



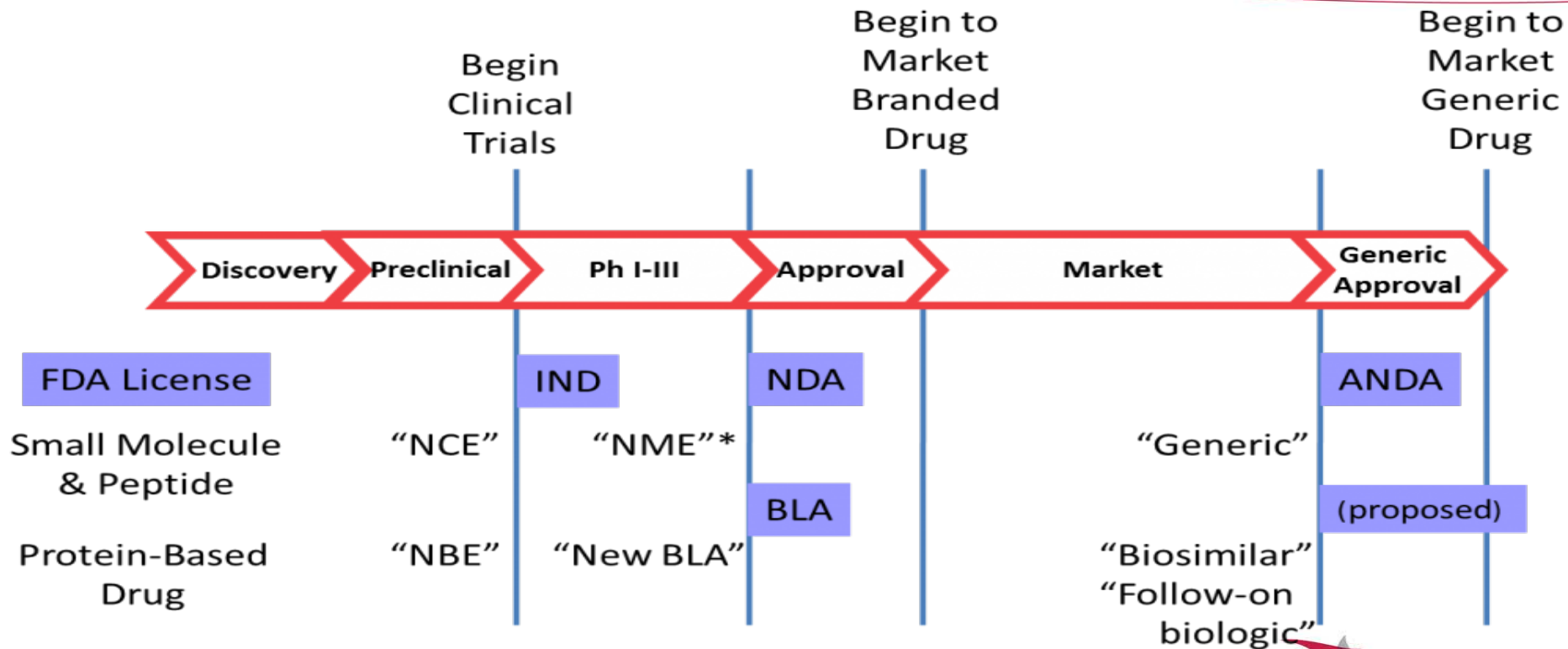
# Precision Medicines & Regulatory Affairs - A changing environment -

