HOW TO MONITOR AND MITIGATE IMMUNOTOXICITY DURING EARLY PHASE CLINICAL TRIALS IN ONCOLOGY?

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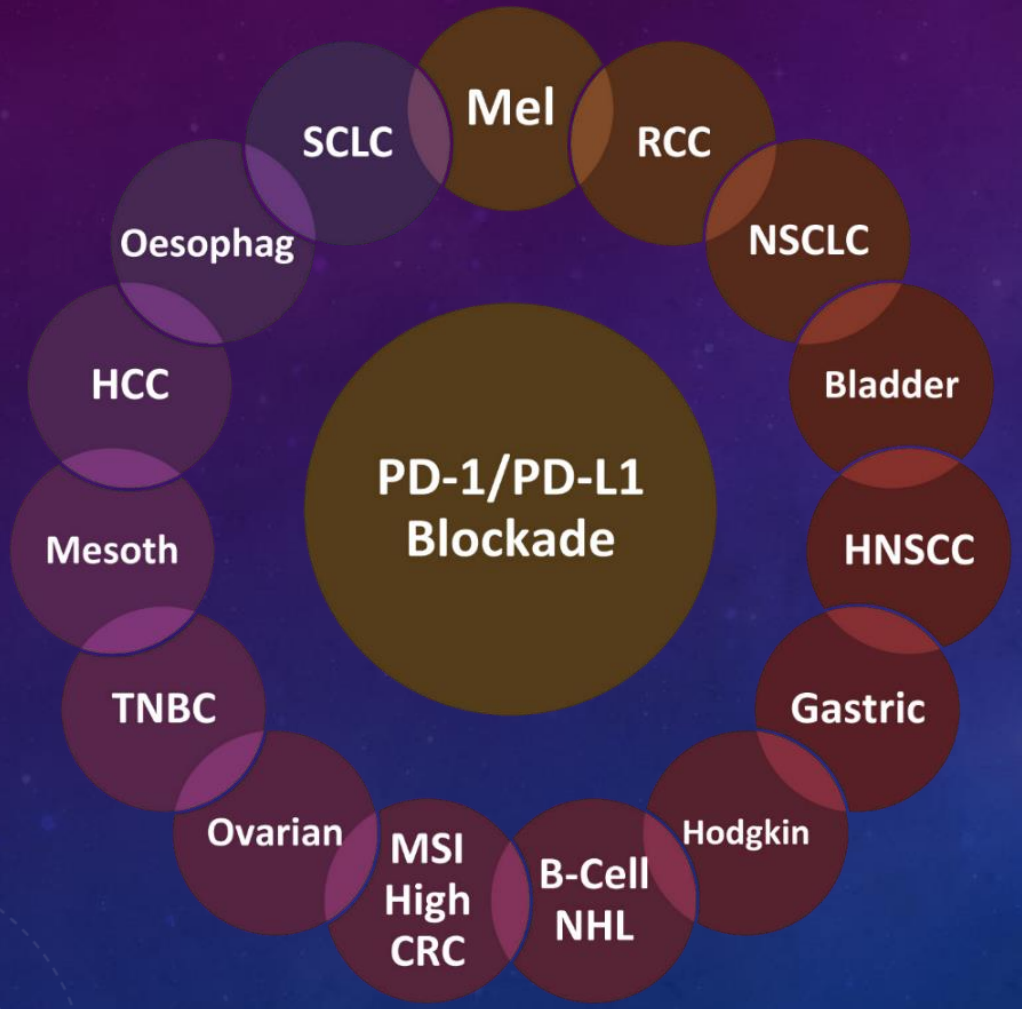
OVERVIEW

- Immuno-oncology(“I-O”) & Immune-related (“IR”) toxicity
  - What is the impact of I-O in the current early phase trial landscape
  - What are the safety related challenges of I-O IMPs in early phase studies?
    - How do they differ from traditional IMPs?
  - What are the challenges inherent in monitoring /managing/ reporting IR AEs?
  - How can we mitigate these risks and design trials that are both safe and efficient?

IMMUNO-ONCOLOGY HAS COME OF AGE

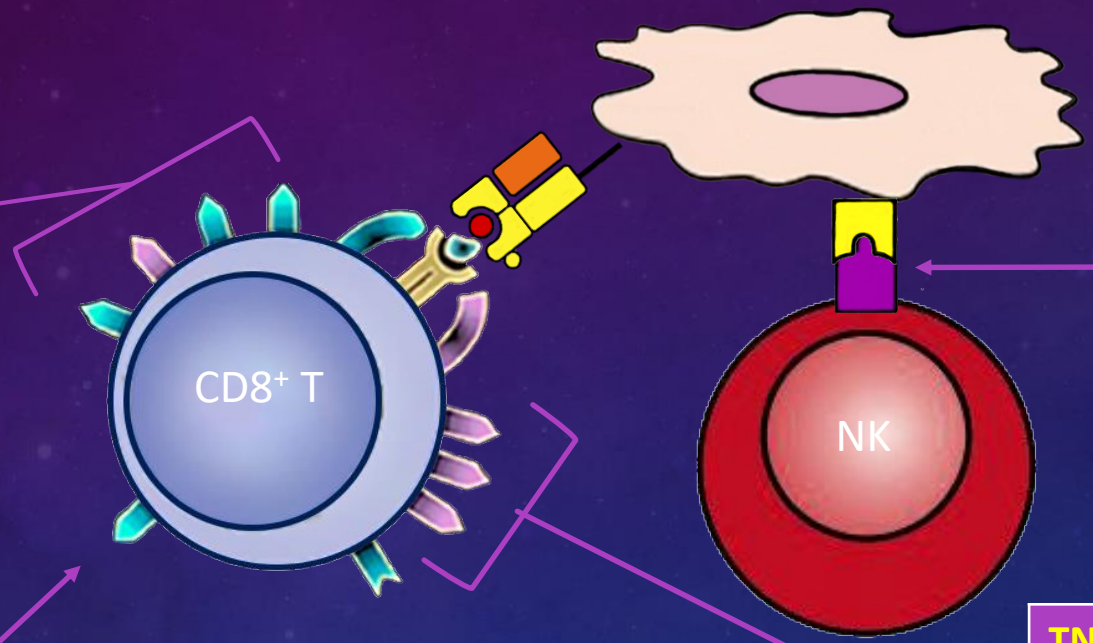


Modified & updated from Michot et al, EJC Feb 2016

- Immune checkpoint inhibitors licensed for use in melanoma, NSCLC, RCC and TCC
- Promising results in trials; potentially >50% of all cancer patients may be eligible for treatment with currently licensed agents

LYMPHOCYTE TARGETING AGENTS IN DEVELOPMENT

CD28/CTLA-Ig family	
Target	**Status**
CTLA-4	Approved
PD 1/PDL1-2	Approved/PII
BTLA	Preclinical
LAG3	Phase II
ICOS	Phase I
TIGIT/CD96	Preclinical



NK agonists	
Target	**Status**
SLAMF7	Approved
KIR	Phase II
NKG2A	Phase II
TIGIT/CD96	Preclinical

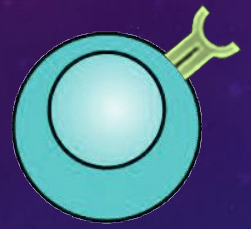
Galectin driven pathways	
Target	**Status**
TIM-3	Phase I
Galectin 1/3/9	Phase II

Cytokines/Chemokines	
Target	**Status**
IFN γ	Approved
IL2	Approved
CXCR4	Phase II
TGFb	Phase II
CCR2	Phase II
CCR4	Approved(Jpn)

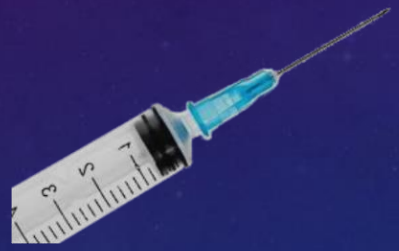
TNF superfamily (& Ligands)	
Target	**Status**
CD40/CD40L	Phase II
OX40	Phase I/II
CD137(4-1BB)	Phase II
GITR	Phase I
CD27/CD70	Phase II

ALSO IN ACTIVE DEVELOPMENT:

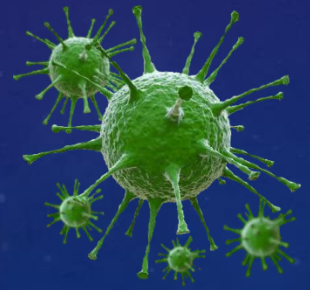
Adoptive T cell therapies (TILs / γδ T cells)



