IQWiG-Herbst-Symposium am 27. und 28. November 2015 in Köln

Frühere Zulassung von Arzneimitteln

Eine Chance für Patienten (?) (!)

Prof. Dr. med. W. Dieter Paar
Medizinische Abteilung
SANOFI
Berlin

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“Sprachverwirrung”

http://www.nuernbergwiki.de/

- Adaptive Licensing
- Adaptive Pathways
- Flexible Licensing
- Conditional marketing authorization
- Conditional approval
- Managed entry agreements (MEAs)
- Coverage with evidence development (CED)
- ……

Adaptive Pathways

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„Adaptive Pathways“: Mögliche Vorteile

- Patienten können früher mit einer neuen Therapie behandelt werden besonders im Fall von Erkrankungen mit „serious unmet need“
- Die Effizienz der Arzneimittelentwicklung kann verbessert werden
- Kleinere Forschungsunternehmen (SME) haben eine größere Chance
- Es werden sofort die „richtigen“ Patienten behandelt, also diejenigen mit größter Aussicht auf Behandlungserfolg

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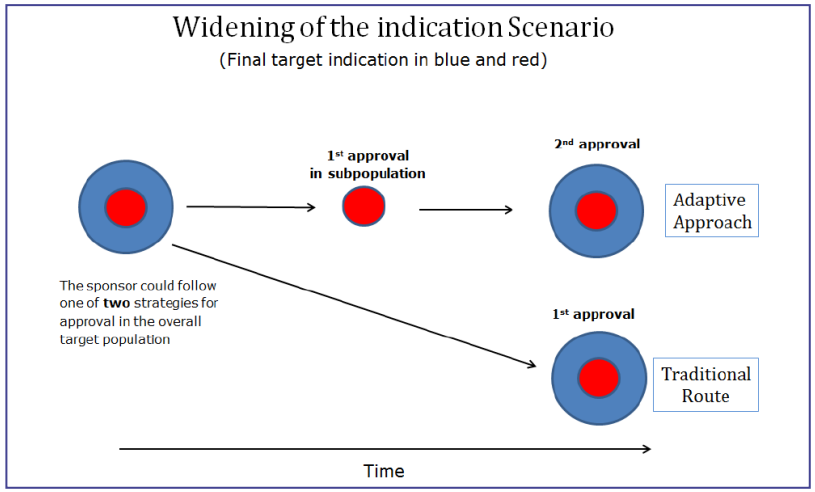
„Adaptive Pathways“: Mögliche Herausforderungen

- Wer definiert den „serious unmet need“?
- Wer definiert die „richtigen Patienten“?
- Haben wir die richtigen Studiendesigns für „adaptive pathways“?
- Wie stellt man sicher, dass nach erfolgter Zulassung auch wirklich nur die „richtigen Patienten“ behandelt werden?
- Wie funktioniert die Erstattung von Patientensubpopulationen?
- Wie wird sichergestellt, dass nach früher Zulassung weiter geforscht wird?
- Was tun, wenn sich der (Zusatz-)nutzen in einer Population im klinischen Alltag relativiert?
- Früher Beginn des Patentablaufs bei noch kleiner Population

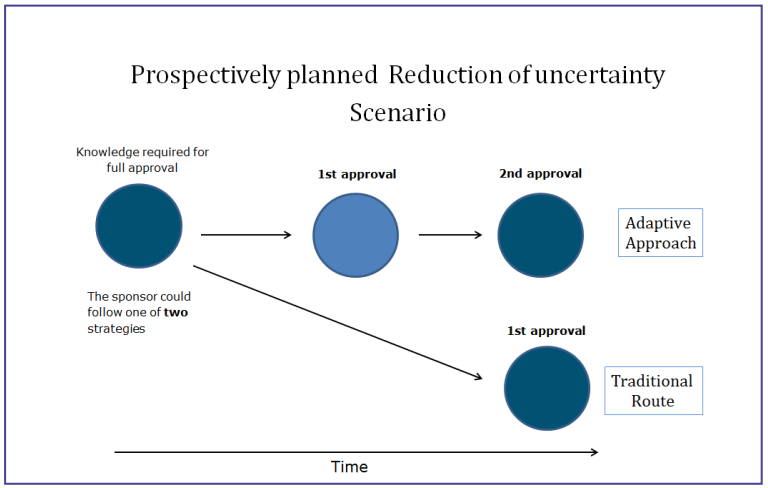
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The sponsor could follow one of two strategies….

Strategy 1



Strategy 2



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EMA/758619/2014

Adaptive Pathways

Gathering pace: adaptive pathways

www.pmlive.com/pharma_intelligence/gathering_pace_adaptive_pathways_631869

EMA looks at how the model could work in practice and picks first drugs for its pilot project

The European Medicines Agency (EMA) has selected six medicines to spearhead its adaptive pathways project, which is trialling a progressive licensing model for new drugs.

- 34 Bewerbungen
- 10 initial ausgewählt
- 6 final ausgewählt

- Ungenaue Beschreibung der Methodik zur Gewinnung von Nachzulassungsdaten

- Endpunkt muss von Zulassung und HTA akzeptiert werden

- „Weg“ von der initialen zur endgültigen Population zu ungenau beschrieben

http://www.pmlive.com/pharma_intelligence/gathering_pace_adaptive_pathways_631869
(3. Februar 2015; Zugriff 25. Oktober 2015)

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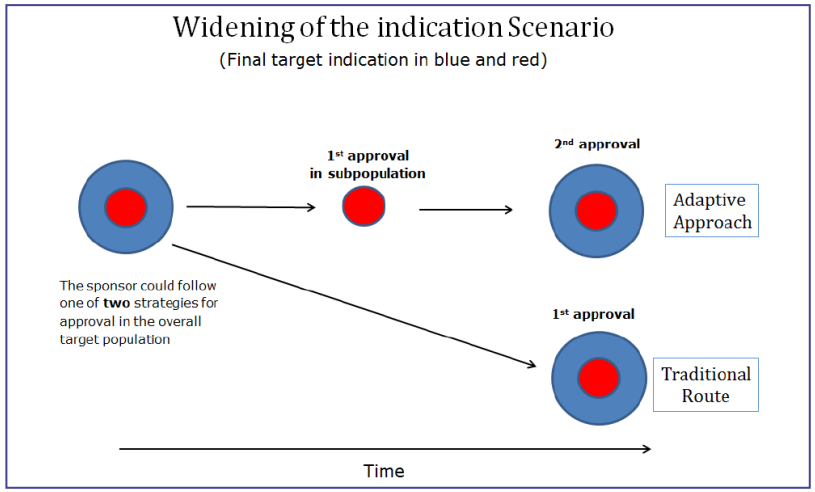
Strategy 1



