De-escalation of immunotherapy. The example of MOIO phase III French clinical trial.

Cancer Drug Development Forum

8 février 2023

Gwenaelle Gravis

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Disclosures

- Speaker bureau: Janssen, Amgen, BMS, IPSEN, AAA, Astra Zeneca, Bayer, Pfizer Merck, Astellas. Recipient: my institution.
- Board: Janssen, Amgen, BMS, Curium, Bayer, Pfizer Merck. Recipient: my institution.
- Expert: BMS, Bayer, Pfizer/ merck. Recipient: my institution.
- Travel expense: Janssen, BMS, Astra Zeneca, Bayer, Pfizer Merck. Recipient: me.
- BMS, Coordinating PI, Financial interest, Institutional

Immunotherapy

- Indications increase in several metastatic cancer types
- Development in (neo) adjuvant setting
- > 8 IO…
- > 20 tumor types…
- Durable response, even after treatment discontinuation
- Immune related adverse events
- Financial expenses

What is the best dosing of IO?

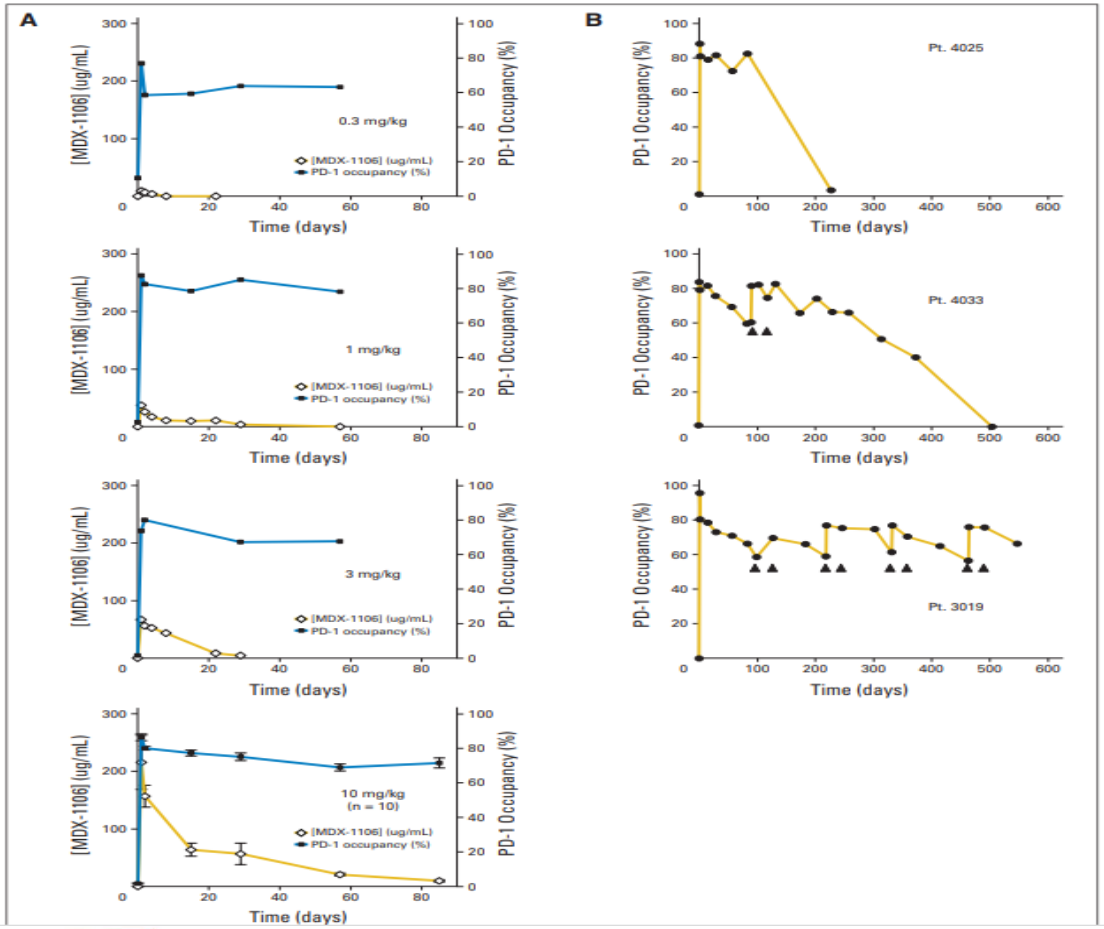
- No maximum Tolerated Dose
- No clear dose response
  - Metrics by IL2 production by T Ly (Pembrolizumab)
  - PD-1 receptor saturation (Nivolumab)
  - Decrease in clearance (20-30%) over time relative to first dose
  - Increase plasmatic level over time

Pharmacodynamics of anti–programmed death-1 (PD-1) monoclonal antibody (MDX-1106)

VOLUME 28 · NUMBER 19 · JULY 1 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates

Julie R. Brahmer, Charles G. Drake, Ira Wollner, John D. Powderly, Joel Picus, William H. Sharfman,



(A) PD-1 occupancy on circulating CD3 T cells after one infusion of MDX-1106 is shown for single patients (Pts.) each receiving 0.3, 1, or 3 mg/kg, and for 10 patients receiving 10 mg/kg (mean standard error of mean; solid squares). Serum concentrations of MDX-1106 at the same time points are indicated (open diamonds).
(B) (B) Long-term PD-1 occupancy analysis in patients receiving one (top panel) or multiple doses (middle and bottom panels) of MDX-1106 at 10 mg/kg. All patients received infusions at day 1; additional infusions are indicated by arrows. Results in (B) middle and bottom panels are representative of five patients receiving multiple doses.

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Different dose/interval

Target	Drug	Body-Weight-Based Dose	Flat Dose	Clinical Applications
CTLA-4	Ipilimumab (YERVOY®)	3 mg/kg Q3W 1 mg/kg Q3W		Metastatic melanoma Cutaneous melanoma Advanced renal cell carcinoma.
PD-1	Nivolumab (OPDIVO®)	3 mg/kg Q2W	240 mg Q2W 480 mg Q4W	Metastatic melanoma Metastatic NSCLC Hodgkin lymphoma Advanced renal cell carcinoma Advanced or metastatic urothelial carcinoma Metastatic colorectal cancer Hepatocellular carcinoma
	Pembrolizumab (KEYTRUDA®)	2 mg/kg Q3W	200 mg Q3W 400 mg Q6W	Melanoma NSCLC Head and neck squamous cell cancer Classical Hodgkin lymphoma Primary mediastinal large b-cell lymphoma Urothelial carcinoma Microsatellite instability-high cancer Gastric cancer Cervical cancer Hepatocellular carcinoma Merkel cell carcinoma
	Cemiplimab (LIBTAYO®)		350 mg Q3W	Metastatic CSCC Locally advanced CSCC
PD-L1	Atezolizumab (TECENTRIQ®)		840 mg Q2W 1200 mg Q3W 1680 mg Q4W	Urothelial Carcinoma NSCLC TNBC Metastatic treatment of TNBC
	Avelumab (BAVENCIO®)	10 mg/kg Q2W	800 mg Q2W	Metastatic Merkel cell carcinoma Advanced or metastatic urothelial carcinoma Advanced renal cell carcinoma (+axitinib)
	Durvalumab (INFINZI®)	10 mg/kg Q2W	750 mg Q2W 1500 mg Q4W	Locally advanced or metastatic urothelial carcinoma Unresectable stage III NSCLC