CAR –T cell therapies



Vaccination approaches

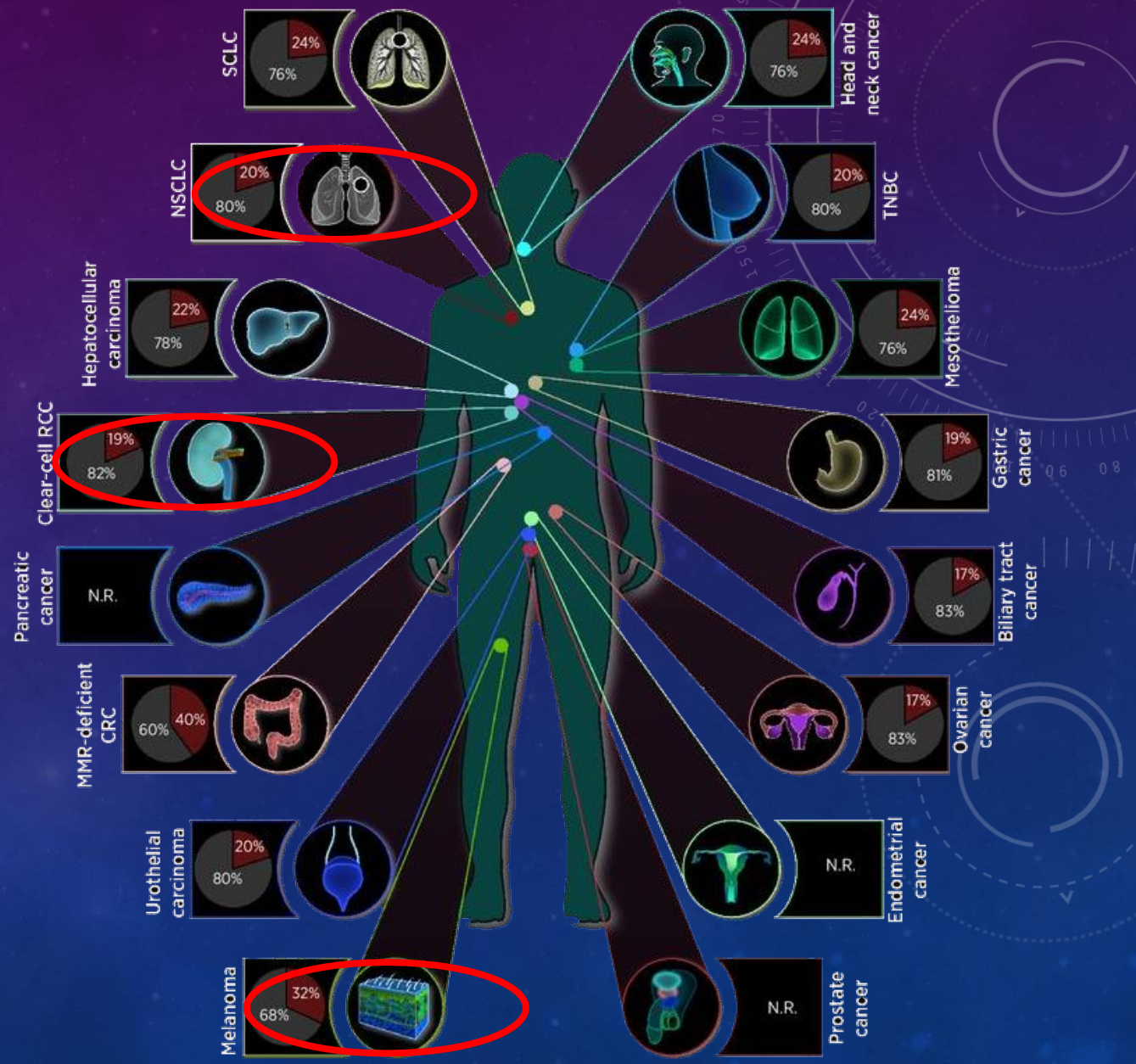


Oncoviral therapies

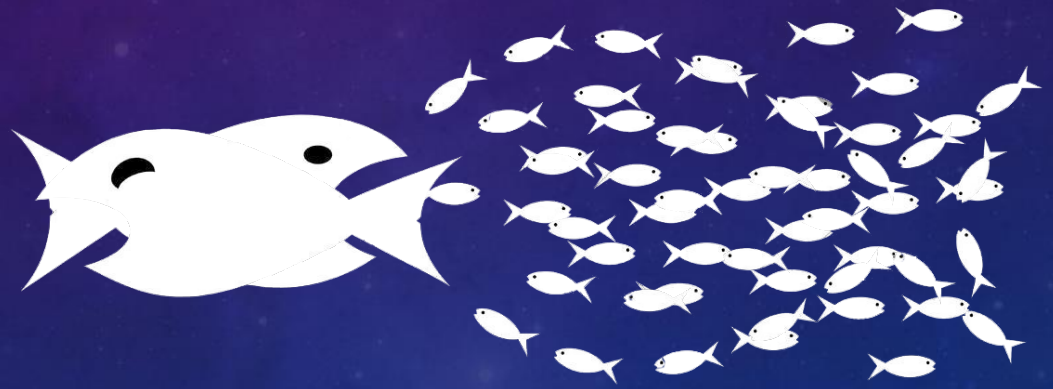
SINGLE AGENT ACTIVITY

Response rates typically <30%

Modified from Chabanon et al CCR; 22(17) Sep 1, 2016

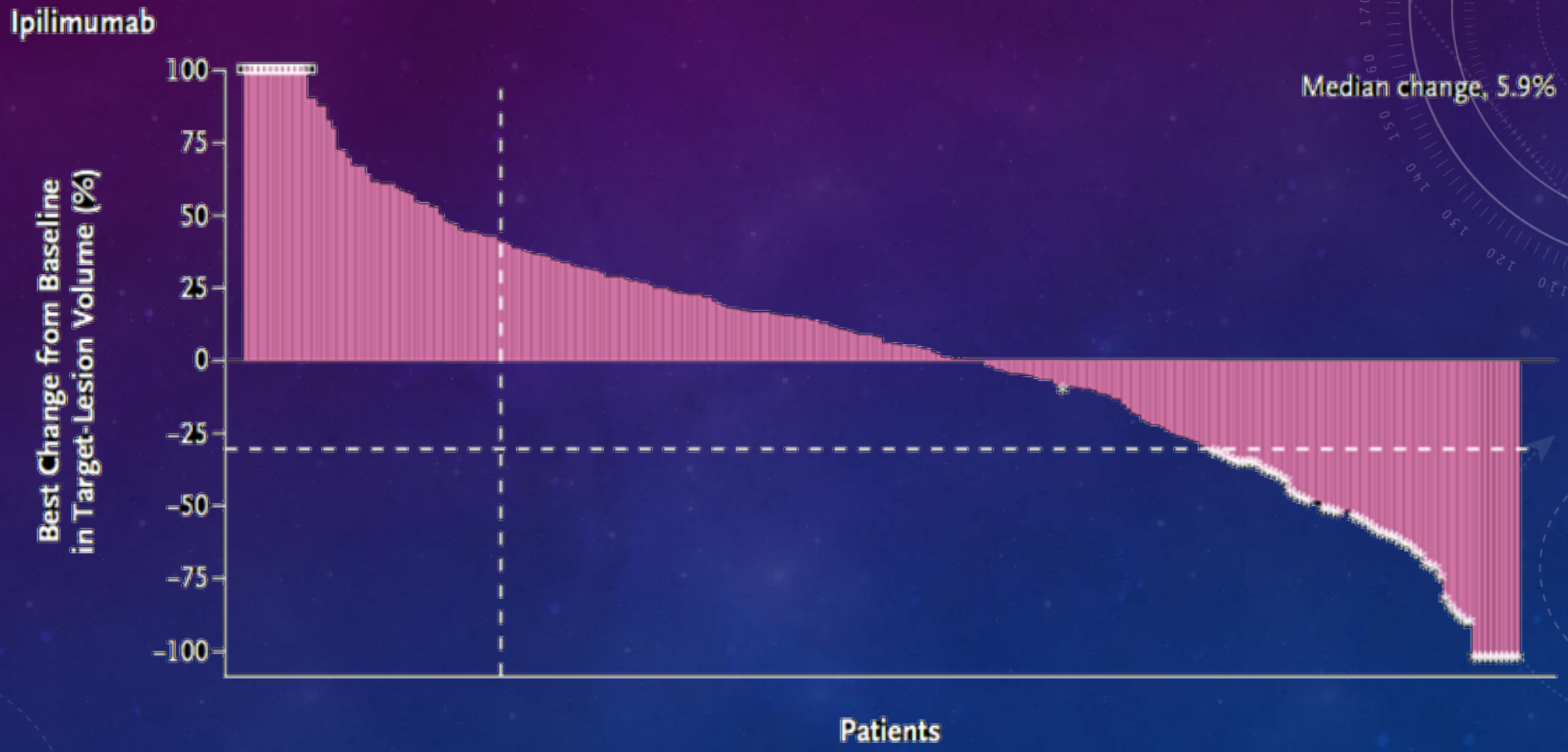


HOW TO COMBAT MULTIPLE CONCURRENT IMMUNE ESCAPE MECHANISMS?



Combinatorial Immunotherapeutics!

CHECKMATE 067



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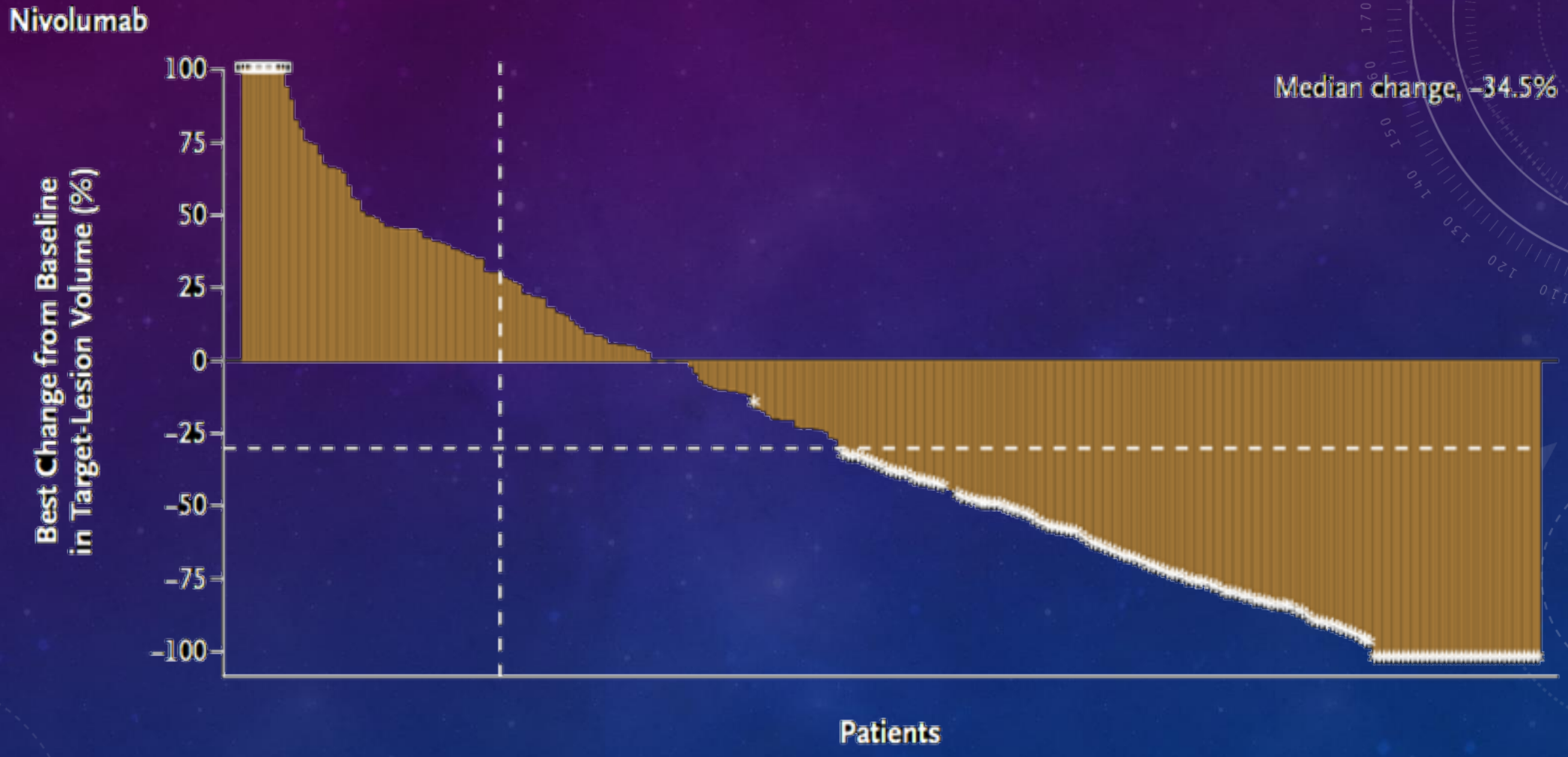

