Precision Medicines & Regulatory Affairs
- A changing environment -

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Dutch Life Sciences conference

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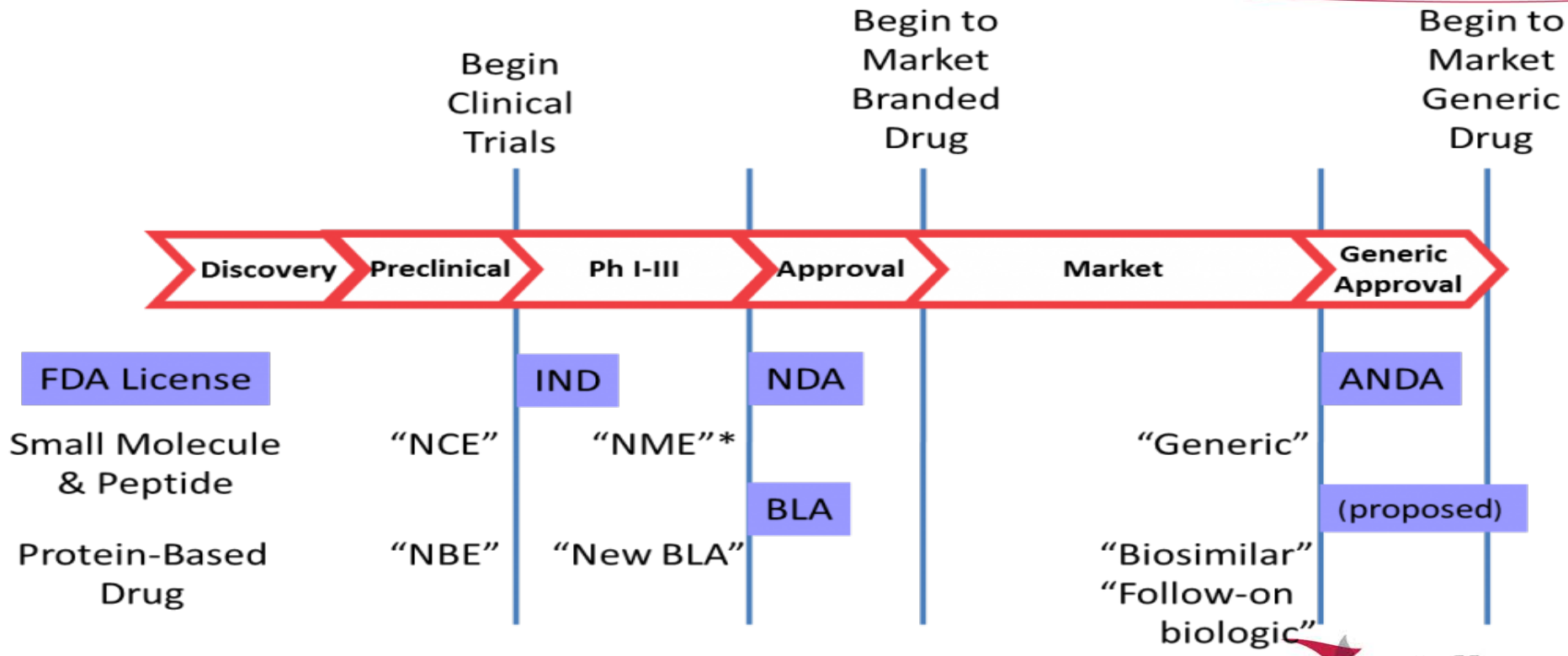
‘Traditional’ Drug Development



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Standard Development Trajectory

	Pre Clinical Testing	FILE IND	Phase I	Phase II	Phase III	FILE NDA	Review	Approval
Years	3.5		1 - 2	2 - 4	4 - 6		1.5	Total = 12 - 17
Test Population	Laboratory and Animal Studies		20 to 100 Healthy Volunteers	100 – 300 Patient Volunteers	1,000 to 3,000 Patient Volunteers		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	