Stef Schutte  
VP & Head Regulatory Affairs EMEA  
Astellas



**Dutch Life Sciences**  
c o n f e r e n c e

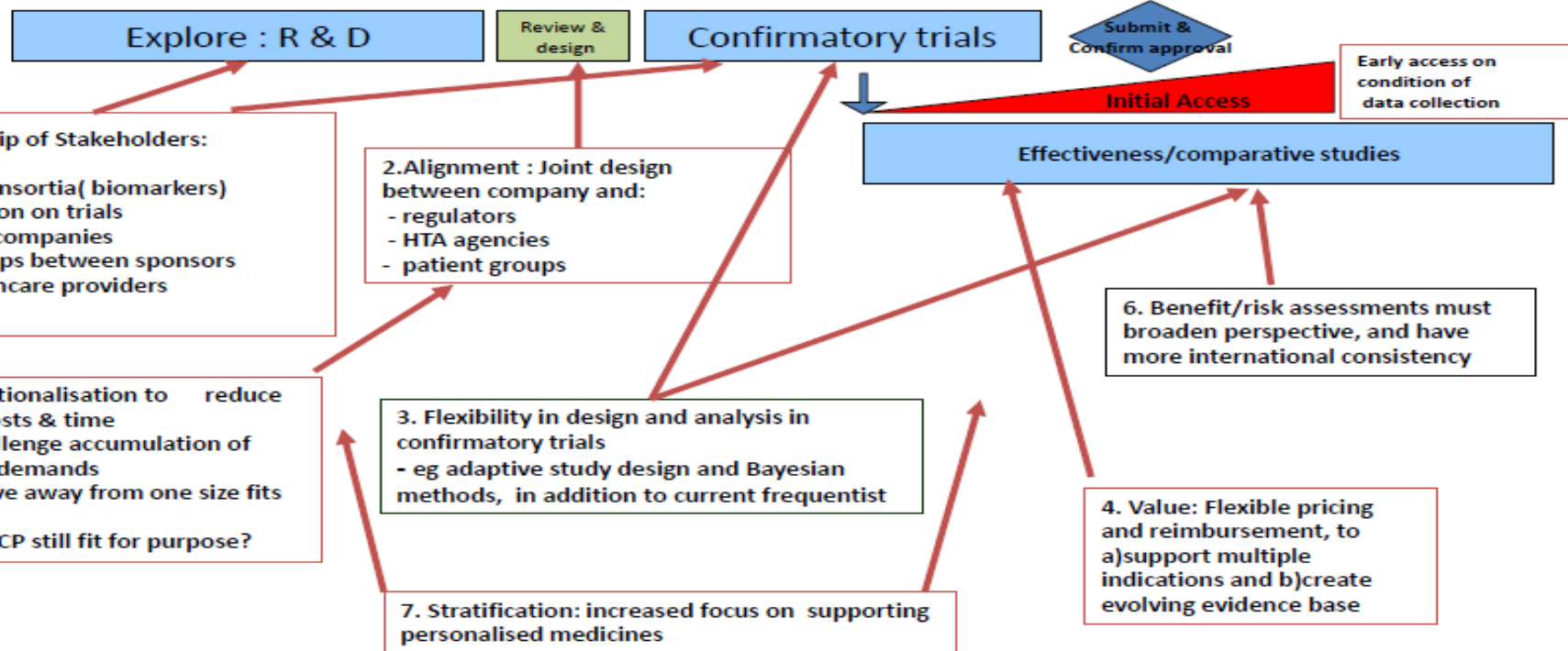
# 'Traditional' Drug Development



# Standard Development Trajectory

	Pre Clinical Testing		Phase I	Phase II	Phase III		Review	Approval
Years	3.5		1 - 2	2 - 4	4 - 6		1.5	Total = 12 - 17
Test Population	Laboratory and Animal Studies	FILE IND	20 to 100 Healthy Volunteers	100 – 300 Patient Volunteers	1,000 to 3,000 Patient Volunteers	FILE NDA	Review Process	Post Marketing Safety Monitoring
Purpose	Assess Safety and Biological Activity		Determine Safety and Dosage	Evaluate Effectiveness. Look for Side Effects.	Verify Effectiveness, Monitor Adverse Reactions from Long-Term Use			Large Scale Manufacturing ----- Distribution ----- Education
% of all new drugs that pass			70% of INDs	30% of INDs	27% of INDs		20% of INDs	

