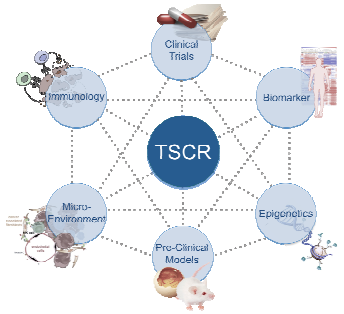

IMMUNO-ONCOLOGY

MERKEL CELL CARCINOMA

Jürgen C. Becker, tscr, DKTK & UK Essen

UV- & Virus-associated Carcinogenesis

Priority Report

Cancer Research

The Distinctive Mutational Spectra of Polyomavirus-Negative Merkel Cell Carcinoma

Paul William Harms[1,2,3], Pankaj Vats[1,4], Monique Elise Verhaegen[3], Dan R. Robinson[1], Yi-Mi Wu[1,2], Saravana Mohan Dhanasekaran[1,2], Nallasivam Palanisamy[1,2,5], Javed Siddiqui[1,2], Xuhong Cao[1,6], Fengyun Su[1], Rui Wang[1,2], Hong Xiao[1,2,5], Lakshmi P. Kunju[1,2], Christopher Keram, Arul M. Chinnaiyan

Abstract

Introduction

3720 Cancer Res; 75(18) Septem

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 3

Mutational landscape of MCPyV-positive and MCPyV-negative Merkel cell carcinomas with implications for immunotherapy

Gerald Goh[1,2], Trent Walradt[3], Vladimir Markarov[4], Astrid Blom[5], Nadeem Riaz[6,7], Ryan Douman, Jonathan Levinsohn[7], Jaehyuk Choi[1,8,10]

[1]Department of Genetics, Yale Sch
[2]Howard Hughes Medical Institute
[3]Department of Dermatology, Yale
[4]Human Oncology and Pathogene
[5]Department of Dermatology, Univ
[6]Department of Radiation Oncolog
[7]Department of Pathology, Univers
[8]Fred Hutchinson Cancer Center,
[9]Department of Dermatology, Vete
[10]Current address: Department of

Correspondence to: Jaehyuk Choi, Richard P. Lifto

Keywords: Merkel cell carcinoma,

Received: August 27, 2015

ABSTRACT

Merkel cell neuroendocrine ca in 80% of cases. sequencing of 49 burden (median of frequent mutation in the chromatin and DNA-damage MCCs harbor few above. In both sub activate the PI3K the Notch pathway relevant in virus-neg gain-of-function mut status predicts deat stage I and II MCCs the tumor neoantige virus-negative MCCs cell lung cancers (n two cancers for wh responses. Collecti virus-negative MCCs

www.impactjournals.com/oncota

Priority Report

Cancer Research

UV-Associated Mutations Underlie the Etiology of MCV-Negative Merkel Cell Carcinomas

Stephen Q. Wong[1], Kelly Waldeck[1], Ismael A. Vergara[1], Jan Schröder[1,2,3], Jason Madore[4], James S. Wilmott[4], Andrew J. Colebatch[1,5], Ricardo De Paoli-Iseppi[4], Jason Li[1], Richard Lupat[1], Timothy Semple[1], Gisela Mir Arnau[1], Andrew Fellowes[1], J. Helen Leonard[6], George Hruby[4], Graham J. Mann[4], John F. Thompson[4], Carleen Cullinane[1], Meredith Johnston[1], Mark Shackleton[1,7], Shahneen Sandhu[1,7], David D.L. Bowtell[1,5,7], Ricky W. Johnstone[1,7], Stephen B. Fox[1,5,7], Grant A. McArthur[1,7], Anthony T. Papenfuss[1,2,7,8], Richard A. Scolyer[9], Anthony J. Gill[9], Rodney J. Hicks[1,7], and Richard W. Tothill[1,5]

Abstract

Introduction

Merkel cell carcinoma (MCC) is a rare but aggressive cutaneous neuroendocrine tumor that occurs most commonly in the fair skinned, elderly, and males with additional risk factors including immunosuppression and excessive sun exposure (1). The Merkel cell polyoma virus (MCV) has been implicated in 80% of MCC cases in the United States and Europe; however, this can differ significantly in other geographic regions such as Australia, where a much lower association with viral infection has been reported (~25%; ref. 2). While the impact of MCV and viral T-antigens on MCC development has been extensively investigated (3), little is known of the etiology of viral-negative tumors.

MCC has propensity for early spread and recurrence and while surgery and radiotherapy can achieve high rates of locoregional control, chemotherapy rarely provides durable responses for distant metastatic disease (4). The deployment of improved targeted therapies is likely to be achieved through a better understanding of MCC biology. Therefore, by applying massively parallel sequencing (MPS), we have searched for cancer gene mutations and somatic copy number alterations (SCNA) within MCC tumors with the view to characterize the genetic landscape of MCC subtypes based on viral association. Furthermore, we have investigated the presence of T-cell infiltrates and PD-L1 expression in MCC tumors, providing a rationale for use of immune checkpoint inhibitors for the treatment of MCC tumors irrespective of viral status.

Materials and Methods

Tumors and cell lines

The discovery cohort consisted of fresh-frozen and archival formalin-fixed paraffin embedded (FFPE) tissue samples

[1]Peter MacCallum Cancer Centre, Melbourne Victoria, Australia, [2]Walter Eliza Hall Institute, Melbourne, Victoria, Australia, [3]Department of Computing and Information Systems, University of Melbourne, Melbourne, Victoria, Australia, [4]Melbourne Institute Australia and the University of Sydney, Sydney, New South Wales, Australia, [5]Department of Pathology, University of Melbourne, Melbourne, Victoria, Australia, [6]QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia, [7]The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia, [8]Department of Medical Biology, University of Melbourne, Melbourne, Victoria, Australia, [9]Cancer Diagnosis and Pathology Research Group Kolling Institute of Medical Research, University of Sydney, Sydney, New South Wales, Australia.

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

Corresponding Author: Richard W. Tothill, Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne, Victoria 3002, Australia. Phone: 61-3-9656-1752; Fax: 61-3-9656-1414; E-mail: richard.tothill@petermac.org

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5228 Cancer Res; 75(24) December 15, 2015

AACR

REPORTS

mains of TRF1 and TRF2, these structural variations emphasize that the TRFH domain is a versatile framework for interactions with different proteins.

The crystal structure of the $TRF2_{TRFH}$–$Apollo_{TRFH}$ complex is corroborated by mutagenesis. Mutations of the conserved hydrophobic residues of Apollo (F504, L506, and P508) or TRF2 (*F120*) completely abolished the interaction both in vitro and in vivo (Fig. 4, F and G). We further assayed the cell

of wild-type and mutant Apollo

hemagglutinin (HA)–tagged pr

telomerase reverse transcript

immortalized human BJ fibrob

wild-type Apollo showed the

mere localization, the L506E

mutant was distributed through

plasm with no obvious accum

meres (Fig. 4H). This resul

structural information and in

binding of Apollo to the TR

TRF2 is required for the telom

of Apollo.

