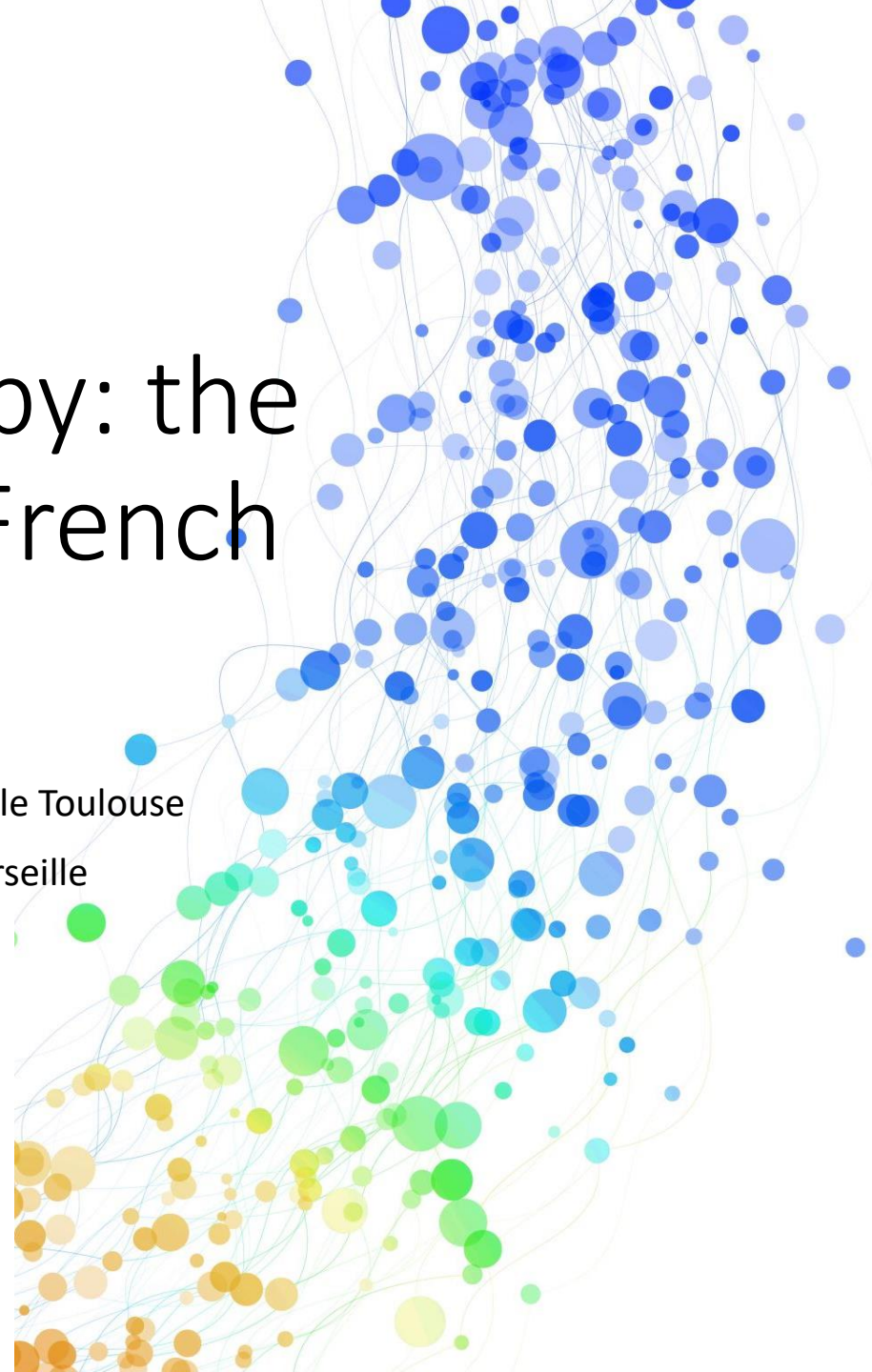
# De-escalating immunotherapy: the example of MOIO phase III French clinical trial

Dr Iphigénie Korakis P.I, Clinical Research Unit-Early Phase Trials, IUCT-Oncopole Toulouse

Dr Gwenaelle Gravis : National Coordinator, Institut Paoli-Calmettes Marseille

Cancer Medicines Forum April 5th 2024



INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

INSTITUT PAOLI-CALMETTES unicancer Marseille

CRCM Centre de Recherche en Cancérologie de Marseille

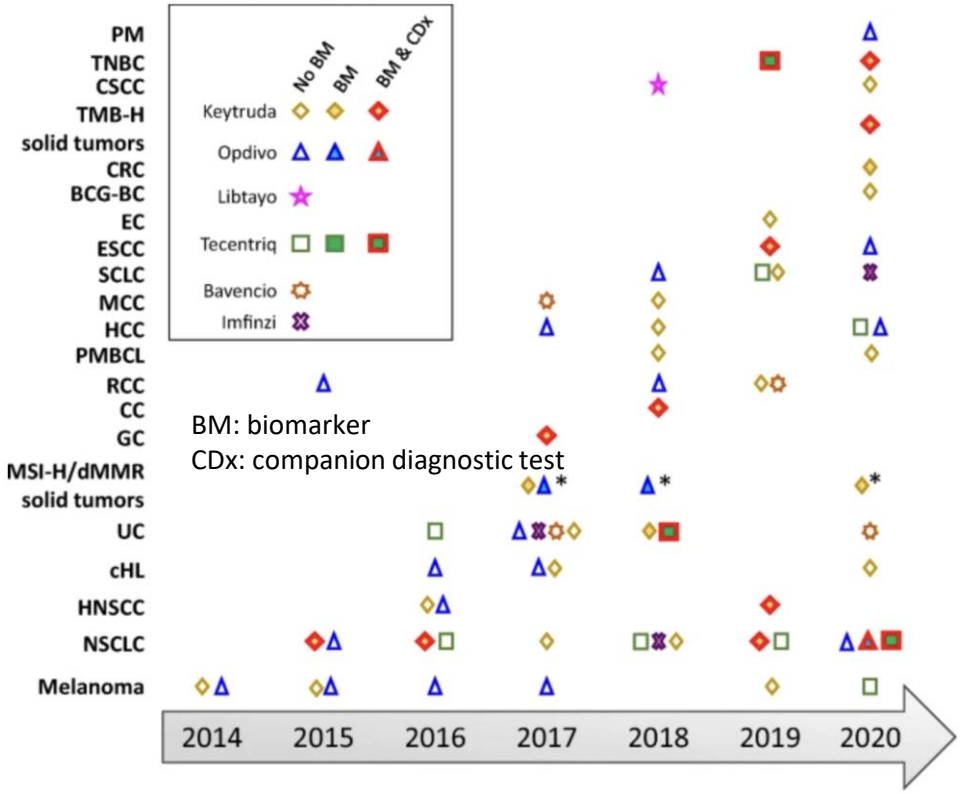
Aix*Marseille université Initiative d'excellence

# Disclosures

- Invited speaker : MSD
- Travel grant : Roche

# Immunotherapy (IO) in the era of personalized medicine

- Over 19 indications in the metastatic setting
- Indications in the neo-adjuvant/adjuvant setting (breast cancer, melanoma, lung).
- Sub-optimal biomarkers to select patients who could benefit (CPS, PDL1, TMB)
- Non-predictable toxicity profile
- Responses sustained after discontinuation
- Cost/time spent at the clinic




FDA approvals for anti PD1/PDL1

*Julianne D. Twomey et al. AAPS Journal 2021*

# PK/PD point of view & commercial aspects

- Maximum tolerated dose was not reached for anti PD1-PDL1
- No dose-response relationship

- PD-1 receptors occupied equally at doses in the 1-10 mg/kg range & persisted up to 80 days, despite falling serum levels of the drug (nivolumab)[1,2]
  - Phase III trials conducted using 3 mg/kg Q2W = 15 times the lowest effective dose.