# New flexible blueprint



# New Regulatory Trends

## Expedited/Adaptive Pathways

US	EU	JP
Breakthrough Therapy Designation	PRIME	SAKIGAKE
Accelerated Approval	Conditional Marketing Authorization	P2 Approval (Oncology only)
Priority Review	Accelerated Assessments	Priority Review
Fast Track Designation	Authorization under exceptional circumstances Adaptive Licensing.	Emergency Approval Public knowledge-based Application



## Expedited Review Programs

### 1 Fast Track Designation

Drug intended to treat a serious condition

Nonclinical or clinical data needed to demonstrate the potential to address unmet medical needs

Requested at any point from IND filing but prior to NDA filing

### 2 Breakthrough Designation

Drug intended to treat a serious condition

Must be preliminary clinical evidence to indicate the drug may substantially improve a clinically significant endpoint compared to available therapies

### 3 Accelerated Approval

Drug must treat a serious condition and generally provide a meaningful advantage over available therapies

Must demonstrate an effect on a surrogate endpoint that is likely to predict a clinical benefit or on a clinical endpoint

### 4 Priority Review

Drug must treat a serious condition and, if approved, offer a significant improvement in safety or effectiveness

Designation assigned only at the time of the original NDA or efficacy filing

# FDA Approval Concepts

There are two ways a medicine can be approved by the FDA.

## STANDARD APPROVAL



OR

## ACCELERATED APPROVAL

If **EARLY TRIAL RESULTS** are especially promising, the FDA can grant **ACCELERATED APPROVAL** to an investigational medicine. This allows patients access while ongoing Phase III studies confirm safety and efficacy.



# Different Options

*For serious and life-threatening diseases, like cancer, the FDA can grant designations to certain medicines that may help accelerate the time to approval.*

## DESIGNATION

### BREAKTHROUGH THERAPY

Drug makers can apply based on clinical data that indicate substantial improvement in one clinically significant endpoint over available medicines

### FAST TRACK

Drug makers can apply based on preclinical or clinical data for a serious condition with a need for new medicines

### PRIORITY REVIEW

The FDA grants priority review to drugs deemed major advancements

## KEY ELEMENTS

### DEDICATED SENIOR MANAGEMENT TEAM

At the FDA helps companies streamline the clinical trial process

### FREQUENT FDA MEETINGS

Help drug makers design clinical trials that are as efficient as possible and meet FDA expectations

### ROLLING REVIEW

Allows drug makers to submit data as they becomes available

### SHORTENED APPLICATION REVIEW TIME\*

Shortens the FDA's review time from 1 year to 8 months

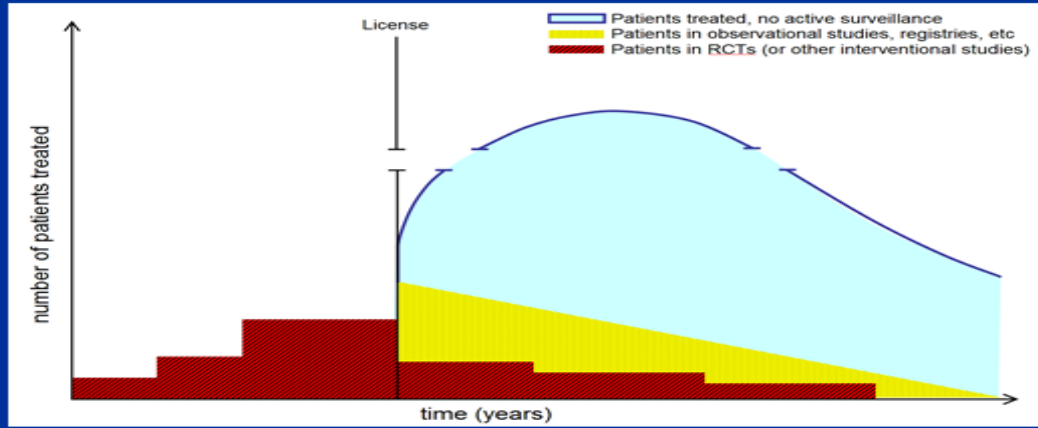
\*Breakthrough Therapy and Fast Track designations have the possibility of shortened review times, it is not guaranteed.



