston, Texas, U.S.A.*

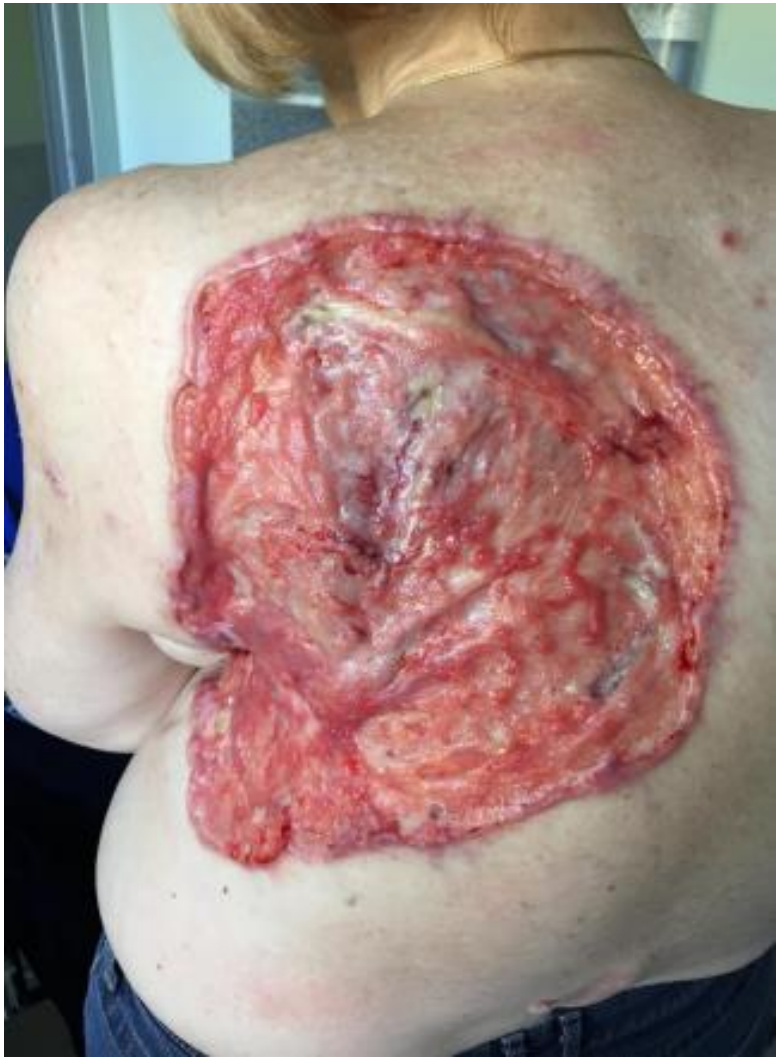


Фото из архива

*** по результатам мета-анализа более 100 пациентов –** ***M. McCusker et al. European Journal of Cancer 50 (2014) 774-783***

Гистологические предикторы

Review

Metastatic basal cell carcinoma: Prognosis dependent on anatomic site and spread of disease☆☆

Margaret McCusker[a,*], Nicole Basset-Seguin[b], Reinhard Dummer[c], Karl Lewis[d], Dirk Schadendorf[e], Aleksandar Sekulic[f], Jeannie Hou[a], Lisa Wang[a], Huibin Yue[a], Axel Hauschild[g]

Table 3
Histology of primary BCC in mBCC cases, 1981–2011.

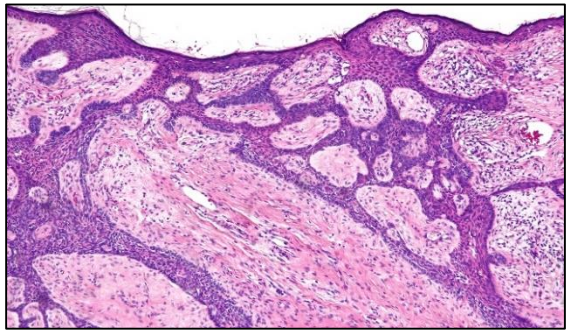
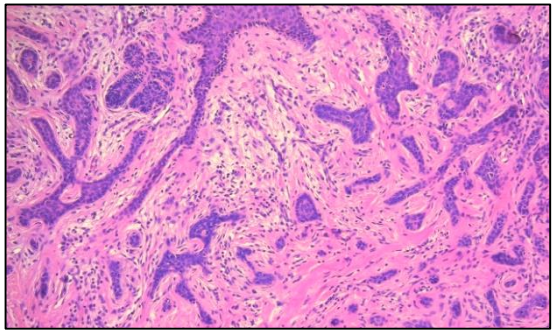
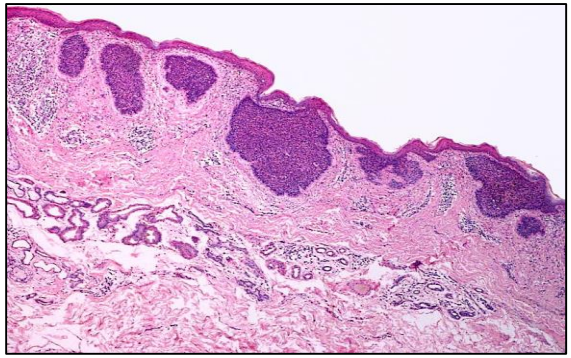
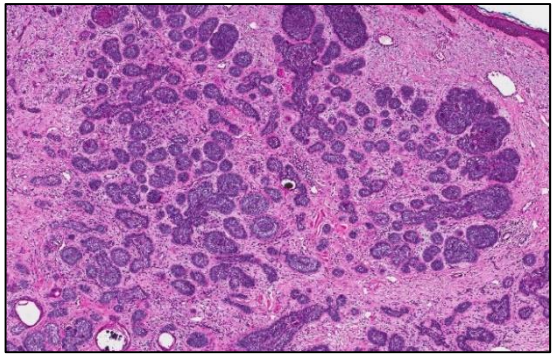
Histology	All cases, *n* (%) (*n* = 100)	Distant metastases, *n* (%) (*n* = 50)	Regional metastases, *n* (%) (*n* = 50)
Basosquamous or metatypical[a]	10 (10.0)	6 (12.0)	4 (8.0)
Infiltrative[b]	14 (14.0)	9 (18.0)	5 (10.0)
Morpheaform[c]	10 (10.0)	5 (10.0)	5 (10.0)
Other[d]	14 (14.0)	6 (12.0)	8 (16.0)
BCC, no subtype specified	52 (52.0)	24 (48.0)	28 (56.0)