We next asked whether

associated proteins might contain

motif suggestive of an intera

TRFH domain of TRF1 or TR

fied this motif in PinX1, origin

a TRF1-interacting protein in

hybrid screen (6). An 11-resid

PinX1 (R287-D-F-T-L-K-P-

referred to as $PinX1_{TRFH}$, cle

$TIN2_{TRFH}$ (fig. S12A), suggest

bind to $TRF1_{TRFH}$ in the same

$TIN2_{TRFH}$. ITC data confirmed

$PinX1_{TRFH}$ interaction, whereas

interaction was observed betw

and $PinX1_{TRFH}$ (fig. S12B). Mut

showed that PinX1-L291 and TRF1-*F142* are critical for the interaction, whereas PinX1-P293 is not (fig. S12C). These results are consistent with those of the $TRF1_{TRFH}$–$TIN2_{TRFH}$ interaction (Fig. 2D) and indicate that PinX1, like TIN2, binds the TRFH domain of TRF1 but not TRF2. Protein sequence database searches showed many instances of telomere-associated proteins containing the F/Y-X-L-X-P motif (fig. S13). Future studies are needed to address

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0022-538X/10/$12.00 doi:10.1128/JVI.02400-09
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Merkel Cell Polyomavirus-Infected Merkel Cell Carcinoma Cells Require Expression of Viral T Antigens[▽]

Roland Houben,[1]† Masahiro Shuda,[2]† Rita Weinkam,[1] David Schrama,[1] Huichen Feng,[2]

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caspases or cha
detected after T
necessary for the
MCC.

Clonal Integ
Human Merk

Huichen Feng, Masahiro Shud

Merkel cell carcinoma (MCC) is
elderly and immunosuppressed
We studied MCC samples by di
between a previously undescrib
Further investigation led to ider
a previously unknown polyoma
sequences were detected in 8 of
various body sites and 4 of 25
DNA was integrated within the
and integration preceded clona
factor in the pathogenesis of M

Polyomaviruses have been
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since the discovery of
virus (MuPyV) by Gross in 195

Merkel cell carcinoma
roendocrine skin cancer
incidence is increasing
exposure and affects pr
pressed patients (5, 11, 1
immune surveillance is
duced cancers and sugg
trigger (9). Recently, a
Merkel cell polyomavir
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MCC tumors collected f
(4, 15, 21, 41). Surveys
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atives for MCV, although
be detected (4, 14, 22, 3

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* Corresponding author. M
gram, University of Pittsbur
Pittsburgh, PA 15213. Phone
E-mail for Yuan Chang: ycha
pwh@pitt.edu.
† R.H. and M.S. contribut
‡ Y.C., P.S.M., and J.C.B.
▽ Published ahead of print

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Current Opinion in Virology

Merkel cell polyomavirus infection and Merkel cell carcinoma

Wei Liu, Margo MacDonald and Jianxin You

Merkel cell polyomavirus is the only polyomavirus discovered to date that is associated with a human cancer. MCPyV infection is highly prevalent in the general population. Nearly all healthy adults asymptomatically shed MCPyV from their skin. However, in elderly and immunosuppressed individuals, the infection can lead to a lethal form of skin cancer, Merkel cell carcinoma. In the last few years, new findings have established links between MCPyV infection, host immune response, and Merkel cell carcinoma development. This review discusses these recent discoveries on how MCPyV interacts with host cells to achieve persistent infection and, in the immunocompromised population, contributes to MCC development.

Address
Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

Corresponding author: You, Jianxin (jianyou@mail.med.upenn.edu)

Current Opinion in Virology 2016, 20:20–27
This review comes from a themed issue on Viruses and cancer
Edited by Ann Moorman and Christian Münz

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Introduction

Merkel cell polyomavirus (MCPyV or MCV) has been linked to the development of a human cancer, Merkel cell carcinoma (MCC) [1**]. MCC, a neuroendocrine carcinoma of the skin, is one of the most aggressive skin cancers, with a disease-associated mortality of 46% [2]. MCC kills more patients than some other well-known cancers such as cutaneous T-cell lymphoma and chronic myelogenous leukemia [3,4].

Excessive exposure to sunlight and ultraviolet (UV) radiation, immune suppression, and advanced age are the major risk factors for MCC skin cancers [5,6]. MCC is therefore more frequently observed among people with fair skin, the elderly, and organ transplant or AIDS patients, with a strong predilection for the sun-exposed skin of the head and neck [5,6]. Clonal integration of MCPyV DNA into the host genome is a causal factor for the development of the majority of MCC tumors [7**].

MCPyV is also an abundant virus frequently detected on healthy human skin, suggesting that its infection is widespread in the general population [8*,9**,10]. Additional studies confirmed that exposure to the virus occurs in 80% or more of the general population [8*,11,12]. Primary infection occurs during childhood. Once acquired, MCPyV becomes a life-long component of the skin flora [13]. The strong association of MCC tumor development with immunosuppression suggests a viral causative link. The discovery of MCPyV in MCC tumors further supports a viral etiology for MCC [1**].

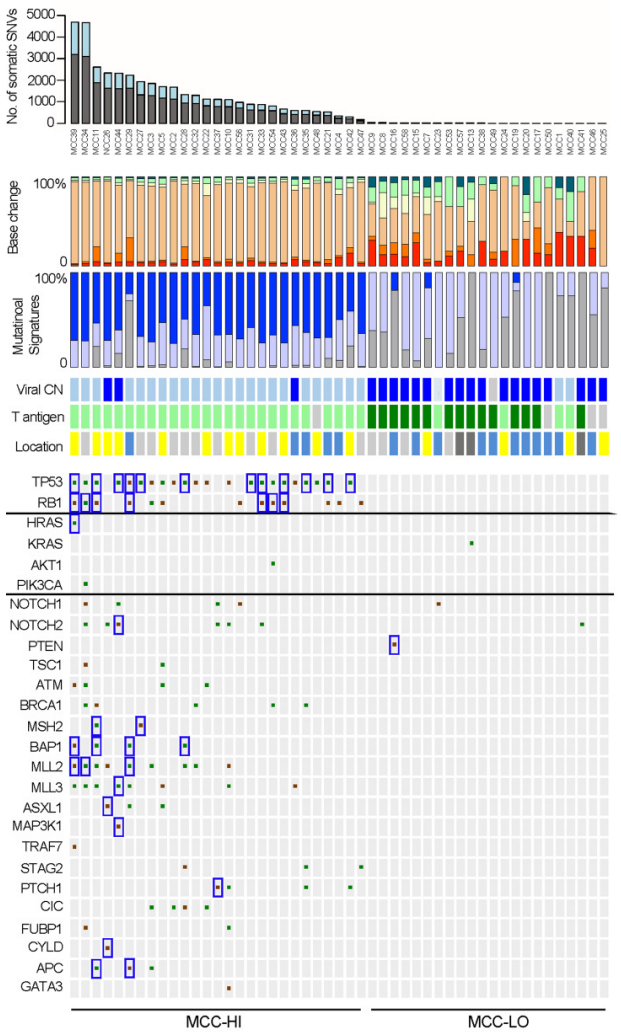
MCPyV is a small DNA virus with a circular, double-stranded DNA (dsDNA) genome of ~5 kb [14]. The viral genome is divided into three major regions: the non-coding regulatory region (NCRR), which contains the viral origin of replication and transcriptional regulatory elements; the early coding region; and the late coding region [14,15]. The early region encodes large T (LT) antigen, small T (sT) antigen, the 57kT antigen, and a protein called alternative LT Open reading frame (ALTO) [14,16**,17**]. The late region encodes the capsid proteins, VP1 and VP2 [18]. During the normal life cycle, the polyomavirus genome is maintained as a circular dsDNA episome (Figure 1).

MCPyV genome and viral T antigens are detected in at least 80% of MCC cases, and expression of the T antigens is restricted to the tumor cells and not the surrounding healthy tissues [1**,19,20*,21–23]. Genetic analysis of MCPyV genome in these MCC tumors revealed that it is clonally integrated into the host cell genome [1**,24]. The viral integration event appears to take place before the clonal expansion of tumor cell proliferation [1**,25–27]. Persistent expression of MCPyV T antigens from the integrated viral genome is required for MCC tumor cells to survive [20*]. Together, these findings provide strong support for a causal role of MCPyV in the development of MCC skin cancer.