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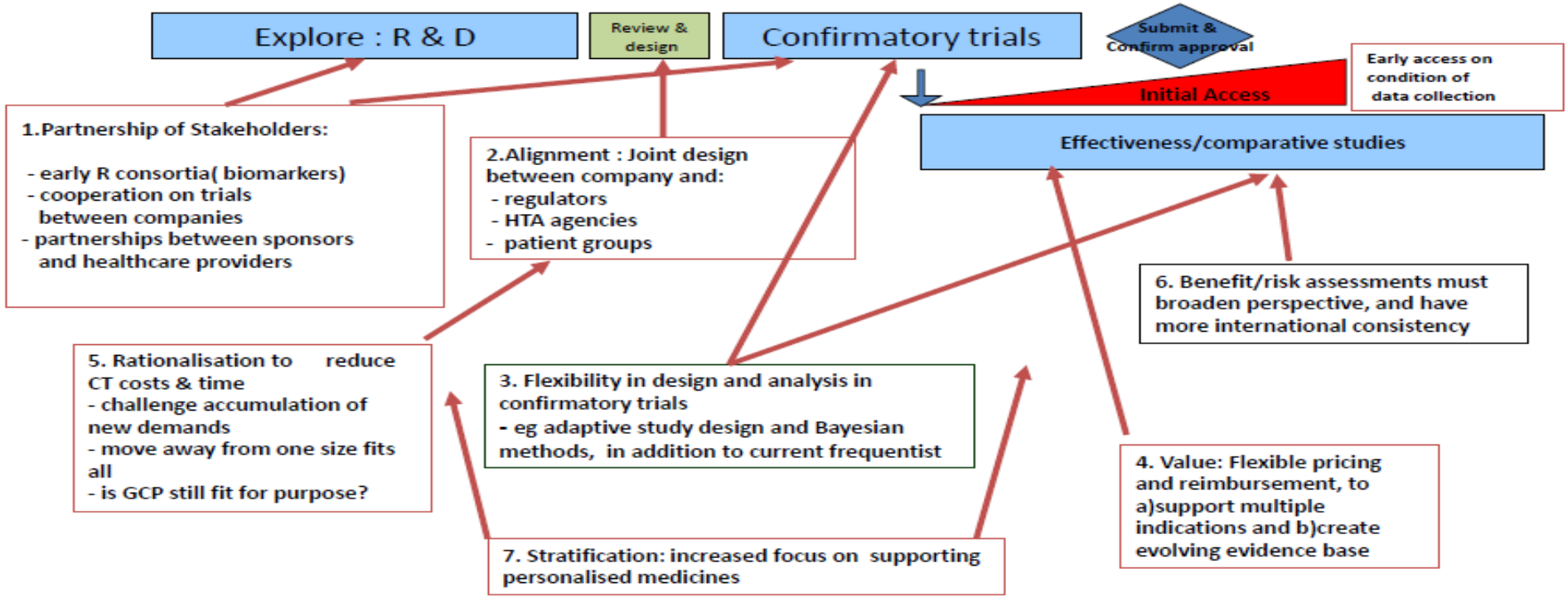
New flexible blueprint



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

5

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

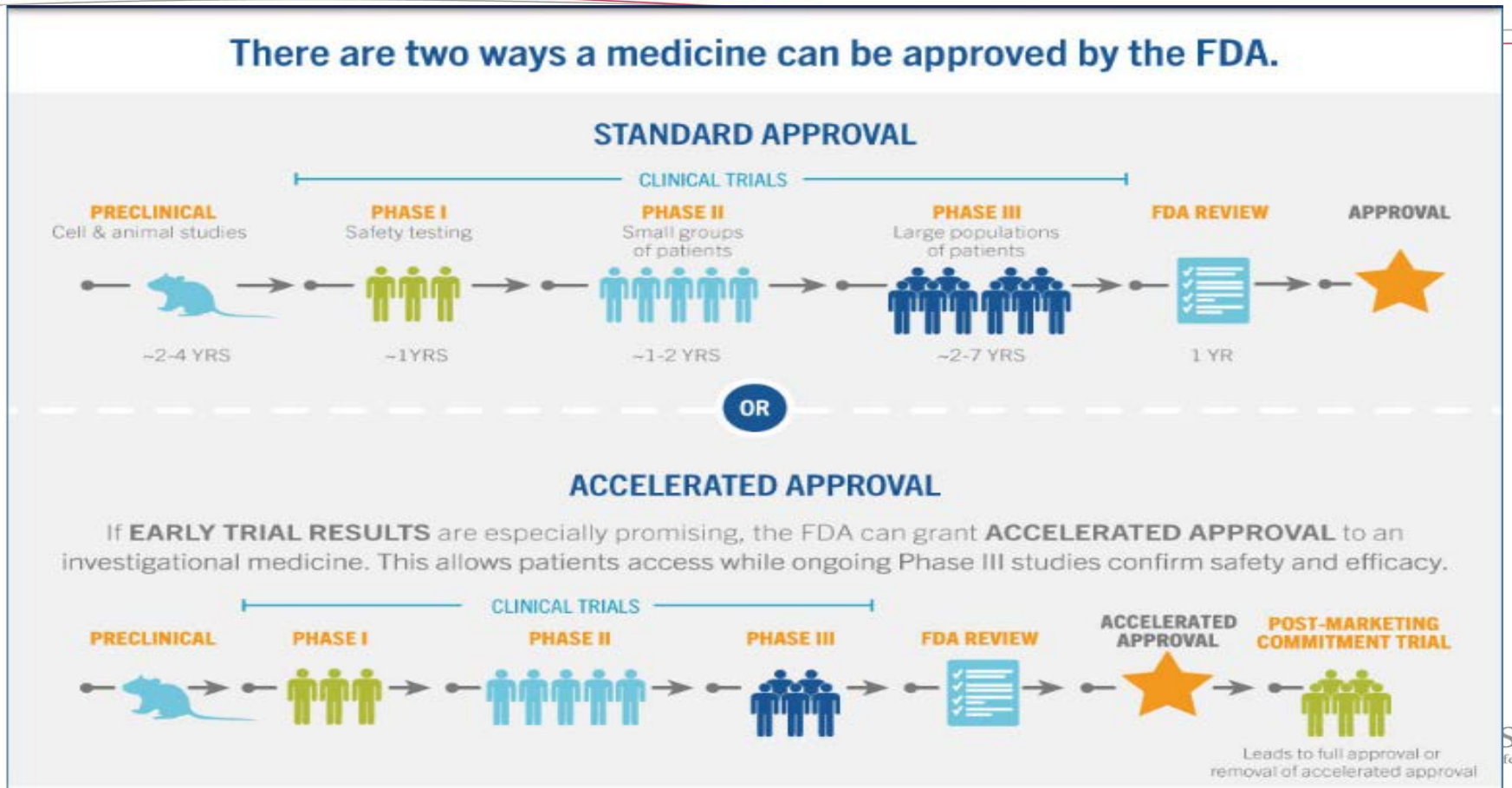
Must demonstrate an effect on a surrogate endpoint that is likely to predict a clinical benefit or on a clinical endpoint