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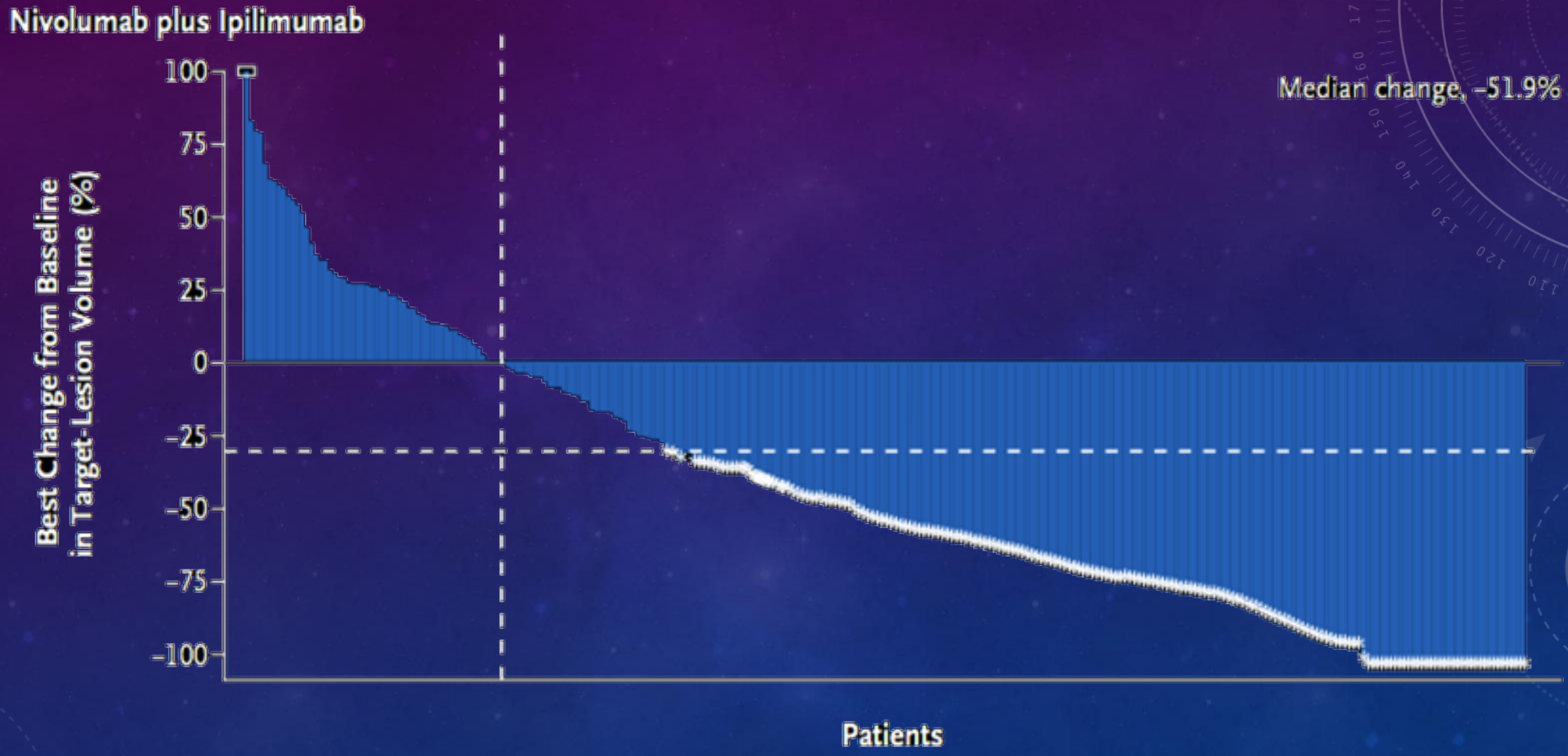


Modified from Larkin et al, N Engl J Med 2015; 373:23-34

COMBINATION THERAPIES IN DEVELOPMENT

	Immunotherapy targets and drugs used		Trial phase	Tumour types	Trial reference
Blockade of T cell inhibition	**Anti-CTLA-4**	**Anti-PD-1**			
	Ipilimumab	Nivolumab	1–3	Melanoma, uveal mel., NSCLC, SCLC, CRC, liver cancer, breast cancer, RCC, lymphoma, multiple myeloma, glioblastoma, gliosarcoma	NCT01844505, 02477826,02538666, 02374242,02060188, 01658878,02453620, 01592370,02210117, 01585194,02311920
	Anti-LAG-3	**Anti-PD-1**			
	LAG525	PDR001	1/2	Advanced cancer	NCT02460224
	BMS-986016	Nivolumab	1/2	Advanced solid tumors	NCT01968109
	REGN3767	REGN2810	1	Advanced cancer	NCT03005782
	Anti-TIM-3	**Anti-PD-1**			
	MBG453	PDR001	1/2	Advanced cancer	NCT02608268
	TSR-022	TBD	1/2	Advanced Solid Tumors	NCT02817633
	Anti-Galectin 3	**Anti-CTLA4**			
	GR-MD-02	Ipilimumab	1	Melanoma	NCT02117362
	Anti-Galectin 3	**Anti-PD-1**			
	GR-MD-02	Pembrolizumab	1	Melanoma	NCT02575404
	Anti-TIGIT	**Anti PDL1**			
	MTIG7192A	atezolizumab	1	Advanced cancer	NCT02794571

COMBINATION THERAPIES IN DEVELOPMENT

	Immunotherapy targets and drugs used		Trial phase	Tumour types	Trial reference
T cell costimulation	**Anti-4-1BB (CD137)**	**Anti-PD-1/PDL1**			
	Urelumab	Nivolumab	1/2	Advanced solid tumors, B cell non-Hodgkin lymphoma	NCT02253992
	PF-05082566	MK3475	1	Advanced solid tumors	NCT02179918
	PF-05082566	Avelumab	2	Melanoma, lung, head and neck cancer	NCT02554812
	Anti-OX40	**Anti-CTLA-4**			
	MEDI6469	Tremelimumab	1/2	Advanced solid tumors	NCT02205333
		Anti-PD-L1			
	MEDI6383	MEDI4736	1	Advanced solid tumors	NCT02221960
	Anti-ICOS	**Anti-PD-1**			
	JTX-2011	**nivolumab**	1/2	Advanced solid tumors	NCT02904226
	Anti-CD27	**Anti-CTLA-4**			
	Varlilumab	Ipilimumab	1/2	Melanoma	NCT02413827
		Anti-PD-1/PDL1			
	Varlilumab	Nivolumab	1/2	Advanced solid tumors	NCT02335918
	Varlilumab	Atezolizumab	1/2	Advanced tumors, RCC	NCT02543645

COMBINATION THERAPIES IN DEVELOPMENT

	Immunotherapy targets and drugs used		Trial phase	Tumour types	Trial reference
Therapeutic Cancer Vaccines	**Peptide vaccines**	**Anti-CTLA-4**			
	6MHP	Ipilimumab	1/2	Melanoma	NCT02385669
		Anti-PD-1			
	6MHP	Pembrolizumab	1/2	Melanoma	NCT02515227
	Tumor cell vaccine	**Anti-CTLA-4**			
	GVAX	Ipilimumab	2	Pancreatic cancer	NCT01896869
		Anti-PD-1			
	GVAX	Nivolumab	2	Pancreatic cancer	NCT02243371
	GM.CD40L	Nivolumab	1/2	Lung cancer	NCT02466568
	Viagenpumatucel-L	Nivolumab	1	NSCLC	NCT02439450
	Vigil	Pembrolizumab	1	Melanoma	NCT02574533
	BCG	Ipilimumab	1	Melanoma	NCT01838200
	Dendritic cell vaccine	**Anti-PD-1**			
	Sipuleucel-T	Pidilizumab	2	Prostate cancer	NCT01420965
	AML fusion vaccine	Pidilizumab	2	AML	NCT01096602
	DNA vaccine	**Anti-PD-1**			
	pTVG-HP plasmid	Pembrolizumab	1/2	Prostate cancer	NCT02499835

COMBINATION THERAPIES IN DEVELOPMENT

	Immunotherapy targets and drugs used		Trial phase	Tumour types	Trial reference
Viro therapy	**Oncolytic virus**	**Anti-CTLA-4**			
	T-VEC	Ipilimumab	1b/2	Melanoma	NCT01740297
		Anti-PD-1			
	T-VEC	Pembrolizumab	1b/3	Melanoma	NCT02263508
IDO inhibitors	**IDO1 inhibitor**	**Anti-PD-1**			
	Epacadostat	Pembrolizumab	1/2	Advanced solid tumors	NCT02178722
		Anti-PD-L1			
	Epacadostat	Durvalumab	1/2	Advanced solid tumors	NCT02318277
	Epacadostat	Atezolizumab	1	NSCLC	NCT02298153
		Anti-CTLA-4			
	Epacadostat	Ipilimumab	1/2	Melanoma	NCT01604889