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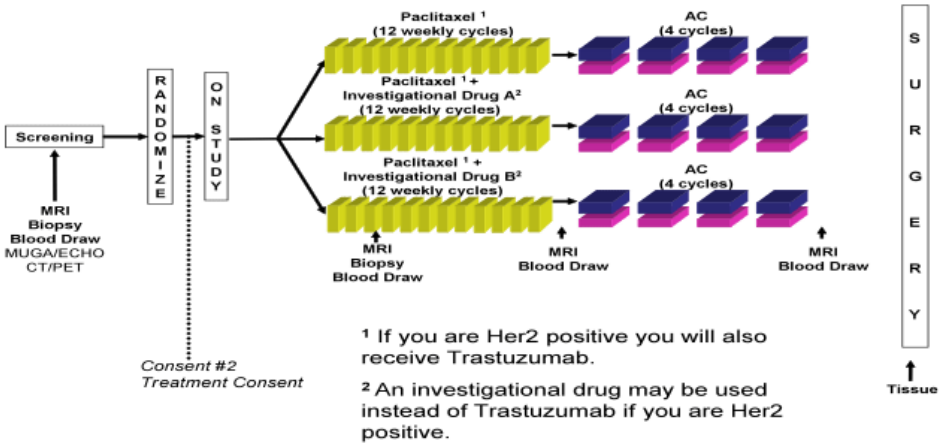
EMA/758619/2014

Design Strategies for Personalized Therapy Trials

I-SPY 2 (Investigations of Serial Studies to predict Your Therapeutic Response with Imaging and Molecular Analysis 2)

- Neoadjuvant trial, high-risk Stage II/III breast cancer
- Primary endpoint: pathologic complete response (pCR)
- An investigational agent can be graduated from the trial at any time with its biomarker signature
- At least 85% Bayesian predictive probability in a randomized 300 patients phase III trial having the same control arm as I-SPY2 and pCR as endpoint



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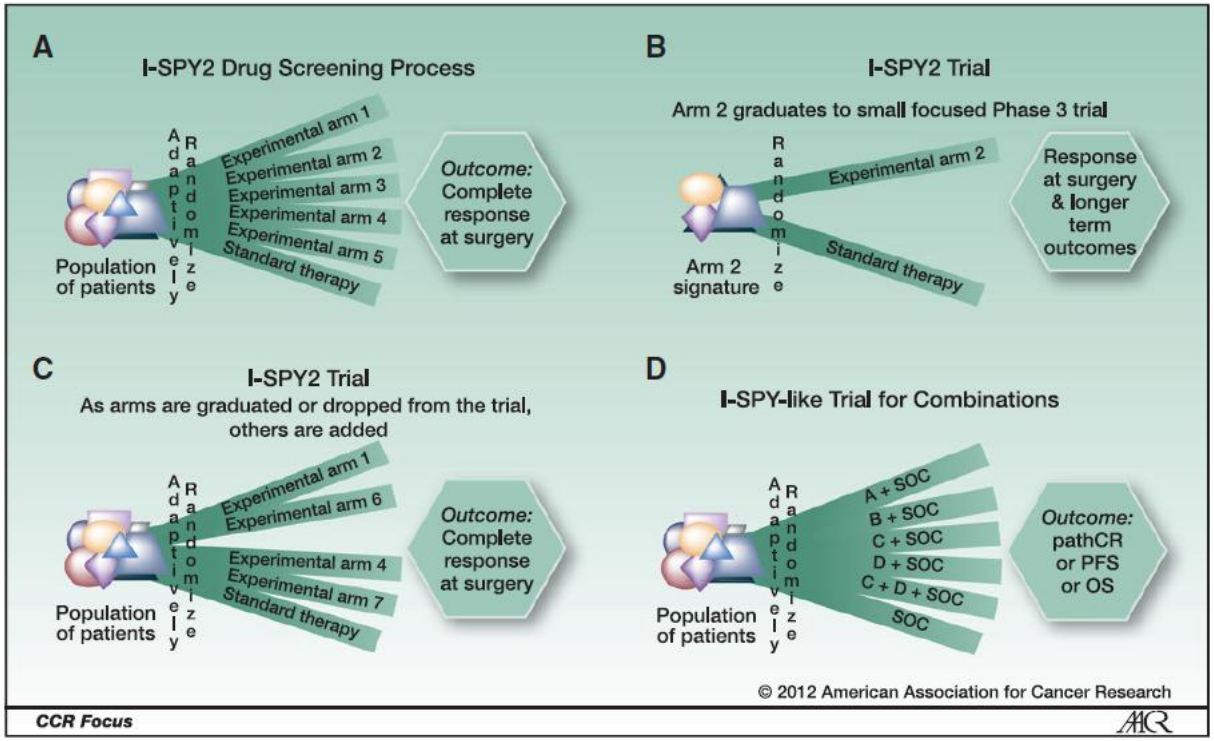
Berry DA et al. Clin Cancer Res. 18: 638-644 (2012)

Design Strategies for Personalized Therapy Trials

I-SPY 2 (Investigations of Serial Studies to predict Your Therapeutic Response with Imaging and Molecular Analysis 2)



Berry DA et al. Clin Cancer Res. 18: 638-644 (2012)

Design Strategies for Personalized Therapy Trials

I-SPY 2 (Investigations of Serial Studies to predict Your Therapeutic Response with Imaging and Molecular Analysis 2)

Condition	Intervention	Phase
Breast Neoplasms Breast Cancer Breast Tumors	Drug: Standard Therapy Drug: AMG 386 Drug: AMG 479 (Ganitumab) plus Metformin Drug: MK-2206 with or without Trastuzumab Drug: AMG 386 and Trastuzumab Drug: T-DM1 and Pertuzumab Drug: Pertuzumab and Trastuzumab Drug: Ganetespib Drug: ABT-888 Drug: Neratinib Drug: PLX3397	Phase 2

Neratinib plus standard neoadjuvant therapy for high-risk breast cancer: Efficacy results from the ISPY 2 TRIAL

HER2+
human epidermal growth factor receptor 2, erb-B2, c-erbB2

Results: Neratinib met the predictive probability criterion in HR/ HER2+, "graduated", and accrual ceased [115 N patients (65 HER2+), 78 concurrently randomized controls (22 HER2+)].

Signature	Estimated pCR Rate (95% probability interval)		Predictive Probability of Success in Phase III	
	Neratinib	Control		
HR-/HER2+	55% (46%-64%)	32% (22%-43%)	94%	78%
HER2+	39% (33%-45%)	23% (15%-30%)	95%	73%
HR+/HER2-	14% (8%-19%)	16% (10%-21%)	39%	12%

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Park JW et al. AACR Annual Meeting 2014 CT227 (modified)

Design Strategies for Personalized Therapy Trials

Successful use of Biomarkers and selected population

- Vemurafenib (BRAF Inhibitor)
- Crizotinib (ALK Inhibitor)

Challenges

- Selection of Biomarker is predominantly based on preclinical studies
- Preclinical Models often do not fully recapitulate the clinical setting
- Suggestion of incorrect prediction
- Incorrect „NO GO“ for further development
- No determination of potential benefit in a biomarker negative population

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Berry DA et al. Clin Cancer Res. 18: 638-644 (2012)

Cetuximab Shows Activity in Colorectal Cancer Patients With Tumors That Do Not Express the Epidermal Growth Factor Receptor (EGRF) by Immunohistochemistry

Table 2. EGFR-Negative Colorectal Cancer Patient Characteristics

Characteristic	Patients		PR Patients	
	No. of Patients	%	No. of Patients	%
Total patients	16	100	4	25
Current age, years				
Median	69		72	
Range	53-82		58-82	
Sex				
Male	11	69	2	50
Female	5	31	2	50
ECOG status				
≤ 2	8	50	2	50
Not documented	8	50	2	50
Cetuximab treatments, No.				
Median	11		15	
Range	1-17		8-17	
Prior treatments, No.				
Median	2		2	
Range	2-5		2-4	
Clinical POD on prior treatment				
Prior irinotecan	15	94	4	100
Prior oxaliplatin	15	94	3	75

Abbreviations: EGFR, epidermal growth factor receptor; PR, partial response; ECOG, Eastern Cooperative Oncology Group; POD, progression of disease.