# Adaptive Licensing

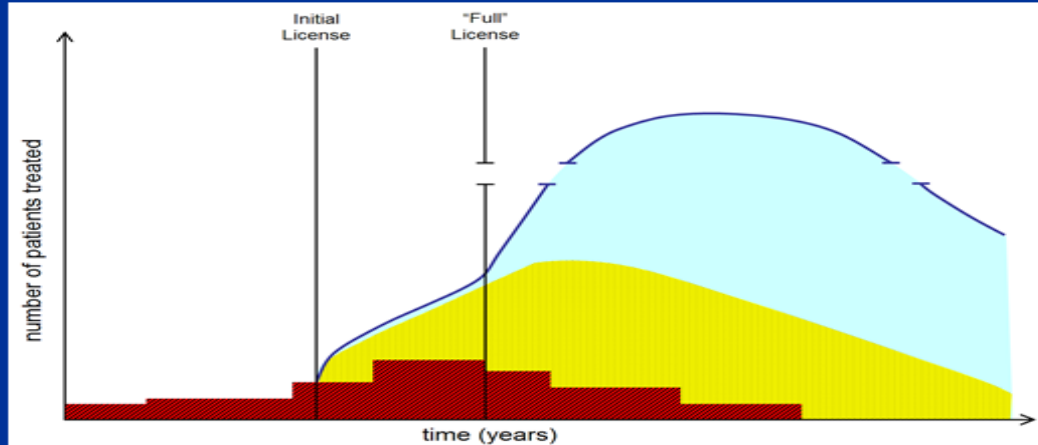


EUROPEAN MEDICINES AGENCY



## Current scenario:

Post-licensing, treatment population grows rapidly; treatment experience contributes little to evidence generation



## Adaptive Licensing:

after initial license, number of treated patients grows more slowly, due to restrictions; patient experience is captured to contribute to real-world information