BCC, basal cell carcinoma; mBCC, metastatic basal cell carcinoma.
[a] One case described as metatypical and morpheaform.
[b] Two cases described as infiltrative and nodular.
[c] One case described as morpheaform and nodular.
[d] Other histologies: adenoid, adenoid cystic and keratotic, clear cell,

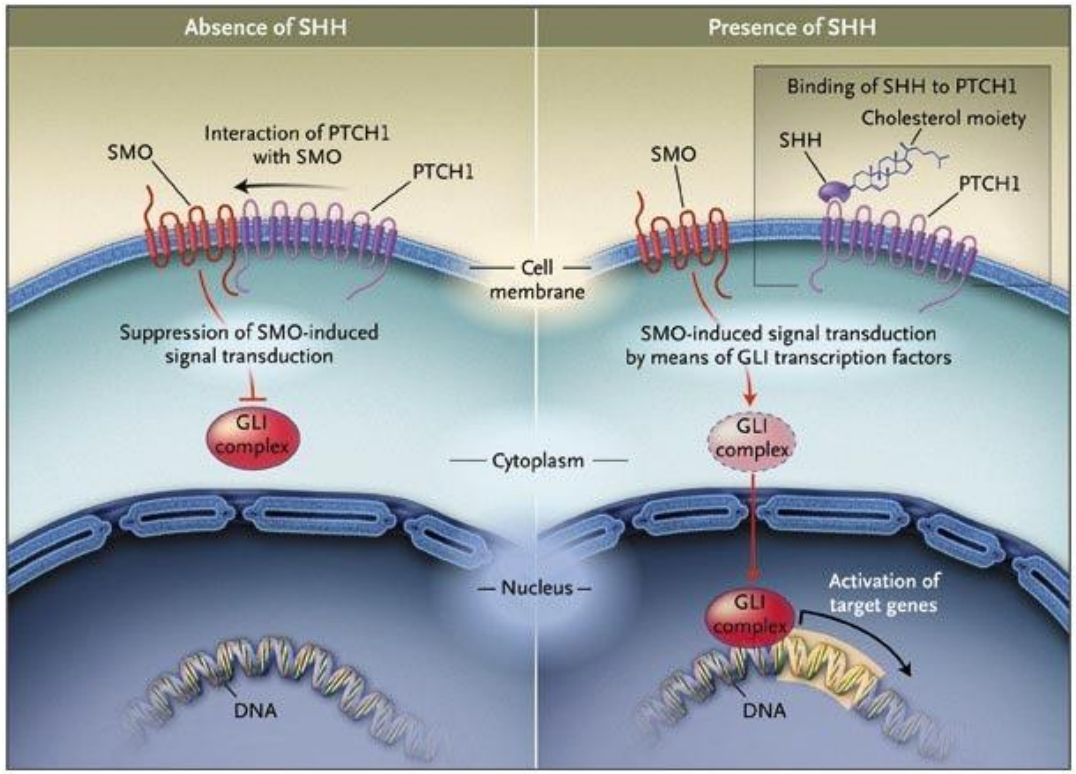
Table 1.01 Histological subtypes of basal cell carcinoma (BCC) stratified by risk of recurrence

Lower risk	Higher risk
Nodular BCC	Basosquamous carcinoma
Superficial BCC	Sclerosing/morphoeic BCC
Pigmented BCC	Infiltrating BCC
Infundibulocystic BCC (a variant of BCC with adnexal differentiation)	BCC with sarcomatoid differentiation
Fibroepithelial BCC	Micronodular BCC

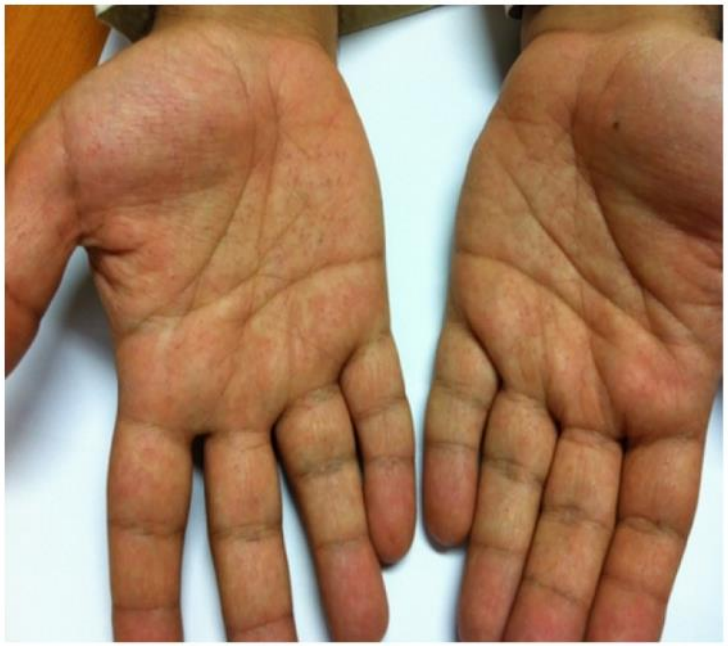
The **WHO Classification of Skin Tumours** is the 11th volume in the 4th edition