Sixteen chemotherapy-refractory, EGFR-negative colorectal cancer patients who received cetuximab in a nonstudy setting were identified.

Fourteen of these patients received cetuximab plus irinotecan, and two received cetuximab monotherapy.

In the 16 patients, four major objective responses were seen (response rate, 25%; 95% CI, 4% to 46%).

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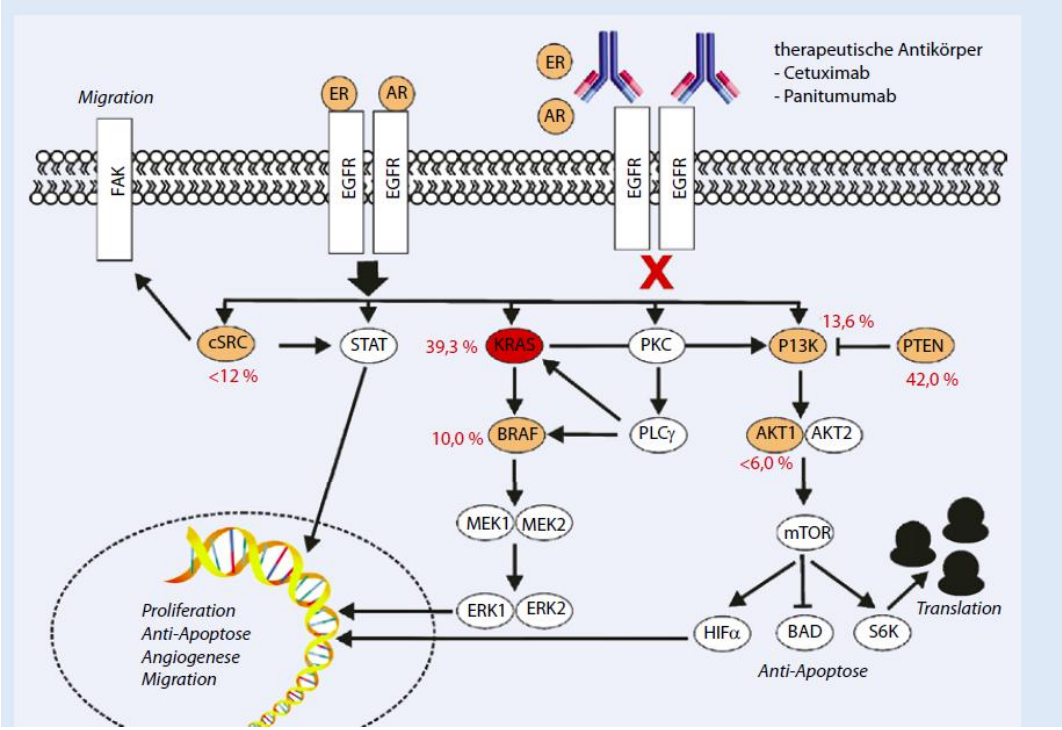
Chung KY et al. J Clin Oncol 23:1803-1810 (2005)

Pathologische Diagnostik für die individualisierte Therapie des Dickdarmkarzinoms

Weitere prädiktive Biomarker für Anti-EGFR-Therapie

Auch bei einem Dickdarmkarzinom mit *KRAS*-Wildtyp sprechen nur etwa 60% der Patienten auf die Anti-EGFR-Antikörpertherapie an, sodass für eine Verbesserung der Individualisierung und Steigerung der Therapieeffizienz weitere prädiktive Biomarker gesucht werden. Mögliche Kandidaten sind *BRAF*-Mutationen, die bei bis zu 10% der Dickdarmkarzinome vorkommen [34], *PI3K*-Mutationen, die bei bis zu 13,6% der Tumoren zu finden sind [34], und ein PTEN-Expressionsverlust, der bei bis zu 42% der Dickdarmkarzinome erwartet wird [14, 17].



Kirchner T, Jung A. Pathologe 31: 16-21 (2010)

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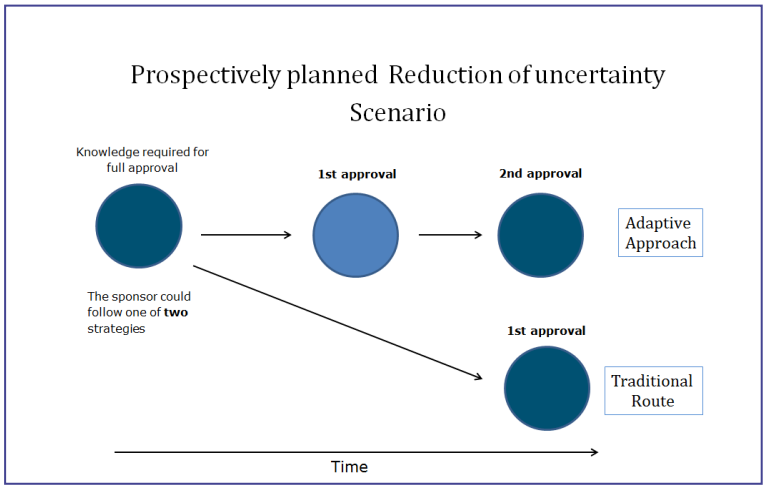
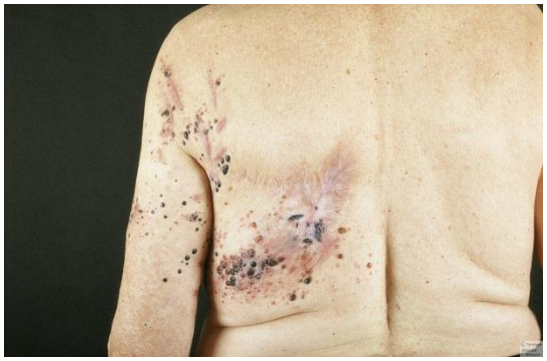
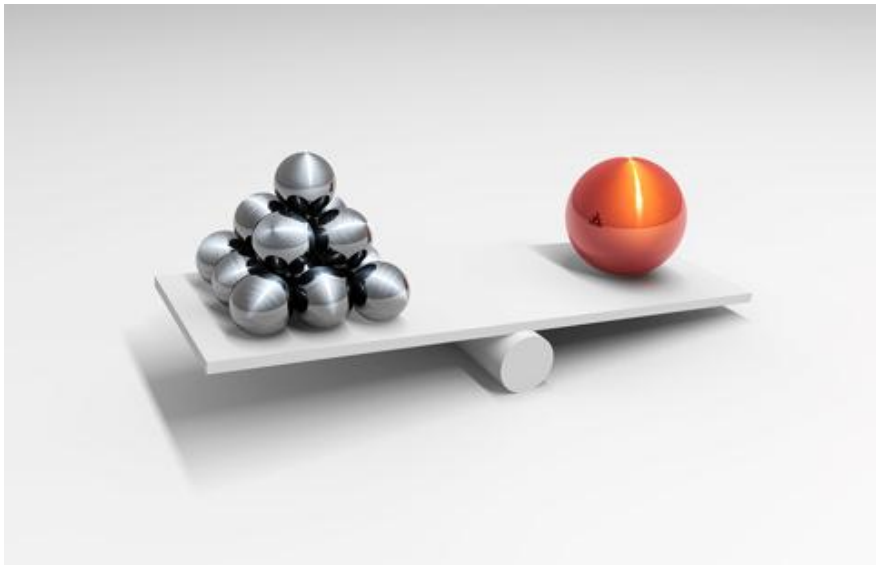
The sponsor could follow one of two strategies….