# Patient selection

## Medicine of the present: one treatment fits all

Cancer patients with e.g. colon cancer



Therapy



Effect



No effect



Adverse effects

## Medicine of the future: more personalized diagnostics

Cancer patients with e.g. colon cancer



Blood, DNA, urine and tissue analysis



Biomarker diagnostics



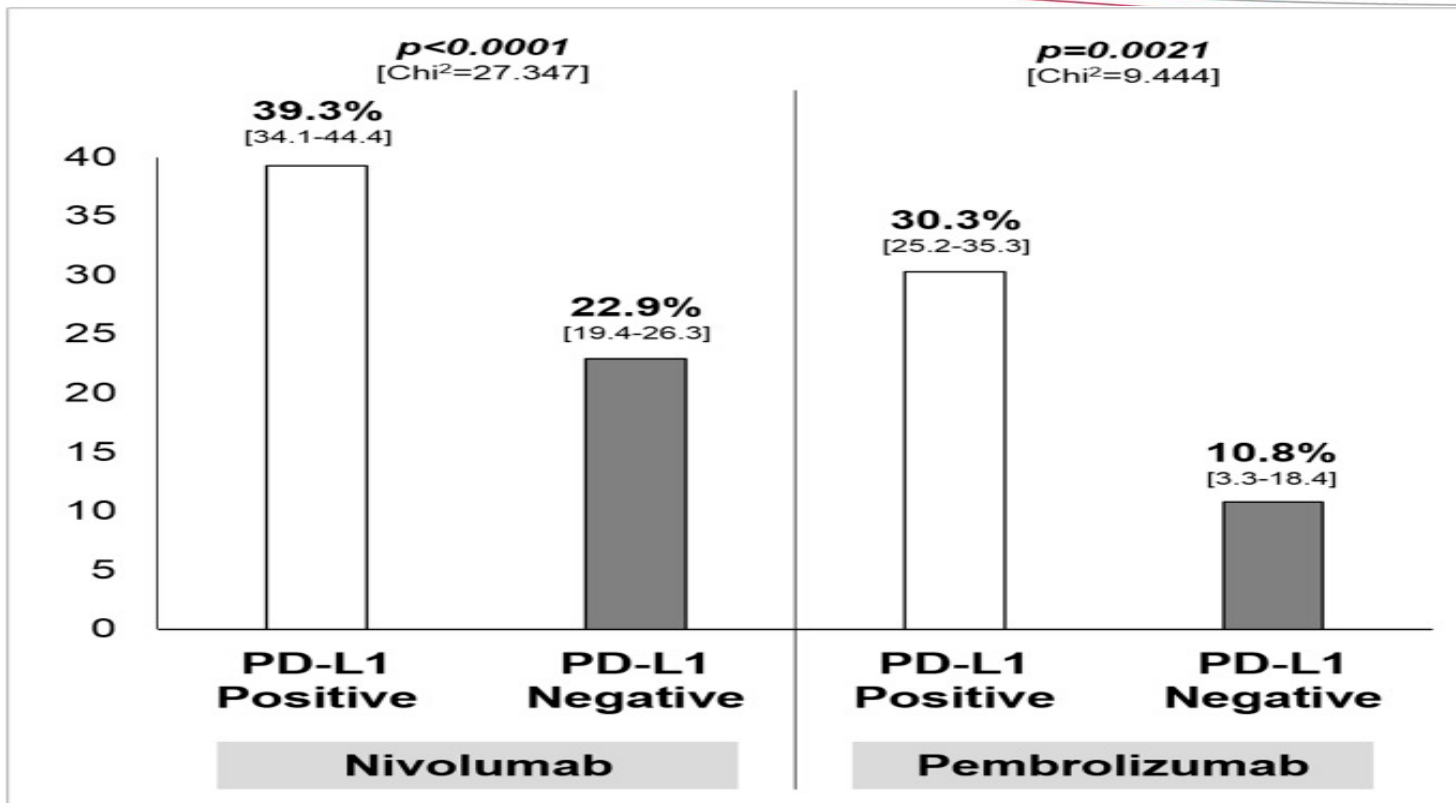
Therapy



Effect

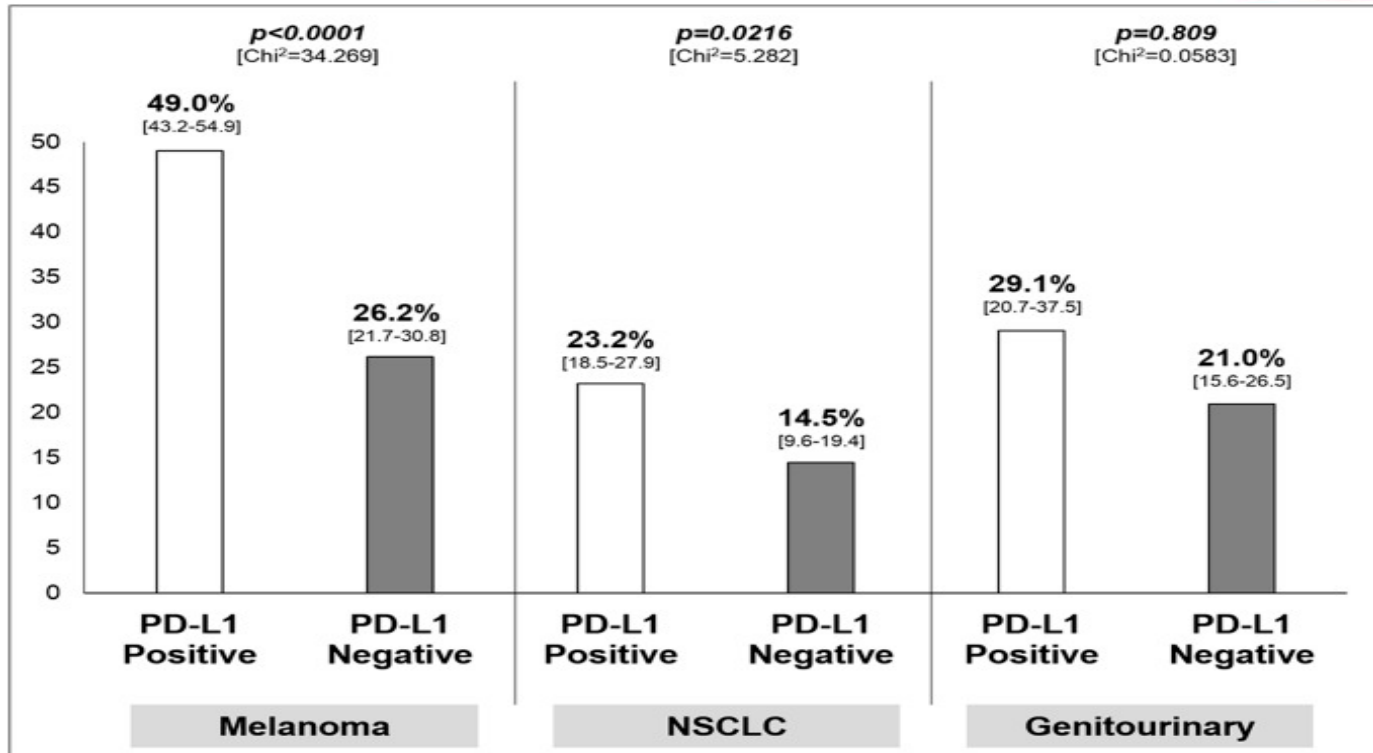
From Bayer Website

# PD-1 Immunotherapy

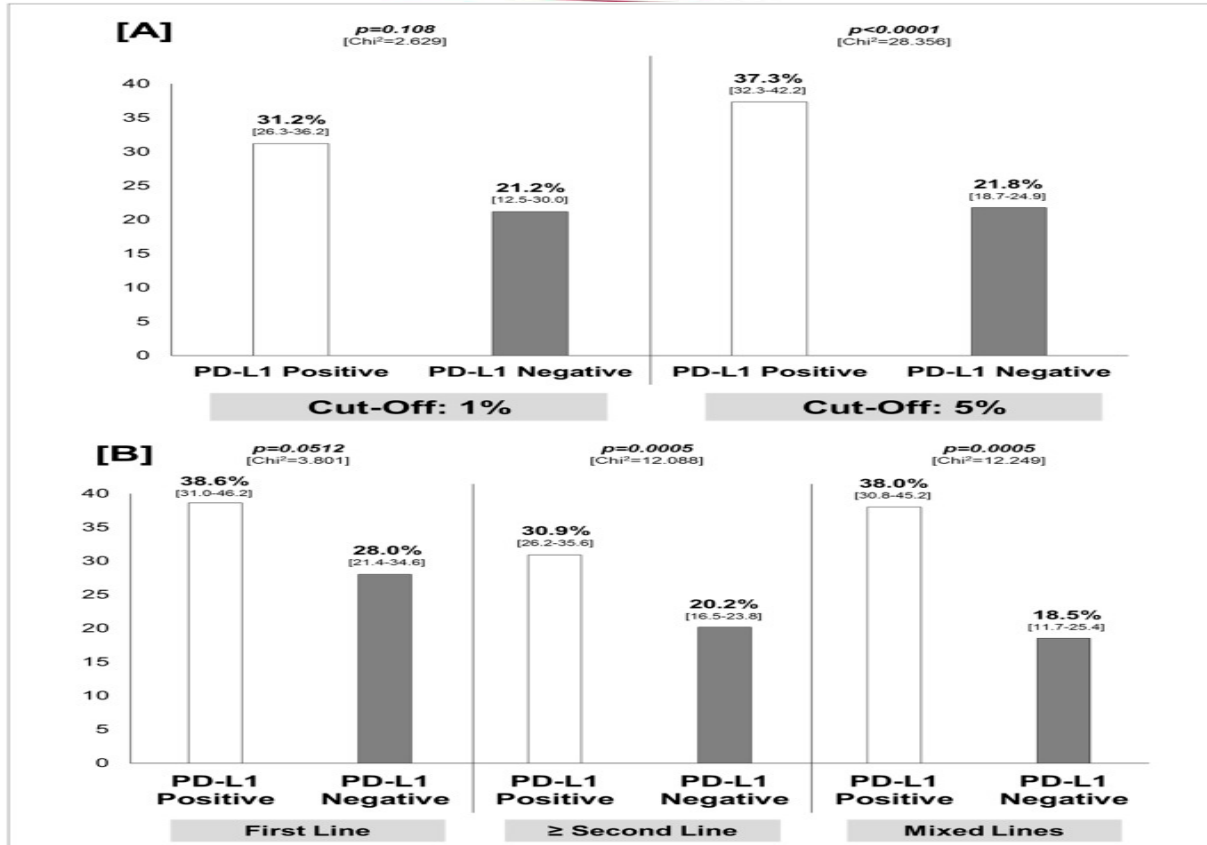


Carbognin et al., Public Library of Science One. 2015; 10(6)

# PD-1 Immunotherapy



# PD-1 Immunotherapy







Carbognin et al., Public Library of Science One. 2015; 10(6)

# Conclusions PD-1 Immunotherapie

- Twenty trials (1,475 patients) were identified.
- A significant interaction ( $p < 0.0001$ ) according to tumor PD-L1 expression was found in the overall sample with an ORR of 34.1% (95% CI 27.6-41.3%) in the PD-L1 positive and 19.9% (95% CI 15.4-25.3%) in the PD-L1 negative population.