4 Priority Review

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

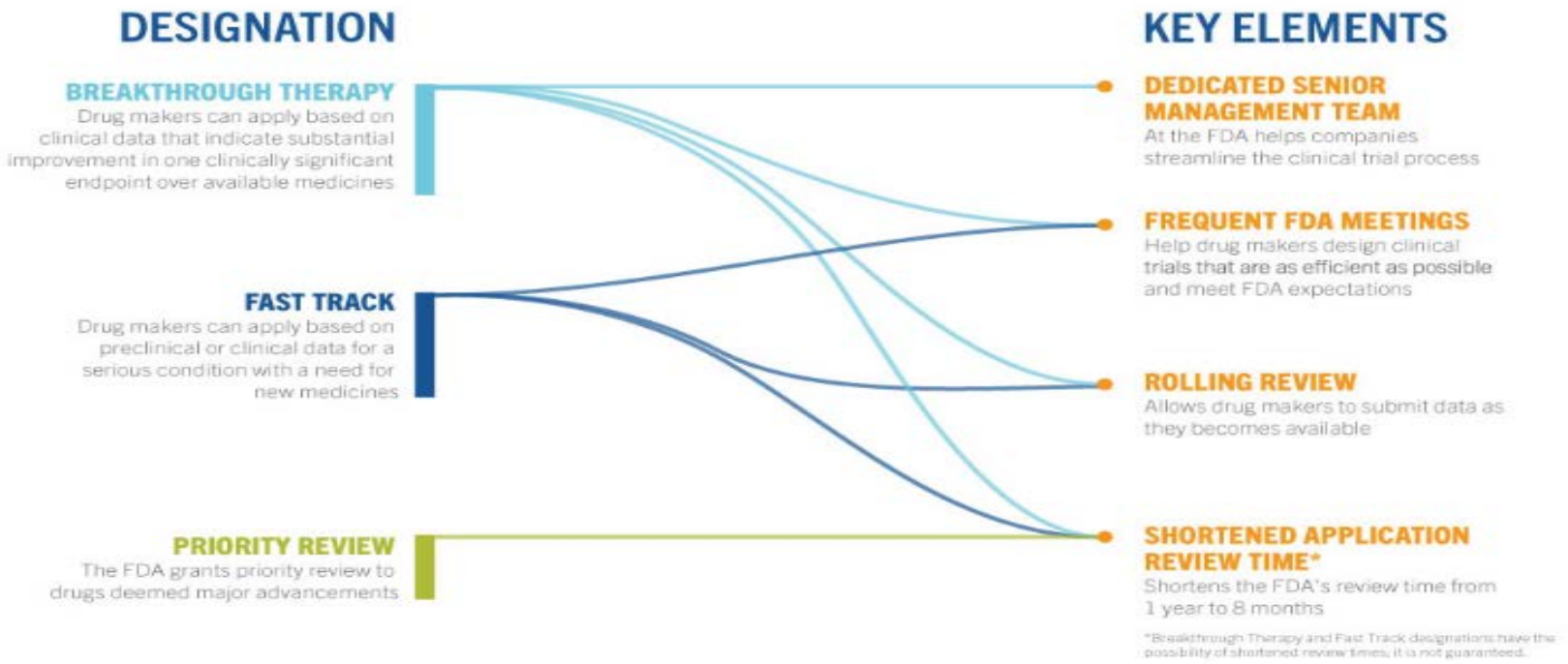
Designation assigned only at the time of the original NDA or efficacy filing