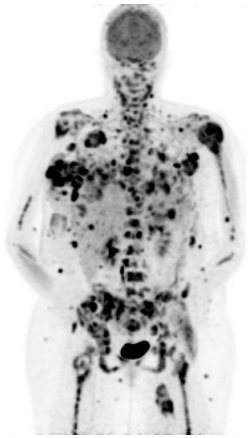
Strategy 2



Abwägung:
Patient mit malignem Melanom







Wirksamkeit einer neuen Behandlung

Sicherheit einer neuen Behandlung

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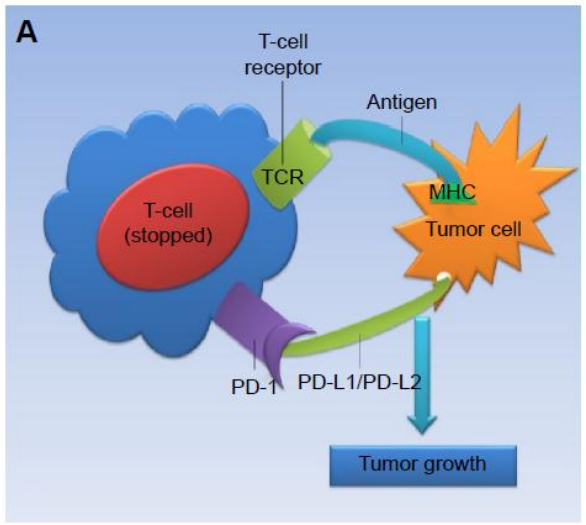
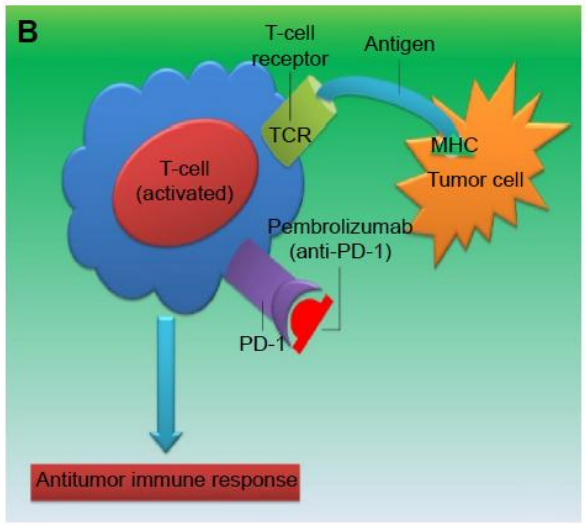
Pembrolizumab (KEYTRUDA®)





G. Improta et al. OncoTargets and Therapy 2015:8 2535-2543

MERCK

Published on *Merck Newsroom Home* (http://www.mercknewsroom.com) on 9/4/14 3:15 pm EDT

Merck Receives Accelerated Approval of KEYTRUDA® (pembrolizumab), the First FDA-Approved Anti-PD-1 Therapy

Release Date:
Thursday, September 4, 2014 3:15 pm EDT

Dateline City:
WHITEHOUSE STATION, N.J.

September 2014

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA FDA

Vorzeitige Zulassung ohne Vergleichsstudie

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Pembrolizumab (KEYTRUDA®)

21 May 2015
EMA/444458/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report **Mai 2015**

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/0000

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Zulassung bei noch laufenden Vergleichsstudien

PAES Auflage
Post Authorisation Efficacy Studies

2.5.4. Conclusions on the clinical efficacy

In conclusion, the overall data support the efficacy of pembrolizumab as monotherapy in both patients that are naïve to ipilimumab treatment and patients that have been previously treated with ipilimumab in melanoma patients with advanced disease. The comparative studies P002 and P006 are still ongoing and only interim results have been submitted. Therefore, the CHMP has imposed two PAES to have the final study reports for studies P002 and P006.

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Pembrolizumab versus Ipilimumab (P006)

(Ipilumab-naive patients)

Trial stopped after at the second interim analysis for efficacy (overall survival)

Median overall survival was not reached in any study group

6 month progression free survival

Hazard ratio for disease progression 0.58 P < 0.001

Estimated 12-month survival rates

hazard ratio for death for pembrolizumab every 2 weeks 0.63; 95% CI, 0.47 to 0.83; P = 0.0005

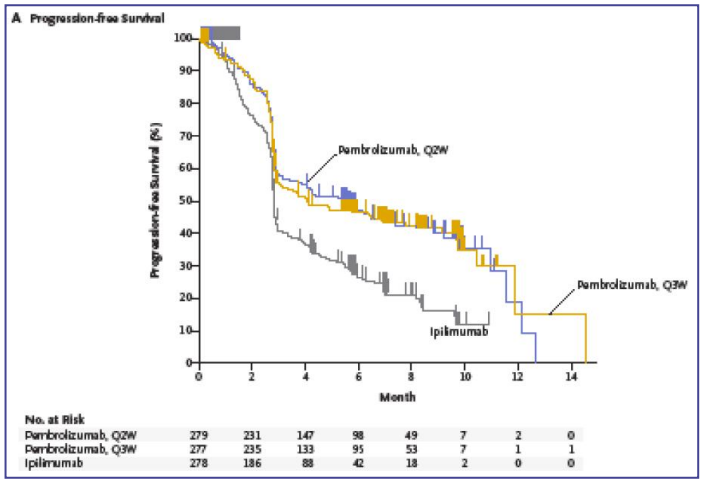
hazard ratio for death pembrolizumab every 3 weeks 0.69; 95% CI, 0.52 to 0.90; P = 0.0036

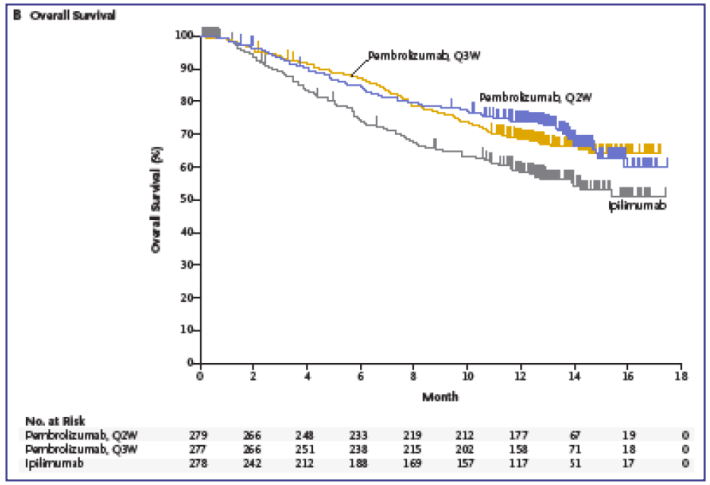
Treatment related adverse events grade 3 to 5

pembrolizumab every 2 weeks 13.3%

pembrolizumab every 3 weeks 10.1%

ipilumab 19.9%





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Robert C et al. N Engl J Med 2015;372:2521-32