COMBINATION THERAPIES IN DEVELOPMENT

	Immunotherapy targets and drugs used		Trial phase	Tumour types	Trial reference
Targeted therapy	**BRAFi + MEKi**	**Anti-PD-1**			
	Dabrafenib + trametinib	Pembrolizumab	1/2	Melanoma	NCT02130466
		Anti-PD-L1			
	Dabrafenib + trametinib	Durvalumab	1/2	Melanoma	NCT02027961
	Dabrafenib + trametinib	Atezolizumab	1	Melanoma	NCT01656642
	EGFRi	**Anti-PD-1**			
	Gefitinib or erlotinib	Pembrolizumab	1/2	NSCLC	NCT02039674
	Gefitinib	Tremelimumab	1	NSCLC	NCT02040064
		Anti-CTLA-4			
	Cetuximab + radiation	Ipilimumab	1	Head and neck cancer	NCT01935921

COMBINATION THERAPIES IN DEVELOPMENT

	Immunotherapy targets and drugs used		Trial phase	Tumour types	Trial reference
Epigenetic therapy	**DNMTi**	**Anti-CTLA-4**			
	SGI-110	Ipilimumab	1	Melanoma	NCT02608437
	HDACi	**Anti-PD-1**			
	Vorinostat	Pembrolizumab	1/1b	RCC	NCT02619253
	Entinostat	Pembrolizumab	1b/2	NSCLC, melanoma	NCT02437136
	Entinostat	Anti-PD-1/CTLA-4 nivolumab + ipilimumab		Breast cancer	NCT02453620
	DNMT + HDACi	**Anti-PD-1**			
	Azacitidine + entinostat	Nivolumab	2	NSCLC	NCT01928576

COMBINATION THERAPIES IN DEVELOPMENT

	Immunotherapy targets and drugs used		Trial phase	Tumour types	Trial reference
Radiotherapy	**Stereotactic body RT**	**Anti-CTLA-4**			
		Ipilimumab	2	Melanoma, liver, lung cancer	NCT01970527 NCT02107755 NCT02239900
		Tremelimumab	1	Unresectable pancreatic cancer	NCT02311361
		Anti-PD-1			
		Nivolumab	2–3	Glioblastoma, triple-negative breast cancer	NCT02617589 NCT02499367
Chemotherapy	**Chemotherapy**	**Anti-PD-1**			
	Temsirolimus, irinotecan, capecitabin	Nivolumab	1/2	Advanced tumors	NCT02423954
	Nab-paclitaxel, gemcitabine, carboplatin	Nivolumab	1	Pancreatic, breast, NSCLC	NCT02309177
	Paclitaxel, carboplatin, pemetrexed	Pembrolizumab	1/2	Lung cancer	NCT02039674
		Anti-CTLA-4			
	Gemcitabine	Ipilimumab	1	Pancreatic cancer	NCT01473940

Modified & updated from Vilgelm et al, JLB vol. 100 no. 2 275-290 (2016)

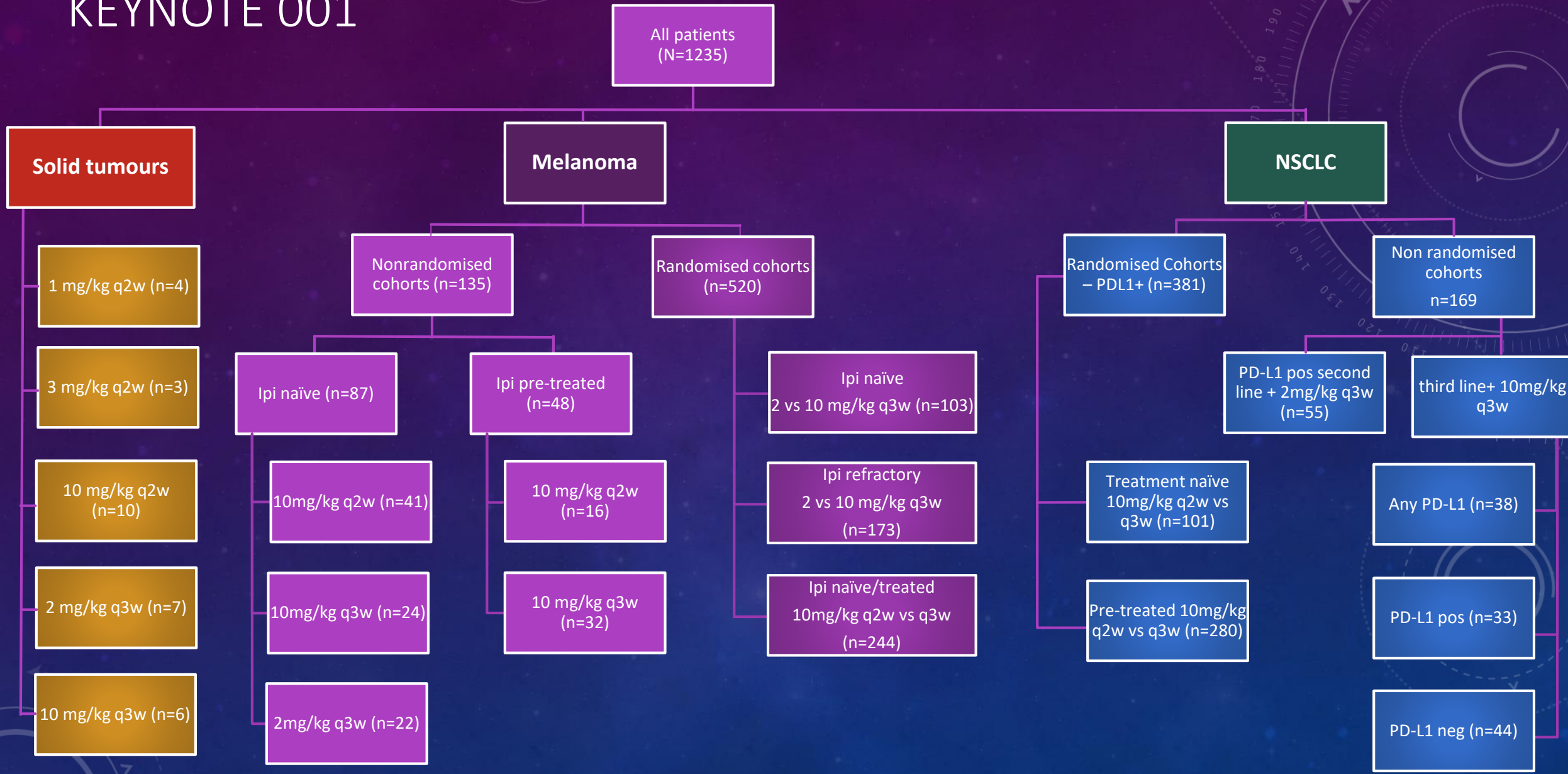
I-O ONCOLOGY PHASE I TRIALS

- 573 recruiting I-O Phase 1 studies currently registered in clicaltrials.gov
  - 375 studies incorporating anti PD-1/PD-L1 agents
  - 19 studies incorporating anti CTLA-4 agents
  - 179 trials incorporating other I-O IMPs / modalities
- 11% of all Phase 1 studies and 20% of all oncology P1 studies!
- Vast majority involve IMP combinations

ONCOLOGY TRIAL PATIENT CHARACTERISTICS

- Highly motivated (& often well informed)
  - Prepared to accept significant morbidity/mortality risks
  - Prepared to accept low/minimal chance of benefit
  - ***Risk of underreporting AEs***
- Limited window of opportunity for individual subjects
- Often heavily pre-treated with long term toxicities
- Long term toxicity monitoring challenging
  - Cross-over to further treatments
  - Short OS due to underlying disease process

KEYNOTE 001



Data from Khoja et al, J Imm Can , **doi :** 10.1186/s40425-015-0078-9

TRENDS IN I-O EARLY PHASE TRIALS

- Increasing use of modular / adaptive designs
  - Expansion cohorts clearly looking at efficacy endpoints
  - Aim for breakthrough designation, accelerated or conditional approval
- MTD very rarely reached
- DLT definition challenging
- Focus on biomarker discovery / validation