- For pembrolizumab: PD-1 receptors were occupied at doses of ≥1 mg/kg for at least 21 days.
  - In phase III trials, pembrolizumab was evaluated at 2 mg/kg every 3 weeks, then changed to 200-mg flat dose[3].

[1]*Topalian S.L et al., NEJM 2012*
[2]*Brahmer J.R et al. JCO 2010*
[3] *Patnaik A et al. Clin Cancer Res. 2015;*

# 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) |

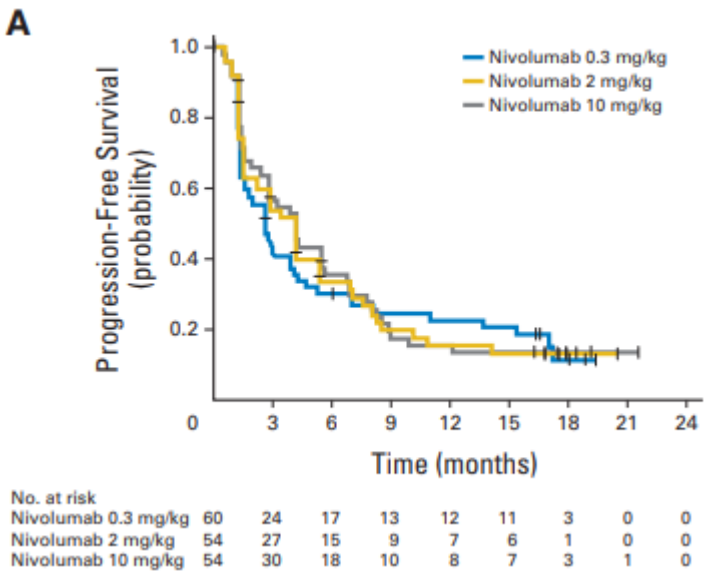
## Nivolumab

| 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) |

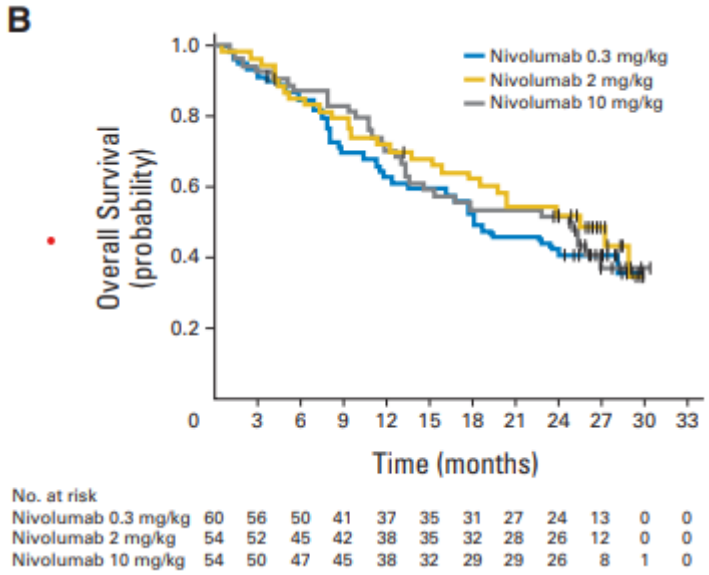
*Renner A et al J of Global Oncol 2019*

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

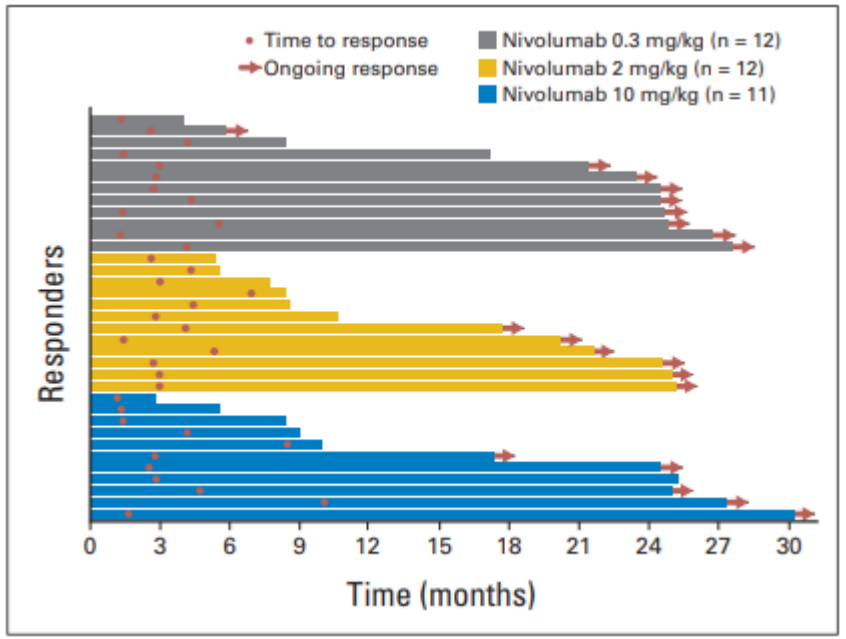
PFS by treatment arm




OS by treatment arm



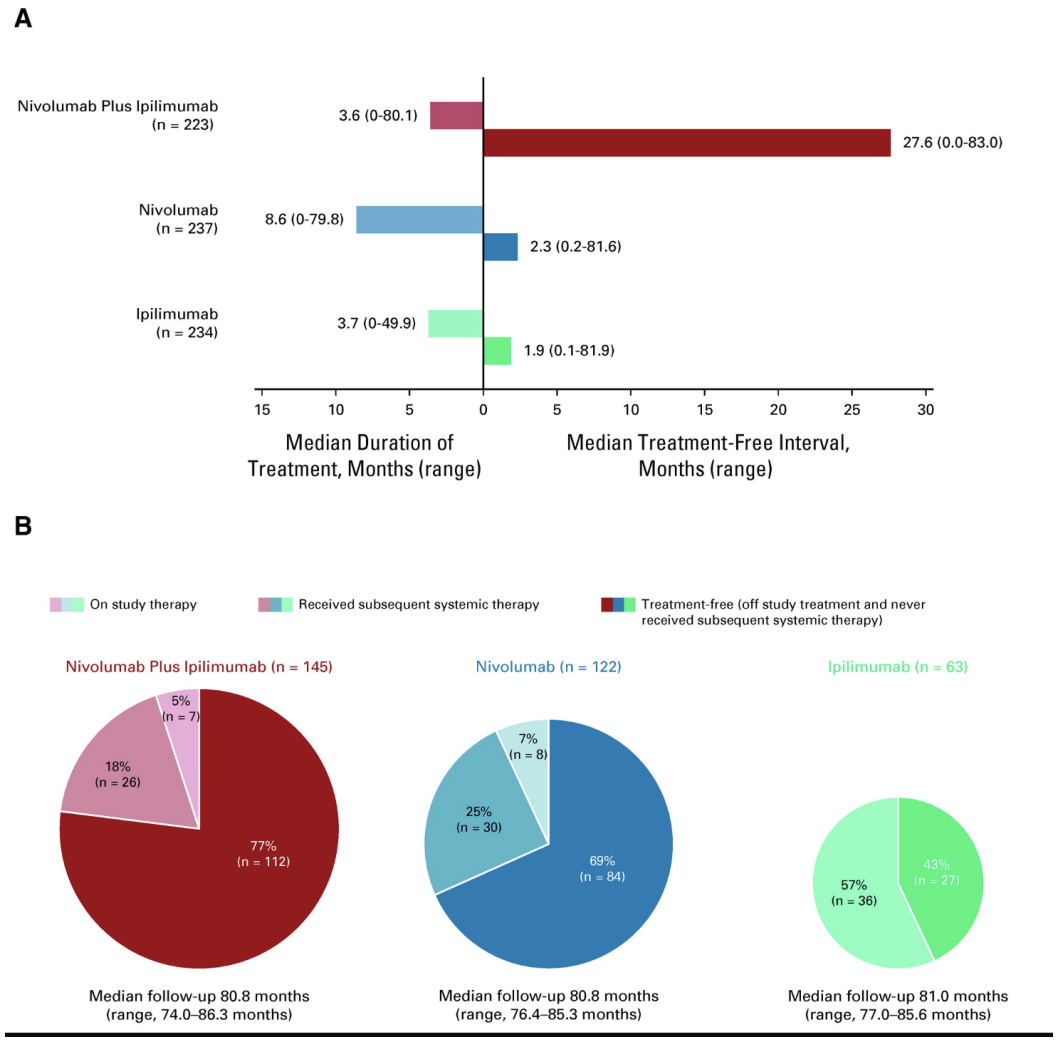

Duration of response by treatment arm




*Motzer, R et al JCO 2014*

# Long-lasting responses: 6.5 year follow-up Checkmate 067 (NIVO / IPI) melanoma

- Median duration of treatment : 3.6 months
- Treatment free interval 27.6 months