FDA Approval Concepts

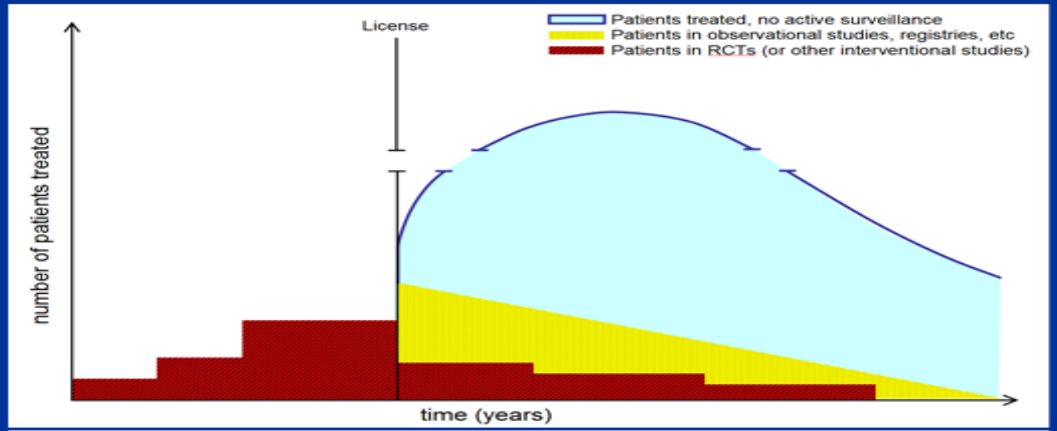


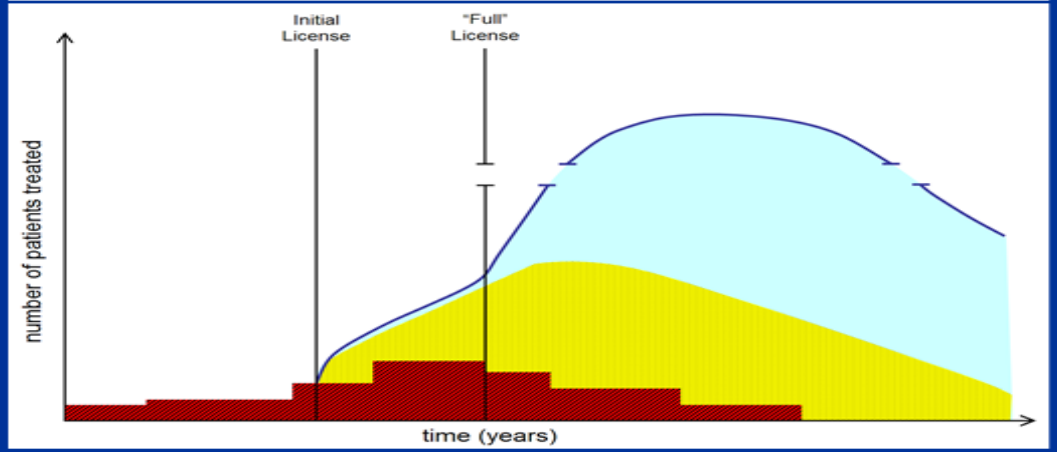
Different Options