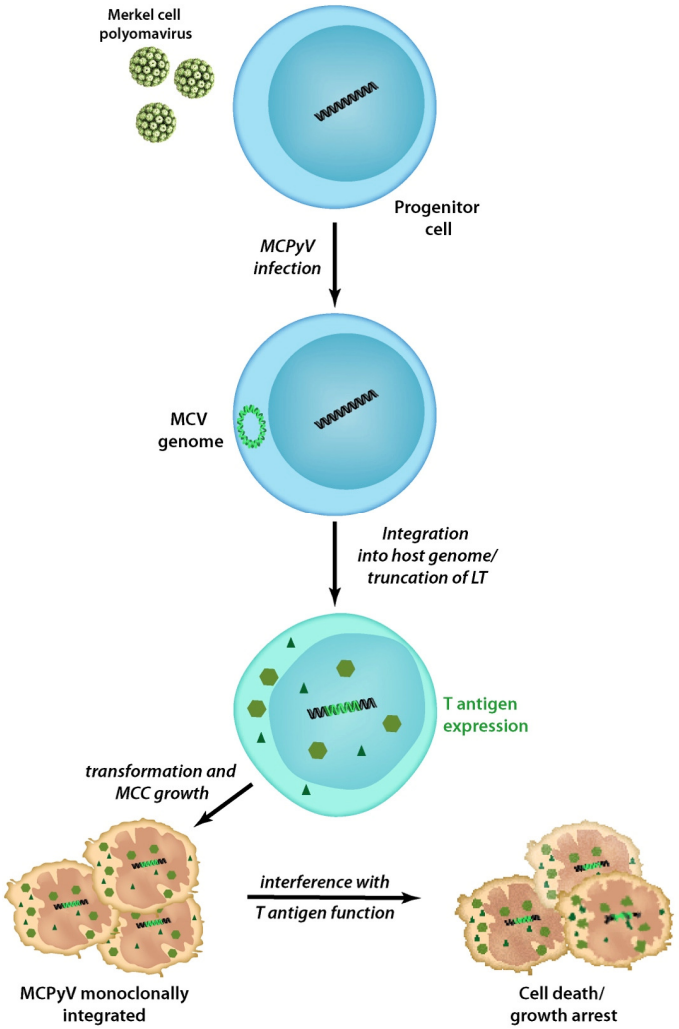
The incidence of MCC has tripled over the past twenty years as the aging population with prolonged sun exposure increases [28]. With the high prevalence of MCPyV infection and an increasing number of MCC diagnoses, there is a need to better understand the biology and oncogenic potentials of MCPyV. In this review, we summarize recent discoveries of the

Current Opinion in Virology 2016, 20:20–27 www.sciencedirect.com

UV- & Virus-asscociated Carcinogenesis



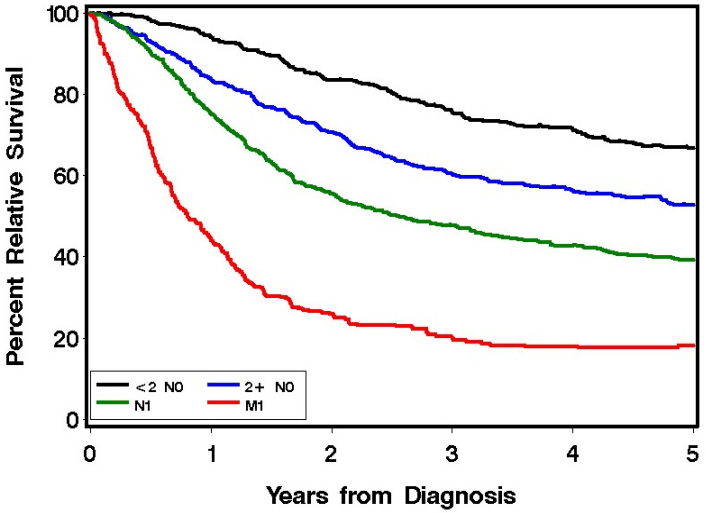
Goh 2015



Schrama 2013

MCC - Prognosis

- tumor stage
  - ☺ stage I < II < III < IV ☹
- gender
  - ☹ males < females ☺
- Localization
  - ☹ head/neck < trunk < extremities ☺
- histological and immunohistological features
  - ☹ small cell size, high mitotic index, high density of blood vessels, loss of MHC class I expression
  - ☺ solar elastosis, inflammatory infiltrate



MCC – Chemotherapie

high objective response rates

- *first line* up to 57%
- *second line* up to 45%
- *third line* up to 20%

but

- **no** controlled randomized trials
- **no** confirmed correlation between objective responses and overall survival
- **no** confirmed correlation between dose intensity and response
- significant rate of **therapy-associated deaths**

MCC - Spontaneous Regressions

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British Journal of Oral and Maxillofacial Surgery 48 (2010) 199–200
BRITISH Journal of Oral and Maxillofacial Surgery
www.bjoms.com
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Short communication
Spontaneous regression of advanced merkel-cell-like small cell carcinoma of the parotid gland

Total Spontaneous Regression of Advanced Merkel Cell Carcinoma after Biopsy: Review and a New Case
Antonio Giovanni Richetta, MD,* Monica Mancini, MD,* Andrea Torroni, MD,† Bruno Lorè, MD,† Giorgio Iannetti, MD,† Barbara Sardella, MD,‡ and Stefano Calvieri, MD*
The authors have indicated no significant interest with commercial supporters.

Merkel Cell Carcinoma of the Eyelid
Review of the Literature and Report of Patients with Merkel Cell Carcinoma Showing Spontaneous Regression
Guy S. Missotten, MD, PhD, D. de Wolff-Rouendaal, MD, PhD, R. J. W. de Keizer, MD, PhD

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Spontaneous regression of Merkel cell carcinoma: a comparative study of TUNEL index and tumor lymphocytes between

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Complete spontaneous regression in Merkel cell carcinoma
Martin J.J. Vesely, Dylan J. Murray, Peter C. Neligan, Christine B. Novak, Patrick J. Gullane, Danny Ghazarian

Extraordinary Case Report
Complete Spontaneous Regression of Metastatic Merkel Cell Carcinoma: A Case Report and Review of the Literature
J. C. Wooff, MD,* J. R. Trites, MD, FRCSC,† N. M. G. Walsh, MD, MRCPI, FRCP (C), FRCPath (UK),* and M. J. Bullock, MD, FRCP (C)*

VOLUME 29 · NUMBER 12 · APRIL 20 2011

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Validation of Intratumoral CD8+ Lymphocyte Invasion As an Independent Predictor of Survival

Kelly G. Paulson, Jayasri G. Iyer, Andrew R. Tegeder, Renee Thibodeau, Janell Schelter, Shinichi Koba, David Schrama, William T. Simonson, Bianca D. Lemos, David R. Byrd, David M. Koelle, Denise A. Galloway, J. Helen Leonard, Margaret M. Madeleine, Zsolt B. Argenyi, Mary L. Disis, Juergen C. Becker, Michele A. Cleary, and Paul Nghiem