- At 6.5 years 77% of the patients were treatment free

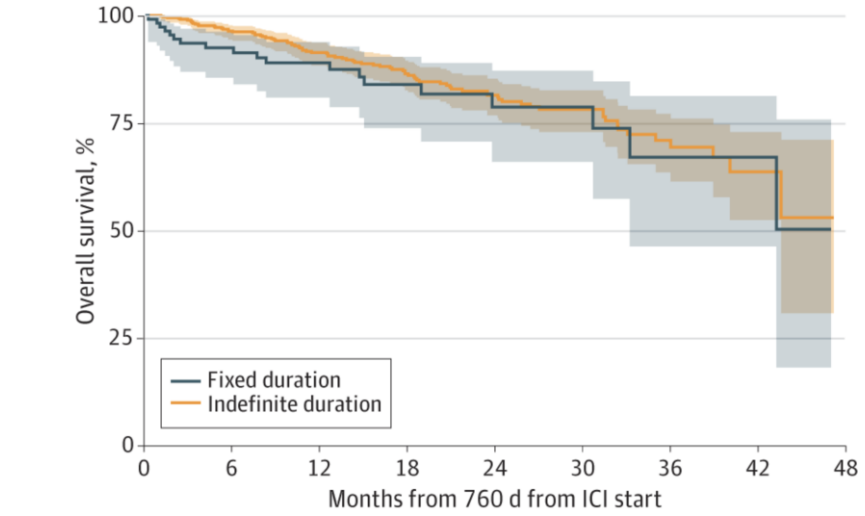



Treatment-free interval and treatment status in patients alive at 6.5 years

*Wolchock et al. JCO 2021*

# How long should we treat patients with IO: NSCLC?

- Retrospective cohort, advanced NSCLC treated by front-line IO
- 706 pts
- Comparison between « fixed duration » = 2 years of IO vs « indefinite duration »
- No statistically significant OS advantage for the indefinite-duration cohort on adjusted analysis




| Survival Characteristic | Fixed duration (n = 113) | Indefinite duration (n = 593) |
|---|---|---|
| **Overall survival probability** | | |
| 3 y (12 mos from 760 d) | 0.89 (0.81-0.94) | 0.91 (0.88-0.94) |
| 4 y (24 mos from 760 d) | 0.79 (0.66-0.87) | 0.81 (0.77-0.85) |
| **Hazard ratio for death** | | |
| Unadjusted | 1.26 (0.77-2.08) | 1 [Reference] |
| *P* value | .36 | |
| Adjusted[a] | 1.33 (0.78-2.25) | 1 [Reference] |
| *P* value | .29 | |