Le Louedec F et al Vaccines 2020

Objective response rate reported in studies with different doses

Pembrolizumab

Cancer Type (No.)	2 mg/kg Once Every 3 Weeks	10 mg/kg Once Every 3 Weeks	10 mg/kg, Once Every 2 Weeks
NSCLC (30)	33 (2/6)	19.2 (55/287)	19.3 (39/202)
NSCLC (32)	18 (62/344)	18 (64/246)	NA
Melanoma (12)	26 (21/81)	26 (20/76)	NA
Melanoma (31)	21 (36/180)	26 (46/181)	NA
Melanoma (33)	NA	32.9 (91/277)	33.7 (94/279)

Nivolumab

Cancer Type (No.)	0.1 mg/kg Once Every 2 Weeks	0.3 mg/kg Once Every 2 Weeks	0.3 mg/kg Once Every 3 Weeks	1 mg/kg Once Every 2 Weeks	3 mg/kg Once Every 2 Weeks	3 mg/kg Once Every 3 Weeks	10 mg/kg Once Every 2 Weeks	10 mg/kg Once Every 3 Weeks
Melanoma (19)	35 (6/17)	28 (5/18)	NA	31 (11/35)	41 (7/17)	NA	20 (4/20)	NA
NSCLC (23)	NA	NA	NA	6 (1/18)	32 (6/19)	NA	18 (7/39)	NA
RCC (23)	NA	NA	NA	24 (4/17)	NA	NA	31 (5/16)	NA
RCC (29)	NA	NA	20 (12/60)	NA	NA	22 (12/54)	NA	20 (11/54)

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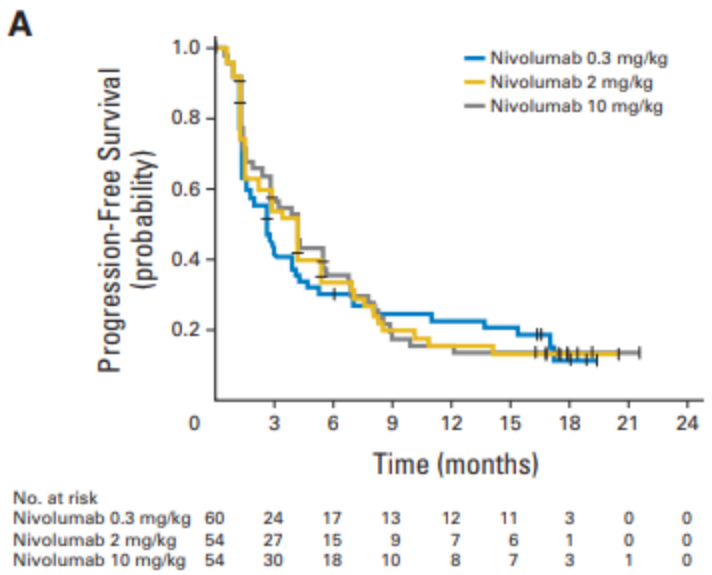
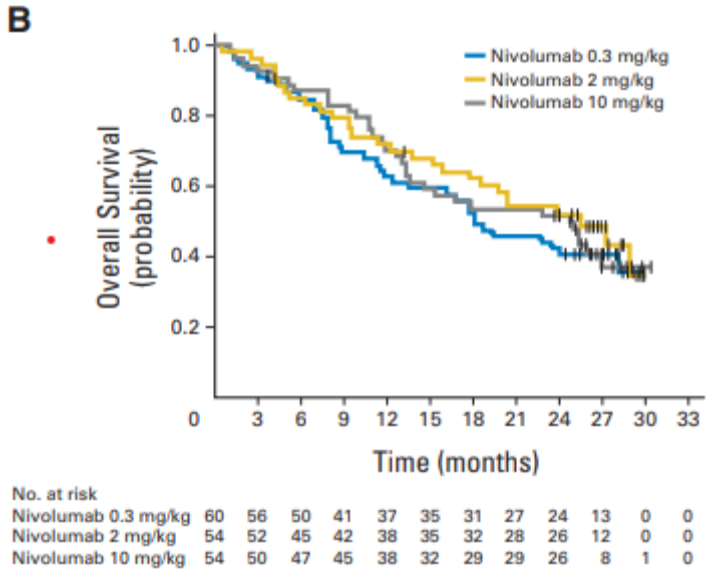
Renner A et al J of Global Oncol 2019

Randomized Phase II evaluated 3 doses of nivolumab for mRCC
No dose-response relationship