- ORR was significantly higher in PD-L1 positive in comparison to PD-L1 negative patients for nivolumab and pembrolizumab, with an absolute difference of 16.4% and 19.5%, respectively.
- A significant difference in activity of 22.8% and 8.7% according to PD-L1 was found for melanoma and NSCLC, respectively, with no significant difference for genitourinary cancer

# Potential Validation Issues

	Has Disease	Doesn't Have Disease
Tested Positive	 <p>True Positive Sensitivity</p>	 <p>FALSE Positive</p>
Tested Negative	 <p>FALSE Negative</p>	 <p>True Negative Specificity</p>

# Regulatory Challenges

- Because of (effective) patient selection, smaller patient subpopulations in studies
- Less data needed for efficacy and consequently smaller safety database. Hence larger uncertainty for benefit/risk evaluation.
- Benefit/Risk evaluation more complex and higher chance for 'wrong' decision in regulatory approval process.
- By patient selection, possible exclusion of patient populations that could benefit!
- Through further patient selection, possible 'orphanization' of many new medicines, with a risk of 'pseudo-specificity'.



# Epilogue

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- Precision Medicines have great opportunity in treating patients better.
- The development and validation of the optimal patient selection test, requires an excellent understanding of the disease and the mechanism of action of the drug.
- Further ‘partnering’ and transparency between health authorities and marketing authorization holder is required to achieve the quickest market access and best products on the market.
- Incorrect or unnecessary patient selection could lead to ‘orphanization’ and not making available effective treatments for patients that could benefit from these.

# Questions?