*Lova Sun et al. JAMA 2023*

# How long should we treat patients with IO: 1st line ccRc?

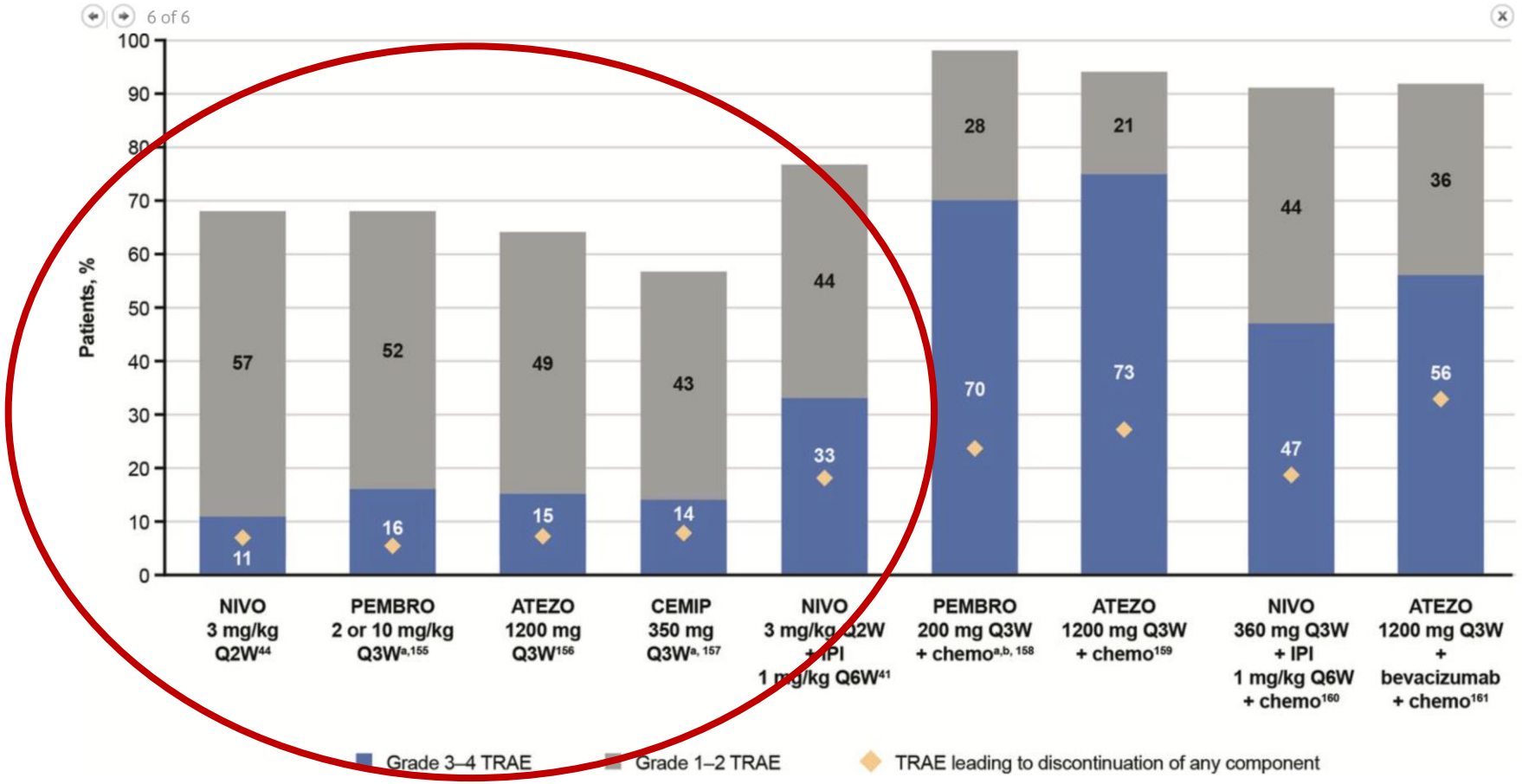
| | Checkmate-214<br>IPI + Nivo (continuously) vs Sutent [1*] | Keynote 426<br>Pembro (2 y) + axi vs Sutent[2] | Checkmate-9eR<br>Nivo (2 y) + Cabo vs Sutent[3] |
|---|---|---|---|
| Median follow –up | 99.1 | 42.8 | 55.6 |
| Median OS<br>HR | 46.7*<br>HR 0.69 | 45,7<br>HR 0.73 | 46.5<br>HR 0.77 |
| Median duration of response | 82.8 | 23.6 | 22 |

**for intermediate and poor risk patients*

*The data on the table is provided for ease of viewing information from different trials. Direct comparison between trials is not intended and should not be inferred*


[1]*Motzer RJ et al Cancer 2022, updated at ASCO GU 2024*
[2]*Rini B et al JCO 2021,*
[3] *Nizar M. Tannir, abstract 363 ASCO GU 2024*

# Toxicity during treatment




***Safety profiles of IO therapies in patients with non-small cell lung cancer (cross-trial comparisons cannot be made due to differences in dosing and methods used to assess TRAEs across studies).***

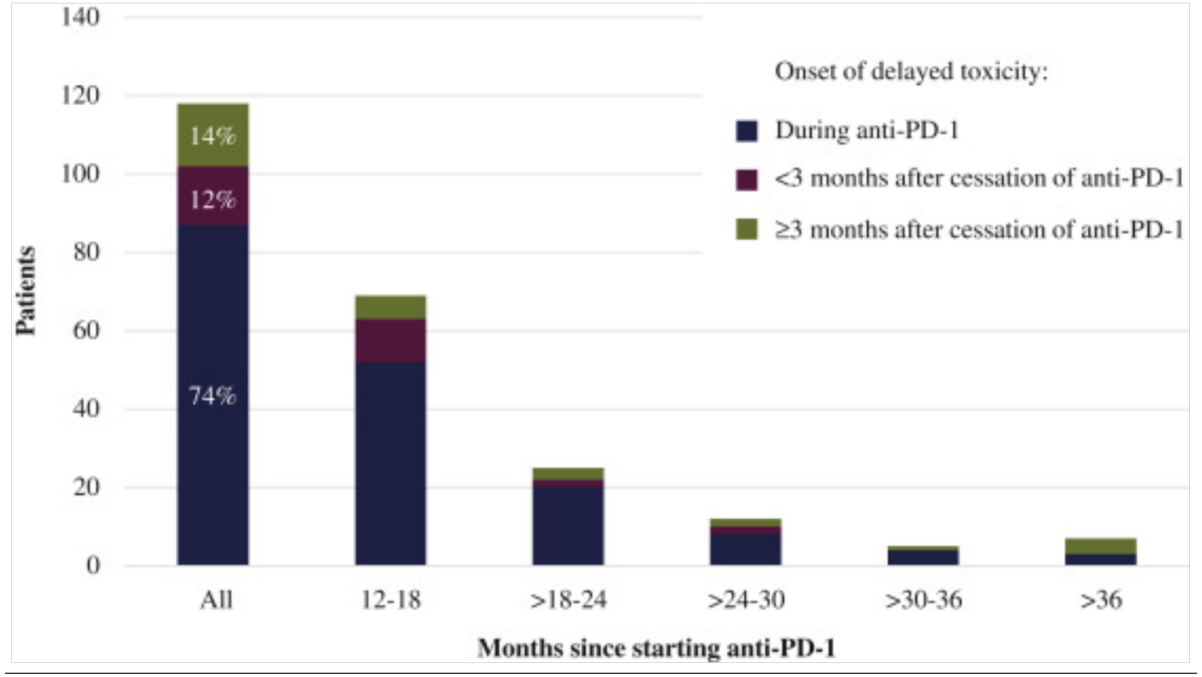
[a]Data for grade 3–4 TRAEs also includes grade 5 TRAEs.
[b]Represents total adverse events, not just TRAEs.
ATEZO, atezolizumab; CEMIP, cemiplimab; chemo, chemotherapy; ICI, immune checkpoint inhibitor; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; QxW, every x weeks; TRAE, treatment-related adverse event.



*Michielin O, Lalani A, Robert C, et al. Journal for ImmunoTherapy of Cancer 2022*

# Delayed immune related AEs (irAEs)

- ❑ Multicentric restrospective analysis (20 centers) melanoma pts treated with anti PD1 mono or CTLA4 combo
- ❑ 118 pts developed a total of 140 delayed irAEs
- ❑ Incidence of 5.3% (95% confidence interval 4.0-6.9, 53/999 patients at sites with available data).
- ❑ Median onset of delayed irAE 16 months (range 12-53 months).