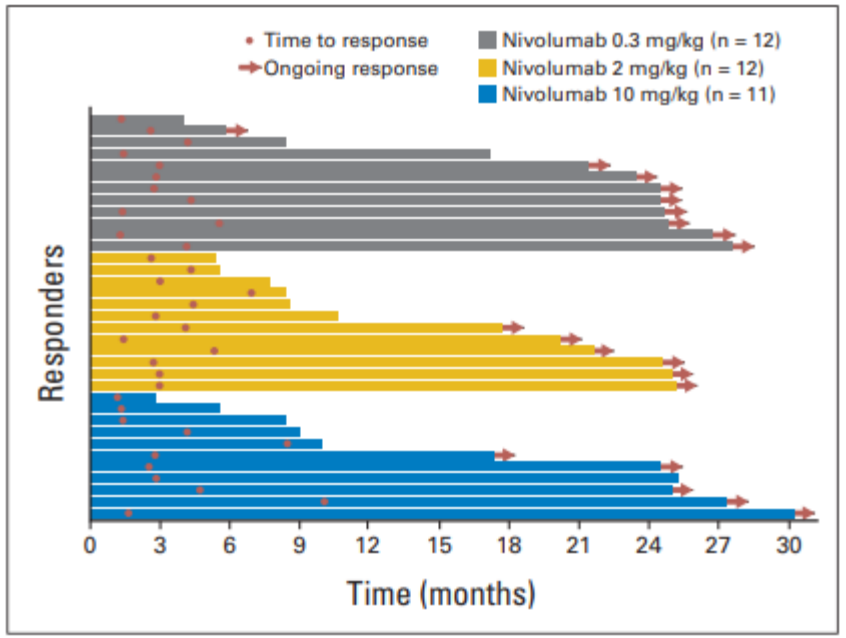
PFS by treatment arm



OS by treatment arm



Duration of response by treatment arm



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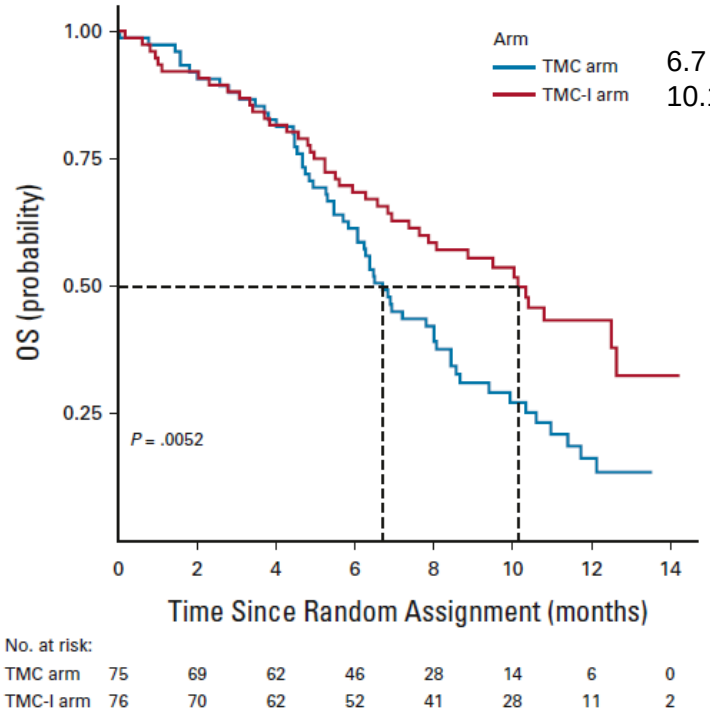
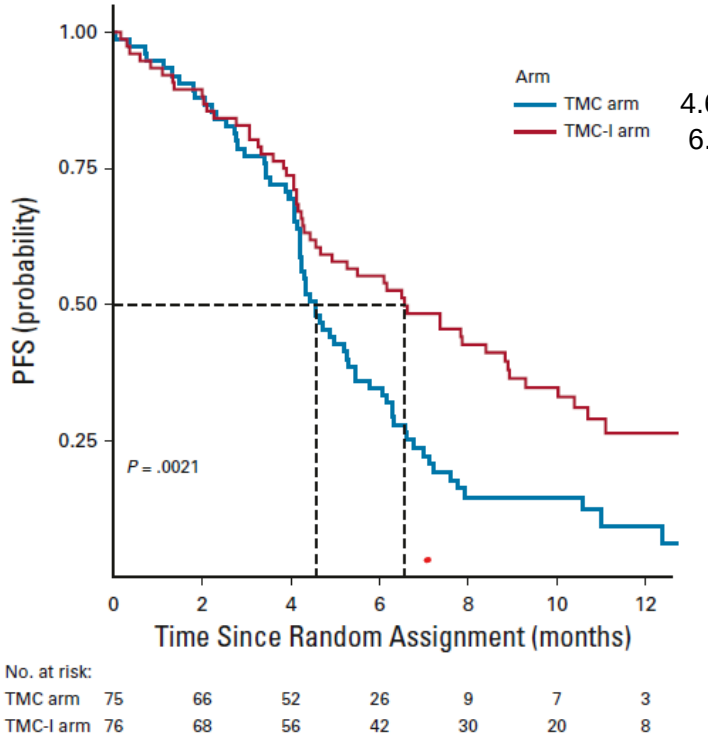
Motzer, R et al JCO 2014

Phase III : metronomic chemotherapy (Metho + Celecoxib + erlotinib)+/- Nivolumab **20 mg/ 3w** in advanced head an neck cancer



6.7 vs
10.1 months (p = .0052)



4.6
6.6 months (p= .0020)

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Patil V-M et al JCO 2022

How long should we give immunotherapy for ?

Renal cell cancer

	Nivo-Ipi# CONTINUOUS (75% arrêt à 22 mo post amdt)	Pembro (2 years) Axi	Pembro (2 years) -Lenva¤	Nivo (2 years) - Cabo
ORR	42%	60%	71%	56%
CR	11%	10%	16%	12%
mDOR	NR	23,6 months	25,8months	23 months

Motzer et al,Cancer 2022; Rini et al, ASCO 2021; Motzer et al, N Eng J Med 2021; Powles et al, ASCO GU 2022.

#*Interm/ high risk*

Metastatic Urothelial carcinoma

	Keynote-045 Pembrolizumab (continuous) vs chemo	Javelin Avelumab (continuous)vs placebo
OS MEDIAN	median 10.1 v 7.2 mo; HR, 0.71; 95% CI, 0.59-0.86	23.8 vs 15.0 mo HR: 0.76 95% CI (0.631-0.915)

Balar A et al Annals oncol 2022, Powles T et al ASCO-GU 2022

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Published OnlineFirst October 8, 2018; DOI: 10.1158/1078-0432.CCR-18-0793

Clinical Trials: Immunotherapy

Clinical Cancer Research

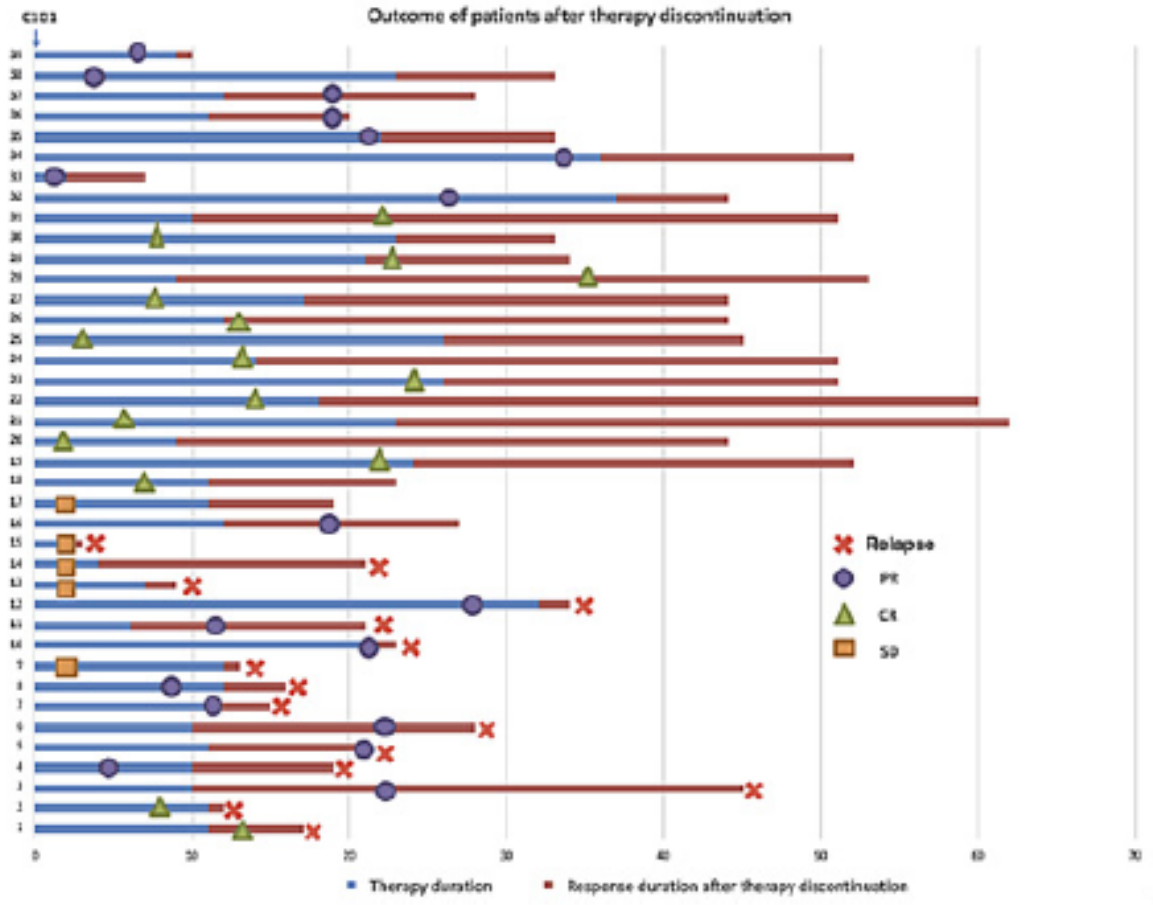
Long-Term Survival in Patients Responding to Anti–PD-1/PD-L1 Therapy and Disease Outcome upon Treatment Discontinuation