Молекулярно-генетические предикторы



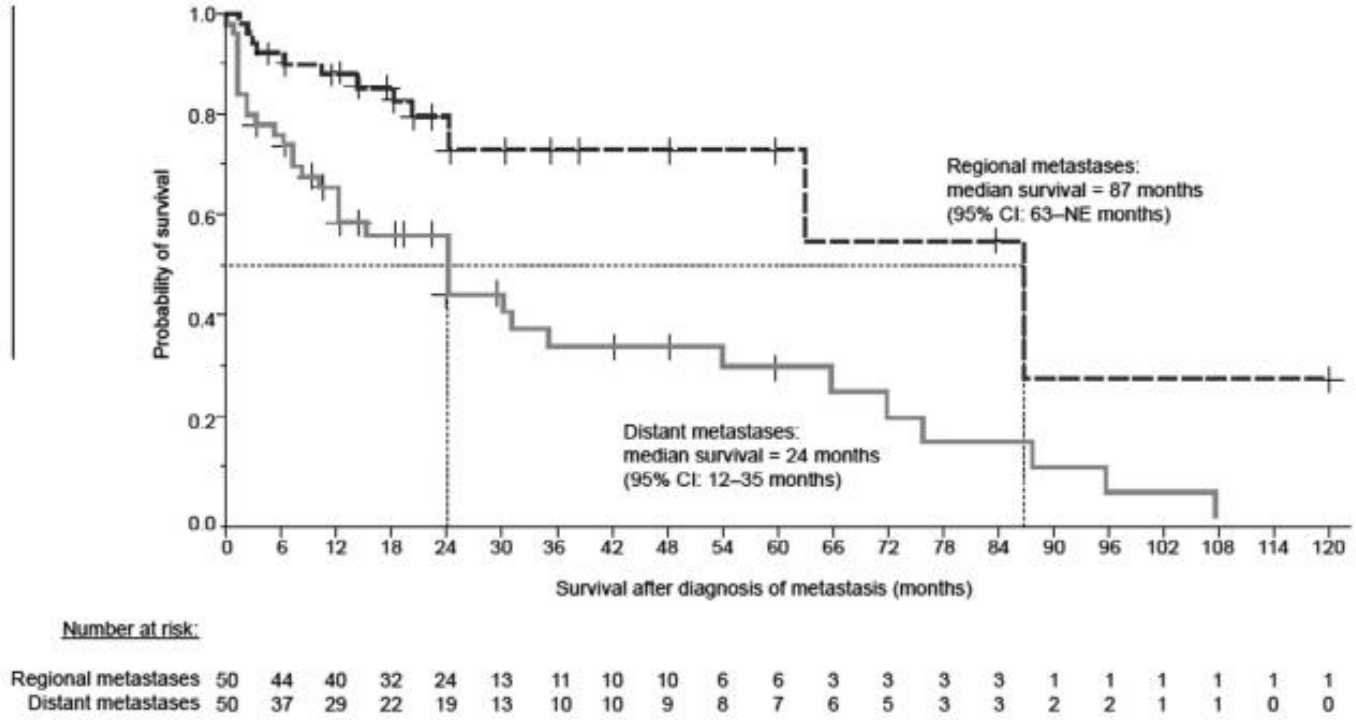
SHH- Sonic hedgehog; PTCH1 - transmembrane proteins patched homologue 1; SMO - smoothened protein



Синдром Горлина-Гольца

Мутации приводящие к утрате функции белка PTCH1 встречаются у 30-40% со спорадическим базальноклеточным раком кожи

Терапевтические опции – крайне скудные



Средняя выживаемость после обнаружения отдалённых метастазов – 24 месяца

Материалы и методы

- Ретроспективный анализ пациентов с базальноклеточным раком кожи 2012 по 2018 год;
- Материалом для исследования послужил консультативный и биопсийный/операционный материал

Критерии включения	Критерии исключения
Первичный очаг и метастаз должны иметь сходное гистологическое строение	Преобладание плоскоклеточного компонента
Первичный очаг должен располагаться в коже	Первичная опухоль располагается в слюнных железах или слизистых
Прямое распространение опухоли опухоли должно быть исключено	

Результаты

- 2 случая метастатической формы базальноклеточного рака из 2727 пациентов (менее 0,1% случаев)

Характеристика	№1	№2
Пол	Женский	Мужской
Дата рождения	1945	1953
Дебют заболевания	2012 год	2008 год
Появление метастазов	2014 год (интервал 2 года)	2018 год (интервал 10 лет)
Локализация первичного очага	подошвенная поверхность правой стопы	передняя грудная стенка
размер опухоли	5.2×3×0,7см	8×5×4 см
Первичное лечение	Лазерная деструкция в 2009 году	Тотальное иссечение в 2008 году
	Тотальное иссечение в 2012 году + лучевая терапия	
Дальнейшее лечение	Висмодегиб (с ноября 2017)+иссечение некоторых опух.узлов	Планируется назначение Висмодегиба