IMMUNE RELATED TOXICITY

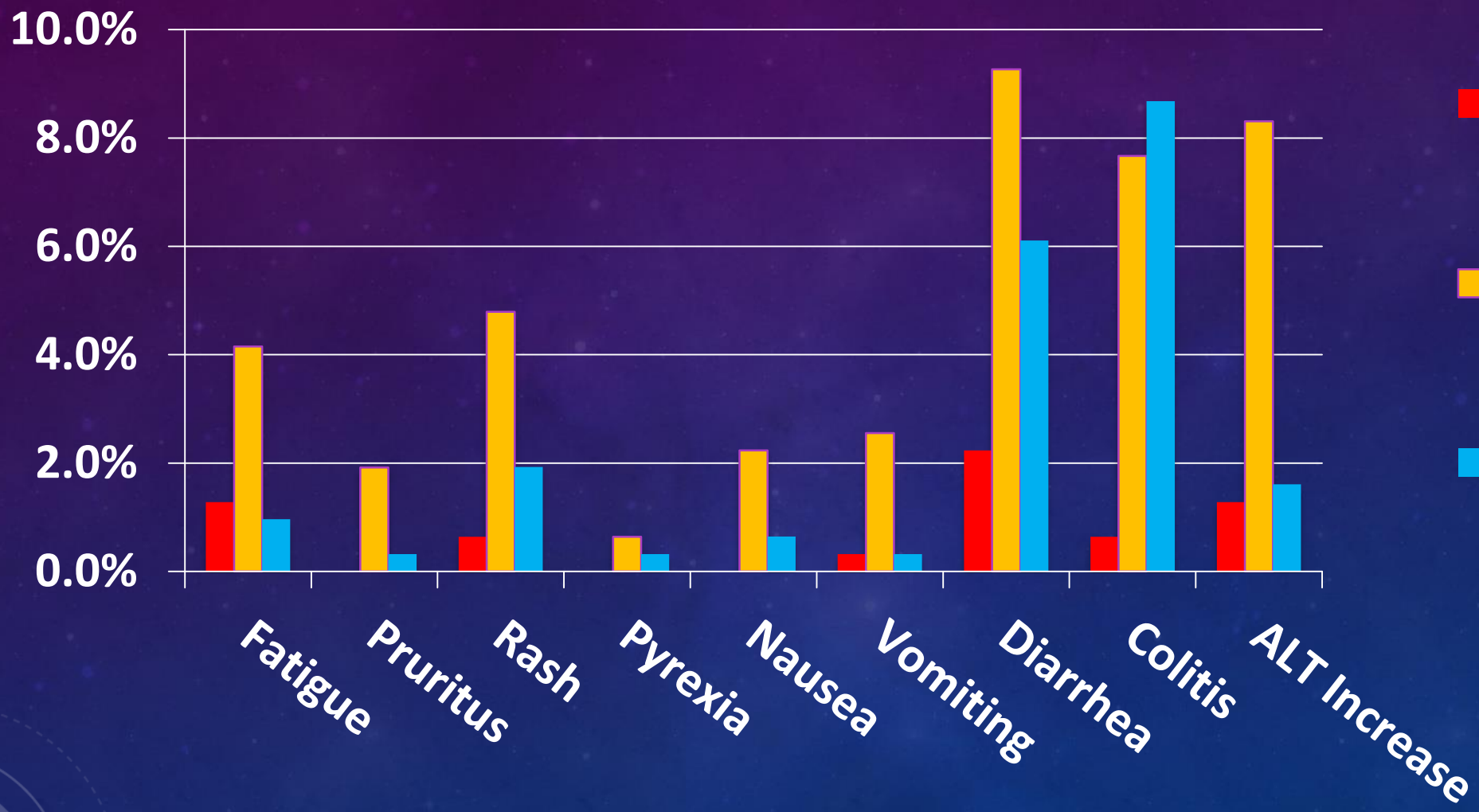
- Any adverse event mediated by the immune system causally related to the IMP
- Can affect any organ system in the body
  - Concurrent toxicities frequent, particularly in the context of combination IT
  - May result in flare / reactivation of pre-existing auto-immune conditions
  - Long recovery time course
    - Can result in irreversible end-organ damage
  - Beyond a certain threshold supportive management insufficient

NIVOLUMAB TOXICITY RATES

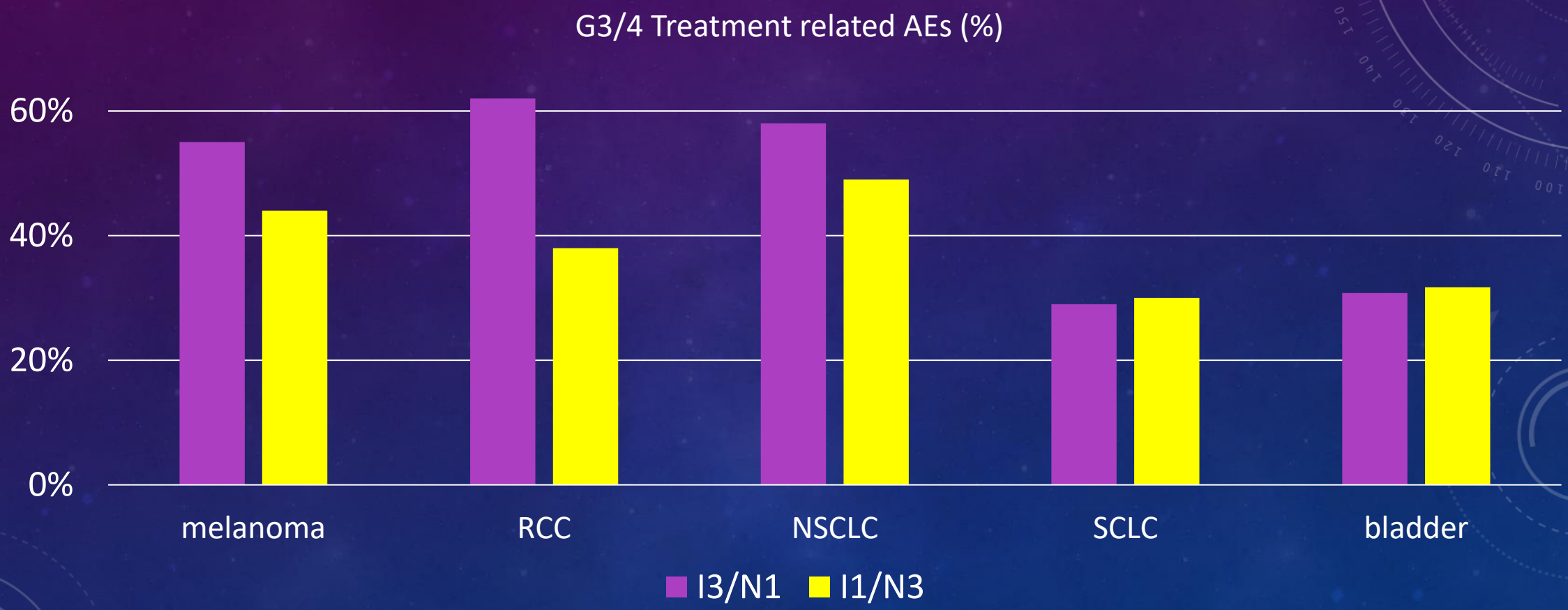
	N=	Colitis	Pneumonitis	Hepatitis	Nephritis	Hypo-thyroidism
NSCLC	418	2.2	3.1	**0.2**	**0.7**	6.5
RCC	406	3.2	**4.4**	1.5	3	8.1
HL(post HSCT)	263	**0.4**	3.4	2.3	**3.8**	9.5
HNSCC	236	0.8	0.8	**0.4**		8.1
urothelial	270	2.6	3.7	1.1	**0.7**	**10.7**
melanoma	576	1	1.9	**2.8**	1.4	5.2

Data from OPDIVO® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017 & Weber et al, JCO 2017, DOI: 10.1200/JCO.2015.66.1389