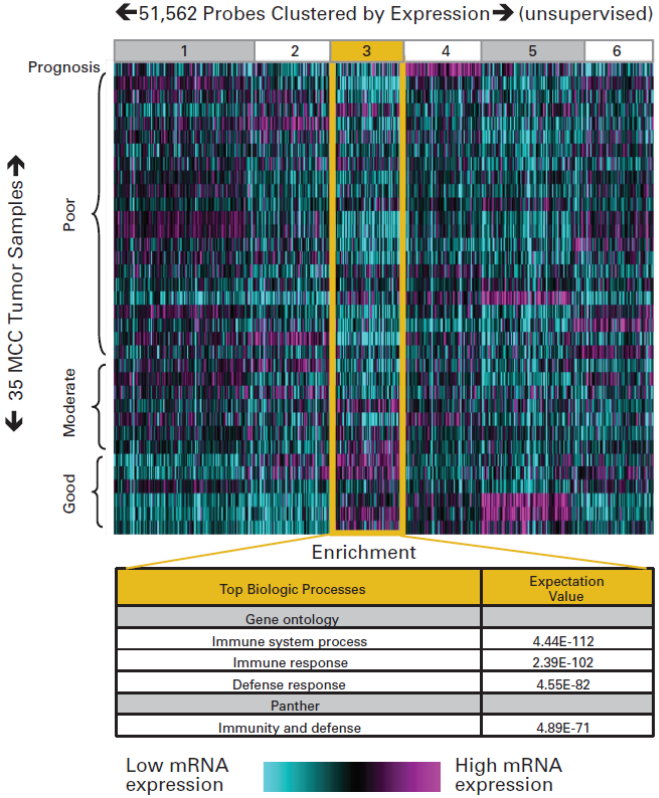
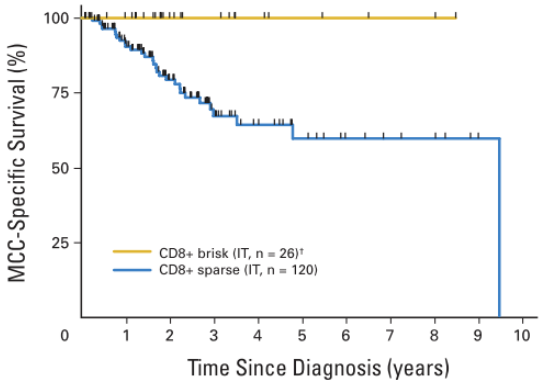


Table 2. Genes Most Highly Upregulated in Good Prognosis Tumors

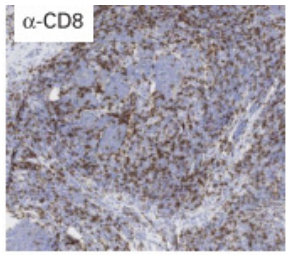
Gene Abbreviation	Gene's Full Name
ALDH1A1	Aldehyde dehydrogenase 1 family, member A1
AMICA1	Adhesion molecule, interacts with CXADR antigen 1
BHLHE41	Basic helix-loop-helix family, member e41
CCL19	Chemokine (C-C motif) ligand 19
CCR2	Chemokine (C-C motif) receptor 2
CD8a	CD8a molecule
CGA	Glycoprotein hormones, alpha polypeptide
CHI3L1	Chitinase 3-like 1
CHIT1	Chitinase 1
CHRNA9	Cholinergic receptor, nicotinic, alpha 9
FAM46C	Family with sequence similarity 46, member C
FBP1	Fructose-1,6-bisphosphatase 1
GZMA	Granzyme A
GZMB	Granzyme B
GZMH	Granzyme H
GZMK	Granzyme K
HLA-DPA1	Major histocompatibility complex, class II, DP alpha 1
HLA-DRB5	Major histocompatibility complex, class II, DR beta 5
IGJ	Immunoglobulin J polypeptide
IGKC	Immunoglobulin kappa constant
ITGBL1	Integrin, beta-like 1
KLRK1	Killer cell lectin-like receptor subfamily K, member 1 (NKG2D)
LYZ	Lysozyme
MMP7	Matrix metallopeptidase 7
POU2AF1	POU class 2 associating factor 1
PROM1	Prominin 1
SLAMF1	Signaling lymphocytic activation molecule family member 1
TMEM200A	Transmembrane protein 200A
TNFRSF17	Tumor necrosis factor receptor superfamily, member 17
TRBC1	T cell receptor beta constant 1

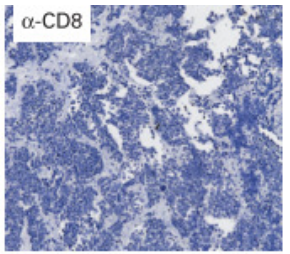
NOTE. The 30 genes in cluster bin 3 (Fig 1) most highly upregulated in good prognosis patients as compared with poor prognosis patients are listed in alphabetical order. Fold overexpression ranged from five- to 13-fold.