Marie-Léa Gauci[1], Emilie Lanoy[2,3], Stéphane Champiat[1,4], Caroline Caramella[5], Samy Ammari[5], Sandrine Aspeslagh[1], Andrea Varga[1], Capucine Baldini[1], Rastilav Bahleda[1], Anas Gazzah[1], Jean-Marie Michot[1], Sophie Postel-Vinay[1], Eric Angevin[1], Vincent Ribrag[1], Antoine Hollebecque[1], Jean-Charles Soria[1], Caroline Robert[3,6], Christophe Massard[1], and Aurélien Marabelle[1,7]

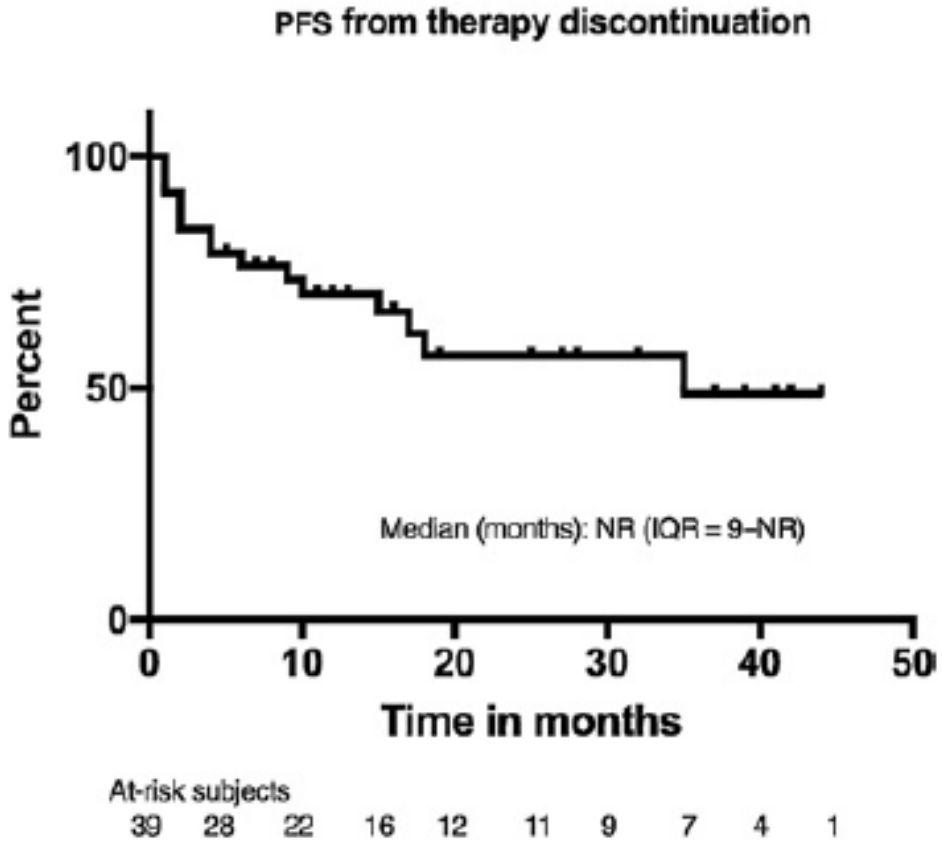
DISCONTINUATION FOR WHOM ?

- 19 cancer types included in different phase I
- 262 pts OR 29%
- Median FU 34 mois

Disease evolution after therapy discontinuation



Response duration after therapy discontinuation

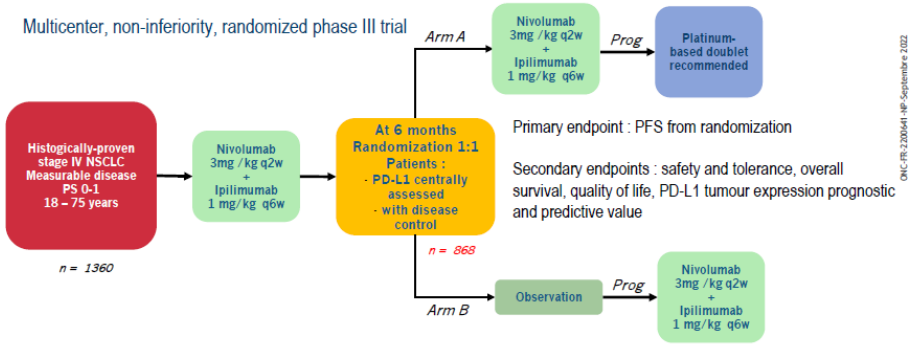


Trial design and endpoints

IFCT-1701 D.I.C.I.P.L.E

Double Immune Checkpoint Inhibitors in PD-L1-positive stage IV non-small Lung CancEr

Multicenter, non-inferiority, randomized phase III trial



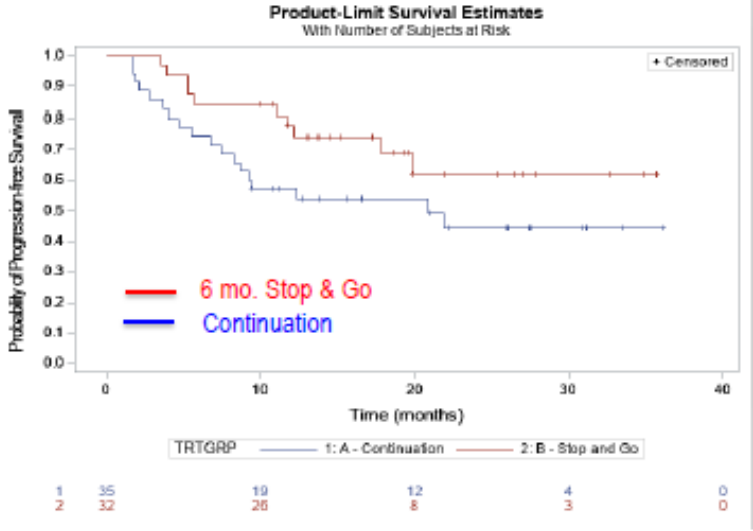
Primary endpoint : PFS from randomization

Secondary endpoints : safety and tolerance, overall survival, quality of life, PD-L1 tumour expression prognostic and predictive value