Pembrolizumab – Nutzenbewertung gemäß § 35a SGB V 12.11.2015

Tabelle 3: Pembrolizumab – Ausmaß und Wahrscheinlichkeit des Zusatznutzens

Frage-stellung	Anwendungsgebiet	Zweckmäßige Vergleichstherapie[a]	Teilpopulation	Ausmaß und Wahrscheinlichkeit des Zusatznutzens
1	vorbehandelte Patienten	Patientenindividuelle Therapie nach Maßgabe des behandelnden Arztes unter Berücksichtigung des Zulassungsstatus und der jeweiligen Vortherapie.	vorbehandelte Patienten, für die Ipilimumab die geeignete Therapie ist	Hinweis auf einen beträchtlichen Zusatznutzen
			vorbehandelte Patienten, für die Ipilimumab nicht die geeignete Therapie ist	Zusatznutzen nicht belegt
2	nicht vorbehandelte Patienten mit einem BRAF-V600-wt Tumor	Dacarbazin oder **Ipilimumab**	-	Anhaltspunkt für einen geringen Zusatznutzen
3	nicht vorbehandelte Patienten mit einem BRAF-V600-mut Tumor	Vemurafenib	-	Zusatznutzen nicht belegt

3 positive Effekte gleicher Wahrscheinlichkeit mit unterschiedlichem Ausmaß in der Kategorie schwerwiegende / schwere Nebenwirkungen

2 positive Effekte gleicher Wahrscheinlichkeit und gleichen Ausmaßes: Mortalität, gesundheitsbezogene Lebensqualität

Bettina Ryll, MD/PhD founded the Melanoma Patient Network Europe after loosing her husband to Melanoma and developed a special interest in patient-centric clinical research and drug development. Bettina's current areas of focus are Adaptive Licensing/ MAPPS , innovative sustainable healthcare models and patient-centered risk/ benefit assessment tools. Bettina lectures and advises on patient-centric drug development; she is member of ASCO and ISPOR and currently holds the Chair of the ESMO Patient Advocacy Working Group.

WORLD HEALTH SUMMIT

„Would you jump out of a plane with a parachute, with a 10% probability of opening?" ……..

Berlin October 11-13, 2015

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WORLD HEALTH SUMMIT

Berlin October 11-13, 2015

„Would you jump out of a plane with a parachute, with a 10% probability of opening?" ..

and what if this plane is close to hit a cliff?

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Adaptive pathways

Arzneimittelsicherheit

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BJCP British Journal of Clinical Pharmacology

Additional safety risk to exceptionally approved drugs in Europe?

Arna H. Arnardottir,[1] Flora M. Haaijer-Ruskamp,[1] Sabine M. J. Straus,[2,3] Hans-Georg Eichler,[4] Pieter A. de Graeff[1,2] & Peter G. M. Mol[1,2]

[1]Department of Clinical Pharmacology, University Medical Centre Groningen, University of Groningen, Groningen, [2]Dutch Medicines Evaluation Board (CBG-MEB), The Hague, [3]Medical Informatics, Erasmus Medical Centre, Rotterdam, the Netherlands and [4]European Medicines Agency, London, UK

Br J Clin Pharmacol 72:490-499 (2011)

Additional safety risk to exceptionally approved drugs in Europe?

- Retrospective cohort study
- 1999-2009
- Frequency and timing of first Direct Healthcare Professional Communication (DHCP)
- 289 new drugs approved
- 46 (16.4%) Exceptional Approval (EC) or Conditional Approval (CA)
- 15% of EC or CA drugs received a DHCP
- 14% of standard approval drugs received a DHCP

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Br J Clin Pharmacol 72:490-499 (2011)

Additional safety risk to exceptionally approved drugs in Europe?

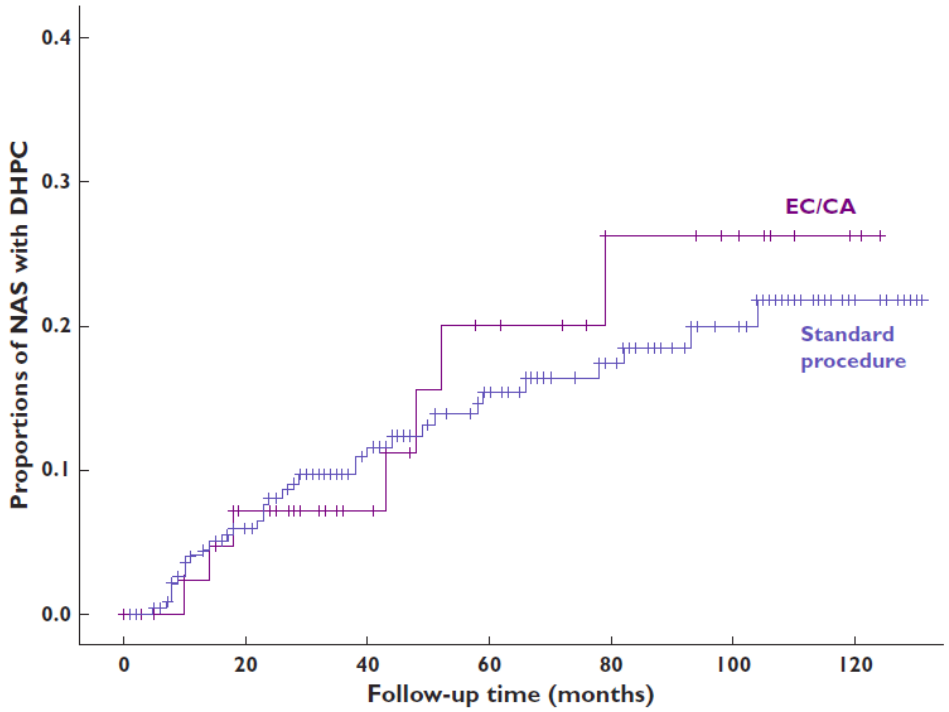

Figure 1

Proportion of new active substances (NAS) that obtained a marketing authorization between 1999 and 2009 under exceptional circumstances/conditional approval (EC/CA) or standard marketing authorizations with or without a Direct Healthcare Provider Communication (DHPC)

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Br J Clin Pharmacol 72:490-499 (2011)

efpia

European Federation of Pharmaceutical Industries and Associations

COMMENT

Priorities for improving drug research, development and regulation

Susan R. Forda, Richard Bergström, Magda Chlebus, Richard Barker and Peter Høngaard Andersen

SANOFI

Nature Reviews Drug Discovery 2013; 12: 247-248

efpia
European Federation of Pharmaceutical Industries and Associations

Priorities for improving drug research, development and regulation (1)

- Redefine diseases by their underlying molecular mechanisms
  - Oestrogen receptor (breast cancer)
  - Human epidermal growth factor receptor 2 (Breast cancer)
- Adapt regulatory framework to new science
  - Improving the regulatory framework for companion diagnostics
  - Collaboration to develop better framework (regulators, patients, pharmaceutical and diagnostic industry)
- Develop new trial design and statistical methods
  - Adaptive approaches while maintaining statistical rigor