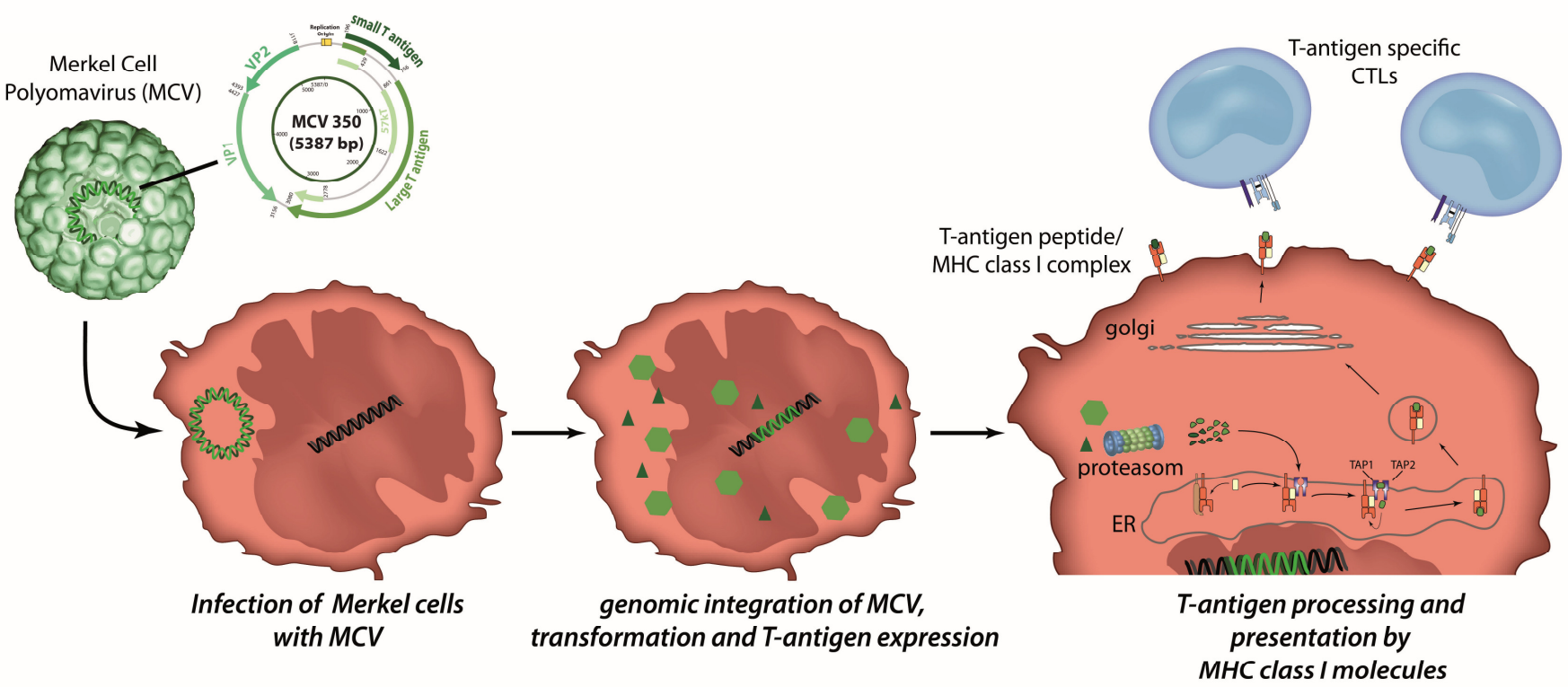
Good Prognosis

Poor Prognosis

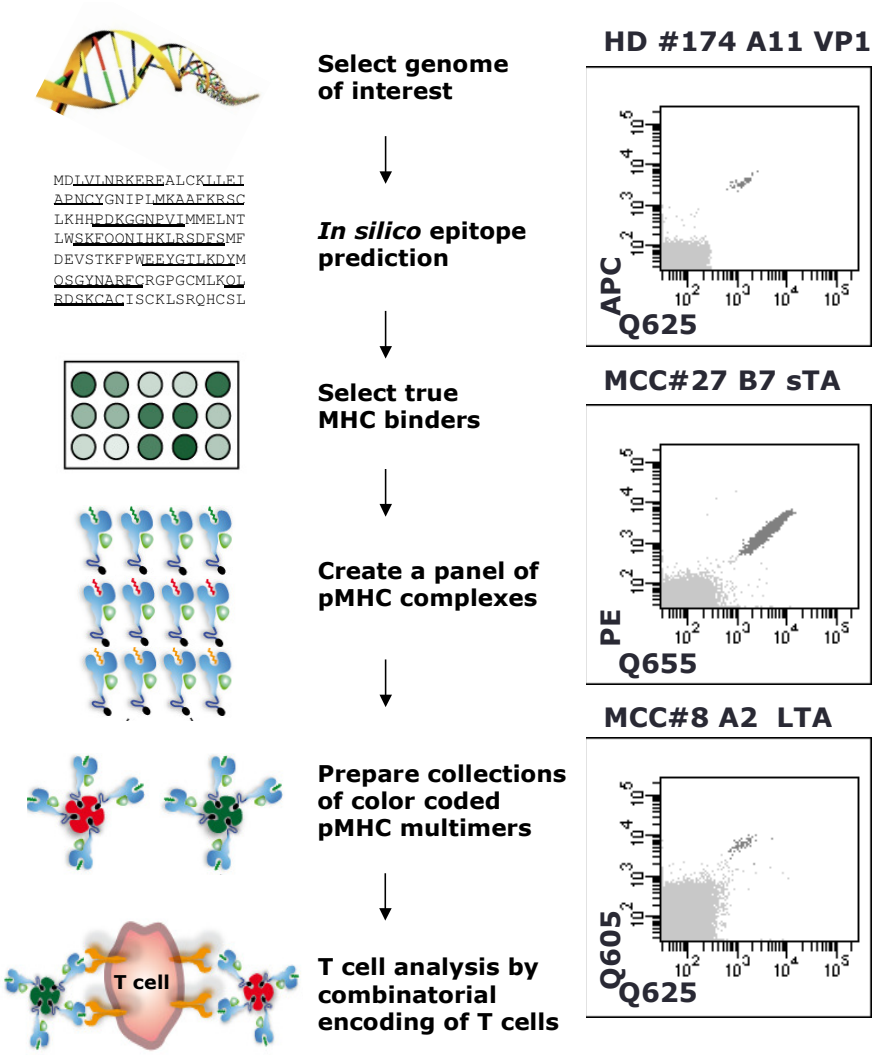




MCPyV derived T-Cell Epitopes

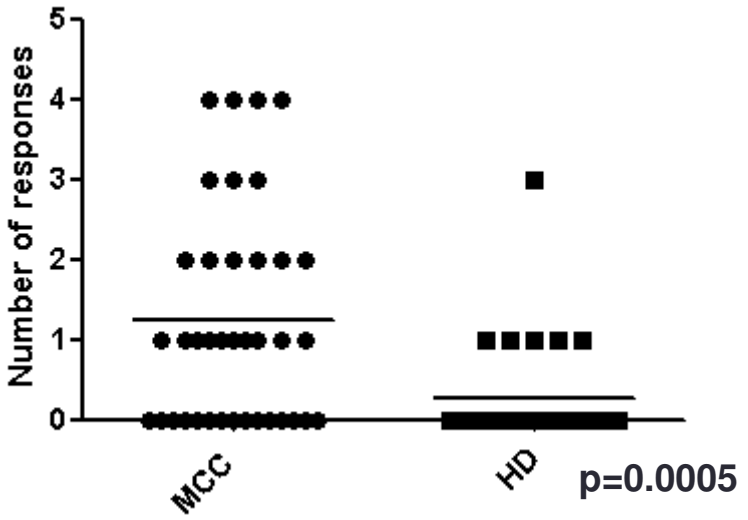


T-Cell Epitopes of MCPyV Encoded Proteins



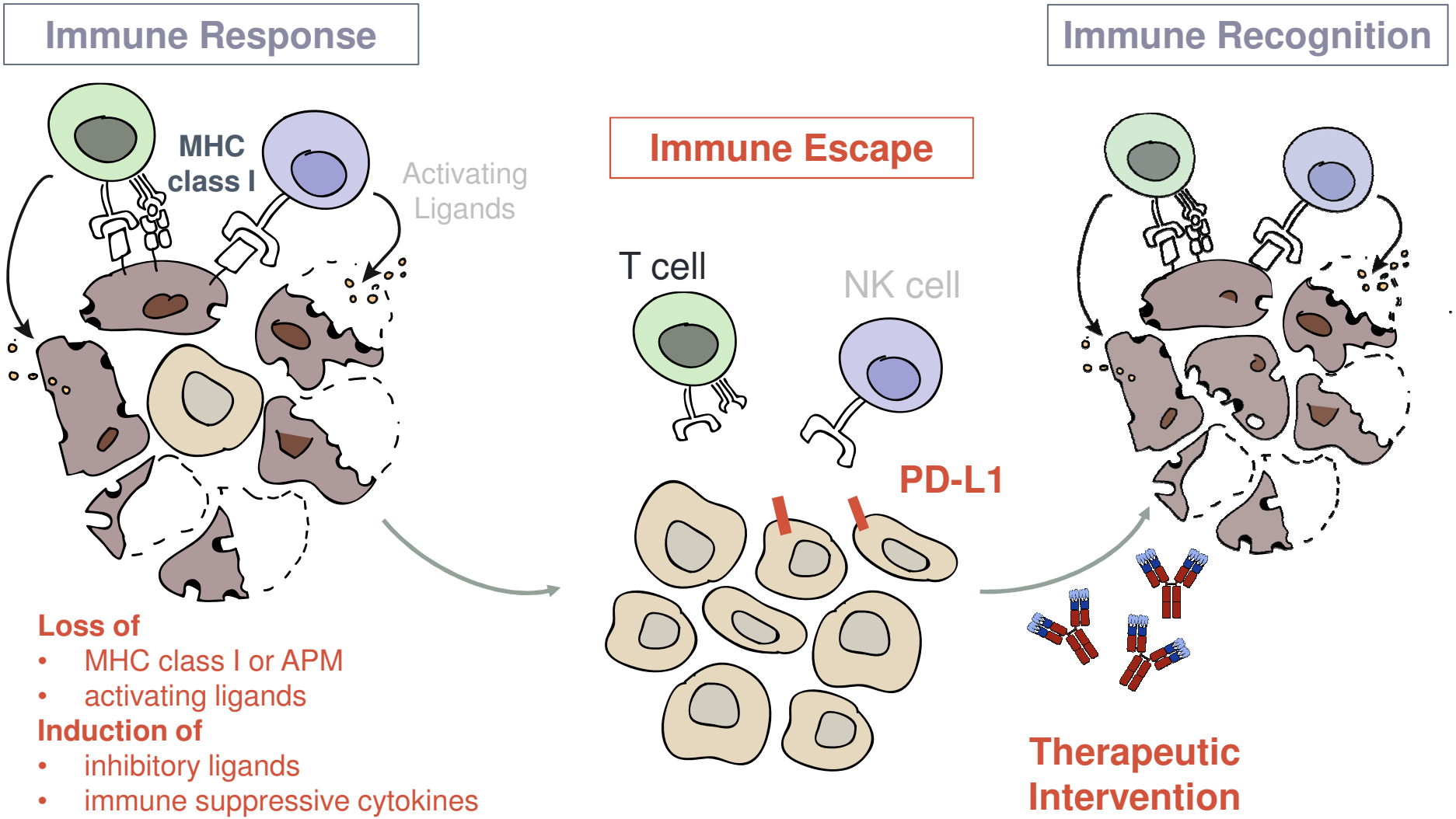
	No.	Responses detected in	frequency
HD	30	6	20%
MCC	38	22	58%