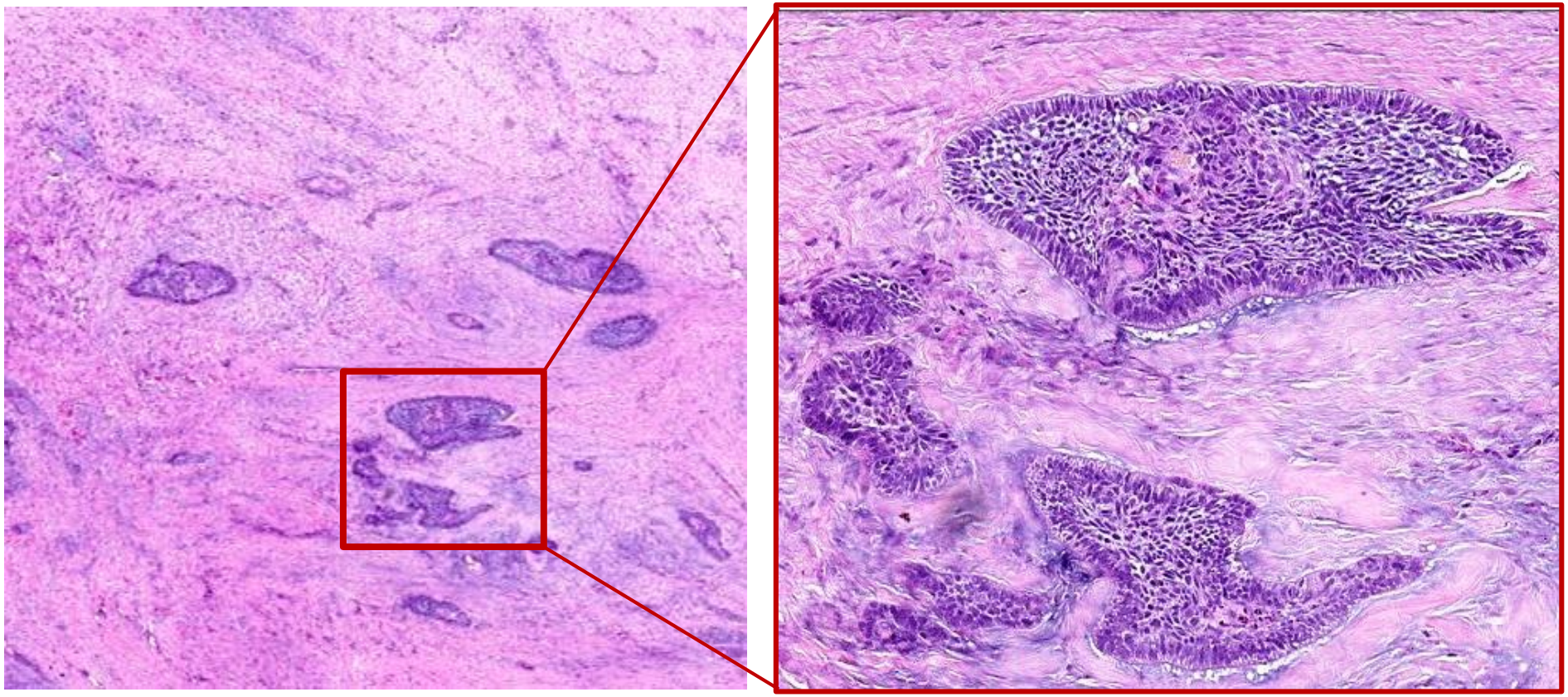
Пациент №1

2012 год
Первичное иссечение опухоли (предоперационная ДЛТ + хирургическое лечение)

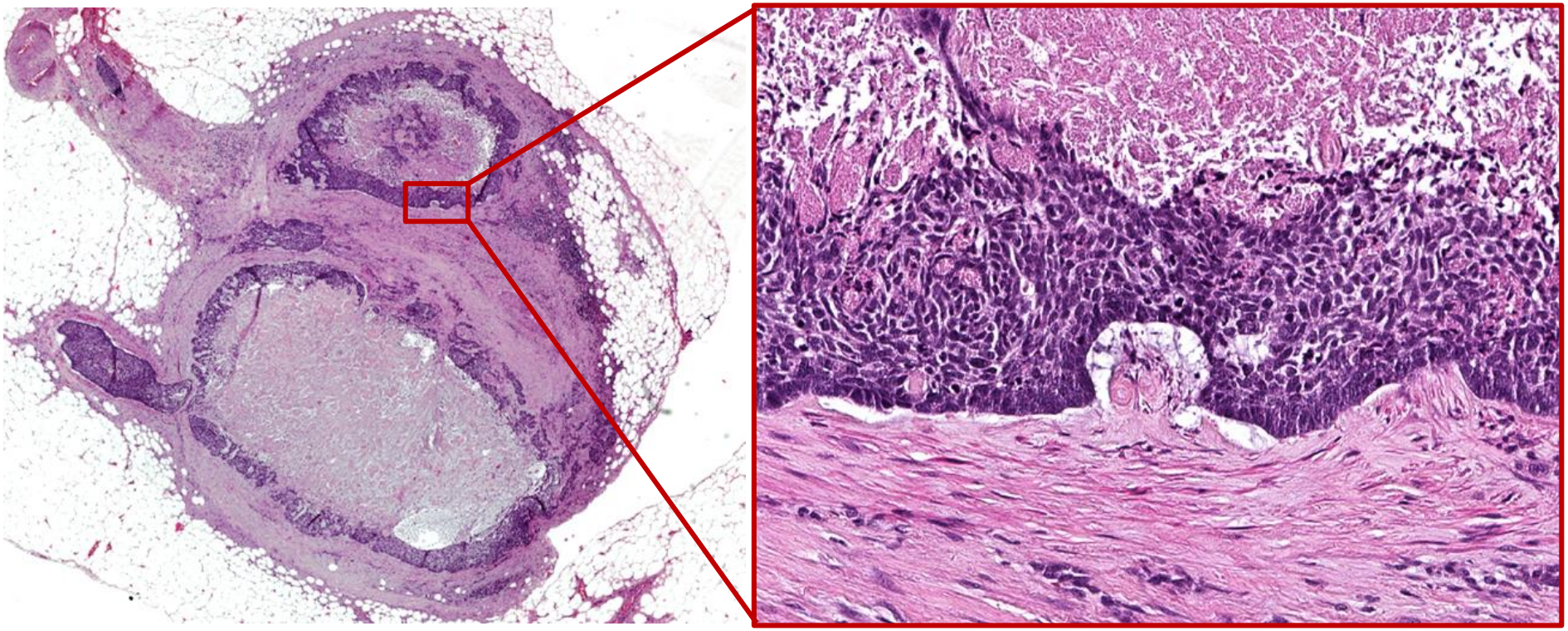
2013 год
Метастазы в паховые и подвздошные лимфатические узлы