Nature Reviews Drug Discovery 2013; 12: 247-248

efpia
European Federation of Pharmaceutical Industries and Associations

Priorities for improving drug research, development and regulation (2)

- Establish agreement on benefit risk assessment by regulatory authorities
  - Benefit established only in a small population
  - Risk when widening the population?
  - EMA versus FDA
- Explore new approaches for granting earlier patient access to important new medicines
  - EU conditional marketing authorization (CA)
  - Progressive Marketing authorization (PMA) (e.g. start with a clearly defined groups of patients based on their genotype)
  - Reimbursement for targeted patients!
- Ensure regulatory operational excellence
- Promote global medicines development
  - ICH update

Nature Reviews Drug Discovery 2013; 12: 247-248

efpia
European Federation of Pharmaceutical Industries and Associations

Medicines Adaptive Pathways to Patients (MAPPs)

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http://efpiamapps.eu/

Medicines Adaptive Pathways to Patients (MAPPs)

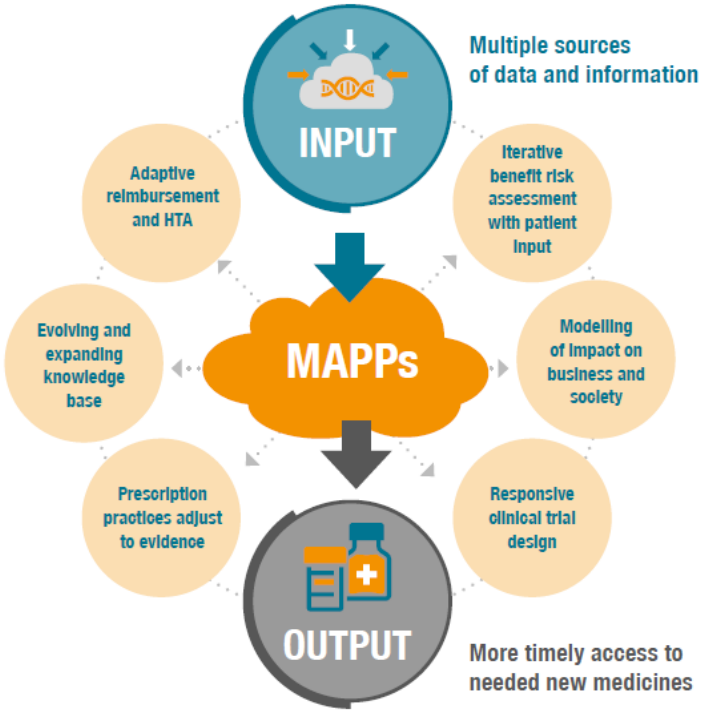
…To Industry, Patients, Payers, Providers, Regulators

MAPPs: What does it mean?

Flexible development and access pathways within the current regulatory framework that balance early patient access, public health and societal benefits.

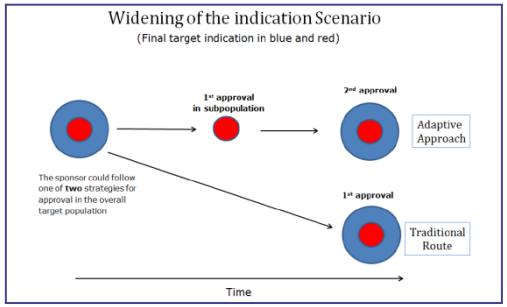
How is MAPPs different from Current Pathways?

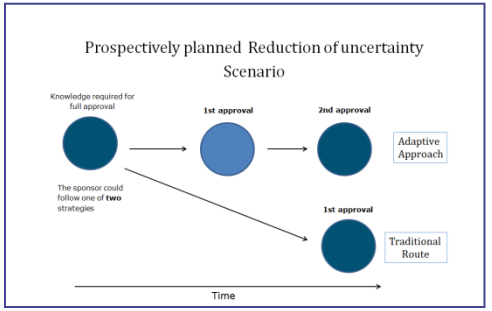
- An early authorisation of a product in a well-defined and targeted patient population with a clear safety and efficacy profile
- The target population is adjusted as additional evidence becomes available
- MAPPs may integrate adaptive clinical trial design, patient centric benefit/risk assessments and continuous re-evaluation as new evidence becomes available
- MAPPs relate to the entire life cycle of a medicine from development, through licensing to patient access

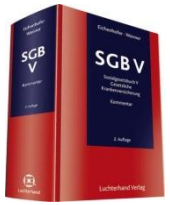


http://efpiamapps.eu/

HEALTH TECHNOLOGY ASSESSMENT







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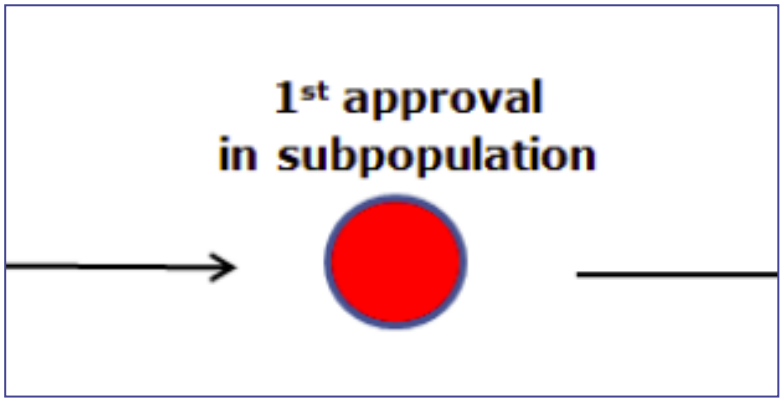
Gedanken des Sponsors…… (eine kleine Auswahl)



- Definition der Subpopulation akzeptiert?
- „unmet need“ für die Subpopulation akzeptiert?
- Diagnose der Subpopulation akzeptiert?
- Subpopulation über „Surrogat Marker“ identifiziert -Okay?
- Subpopulation über „Genetik“ definiert- Okay?
- Erstattungsverhandlung nur für die Subpopulation?
- Erstattungsbetrag für die Subpopulation?
- Größe der Subpopulation?