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



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

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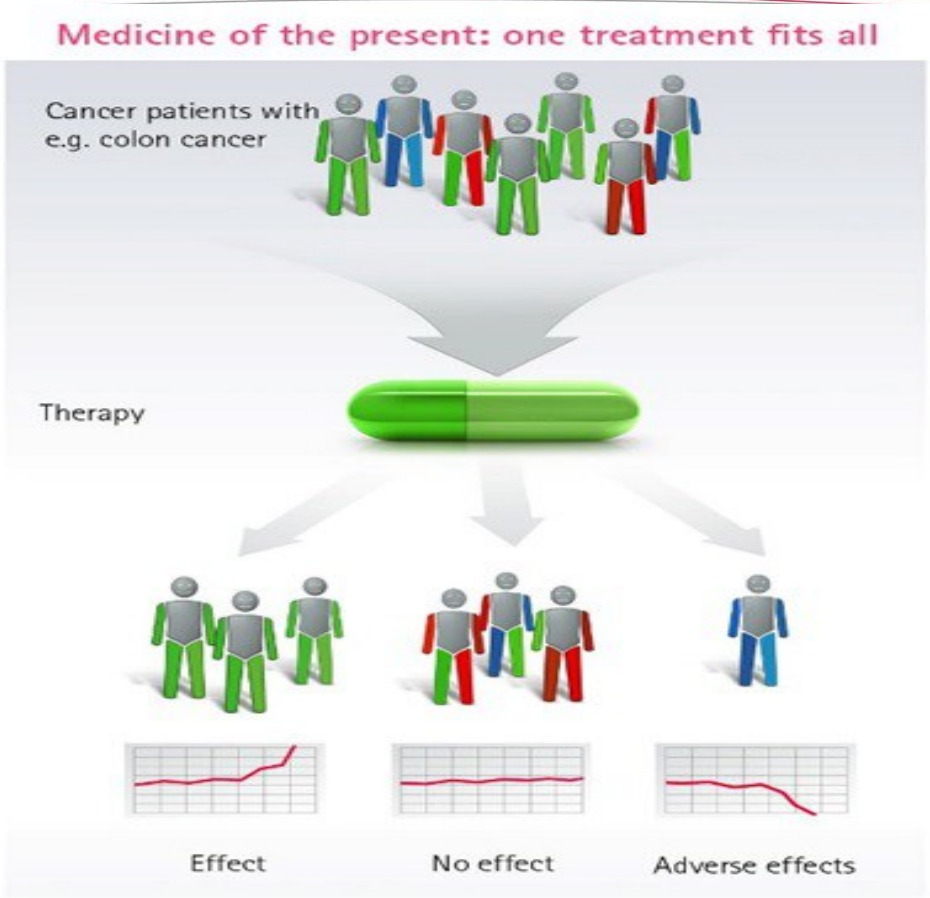
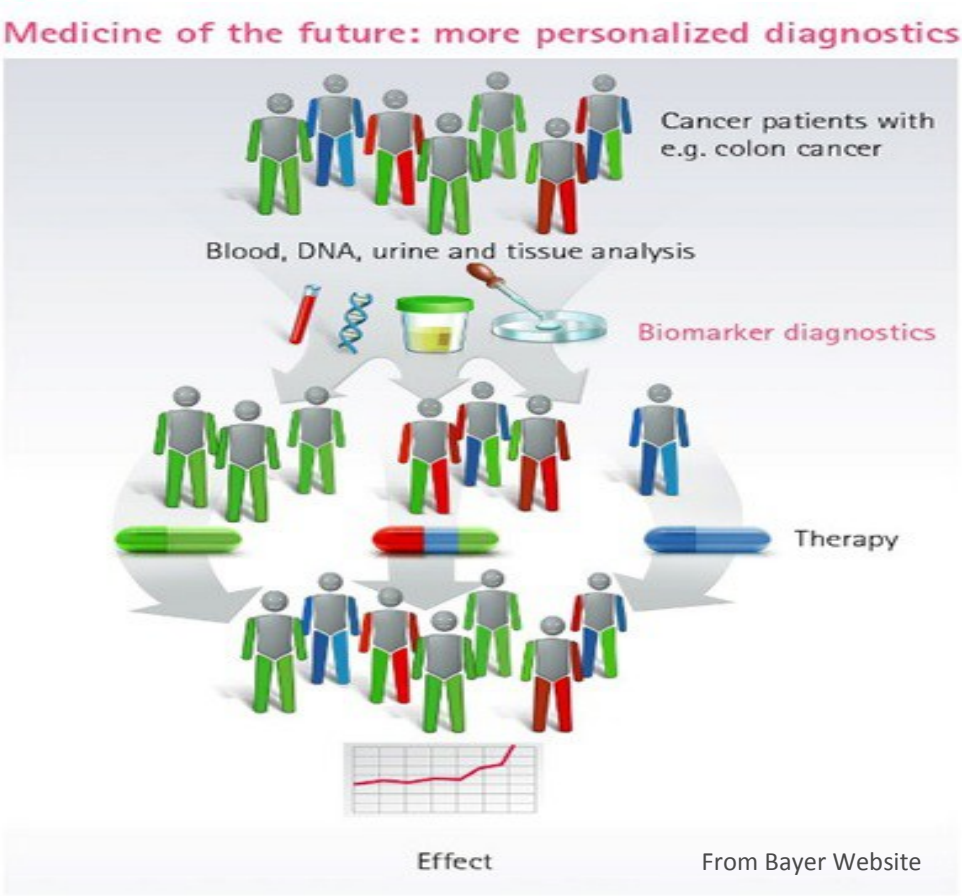
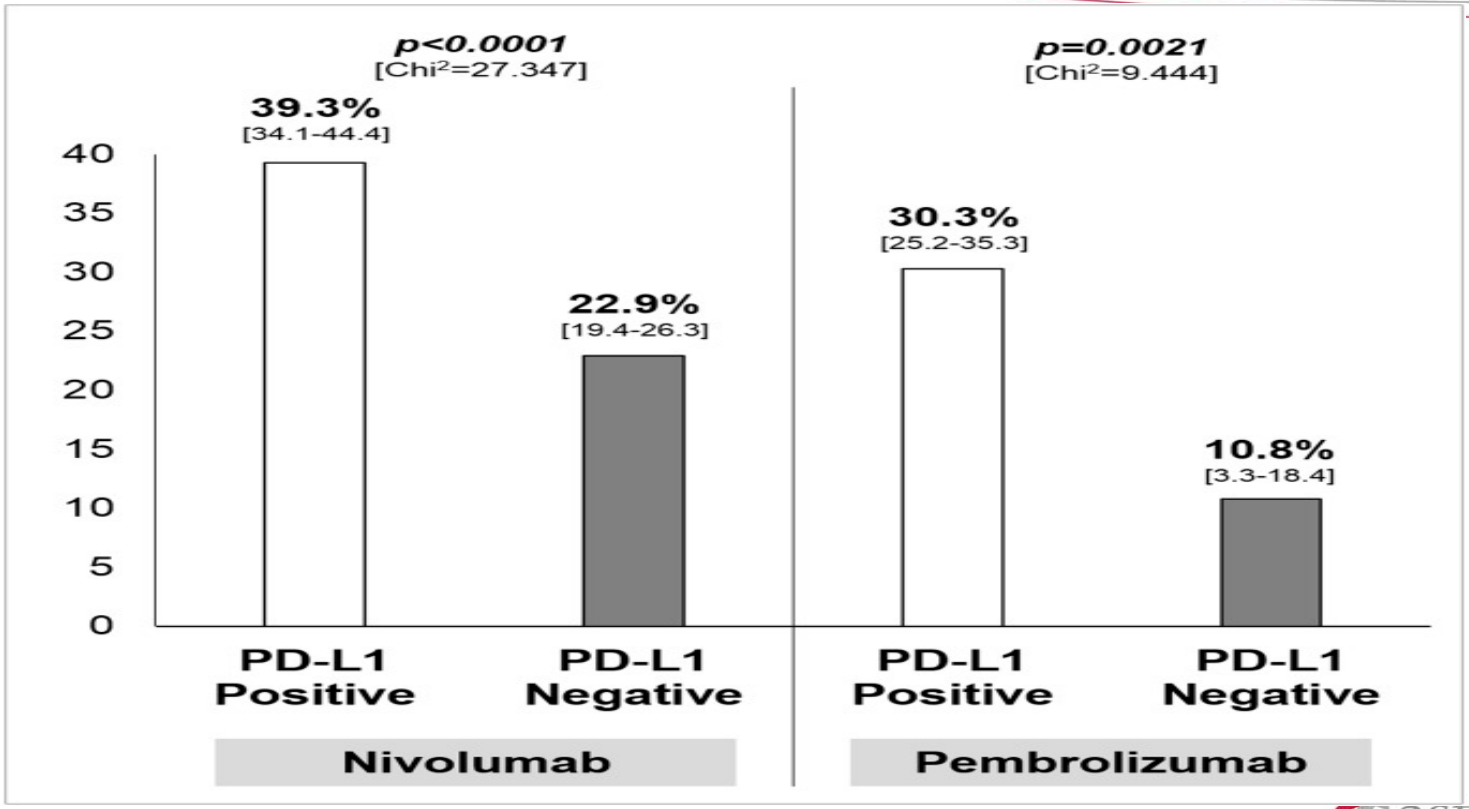
Patient selection