2017 год
Множественные метастазы в лёгкие и сигмовидную кишку

2018 год
Смерть

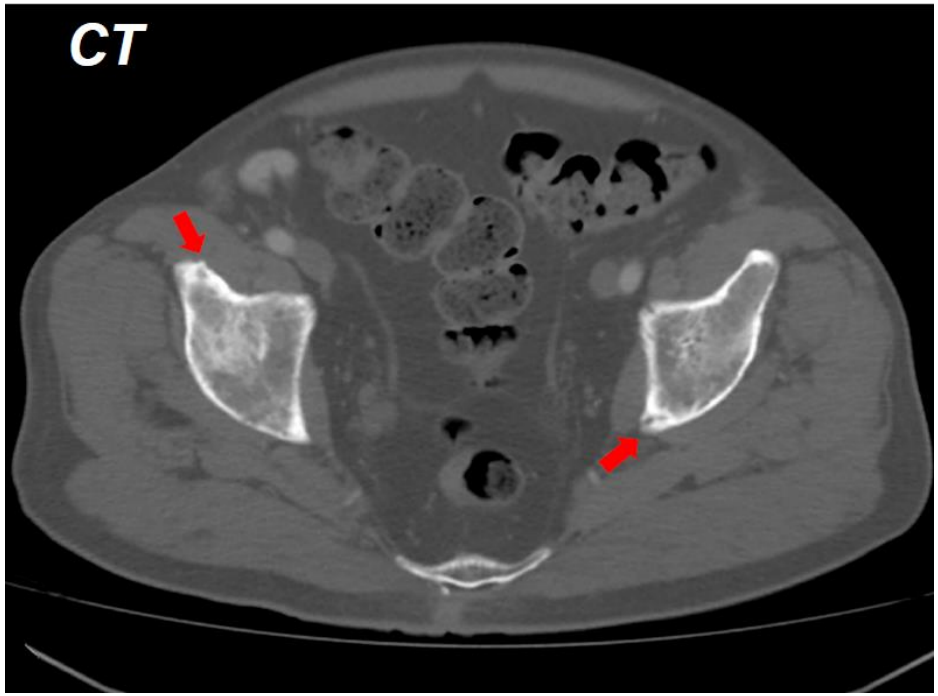


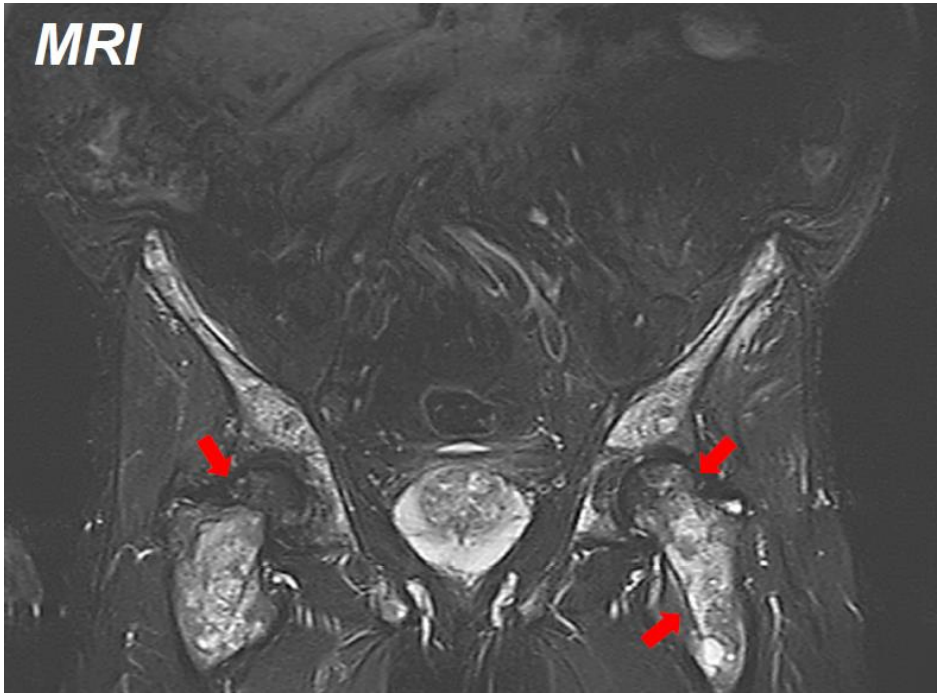
Пациент №1



Подвздошный лимфатический узел