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Marketing Authorization under exceptional circumstances Lometapide (Lojuxta®)

Oral small molecule inhibitor of microsomal triglyceride transfer protein (MTP)

Treatment of homozygous familial hypercholesterolemia

Article 14(8) of Regulation (EC) No 726/2004

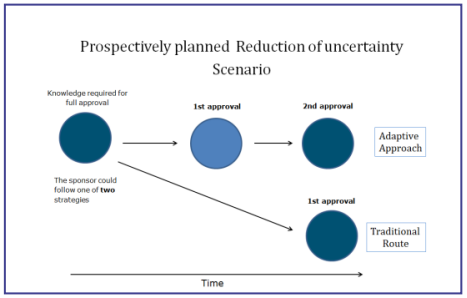
- **Indication is rarely**
- Comprehensive evidence is difficult to be provided
- Subject to specific obligations and conditions
  - the applicant will have to conduct a **prospective observational cohort study (registry)** to **further assess the safety** of lomitapide in the treatment of patients with HoFH and to **further assess** the long-term effectiveness of lomitapide in usual care.
  - the medicinal product in question **may** be supplied on **restricted medical prescription** only
  - the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in Question are as yet inadequate in certain specified respects.
  - Risk minimization measures
  - annual assessment

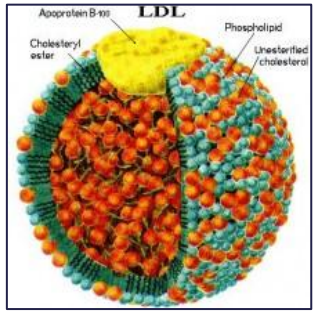
Lomitapid: Nutzenbewertung gemäß §35a SGBV (IQWiG Bericht Nr. 324)

Tabelle 3: Lomitapid – Ausmaß und Wahrscheinlichkeit des Zusatznutzens

Anwendungsgebiet	**Zweckmäßige Vergleichstherapie**[a]	**Ausmaß und Wahrscheinlichkeit des Zusatznutzens**
erwachsene Patienten mit HoFH, bei denen medikamentöse und diätische Optionen zur Lipidsenkung **ausgeschöpft** worden sind und die **keine LDL-Apheresebehandlung** erhalten	LDL-Apherese (als „ultima ratio“ bei therapierefraktären Verläufen) ggf. mit begleitender medikamentöser lipidsenkender Therapie	Zusatznutzen nicht belegt
erwachsene Patienten mit HoFH, bei denen medikamentöse und diätische Optionen zur Lipidsenkung **ausgeschöpft** worden sind und die **zugleich eine LDL-Apheresebehandlung** erhalten		Zusatznutzen nicht belegt
erwachsene Patienten mit HoFH, bei denen medikamentöse und diätische Optionen zur Lipidsenkung **nicht ausgeschöpft** worden sind	maximal tolerierte medikamentöse und diätische Therapie zur Lipidsenkung	Zusatznutzen nicht belegt
a: Dargestellt ist jeweils die vom G-BA festgelegte zweckmäßige Vergleichstherapie. G-BA: Gemeinsamer Bundesausschuss; HoFH: homozygote familiäre Hypercholesterinämie; LDL: Low Density Lipoprotein		

LDL-C Senkung durch PCSK-9 Inhibition (z.B. Alirocumab)





EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 December 2013
EMA/CHMP/748108/2013
Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products in the treatment of lipid disorders

The requirement of clinical studies showing beneficial outcome on morbidity and mortality during registration largely depends on the mechanism of action and the pharmacological class of the medicinal product and the target population. Such studies are not foreseen for the registration of a new HMG-CoA reductase inhibitor. **For other medicinal products acting on LDL-C, at least a detrimental effect on mortality and morbidity should be excluded prior to registration** (see section 7.2). Until clinical trial data are available, it should be specifically mentioned in the Summary of product characteristics (SmPC) that beneficial effects on mortality and morbidity have not been evaluated.

For medicinal products modifying lipid parameters **other than LDL-C, demonstration of a positive clinical outcome in terms of morbidity and mortality is required.**

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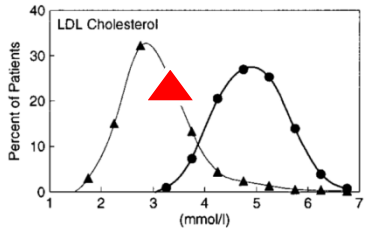
LDL-C Senkung durch PCSK-9 Inhibition (z.B. Alirocumab)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Indication for LDL-C lowering after failure of diet and maximum tolerated dose of statin alone or in combination with other lipid lowering therapies or when statins are contraindicated

4 S Studie



Pat. SK, m, 48 Jahre, Z.n. VWI Dez. 2014,
BMI 24, RR 135/80 mmHg, LDL-C unter 40 mg Atorvastatin 135 mg/dl

Editorial

Strategies to overcome statin intolerance

Pat. U.H., w, 54 Jahre, Z.n. Apoplex Juni 2013, BMI 28, RR 150/85 mmHg,
Juni-August 2013: 40 mg Atorvastatin, Myopathie, September-November 2013 20 mg Fluvastatin Myopathie, keine Interaktionen, jetzt 10 mg Ezetemib, LDL-C 130 mg/dl

Pat. T.G., w, 35 Jahre, heFH, wöchentliche Apherese seit 3 Jahren, LDL-C vor Apherese unter zusätzlicher maximal verträglicher lipidsenkender Therapie und Diät 162 mg/dl
mg/dl

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LDL-C Senkung durch PCSK-9 Inhibition (z.B. Alirocumab)

HEALTH TECHNOLOGY ASSESSMENT

Argument 1: LDL-C genetisch kausal

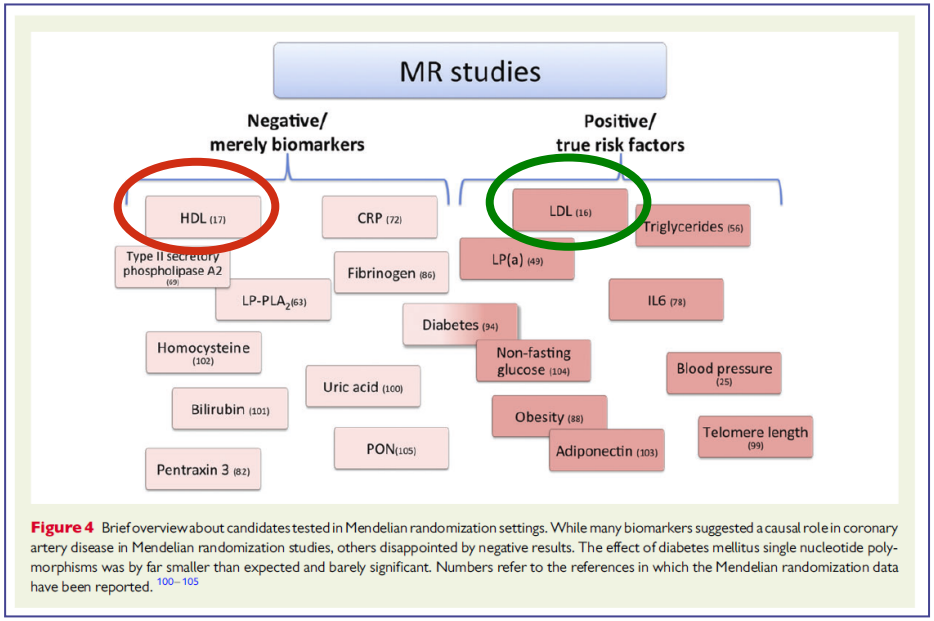

Figure 4 Brief overview about candidates tested in Mendelian randomization settings. While many biomarkers suggested a causal role in coronary artery disease in Mendelian randomization studies, others disappointed by negative results. The effect of diabetes mellitus single nucleotide polymorphisms was by far smaller than expected and barely significant. Numbers refer to the references in which the Mendelian randomization data have been reported. [100–105]

Jansen H, Samani NJ, Schunkert H. EHJ 35:1917-1924 (2014)