p=0.038

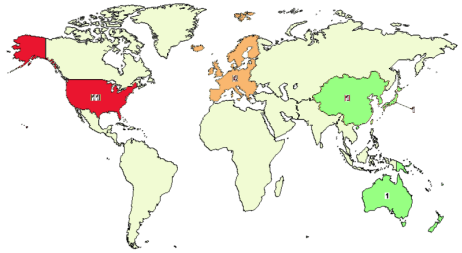


Lyngaa, et al. *Clin Cancer Res 2014*

Cancer Immune Surveillance



MCC: Klinische Studien



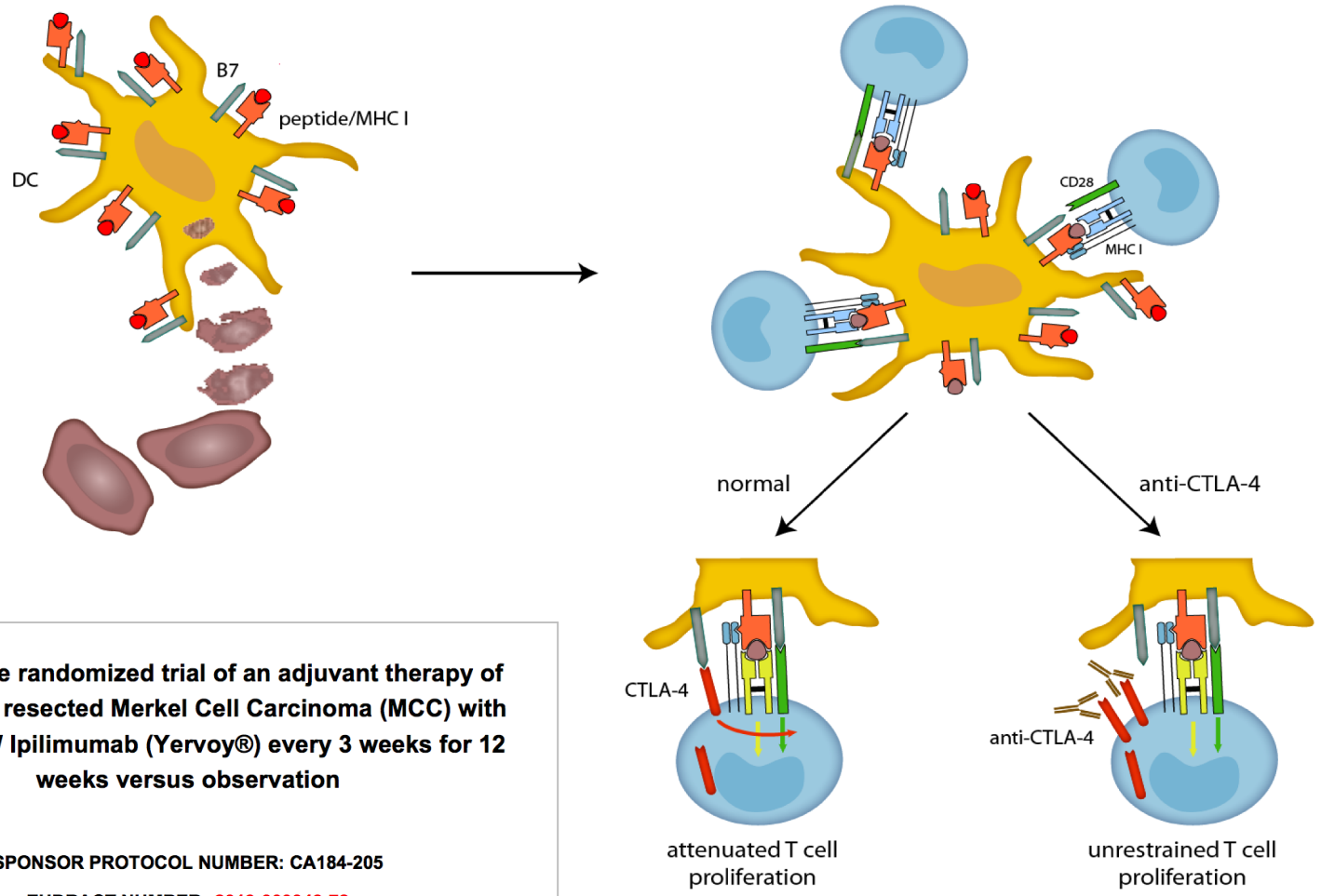
Studiennummer	Drug	Behandlung	Kombination	Mechanismus	Status	Patienten	Phase
NCT02054884	F16-IL-2	Antikörper-IL-2-Fusionsprotein	Paclitaxel	IL-2 transport ins Tumorstroma	rekrutiert	45/90	2
NCT02465957	aNK	Transfer von aktivierten NK-92 Zellen	-	NK-Zell vermittelte Lyse von Tumorzellen	rekrutiert	24	2
NCT01440816	IL-12-Plasmid	IL-12-DNA Elektroporation	-	Verstärkt TH1-Antworten, erhöht IFN-γ und zytolytische Aktivität	aktiv	15	2
NCT02267603	Pembrolizumab	Anti-PD-1	-	Blockiert inhibitorische Signale an $CD8^+$ T- Zellen	rekrutiert	50	2
NCT02488759 (virus ass. Tumors)	Nivolumab	Anti-PD-1	-	Blockiert inhibitorische Signale an $CD8^+$ T- Zellen	aktiv	199	1/2
NCT02155647	Avelumab	Anti-PD-L1	-	Blockiert inhibitorische Signale an $CD8^+$ T- Zellen	aktiv	88	2
NCT02196961	Ipilimumab	CTLA-4 blockierender Antikörper	-	Blockiert CTLA-4 vermittelte Aktivierung von Immunantworten	rekrutiert	222	2
NCT01758458	$CD8^+$ T cells	Adoptive T-Zell-Therapie	Aldesleukin	Expansion und Aktivierung von tumor-reaktiven Lymphozyten	rekrutiert	16	1/2
NCT02035657	GLA-SE	Toll-like Rezeptor-4 Agonist	-	Immunstimulation	aktiv	10	1
NCT02036476	Cabozantinib	Rezeptortyrosinkinase-Inhibitor	-	Inhibition des Tumorzellwachstums	rekrutiert	12	2
NCT02514824	MLN0128	mTOR Kinase-Inhibitor	-	Inhibition des Tumorzellwachstums	rekrutiert	34	1/2
NCT02351128	Lanreotide	Somatostatin-Analogon	-	Inhibition des Tumorzellwachstums	rekrutiert	35	2