Пациент №2





Пациент №2

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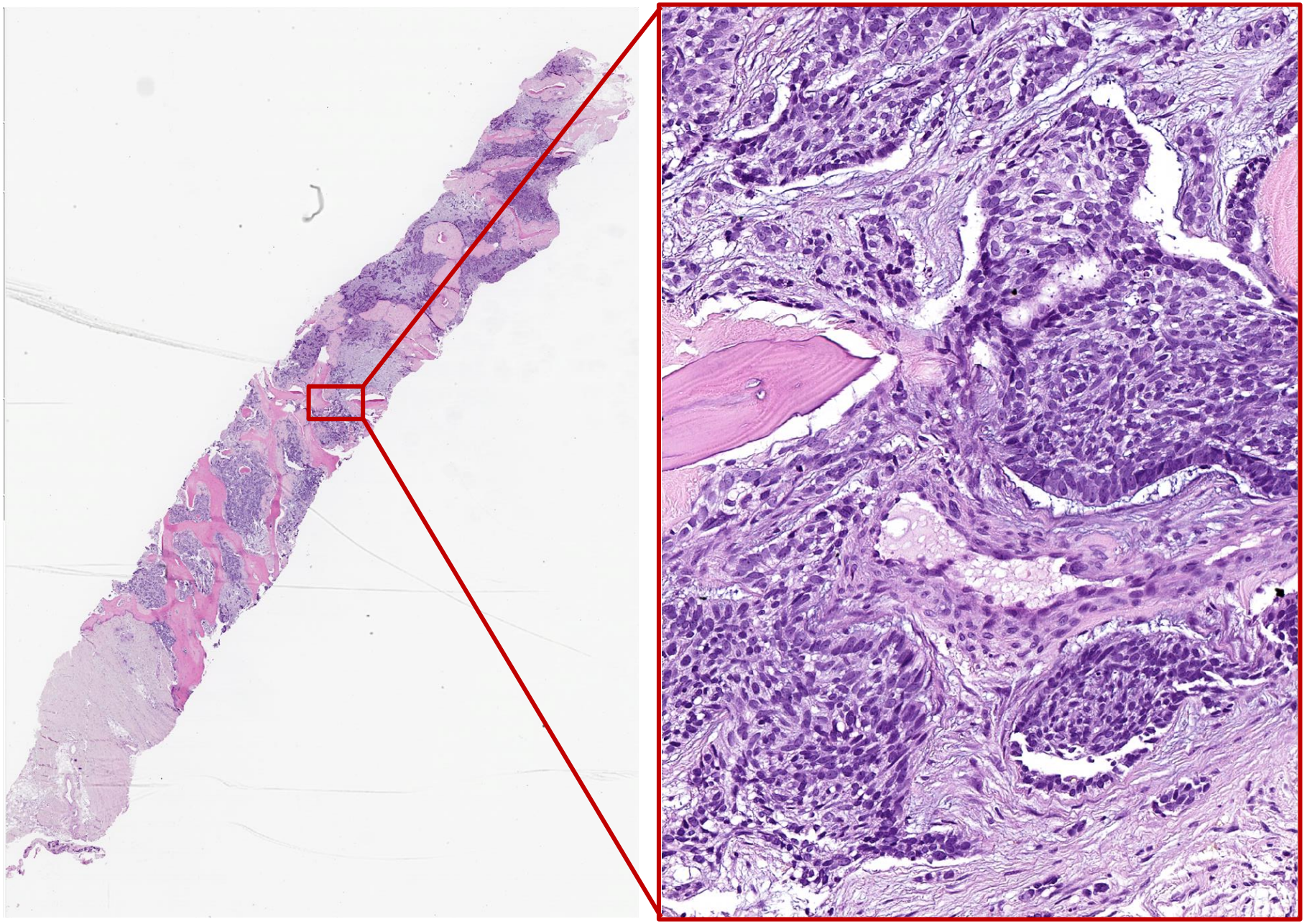

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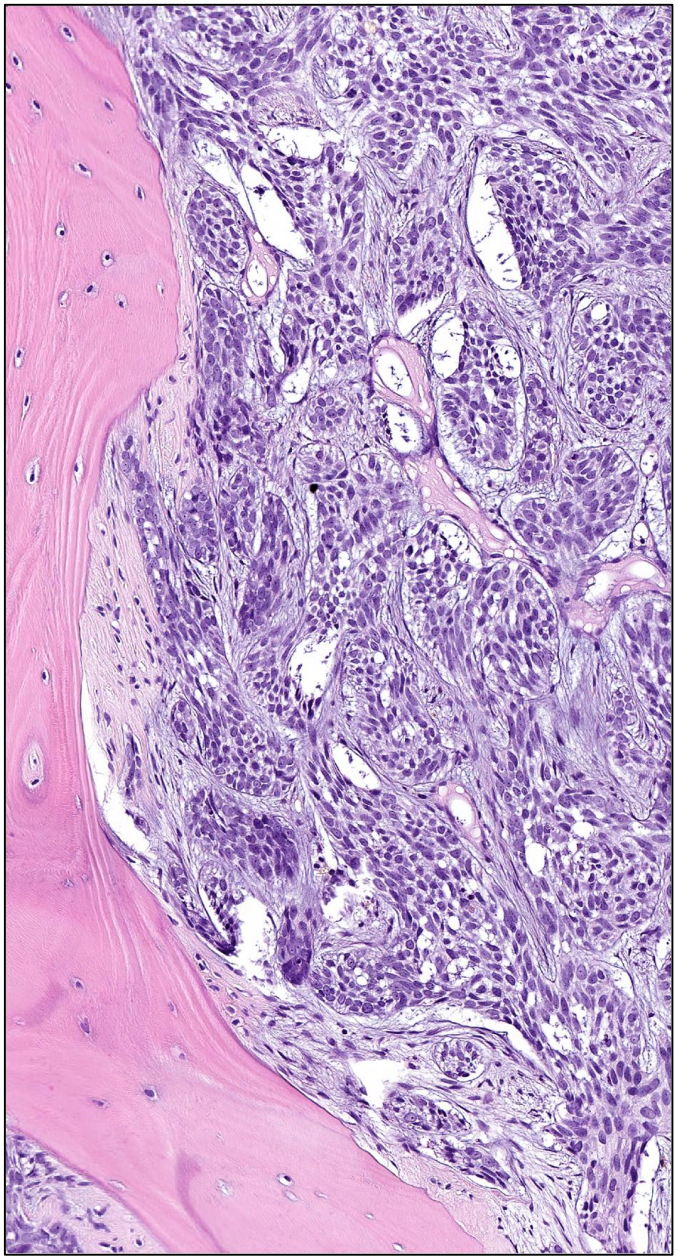