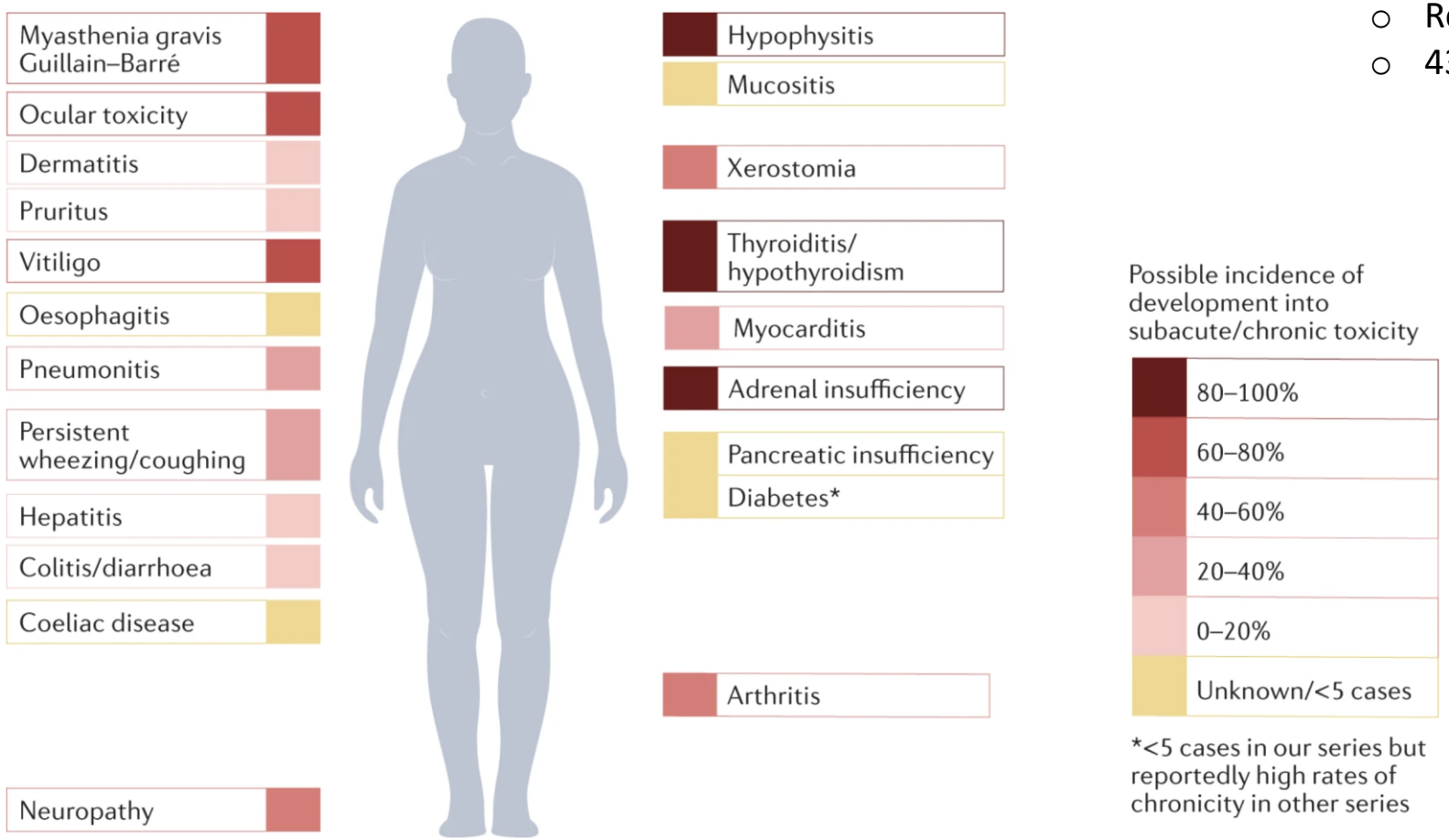



Delayed ≠ mild

- 55 grade ≥ III
- Requiring steroids ( 80 pts) +/- other immunesuppressive agent
- 2 deaths (encephalitis, multiple organ related irAE)