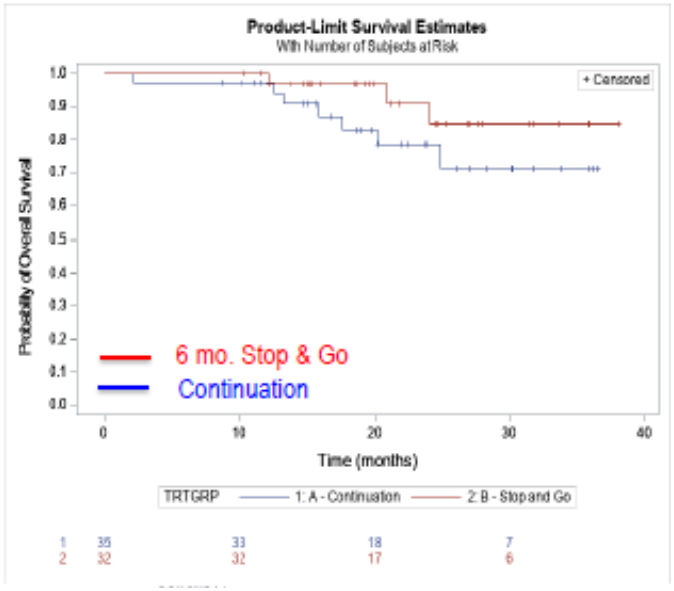
Presented by Gerard Zalcman, M.D. Bichat Hospital (APHP), Paris, France

	A - Continuation (N=35)				B - Stop & Go (N=34)			
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any adverse event	35 (100%)	15 (42.9%)	4 (11.4%)	0 (0%)	32 (94.1%)	11 (32.4%)	1 (2.9%)	1 (2.9%)
Immune-related adverse event (irAE)	31 (88.6%)	9 (25.7%)	0 (0%)	0 (0%)	28 (82.4%)	4 (11.8%)	0 (0%)	0 (0%)
Serious Adverse Event (SAE)	15 (42.9%)	9 (25.7%)	0 (0%)	0 (0%)	8 (23.5%)	6 (17.6%)	0 (0%)	1 (2.9%)

PFS



OS



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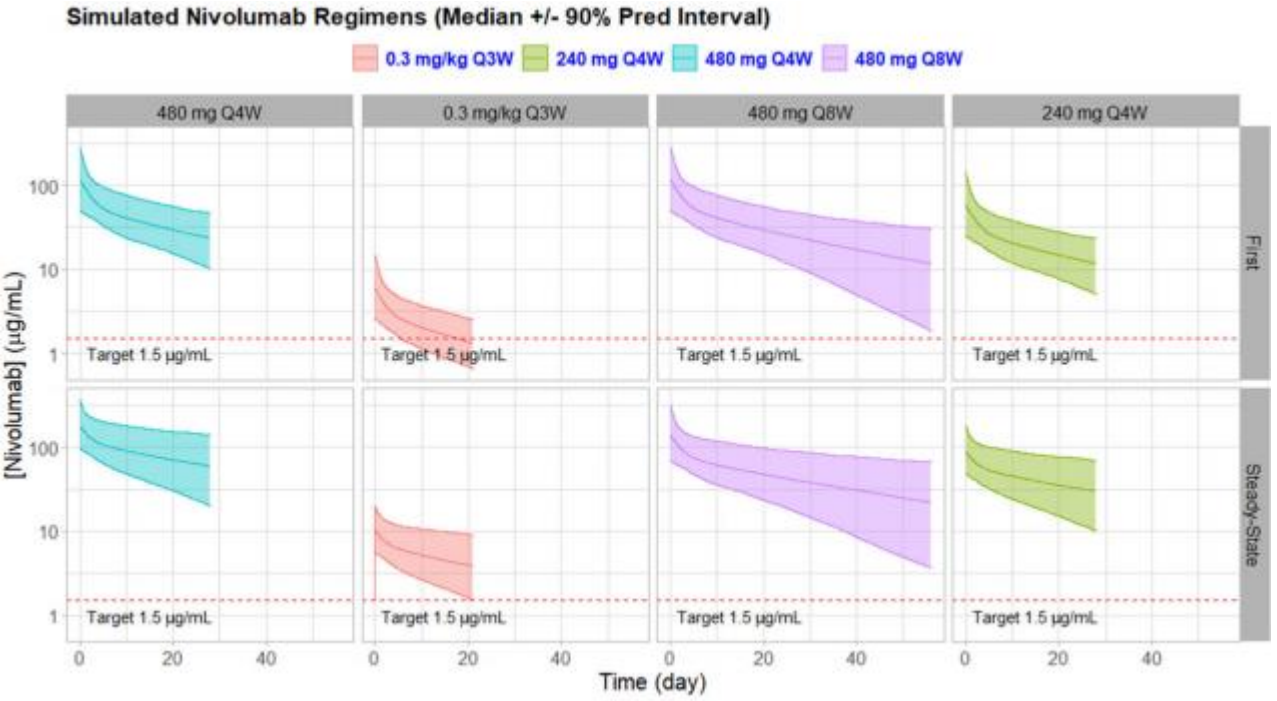
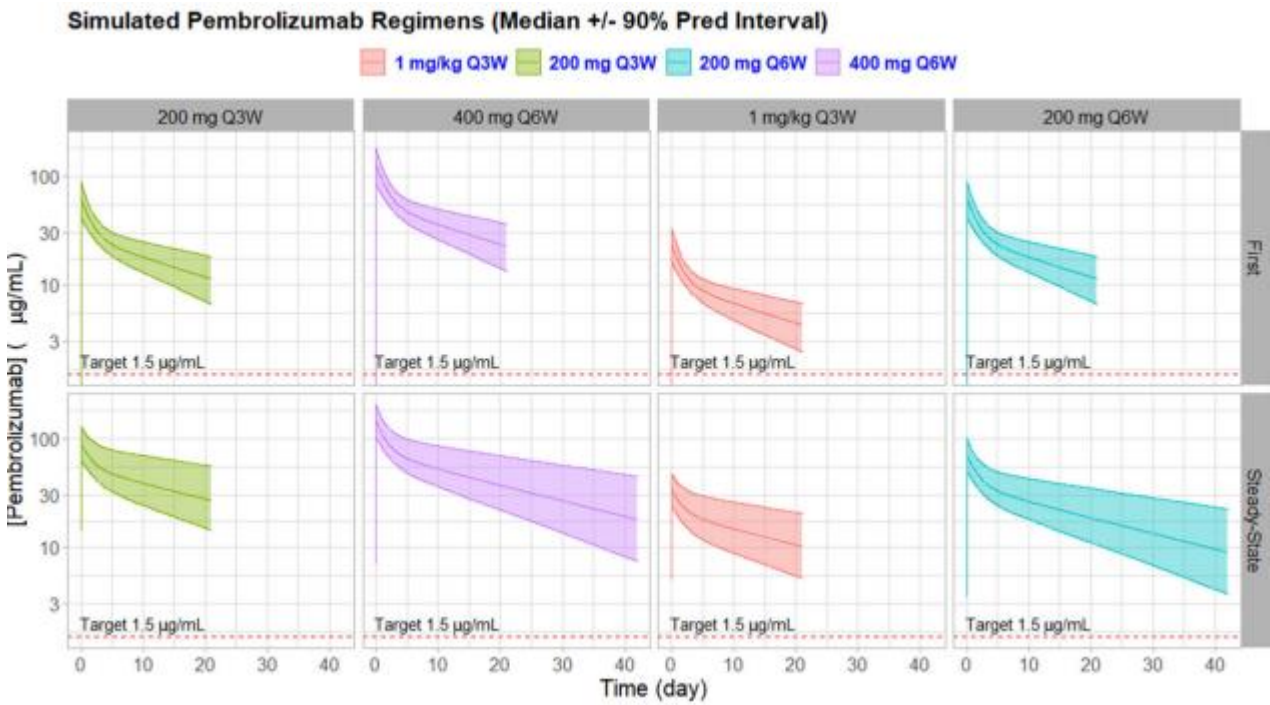
Zalcman et al ESMO 2022