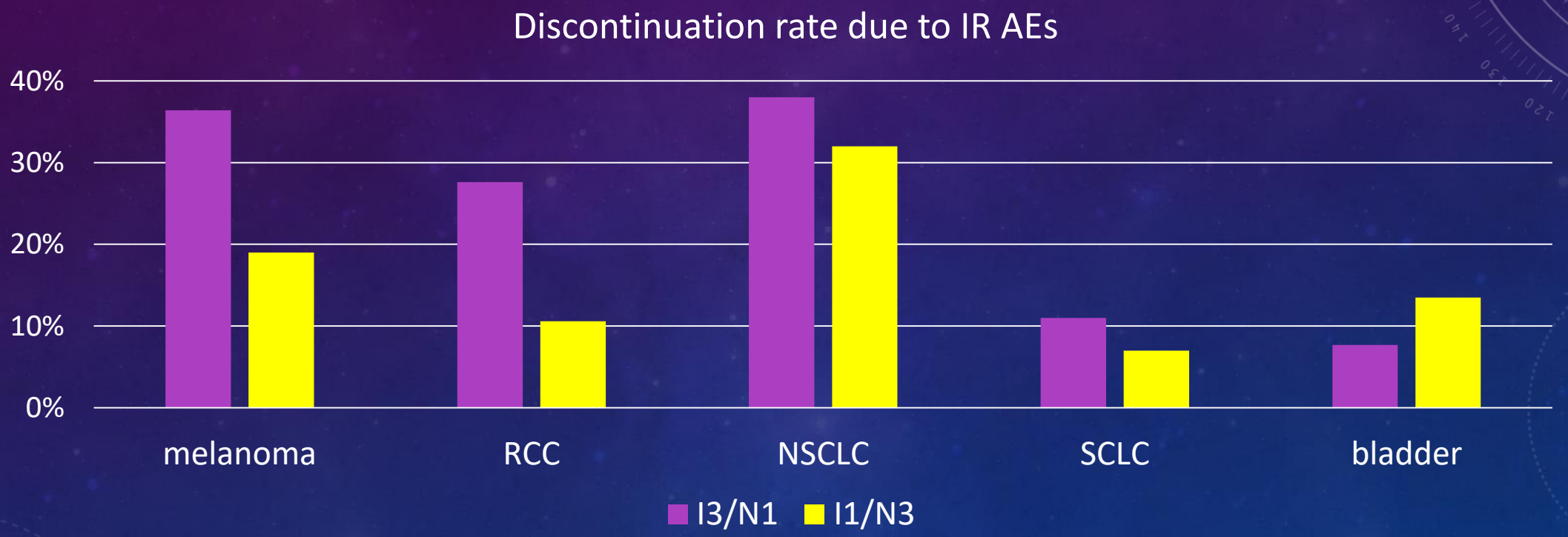
CHECKMATE 067- GRADE 3-4 TOXICITIES



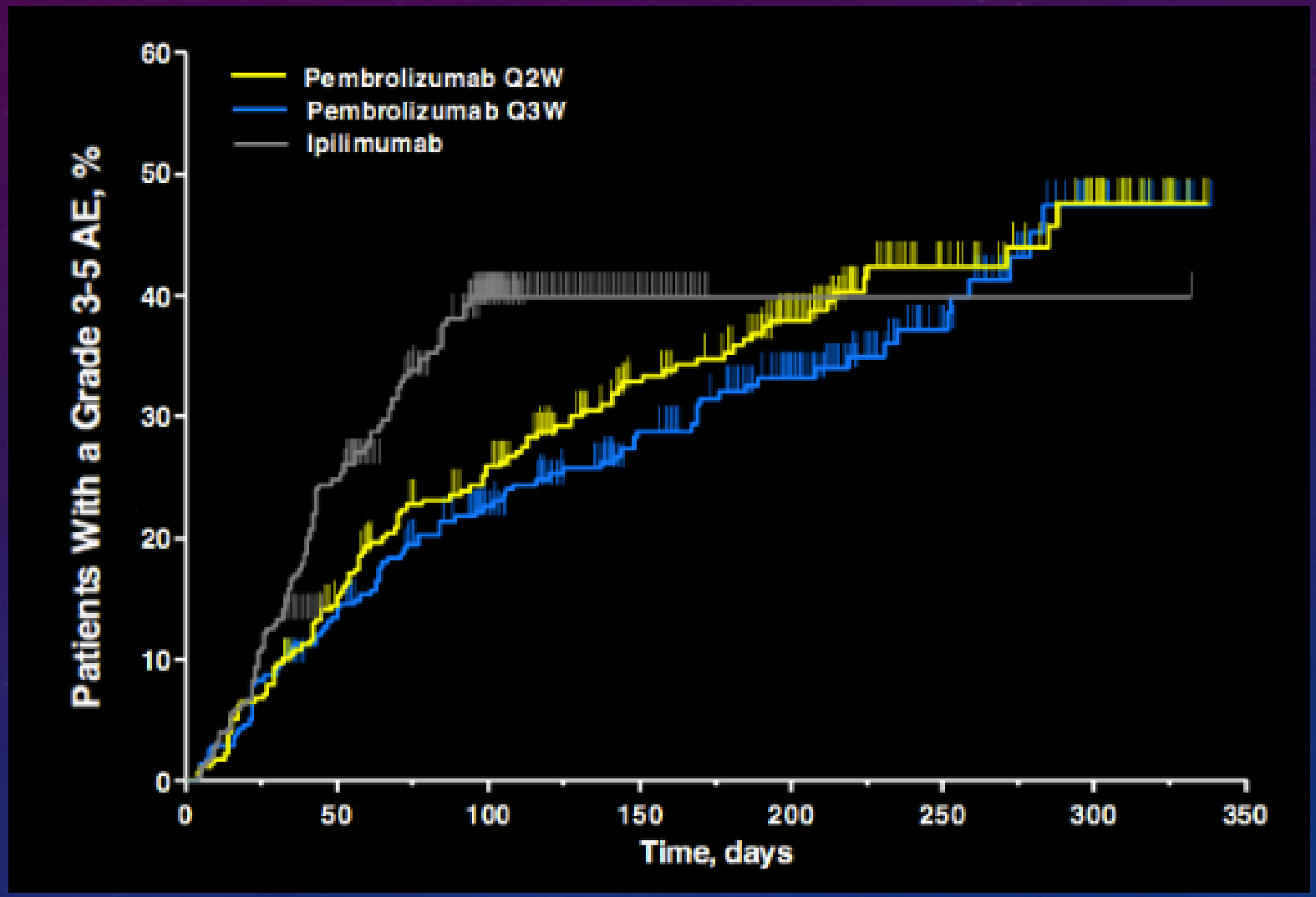
COMBINATION IMMUNOTHERAPY TOXICITY



IR-TOXICITY RELATED DISCONTINUATION

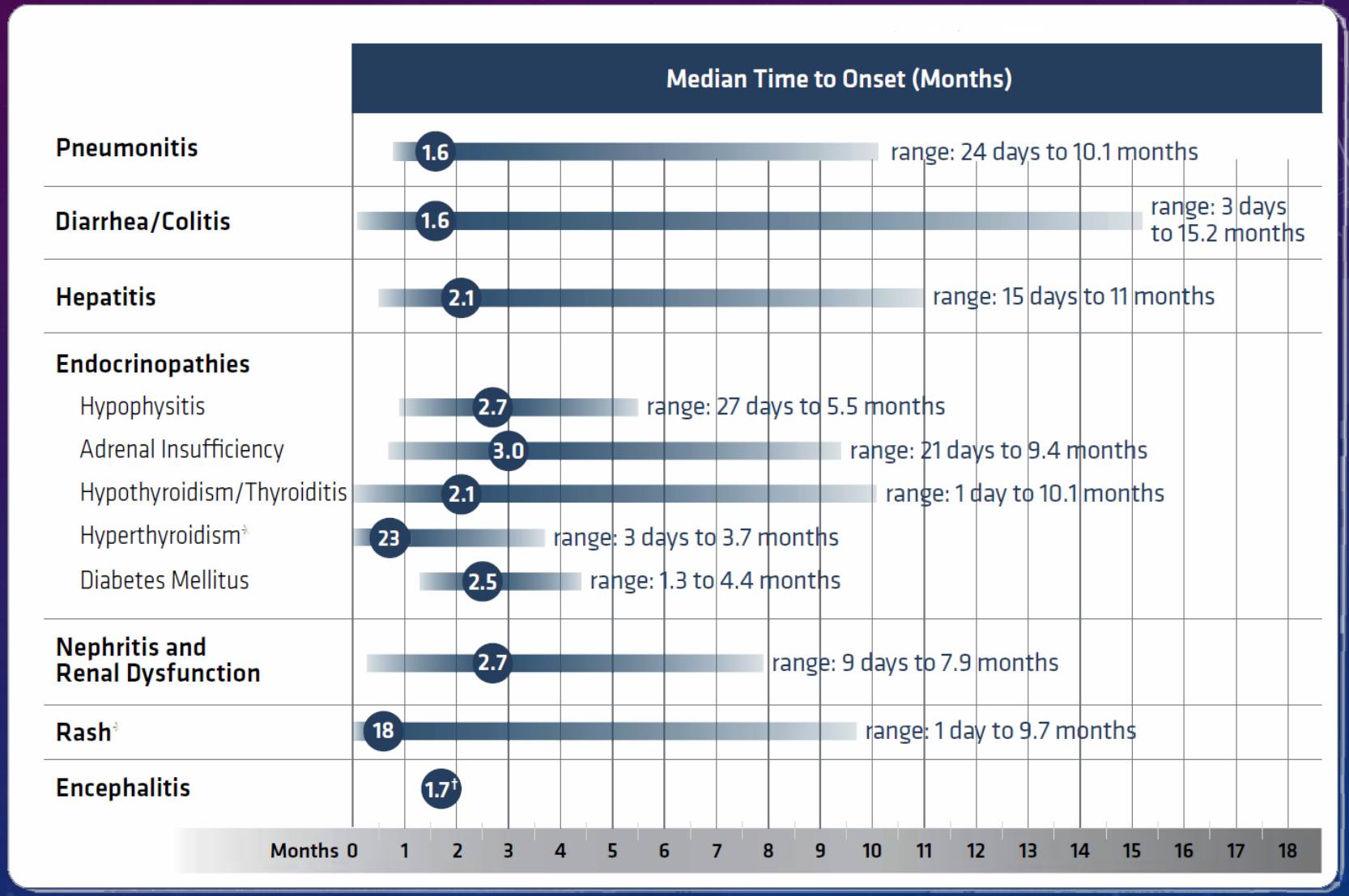


TIME TO ONSET OF SEVERE ADVERSE EVENTS



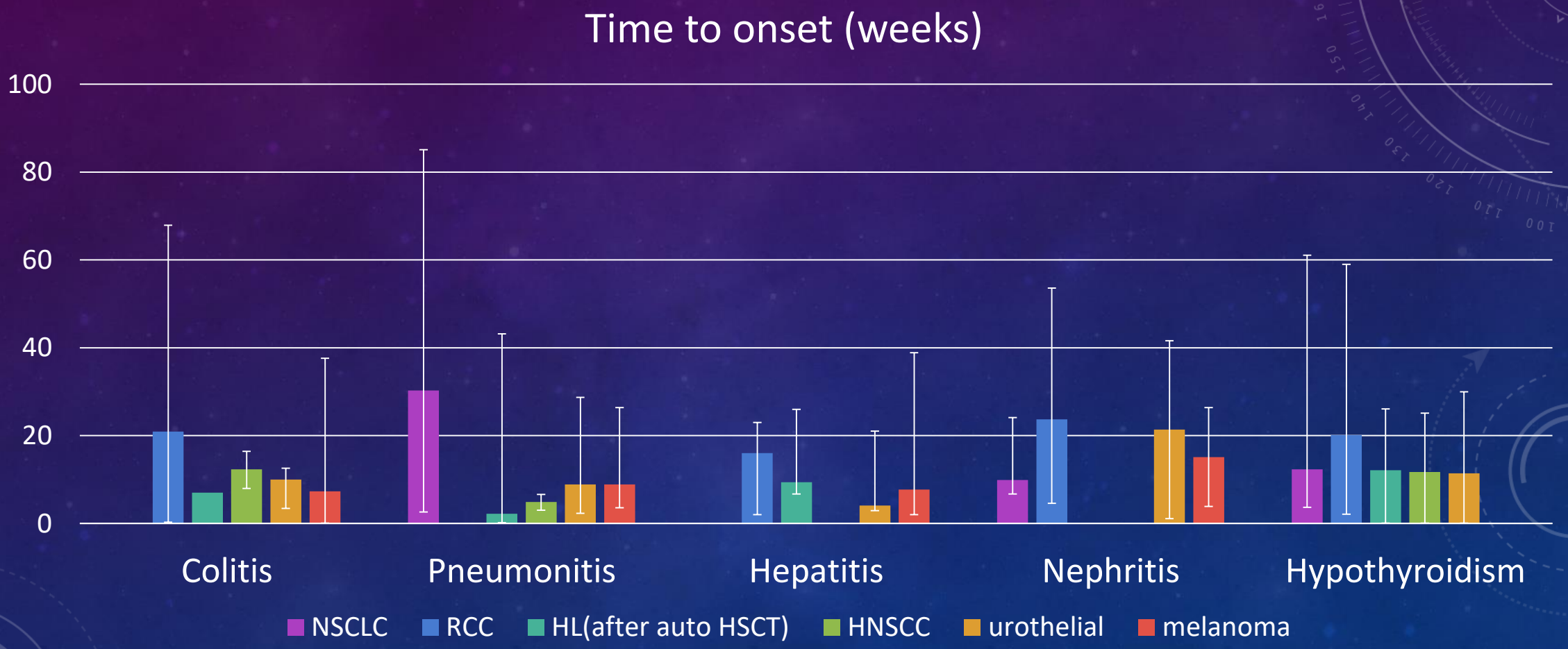
Modified from Robert et al NEJM 19.4.2015

IPILIMUMAB & NIVOLUMAB IN MELANOMA



Aggregated data from CHECKMATE 067 & 069; Modified from OPDIVO® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.