*Owen CN et al. Ann Oncol. 2021*

# Chronic toxicity persisting >12 weeks after discontinuation

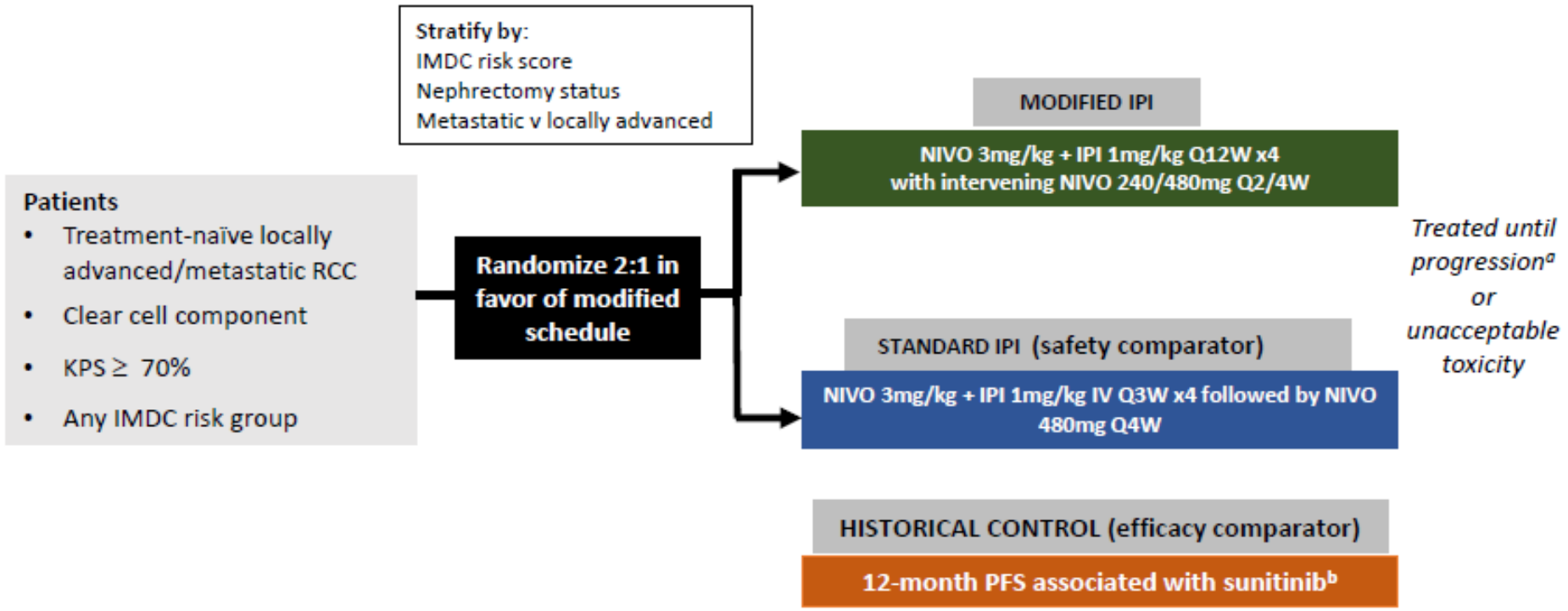



- Retrospective study 387 pts, melanoma
- 43% pts experienced chronic toxicity

Johnson, D.B. et al, JAMA Oncol. 2021

# Dose de-escalation to reduce toxicity

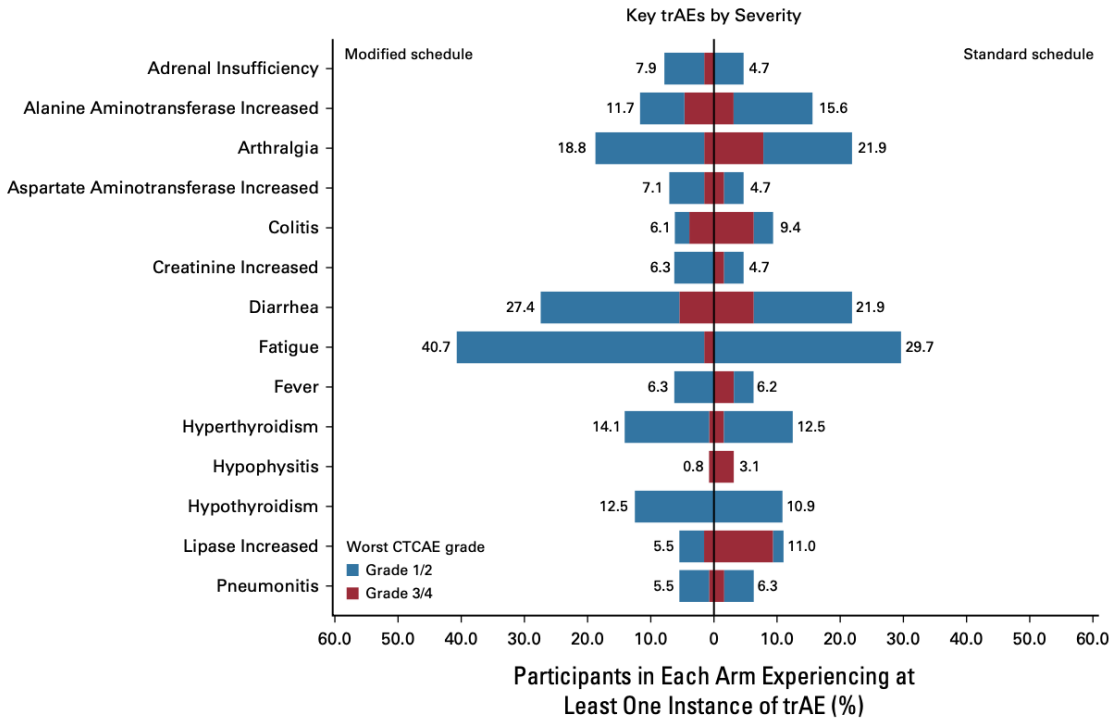
## PRISM: Study design




[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

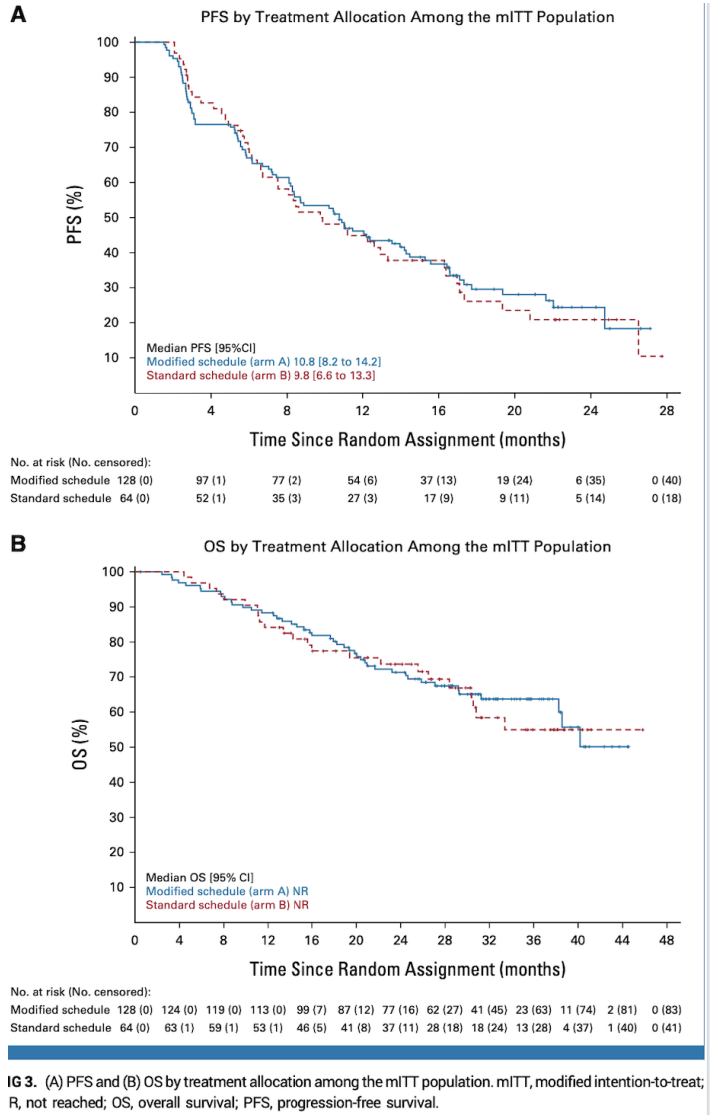
# Primary objective: decrease in toxicity

- Grade ≥ 3 AEs 32.8% in the modified schedule v 53.1% odds ratio, 0.43 [90% CI, 0.25 to 0.72]; P = 0.0075




# Secondary objective: PFS, OS

N=195, 2 year- follow-up



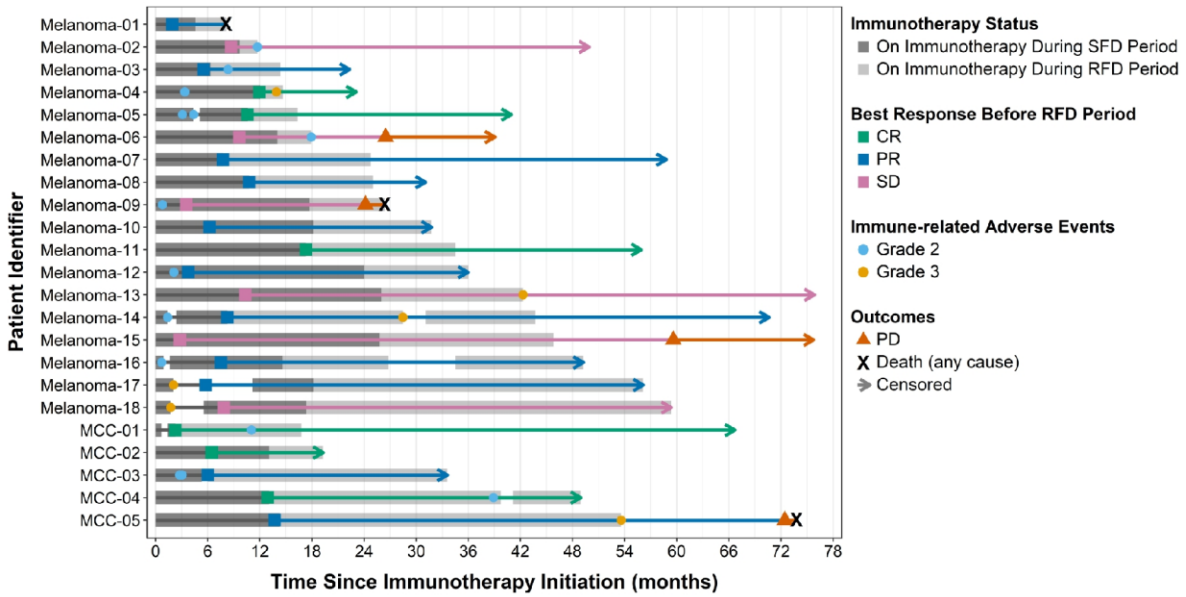

IG 3. (A) PFS and (B) OS by treatment allocation among the mITT population. mITT, modified intention-to-treat; R, not reached; OS, overall survival; PFS, progression-free survival.