Pharmacokinetic Simulation Analysis of Less Frequent Nivolumab and Pembrolizumab Dosing





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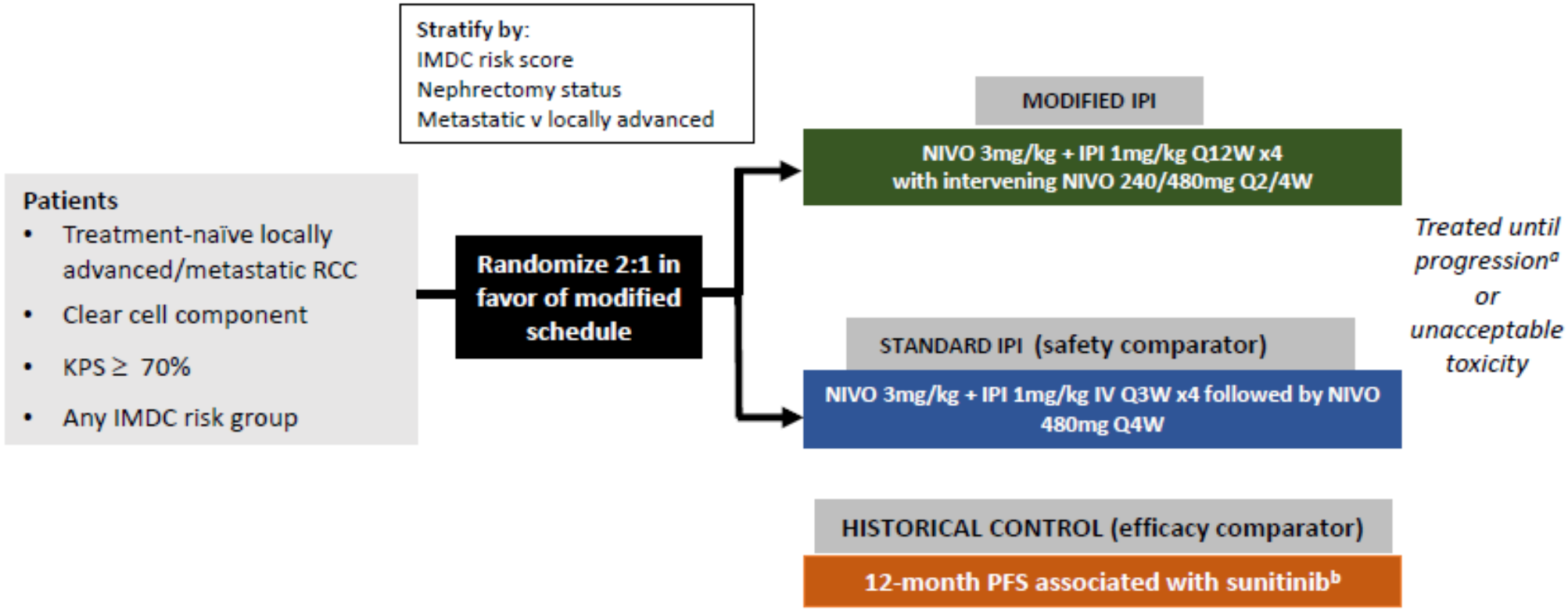
Peer CJ et al J Clin Pharmacol. 2022

What is the best frequence of administration ?

PRISM: Study design

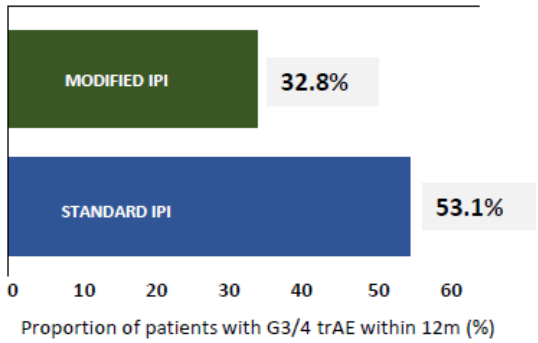


[a] patients were allowed to continue treatment beyond RECIST defined progression if clinically stable and tolerating therapy

[b] Motzer RJ et al. *N Eng J Med* 2013;14:141-8

Q2, 3, 4, 12W – every n weeks; KPS – Karnofsky Performance Status; IMDC – International Metastatic RCC Database Consortium

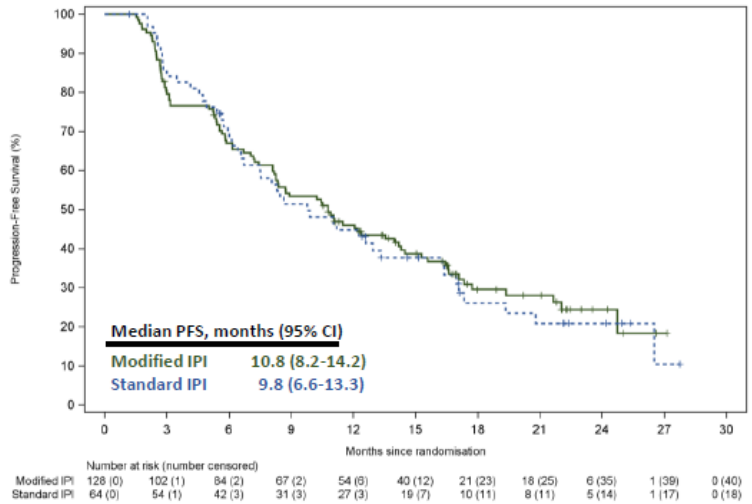
Primary endpoint: Proportion of patients with G3/4 trAE within 12m



Δ -20.3% (90%CI -32.6, -8.0)

OR 0.43 (90% CI 0.25-0.72); p = 0.0075

Progression-free survival: modified ITT

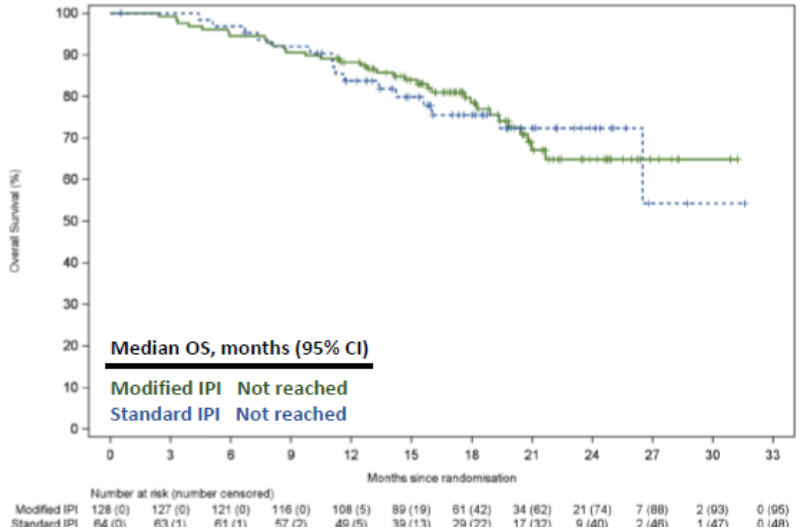


12m PFS rate (90% CI)	
Modified IPI	46.1% (38.6%, 53.2%)
Historical rate	39.7%*

*based on 9m median PFS with sunitinib in COMPARZ trial[a]

The study was not designed to allow formal comparison of PFS between treatment arms, only against historical control.