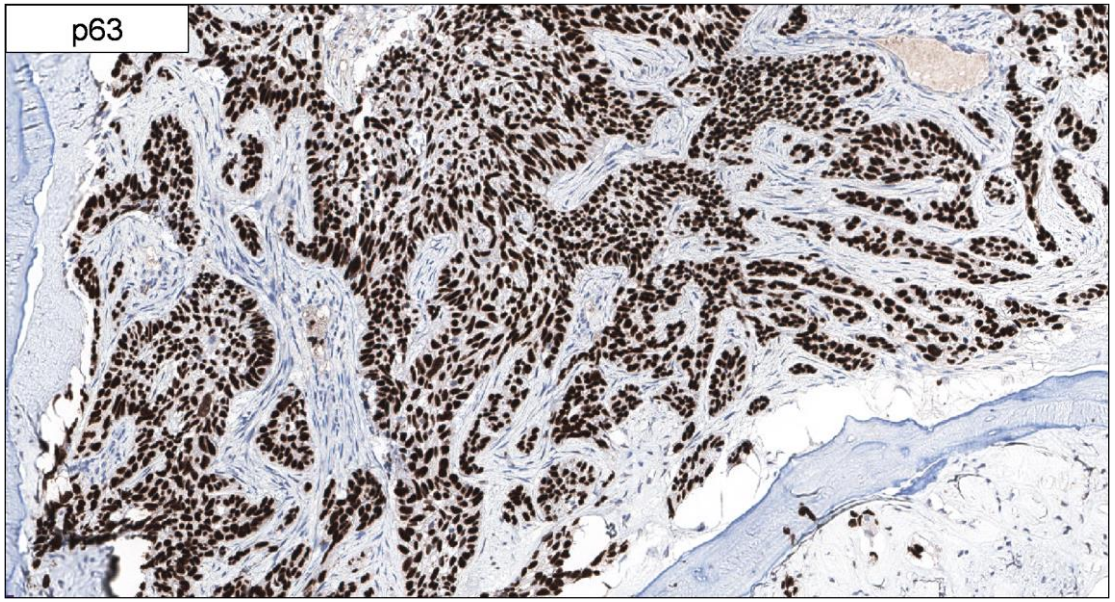

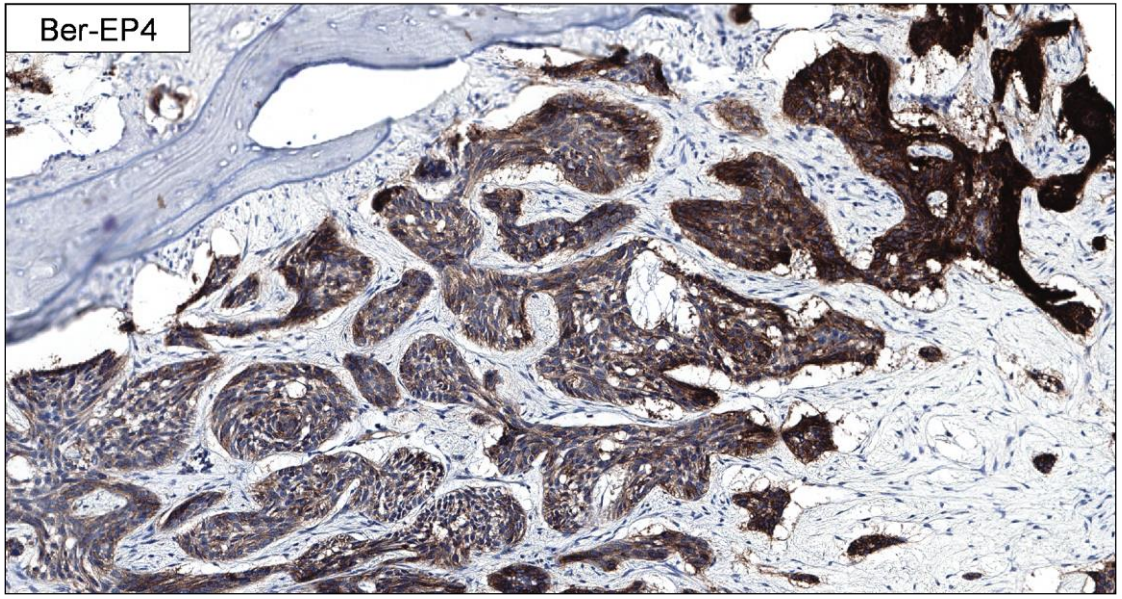

Пациент №2

Результаты широкопанельного секвенирования нового поколения (NGS)

Genomic Signatures

Microsatellite status - MS-Stable

Tumor Mutational Burden - TMB-Intermediate (9 Muts/Mb)

Gene Alterations

For a complete list of the genes assayed, please refer to the Appendix.

ARID1A **A142fs*76 - subclonal**†

CDKN2A/B **loss**

MTAP **loss**

NOTCH3 **truncation intron 2**

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† See About the Test in appendix for details.

0 Therapies approved in the EU

0 Therapies with Lack of Response

6 Clinical Trials

FOUNDATION MEDICINE®

Genetico

Пациент №2

Результаты широкопанельного секвенирования нового поколения (NGS)

Nivolumab Alone or Plus Ipilimumab for Patients With Locally-Advanced Unresectable or Metastatic Basal Cell Carcinoma

ClinicalTrials.gov Identifier: NCT03521830

Recruitment Status : Recruiting
First Posted : May 10, 2018
Last Update Posted : December 6, 2018
See Contacts and Locations

Sponsor:
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Information provided by (Responsible Party):
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Tracking Information	
First Submitted Date ICMJE	April 30, 2018
First Posted Date ICMJE	May 10, 2018
Last Update Posted Date	December 6, 2018
Actual Study Start Date ICMJE	November 27, 2018
Estimated Primary Completion Date	November 2023 (Final data collection date for primary outcome measure)
Current Primary Outcome Measures ICMJE (submitted: April 30, 2018)	Objective Response Rate [Time Frame: 5 years] Objective response rate per the revised Response Evaluation Criteria in Solid Tumors (RECIST 1.1)
Original Primary Outcome Measures ICMJE	*Same as current*
Change History	Complete list of historical versions of study NCT03521830 on ClinicalTrials.gov Archive Site
Current Secondary Outcome Measures ICMJE (submitted: April 30, 2018)	• progression-free survival [Time Frame: 5 years] duration of time from start of treatment to time of progression or Basal Cell Carcinoma specific death, whichever occurs first • duration of response [Time Frame: 5 years] duration of time that measurement criteria are met for Complete Response or Partial Response (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented • overall survival [Time Frame: 5 years] measured from the time of enrollment until death