Vasudev N et al., JCO 2023

# 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 |

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

# Current trials with de-escalation strategies

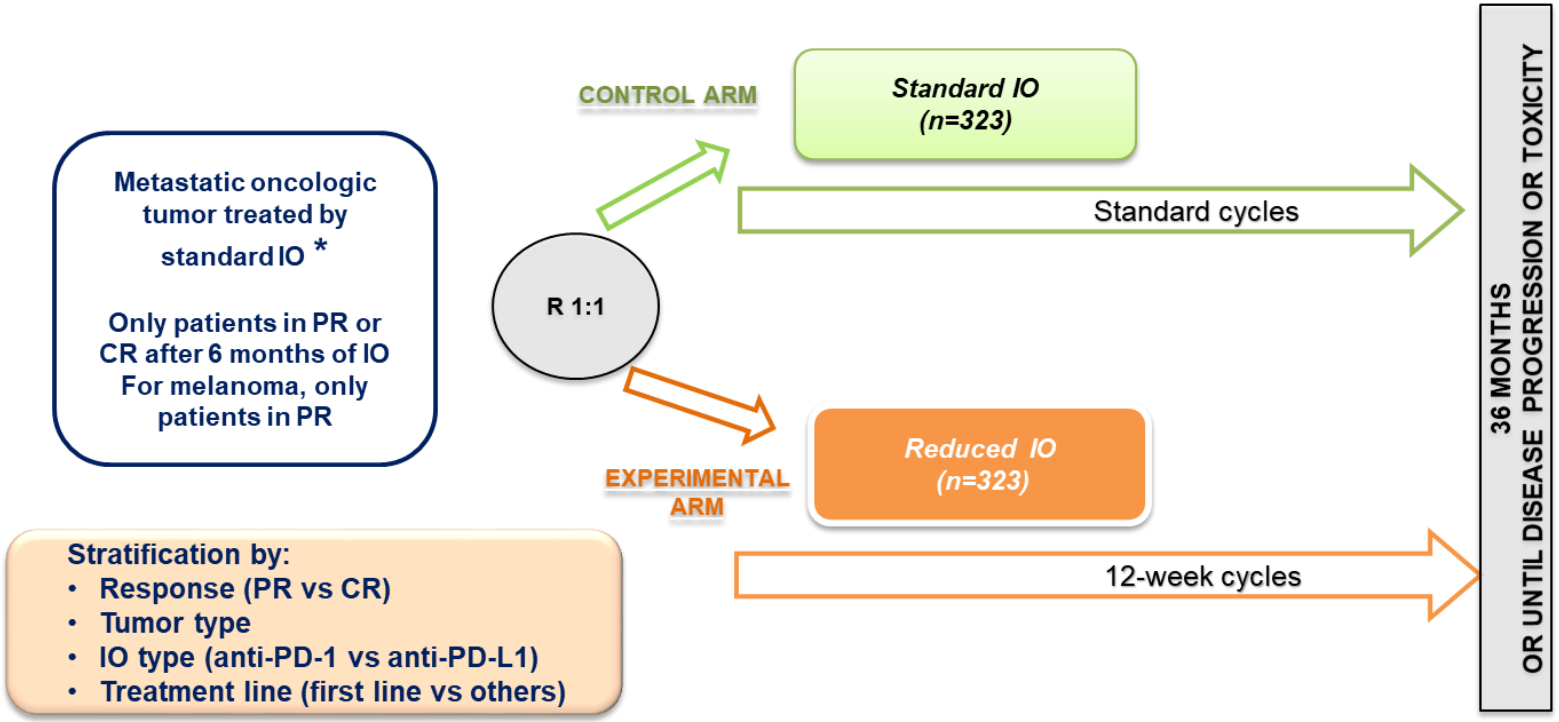
| Type | Trial | Indication | Design | Planned *n* | Country | Registration number |
|---|---|---|---|---|---|---|
| Early cessation | DANTE | Melanoma | Randomized between stop at 1 year vs continue to 2 years in responding patients | 1,208 | UK | ISRCTN15837212 |
| | STOP-GAP | Melanoma | Randomized between stop at response (restart at progression) vs continuous treatment to 2 years | 614 | Canada | NCT02821013 |
| | SAFE STOP | Melanoma | Stop on complete response, single-arm cohort, PFS at 2 years | 200 | The Netherlands | NL7293 (NTR7502) |
| | PET-STOP | Melanoma | Stop on PET-CR, single-arm cohort, PFS | 150 | USA | NCT04462406 |
| | SAVE | NSCLC | ICI after chemotherapy randomized to stop at 1 year vs continuation | 216 | Japan | JCOG1701 |
| | STOP | Renal cell carcinoma | ICI responding at 1 year randomized to stop at 1 year vs continuation | 216 | Japan | JCOG1905 |
| | DIAL | NSCLC | Randomized between 6 months and 2 years of pembrolizumab after chemotherapy | 114 | France | NCT05255302 |
| | OPTIMICE-pCR | TNBC | Observation vs adjuvant ICI after chemo- immunotherapy combination | 1,295 | USA | TBC |
| Extended interval | NCT04295863 | Any | 1x vs 2x SOC interval | 264 | USA | NCT04295863 |
| | REFINE | Basket (renal) | MAMS initially 1x vs 2x SOC interval expanding to 3x | 160 | UK | NCT04913025 |
| | MOIO | Any | SOC vs 12 weeks | 656 | France | NCT05078047 |
| | REFINE-Lung | NSCLC | MAMS initially pembrolizumab 6 vs 12 weeks | 1,750 | UK | NCT05085028 |
| | NCT04032418 | NSCLC | Pembrolizumab 3 vs 12 weeks after combination chemotherapy | 152 | USA | NCT04032418 |
| | PULSE | NSCLC | Pembrolizumab 3 vs 6 weeks after combination chemotherapy | 1,100 | France | TBC |
| Low dose | NVALT-30 Dedication | NSCLC | Randomized between pembrolizumab and pembrolizumab 25% dose reduction | 750 | The Netherlands | EudraCT 2020-000493-15 |
| | CTRI-DELLI | HNSCC | Low-dose nivolumab (20 mg twice weekly) vs chemotherapy | TBC | India | CTRI/2020/02/023441 |

ICI, immune checkpoint inhibitors;
MAMS, multi-arm, multi-stage;
SOC, standard of care;
TBC, to be confirmed