NIVOLUMAB AE KINETICS



Data from OPDIVO® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017 & Weber et al, JCO 2017, DOI: 10.1200/JCO.2015.66.1389

IR TOXICITY – IMPORTANT CONSIDERATIONS

- Toxicity may be long term and/or irreversible(duration of action far exceeding half life)
- Predicting nature and intensity of combinatorial toxicity from single agent toxicity is challenging
- Toxicity depends not only on agent(s) and total dose but also on
  - Scheduling
  - Individual patient characteristics (age, HLA type, micriobiome, tumour load etc)
  - Specific indication (tumour type)
- Cancer patients immune systems are NOT normal

PREDICTING TOXICITY: PRECLINICAL STUDIES

- Animal models problematic
  - Immunocompromised hosts innately unsuitable
  - Immune system make-up different (e.g. CD28 expression patterns – cf TGN1412)
- In vitro/ex-vivo models cannot fully recapitulate complexity of immune system & large intra & inter-subject variability
- Too early for in-silico models to be of use

TGN1412 – A CAUTIONARY TALE

In vivo – cynomolgous monkeys

- 100% sequence homology, equivalent binding affinity & tissue staining
- CD4 EM T cells do not express CD28
- Naïve/CM T cells require costimulation

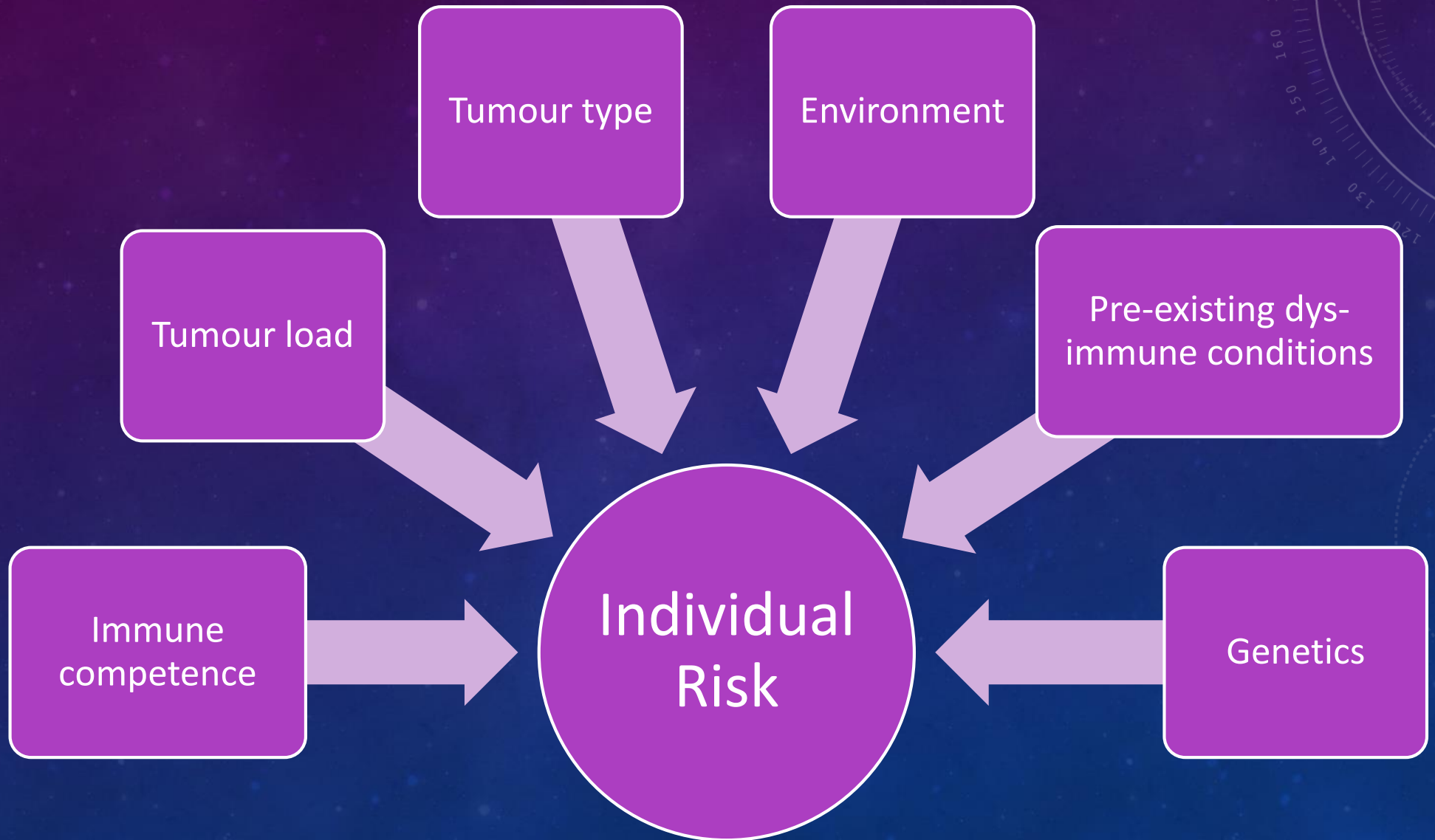
In vitro- human PBMCs

- Used TGN1412 in solution
- CD4 EM T cells found predominantly in tissues

Starting dose

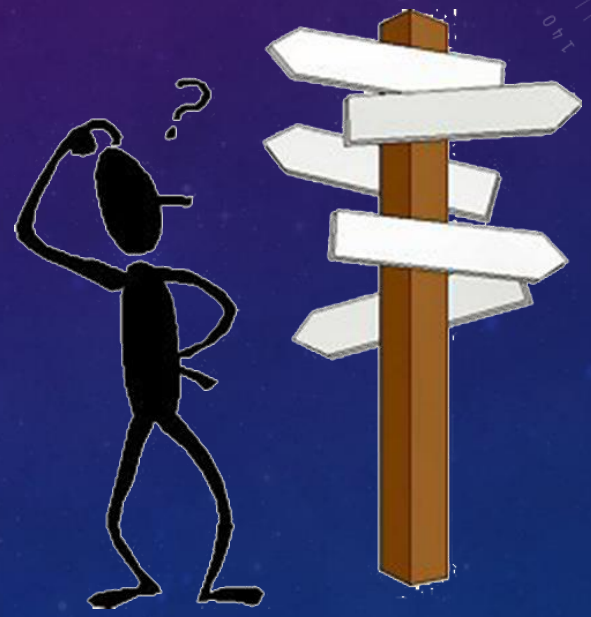
- 1/500 of no-observable adverse effect dose in monkeys
- 45-80% receptor occupancy in humans

PREDICTING TOXICITY: PATIENT CHARACTERISTICS



PREDICTING TOXICITY: BIOMARKERS

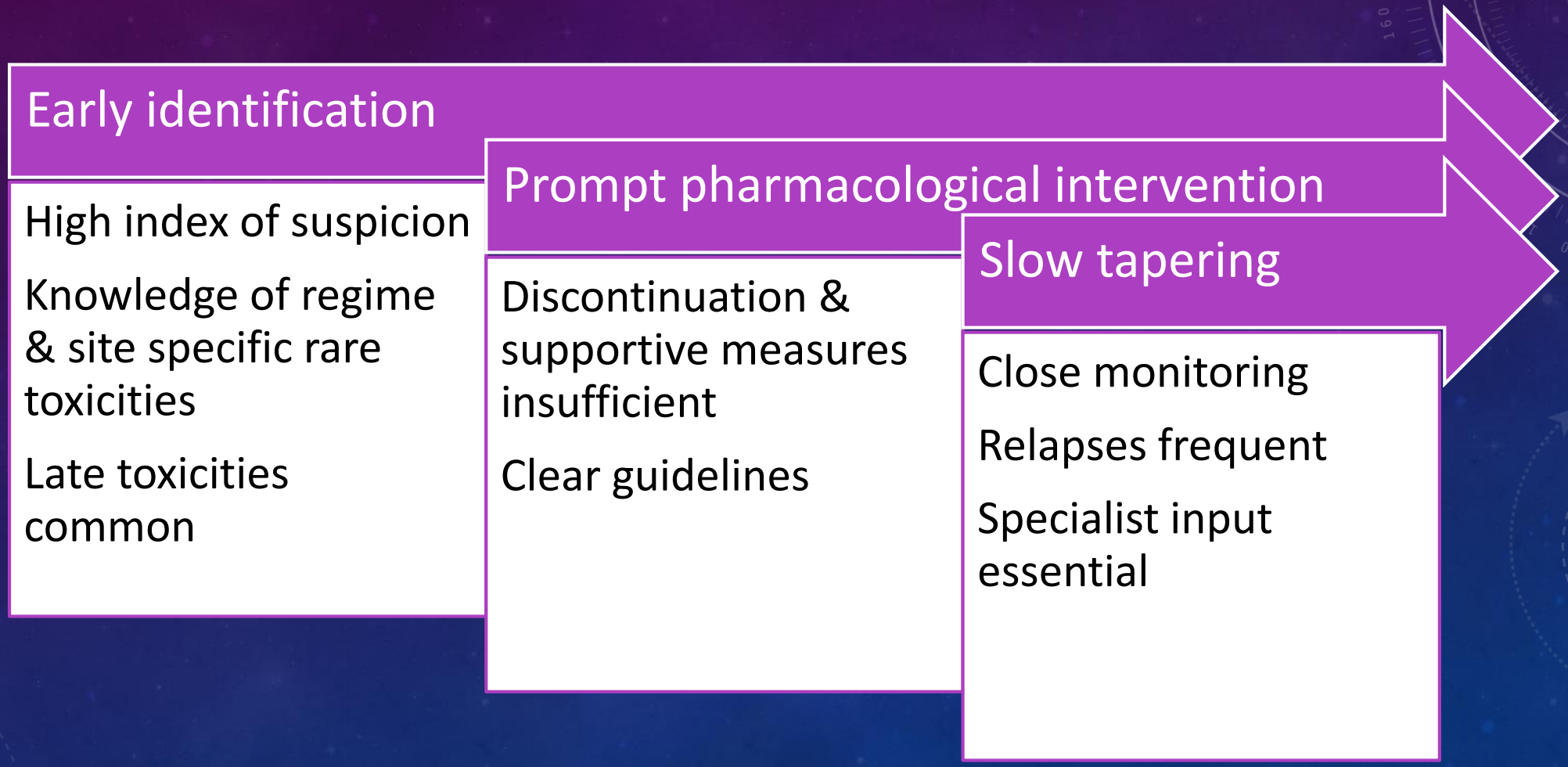
- Genetic predisposition
  - Polymorphisms e.g CTLA 4
  - HLA haplotypes
- Microbiome
- IL17 / eosinophil count
- Gene Expression Profiling