Immuntherapie

Andere

www.clinicaltrial.gov (Februar 2016)

NCT02196961: Ipilimumab Adjuvant



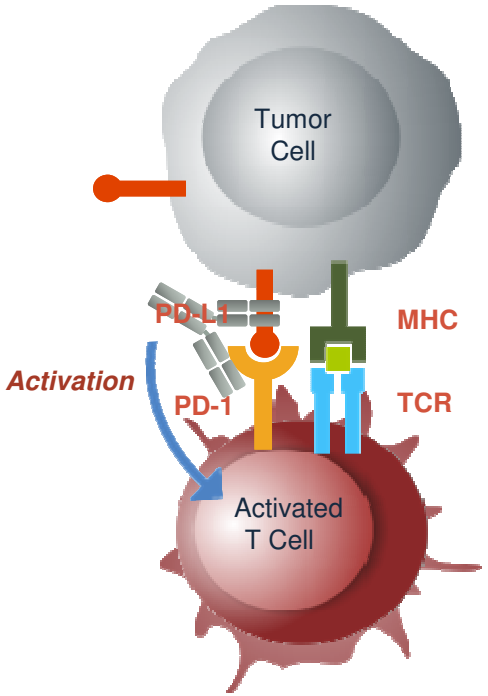
Prospective randomized trial of an adjuvant therapy of completely resected Merkel Cell Carcinoma (MCC) with 3mg/kg BW Ipilimumab (Yervoy®) every 3 weeks for 12 weeks versus observation

SPONSOR PROTOCOL NUMBER: CA184-205

EUDRACT NUMBER: 2013-000043-78

Anti PD-1 for advanced MCC

- Multicenter, Phase II, single arm of pembrolizumab, 2mg/kg q3wks as **first line** therapy
- PI: Paul Nghiem and the Cancer Immunotherapy Trials Network (CITN), CTEP
- ClinicalTrials.gov Identifier: NCT02267603



The NEW ENGLAND JOURNAL of MEDICINE

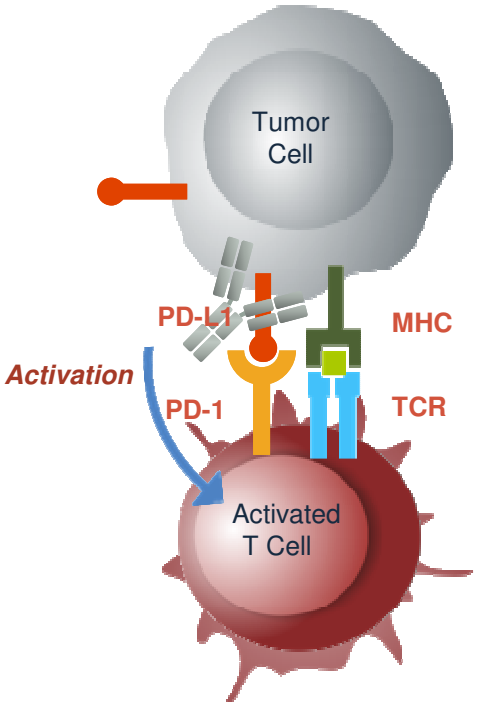
ORIGINAL ARTICLE

PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma

Paul T. Nghiem, M.D., Ph.D., Shailender Bhatia, M.D., Evan J. Lipson, M.D., Ragini R. Kudchadkar, M.D., Natalie J. Miller, B.A., Lakshmanan Annamalai, D.V.M., Ph.D, Sneha Berry, M.S., Elliot K. Chartash, M.D., Adil Daud, M.B., B.S., Steven P. Fling, Ph.D., Philip A. Friedlander, M.D., Harriet M. Kluger, M.D., Holbrook E. Kohrt, M.D., Ph.D.,* Lisa Lundgren, M.S., Kim Margolin, M.D., Alan Mitchell, M.Sc., Thomas Olencki, D.O., Drew M. Pardoll, M.D., Ph.D., Sunil A. Reddy, M.D., Erica M. Shantha, M.D., William H. Sharfman, M.D., Elad Sharon, M.D., M.P.H., Lynn R. Shemanski, Ph.D., Michi M. Shinohara, M.D., Joel C. Sunshine, M.D., Ph.D., Janis M. Taube, M.D., John A. Thompson, M.D., Steven M. Townson, Ph.D., Jennifer H. Yearley, D.V.M., Ph.D., Suzanne L. Topalian, M.D., and Martin A. Cheever, M.D.

Anti-PD-L1 for advanced MCC

- Phase II, single arm of avelumab 10 mg/kg q2wks as **second line** therapy
- Multicenter US and Europe
- PI: Howard Kaufman, Rutgers University
- ClinicalTrials.gov identifier: NCT02155647



Articles

Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial

Howard L Kaufman, Jeffery Russell, Omid Hamid, Shailender Bhatia, Patrick Terheyden, Sandra P D'Angelo, Kent C Shih, Céleste Lebbé, Gerald P Linette, Michele Milella, Isaac Brownell, Karl D Lewis, Jochen H Lorch, Kevin Chin, Lisa Mahnke, Anja von Heydebreck, Jean-Marie Cuillerot, Paul Nghiem

Summary

Background Merkel cell carcinoma is a rare, aggressive skin cancer with poor prognosis in patients with advanced disease. Current standard care uses various cytotoxic chemotherapy regimens, but responses are seldom durable. Tumour oncogenesis is linked to Merkel cell polyomavirus integration and ultraviolet-radiation-induced mutations, providing rationale for treatment with immunotherapy antibodies that target the PD-L1/PD-1 pathway. We assessed treatment with avelumab, an anti-PD-L1 monoclonal antibody, in patients with stage IV Merkel cell carcinoma that had progressed after cytotoxic chemotherapy.

Lancet Oncol 2016

Published Online
September 1, 2016
http://dx.doi.org/10.1016/S1470-2045(16)30364-3

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(16)30441-7

NCT02155647 - Avelumab
Effective for therapy resistant MCC

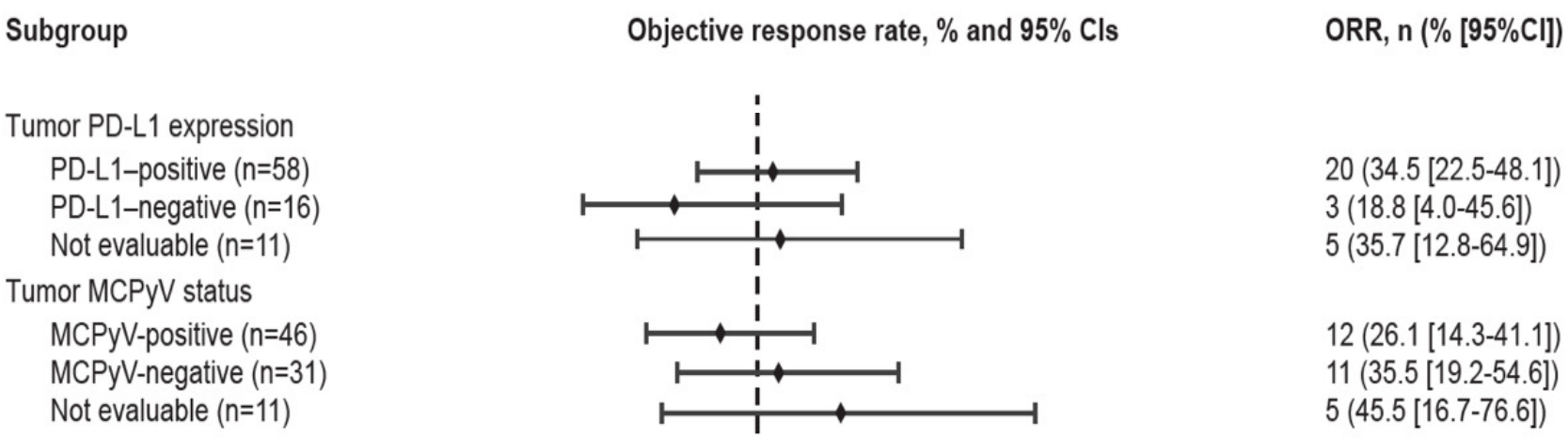
BOR by RECIST v1.1* (n=88)	
Complete response, n (%)	8 (9.1)
Partial response, n (%)	20 (22.7)
Stable disease, n (%)	9 (10.2)
Progressive disease, n (%)	32 (36.4)
Non-CR/non-PD, n (%)	1 (1.1)
Non-evaluable, n (%)	18 (20.5)
Objective response rate, % (95.9% CI)†	**31.8 (21.9, 43.1)**