*Ian Hirsch et al., Nature Medicine 2022*

# 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**

*Gravis G et al., BMC cancer 2023*
*PHRC 2020*

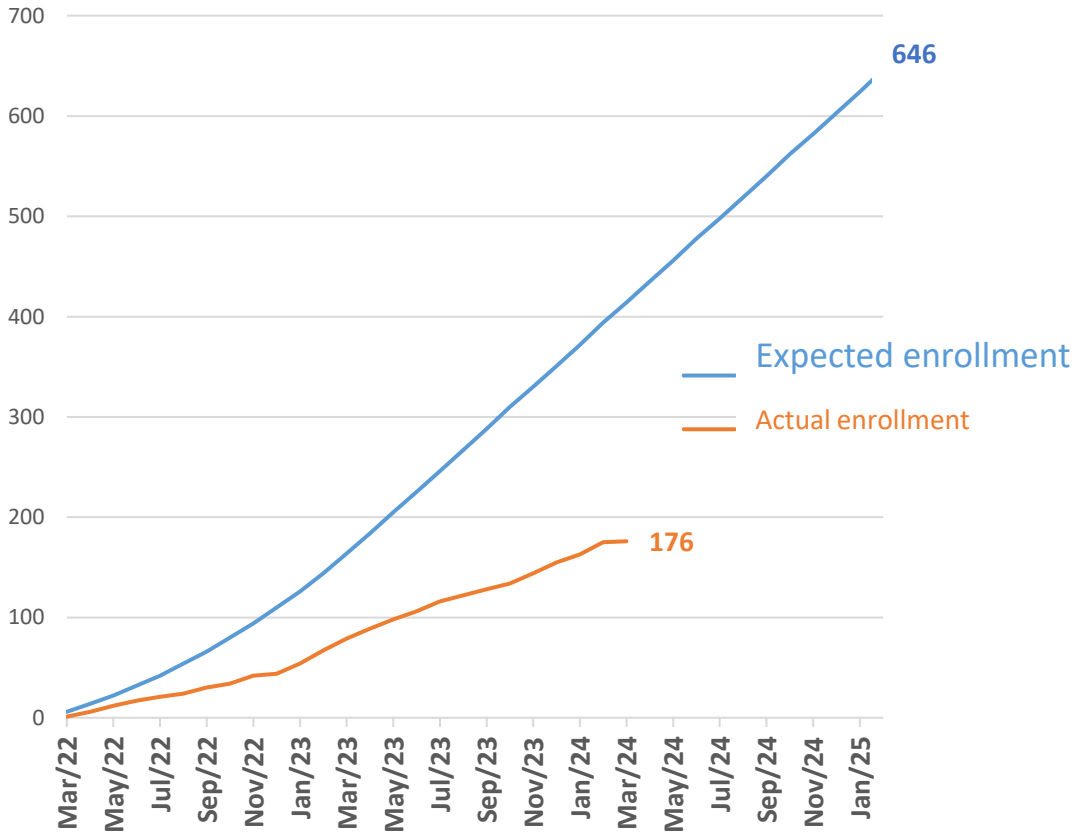
# MOIO: Outcome measures

- **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
- **Translational study**
  - Immune monitoring: identify immune biomarkers of long-term response allowing IO dose reduction
  - PK study
  - Circulating tumor DNA study

*Gravis G et al., BMC cancer 2023*
*PHRC 2020*

# MOIO: recruitment status

- 176 pts enrolled in 31 centres:
  - 87 pts in the reduced frequency IO arm
  - 89 pts in the standard IO arm

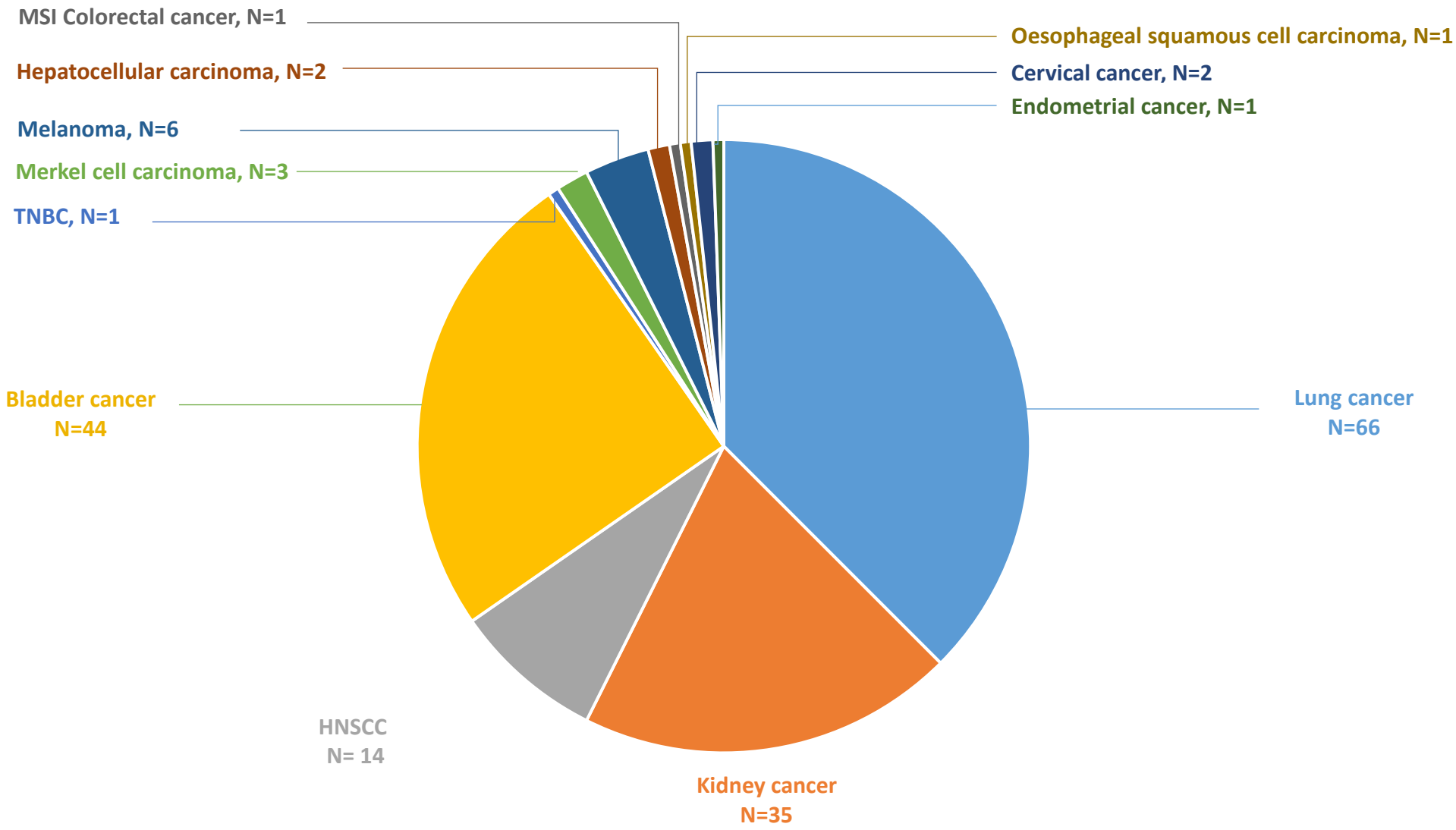



Current recruitment rate : 10-11 pts/month

** Updated inclusion rates 07/03/2024*

Immuno-Oncology Group unicancer

# MOIO: recruitment status




Immuno-Oncology Group
unicancer

** Updated inclusions 07/03/2024*

# Why academic trials need to investigate different IO administration?

- The dose is unknown
- The duration is unknown
- The interval of administration is unknown
- Avoiding overtreatment and minimize unnecessary toxicities (some high and chronic)
- The financial burden is high
- Better prediction of treatment effectiveness is needed