Argument 2: PCSK-9 genetisch kausal

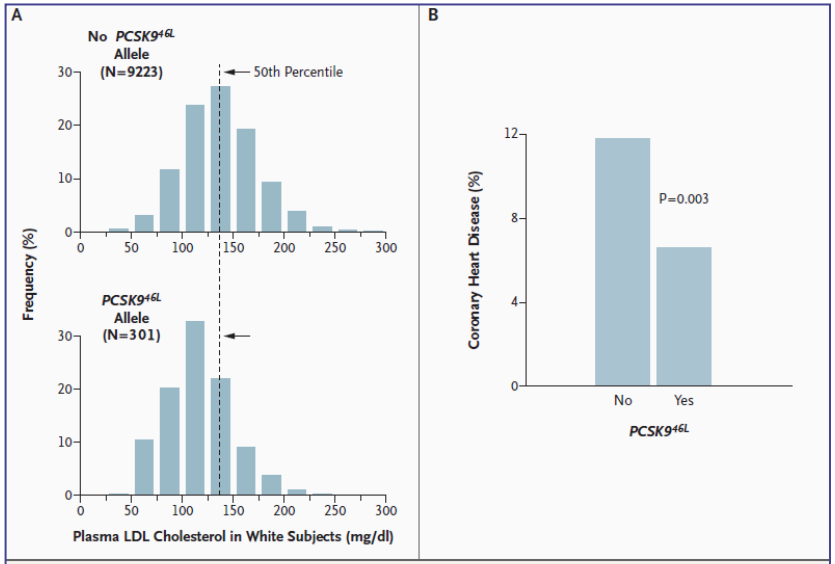

Figure 2. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Events (Panel B) among White Subjects, According to the Presence or Absence of a *PCSK9 46L* Allele.

Cohen JC et al. N Engl J Med 2006;354:1264-72

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LDL-C Senkung durch PCSK-9 Inhibition (z.B. Alirocumab)

HEALTH TECHNOLOGY ASSESSMENT

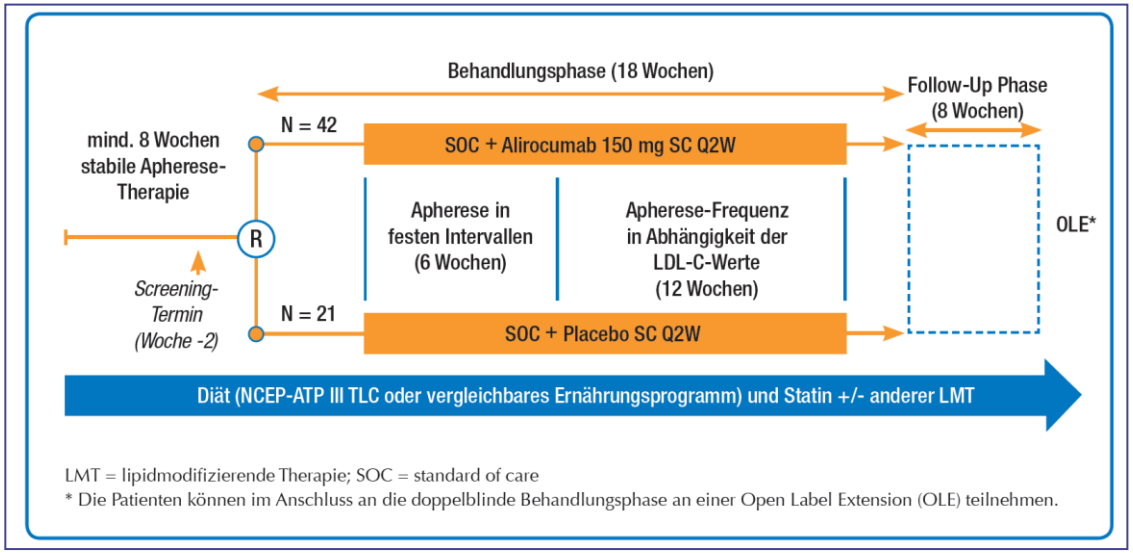
RCT Evidenz „echte“ Statinintoleranz

Original Article

Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial

Moriarty PM et al. J Clin Lipidol (2015) http://dx.doi.org/10.1016/j.jacl.2015.08.006

RCT Evidenz Lipidapherese



https://www.clinicaltrials.gov/ct2/show/NCT02326220?term=alirocumab&rank=6

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LDL-C Senkung durch PCSK-9 Inhibition (z.B. Alirocumab)

HEALTH TECHNOLOGY ASSESSMENT

Erste Outcome Daten aus der Phase III

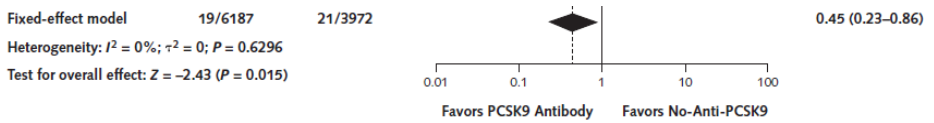
Annals of Internal Medicine REVIEW

Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia

A Systematic Review and Meta-analysis

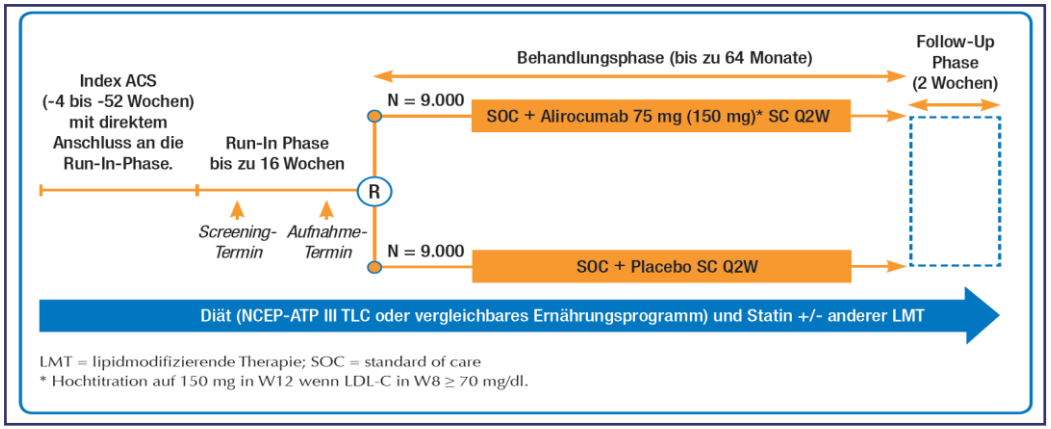
Eliano Pio Navarese, MD, PhD; Michalina Kołodziejczak, MD; Volker Schulze, MD; Paul A. Gurbel, MD; Udaya Tantry, PhD; Yingfeng Lin, MD; Maximilian Brockmeyer, MD; David E. Kandzari, MD; Julia M. Kubica, MD; Ralph B. D'Agostino Sr., PhD; Jacek Kubica, MD, PhD; Massimo Volpe, MD; Stefan Agewall, MD; Dean J. Kereiakes, MD; and Malte Kelm, MD

Figure 2. Cardiovascular mortality.



Navarese EP et. al. Ann Int Med 2015 doi:10.7326/M14-2957

Laufende Outcomestudie



https://www.clinicaltrials.gov/ct2/show/NCT01663402?term=alirocumab&rank=7

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“the safest drug that no one can afford or that arrives too late is of no benefit to a patient”

Zitat eines Patientenvertreters auf dem HTAi policy forum 2014, Washington, DC

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