2/8 CRs occurred in patients with visceral disease

* Confirmed best overall response according to independent review committee assessment.
† A repeated CI for ORR (95·9% CI for the primary analysis) was calculated to account for the group sequential testing approach.

J Clin Oncol. 2016;34 (suppl; abstr 9508).

Neither MCPyV nor PD-L1 status predict response to Avelumab



Avelumab: Toxicity and side effects

n=88	Any grade n (%)	Grade 3 n (%)
Any TRAE	62 (70.5)	**4 (4.5)**
Fatigue	21 (23.9)	**0**
Infusion-related reaction†	15 (17.0)	**0**
Diarrhea	8 (9.1)	**0**
Nausea	8 (9.1)	**0**
Asthenia	7 (8.0)	**0**
Rash	6 (6.8)	**0**
Decreased appetite	5 (5.7)	**0**
Maculopapular rash	5 (5.7)	**0**

* Based on the worst grade per patient.
† composite definition with 5 different MedDRA terms. Signs and symptoms of a potential infusion-related reaction (eg, fever, chills, or rigors) reported on the day of infusion were queried with investigators to ascertain whether an AE of “infusion-related reaction” should be recorded.

BMS CA 209-358 (Nivo)

Non-Comparative, Two-Cohort, Single Arm, Open-Label, Phase 1/2 Study of Nivolumab (BMS-936558) in Subjects with

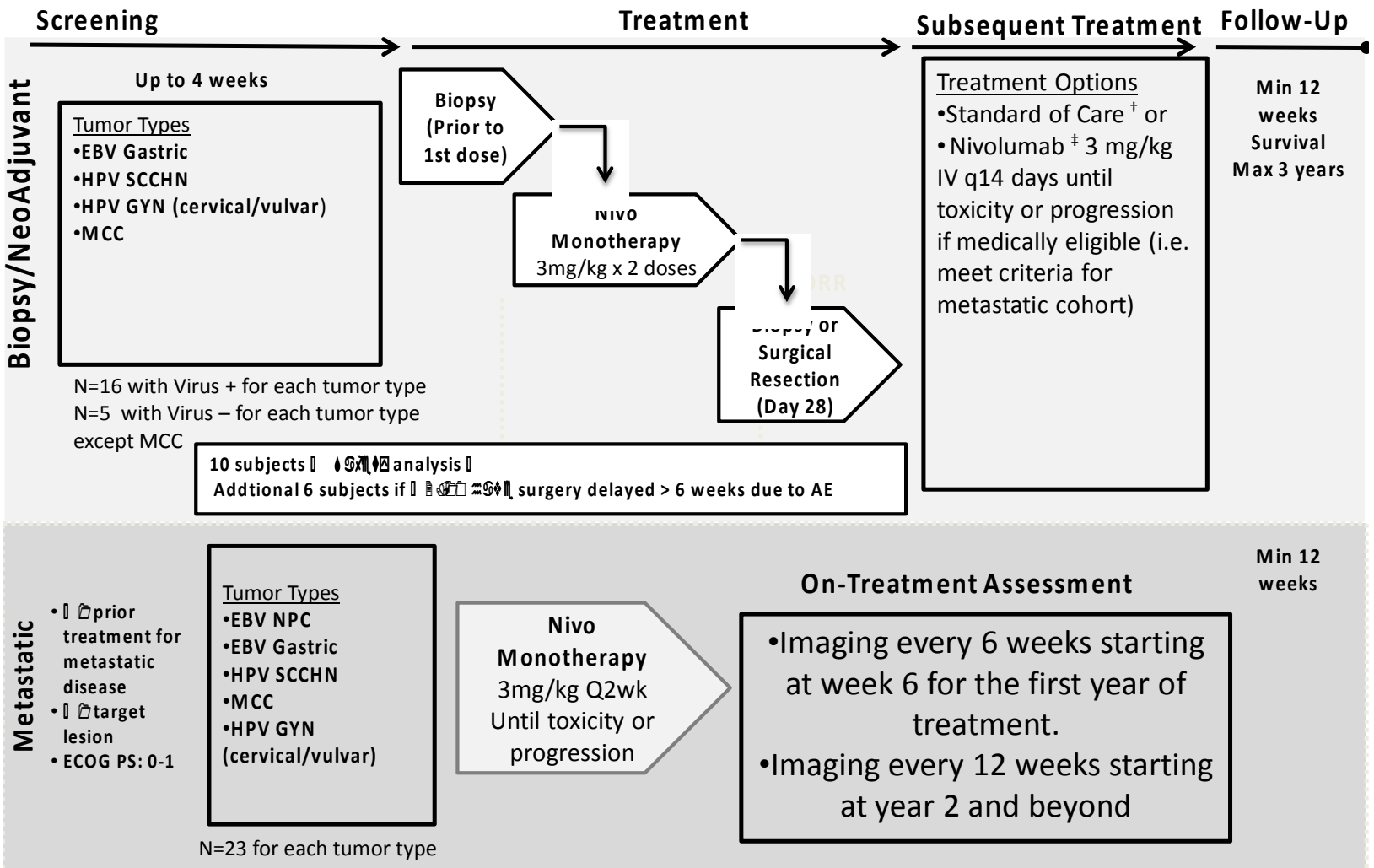
Virus-positive Solid Tumors

ClinicalTrials.gov - NCT02488759

Cohort A (Biopsy / Neoadjuvant): 84 subjects prior to surgery

Cohort B (Metastatic): 115 subjects with recurrent or metastatic disease who have had one prior line of therapy for recurrent or metastatic disease

BMS CA 209-358 (Nivo)



Σummary

- MCC is an immunogenic tumor eliciting adaptive T cell responses
- Immune responses impact the course of disease
- MCC is prone to multiple immune escape mechanisms
- PD-L1 is expressed on MCC cells, stroma cells or both and appear to be a prognostic marker depending on which cell expresses it
- **PD-1/PD-L1 immune checkpoint blockade is an efficient therapeutic option!**

immomec

IMmune MOdulating strategies for treatment of MErkel cell Carcinoma

8TH INTERNATIONAL CONGRESS ON
HPV & POLYOMAVIRUS IN SKIN CANCER
16-18 NOVEMBER 2016 MECC MAASTRICHT, THE NETHERLANDS

Wednesday 16 November, 09.00-16.30, Maastricht

International Symposium on the Immunology and Immunotherapy of Merkel cell Carcinoma

Confirmed Speaker:

Christopher Bichakjian - Jürgen C. Becker - James DeCaprio
Nicole Fischer - Axel zur Hausen - Rikke Lyngaa - Paul Nghiem
Cathrin Ritter - David Schrama - Andreas Stang - Masahiro Shuda

SEVENTH FRAMEWORK PROGRAMME