Overall survival: modified ITT



12m OS rate (95% CI)	
Modified IPI	88.3% (81.2, 92.8)
Standard IPI	83.7% (71.8, 90.1)

Vasudev et al ESMO 2021

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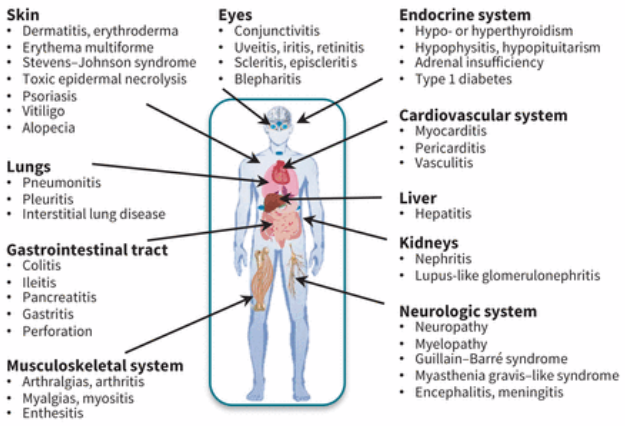
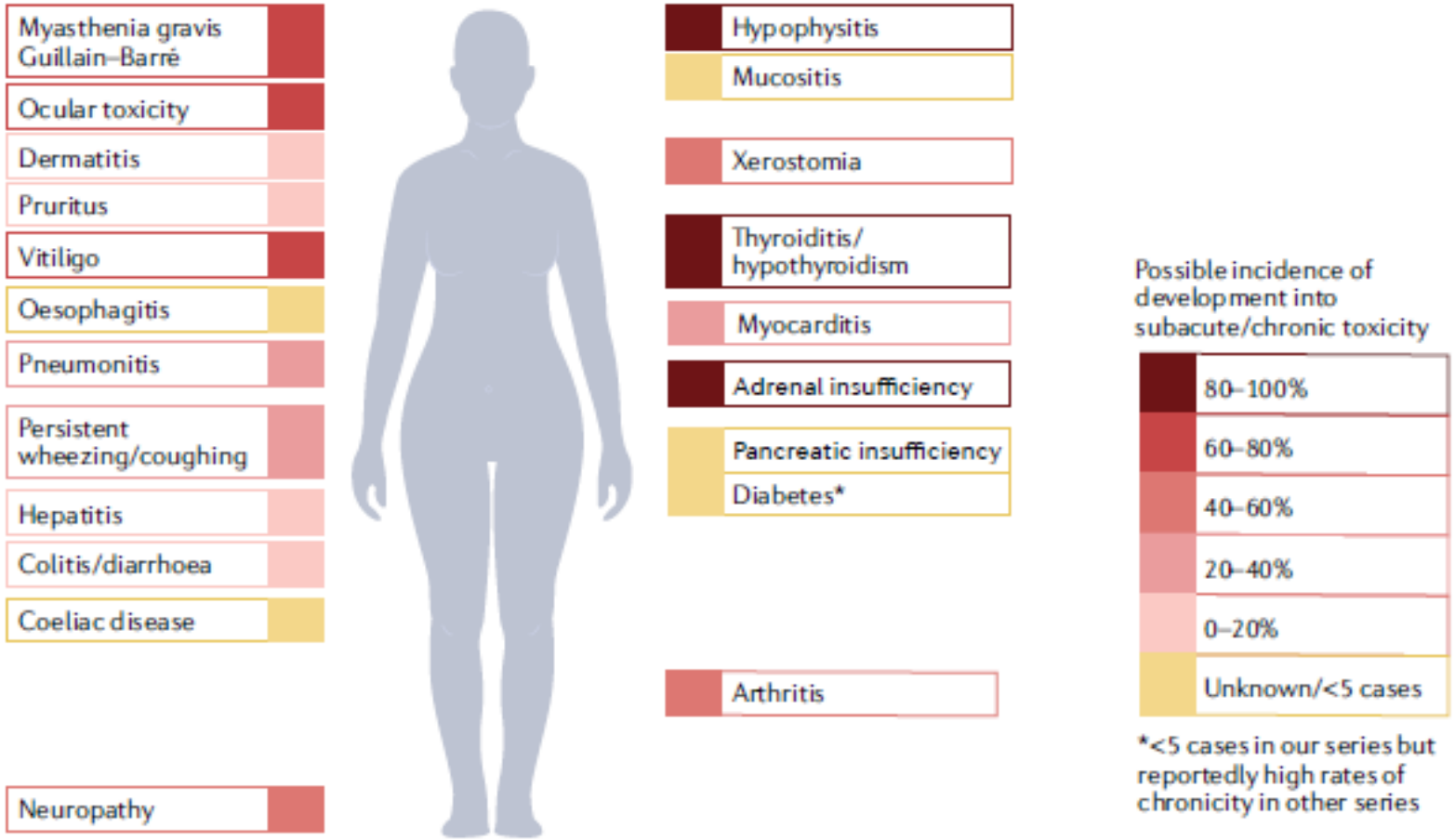
De-escalation: Impact on toxicity

Spectrum of immune related adverse events



Possible frequencies of chronic* immune-checkpoint inhibitor-induced toxicities



*persisting for at least 12 weeks beyond treatment cessation

Douglas B. Johnson et al NAture Reviews | CLInIcAL OncoLogy 2022

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De-escalation: Impact on costs