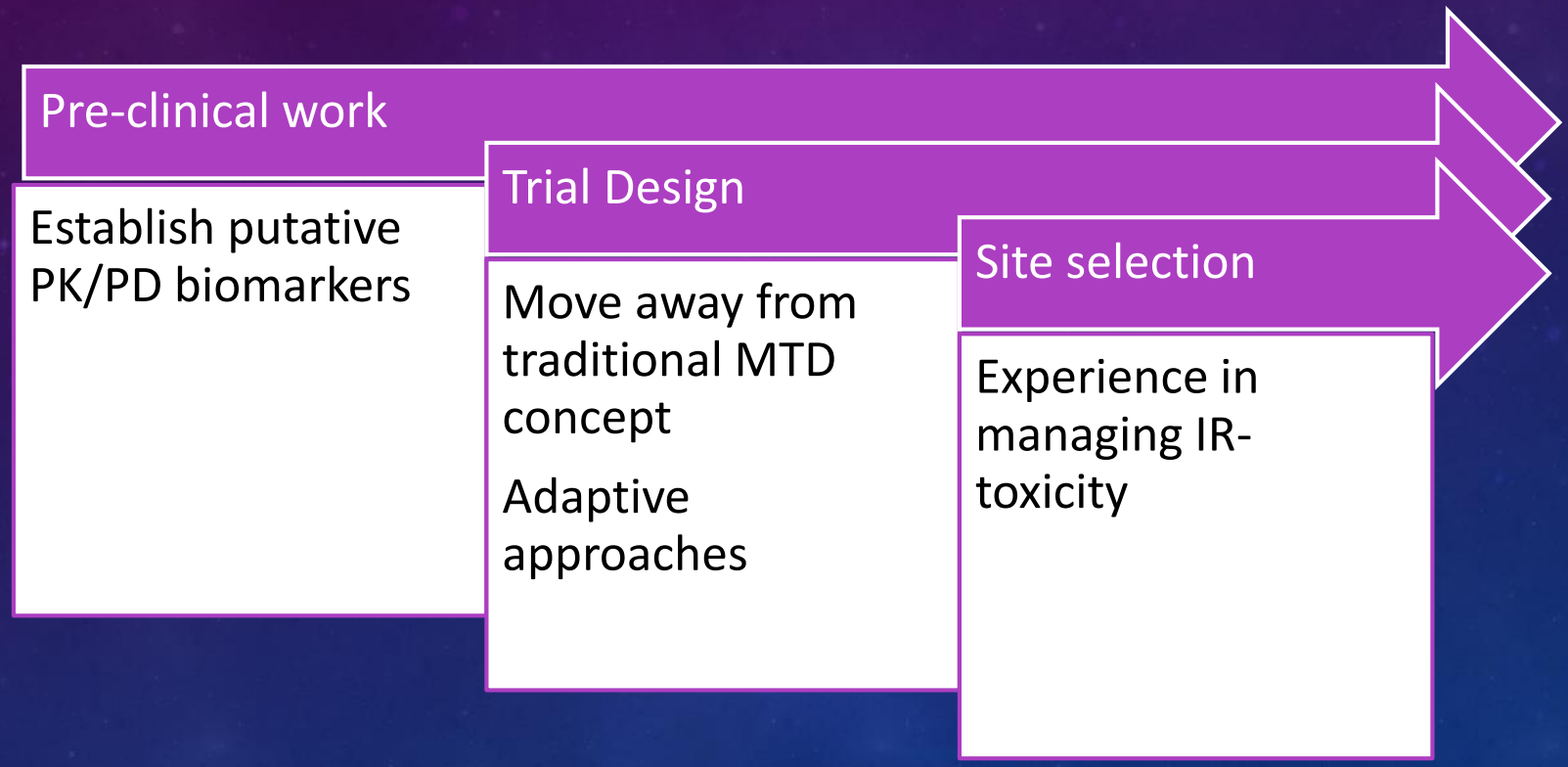
IDENTIFYING IR TOXICITY

- Early symptoms non-specific
  - Often mimic other conditions
  - Screening essential
- Specialist input & investigations required
- Late presentations not unusual

MANAGING IR TOXICITY



MITIGATING IR TOXICITY

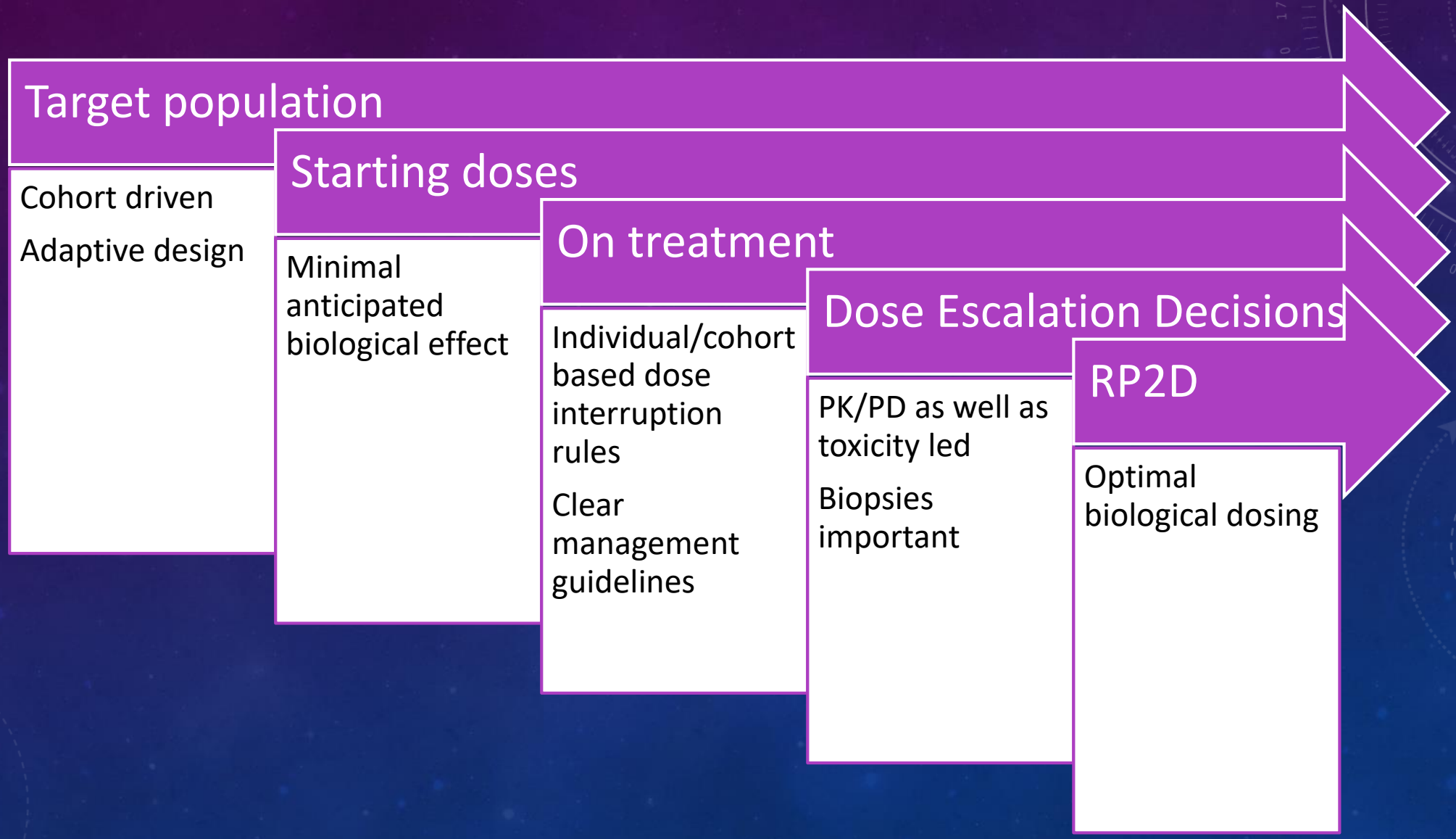


MITIGATING IR TOXICITY – PRE CLINICAL DEVELOPMENT

Right target	• Strong link between target pathway & disease
Right tissue	• Understanding of tissue specific PK/PD
Right safety	• Human data (ex vivo/in vitro) essential
Right patients	• Determine subgroups more at risk of toxicity

Biomarkers essential!

MITIGATING IR TOXICITY- TRIAL DESIGN



EXAMPLE MANAGEMENT GUIDELINES

Grade 1 (mild)	• Manage symptomatically
Grade 2 (moderate)	• Initially manage symptomatically • If ***persistent*** interrupt treatment + commence steroids (pred 0.5-1 mg/kg)
Grade 3-4 (severe)	• **Interrupt** treatment (possibly permanently) • Hospitalise, investigate & com mence ***immunomodulating*** treatment

MITIGATING IR TOXICITY – SITE SELECTION

- Competence & Experience in dealing with IR-AEs
- Sufficient resources for increased workload caused by adaptive/ multi-arm designs
- High level cross- specialty support
- Capability for collection & processing of PK/PD samples

IR- TOXICITY: OPEN CHALLENGES

- Large variability across patient groups & within individual patients at different time-points
- Late onset severe toxicities
- Underestimates of rare toxicities
  - Difficult to detect even in large Phase I studies with heterogeneous multiple expansion cohorts
  - Proper Phase III / post marketing authorisation studies essential
- Prediction of combinatorial toxicity
- Transparency and communication

SUMMARY

- IO has accelerated a paradigm shift in early phase trial design
- Lack of suitable animal & in vitro models pose significant safety related challenges
- Pressing need for predictive biomarkers
- Careful trial design and management critical to mitigate toxicity concerns