From Bayer Website

PD-1 Immunotherapy



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

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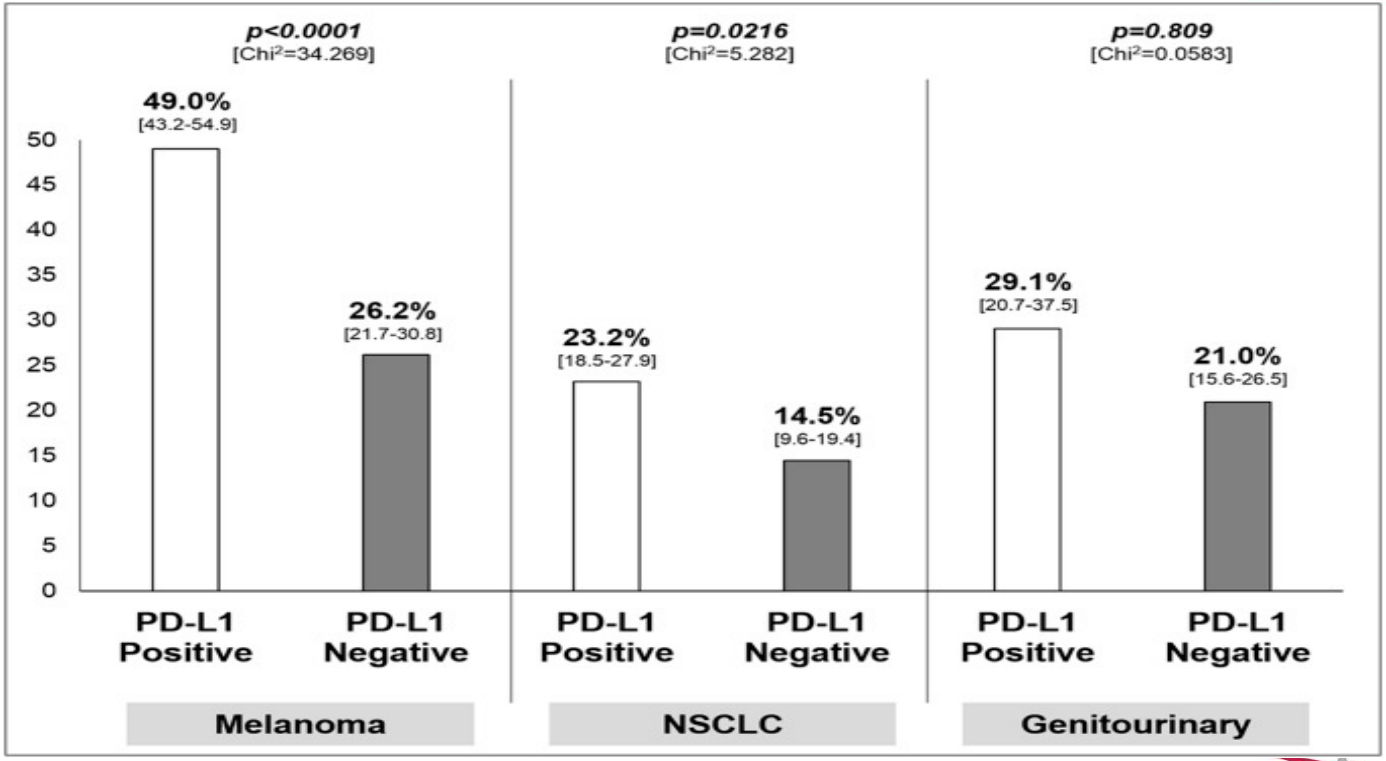

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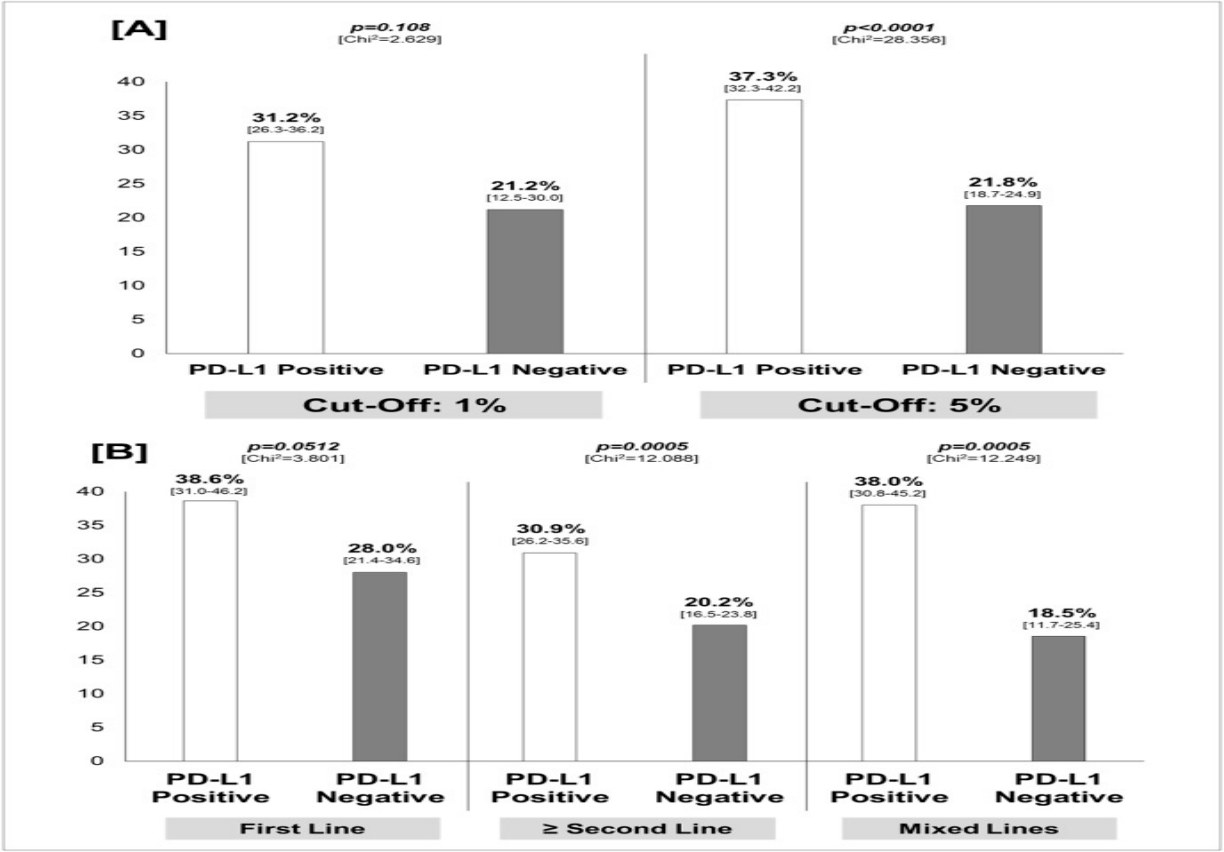