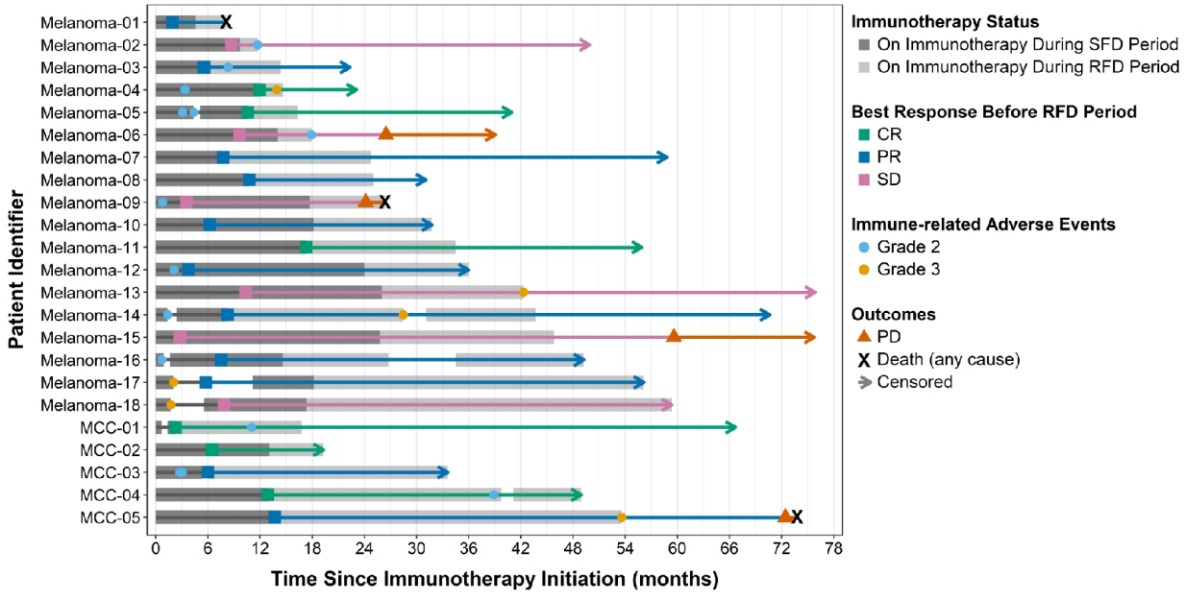
Dose and cost estimations for Nivolumab

Nivolumab	0.1 mg/kg Once Every 2 Weeks	0.3 mg/kg Once Every 2 Weeks	1 mg/kg Once Every 2 Weeks	3 mg/kg Once Every 2 Weeks	240 mg Once Every 2 Weeks
Mg per cycle	8	24	80	240	240
Cost per cycle (USD)	205	615	2,051	6,153	6,153
Cost per year (USD)	4,922	14,766	49,221	147,663	147,663
Relative cost versus std (%)	3	10	33	100	100
Patients treated versus std (No.)	30	10	3	1	1

Renner A et al J of Global Oncol 2019

Extended duration of anti-PD-1 therapy, using reduced frequency dosing, in patients with advanced melanoma and Merkel cell carcinoma

Lisa May Ling Tachiki[1,2], Karly Williams Silva[1], Daniel S Hippe[1,2], Dane Fritzsche[2], Aleksandra Raczka[2], Andrea Perdue[1,2], Julia Majovski[1,2], Alexandra Spallone[1,2], Daniel A Goldstein[3], Paul T Nghiem[1,2], John A Thompson[1,2], Evan Thomas Hall[1,2], Shailender Bhatia[1,2]
[1]University of Washington, Seattle, WA, [2]Fred Hutchinson Cancer Center, Seattle, WA, [3]Rabin Medical Center, Petah Tikva, Israel



	Total savings in 15 patients	Median savings per patient
Drug costs	$1,124,464.63	$71,888.60
Travel costs to patient	$3,317.44	$127.76
Clinic time saved	384 hrs	28 hrs

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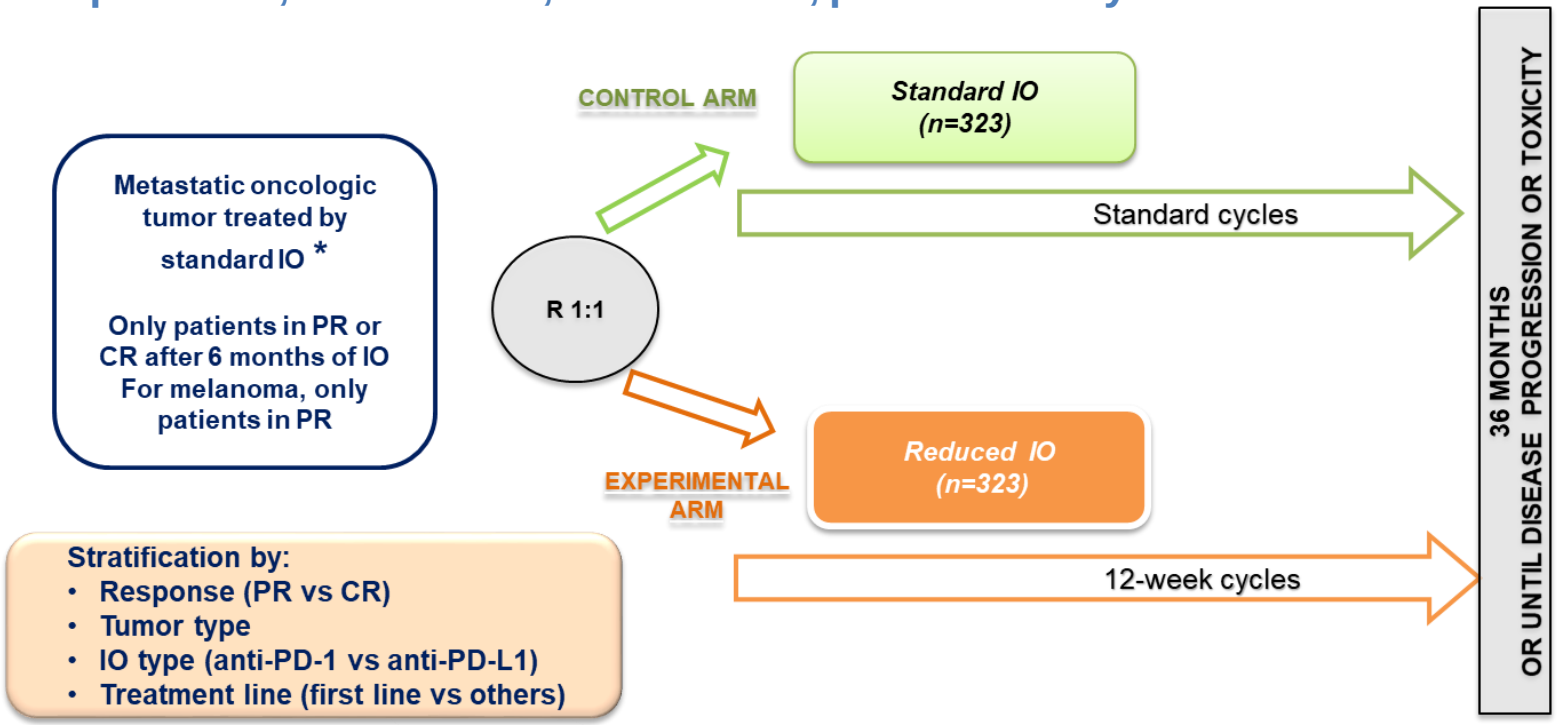
2022 ASCO Annual Meeting | ***Abstract ID:*** *2588*

MOIO: Study design

- **Open label, randomized, multicentric, phase III study**



IO monotherapy or in combination
**Except mRCC patients with IMDC favourable risk treated TKI/IO combination*

INCLUSION PERIOD: **36 months**

TREATMENT DURATION: Until disease progression, unacceptable toxicity, death, patient's choice or investigator's decision

FOLLOW UP PERIOD: 36 months

OVERALL TRIAL ESTIMATED DURATION : 72 months

PHRC 2020

MOIO: Outcome measures

- **Primary objective**
  - The primary endpoint is the hazard ratio of progression-free survival. HR: 1,3 with 5% level of significance and 90% power
- **Secondary objectives**
  - Cost-effectiveness
  - Efficacy evaluation:
    - Immune PFS
    - objective response rate overall survival
    - duration of response at 12 months post-randomization
  - Quality of life
  - Anxiety and fear of relapse using specific questionnaires
  - Safety profile
- **Translationnal study**
  - Immune monitoring: identify immune biomarkers of long-term response allowing IO dose reduction
  - PK study
  - Circulating tumour DNA study

Why academic trials need to investigate different IO administration

- The level of dose is unknown
- The duration is unknown
- The interval of administration is unknown
- Avoiding overtreatment, some patients need less (RC/RP)
- Minimize unnecessary toxicities (some high and chronic)
- The financial burden is high
- Better prediction of treatment effectiveness is needed

THANK YOU FOR YOUR ATTENTION

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