Пациент №2

Результаты широкопанельного секвенирования нового поколения (NGS)

GENE
ARID1A

ALTERATION
A142fs*76 - subclonal

POTENTIAL TREATMENT STRATEGIES

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620; 1 patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[38-39]. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to inhibitors of EZH2[40-41], which are under investigation in clinical trials. Other studies have reported that loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[42-44]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy in patients with ovarian clear cell carcinoma[45-46] and to 5-fluorouracil (5-FU) in CRC cell lines[47].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (36%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma (CRC), and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2018)[48-53]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[54-57], CRC[58-60], and gastric cancer[61-65]. ARID1A protein loss is associated with tumors of poor histological grade for

GENE
CDKN2A/B

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[87-90]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[91-92], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[93-99]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[100-101], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

Multiple studies have reported loss of heterozygosity of the CDKN2A/B locus in basal cell carcinoma (BCC) cases[102-104]. Upregulation of CDKN2A (both the p16INK4a- and p14ARF-encoding loci) and CDKN2B mRNA levels as well as increased p16INK4a, p14ARF, and p15INK4b expression in BCC cases have been detected in several studies[102-103,105-108]. Increased p16INK4a expression has been associated with invasive capacity in BCC samples; higher expression was observed on the invasive front compared to other areas of the tumors[109-110].

PRF# 507548

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

Inactivation of MTAP is being explored for specific metabolic vulnerabilities. In preclinical cancer models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, providing competition to purine poisons lacking in MTAP-deficient cells[143-151]. However, such combination approaches are not being clinically tested, and a Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy in 65 patients with MTAP-deficient cancers reported no responses and stable disease in 24% of patients[152]. Other approaches have been described in preclinical studies[153-155], but these have not been clinically tested.

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[156-157]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[158], gastrointestinal stromal tumors[159], mantle cell lymphoma (MCL)[160], melanoma[161-162], gastric cancer[163], myxofibrosarcoma[164], nasopharyngeal carcinoma[165], ovarian carcinoma[156] and non-small cell lung cancer[166]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[167] or in astrocytoma[168]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[169], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[170].

GENE
NOTCH3

ALTERATION
truncation intron 2

POTENTIAL TREATMENT STRATEGIES

Several approaches for inhibiting NOTCH3 signaling are being developed, including neutralizing NOTCH antibodies such as OMP-59R5[182], which targets NOTCH2 and NOTCH3, and pan-Notch inhibitors, such as gamma-secretase inhibitors (GSI)[183-185]. A Phase 1b study of OMP-59R5 in combination with gemcitabine and nab-paclitaxel has shown promising efficacy (up to 50% partial response) in patients with untreated metastatic pancreatic cancer[186]. A Phase 1b study of OMP-59R5 in combination with etoposide and cisplatin for small cell lung cancer reported a median progression free survival of 124 days and 84% overall response rate[187]. The GSI BMS-906024 inhibits NOTCH activity in vitro and exhibits anti-tumor activity in xenograft models of leukemia and triple negative breast cancer harboring NOTCH1 and NOTCH3 activating mutations or overexpression[188]. These agents are being investigated in preclinical studies and early clinical trials in various tumor types[189]. These approaches would not be relevant in the context of inactivating alterations, as seen here.

FREQUENCY & PROGNOSIS

NOTCH3 mutations have been reported in 10% (7/70) of basal cell carcinoma samples (COSMIC, Apr 2019). Published data investigating the prognostic implications of

Пациент №2

Результаты широкопанельного секвенирования нового поколения (NGS)

GENE
ARID1A

ALTERATION
A142fs*76 - subclonal

RATIONALE
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors.

NCT02264678		**PHASE 1/2**
Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents		**TARGETS** ATR, PARP, PD-L1
LOCATIONS: California, New York, Saint Herblain (France), Villejuif (France), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), London (United Kingdom), Manchester (United Kingdom), Sutton (United Kingdom)		
NCT02157792		**PHASE 1**
M6620 First in Human Study		**TARGETS** TOP1, TOP2, ATR
LOCATIONS: Manchester (United Kingdom), Newcastle Upon Tyne (United Kingdom), Oxford (United Kingdom), Massachusetts, Ohio, Sutton (United Kingdom), Texas, Virginia, London (United Kingdom)		
NCT03641547		**PHASE 1**
M6620 Plus Standard Treatment in Oesophageal and Other Cancer		**TARGETS** ATR
LOCATIONS: Glasgow (United Kingdom), Oxford (United Kingdom)		
NCT02487095		**PHASE 1/2**
Trial of Topotecan With VX-970, an ATR Kinase Inhibitor, in Small Cell Cancers		**TARGETS** ATR
LOCATIONS: Maryland		
NCT02595931		**PHASE 1**
ATR Kinase Inhibitor VX-970 and Irinotecan Hydrochloride in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery		**TARGETS** ATR
LOCATIONS: California, Connecticut, Florida, Massachusetts, Michigan, Missouri, North Carolina, Pennsylvania, Tennessee		
NCT02723864		**PHASE 1**
Veliparib (ABT-888), an Oral PARP Inhibitor, and VX-970, an ATR Inhibitor, in Combination With Cisplatin in People With Refractory Solid Tumors		**TARGETS** PARP, ATR
LOCATIONS: Maryland, Massachusetts, Texas		

Благодарности

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