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Conclusions PD-1 Immunotherapie

- 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

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Potential Validation Issues

	Has Disease	Doesn't Have Disease
Tested Positive	 True Positive Sensitivity	 FALSE Positive
Tested Negative	 FALSE Negative	 True Negative Specificity

Regulatory Challenges

- Because of (effective) patient selection, smaller patient subpopulations in studies
- Less data needed for efficacy and consequently smaller safety databse. Hence larger uncertainty for benefit/risk evalaution.
- 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 selcetion, possible ‘orphanization’ of many new medicines, with a risk of ‘pseudo-specificity’.

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Epilogue

- 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.

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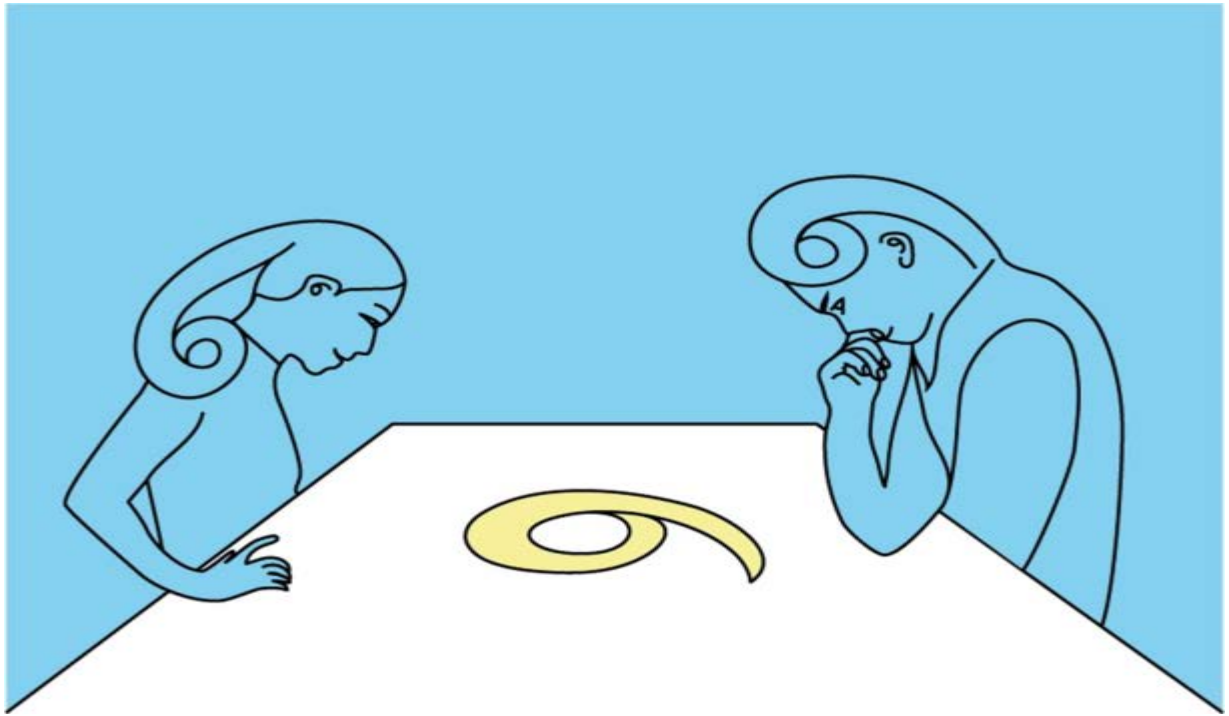
Questions?



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