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Checkpoints inhibitors (CPIs) in the early setting of solid cancers : Promising findings and perspectives -

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ULB iris

OUTLINE

- **Rationale for immunotherapy use in the early setting**
- Adjuvant checkpoint blockade
- Neoadjuvant checkpoint blockade
- Perspectives for development of CPis in the early setting
- Conclusions

Introduction

- CPIs transformed the treatment of patients with advanced cancers
- Several drugs approved for treatment across many subtypes
- **Next logical steps :** Explore the potential of CPis, such as PD-1/PD-L1 inhibitors, in a curative setting to improve patients outcome

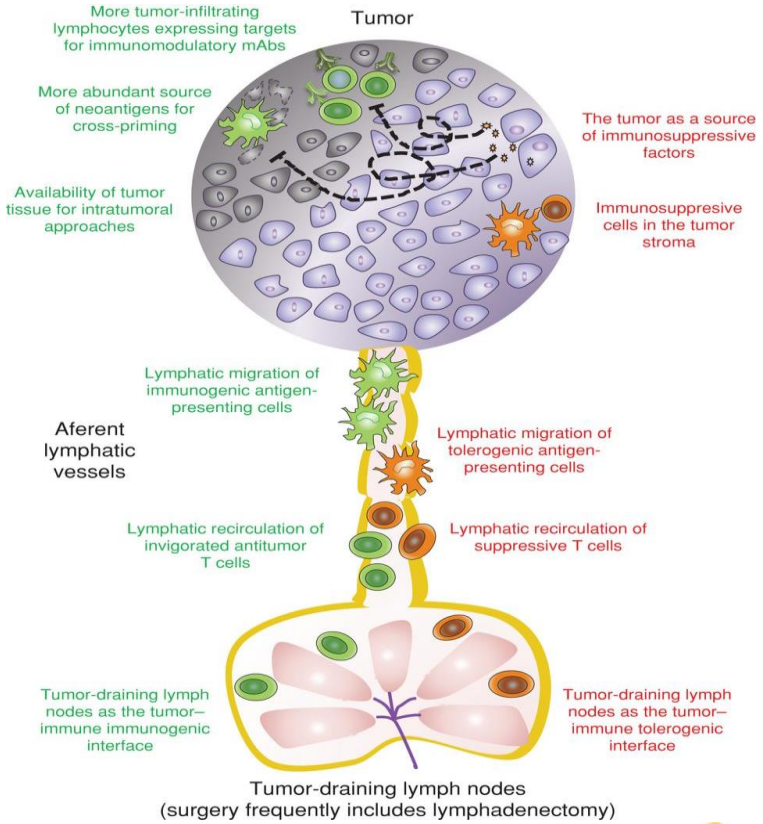
Objectives of systemic treatments in the early setting

- Improve surgical outcomes (neoadjuvant setting)
- Reduce the risk of distant recurrence
- Eradication of micrometastases
- Increase response to definitive radiotherapy (cRT)

Hypothesis: Immunotherapy serves as a primer for systemic antitumor responses, activating tumor-specific T cells that seek out distant micrometastases.

RATIONALE FOR NEOADJUVANT vs ADJUVANT IMMUNOTHERAPY

- **Presence of TiLs** that are often expressing the targets for the immunomodulatory mAbs
- **Abundance of tumor antigens available for cross-priming** at the time of immunotherapy.
- Recirculation of **reinvigorated T lymphocytes** out of the primary tumor infiltrate to tackle micrometastatic disease.
- **Preclinical studies - Short course of neoadjuvant immunotherapy significantly improved survival** compared to adjuvant administration



Ignacio Melero et al. Cancer Discov 2016;6:1312-1314

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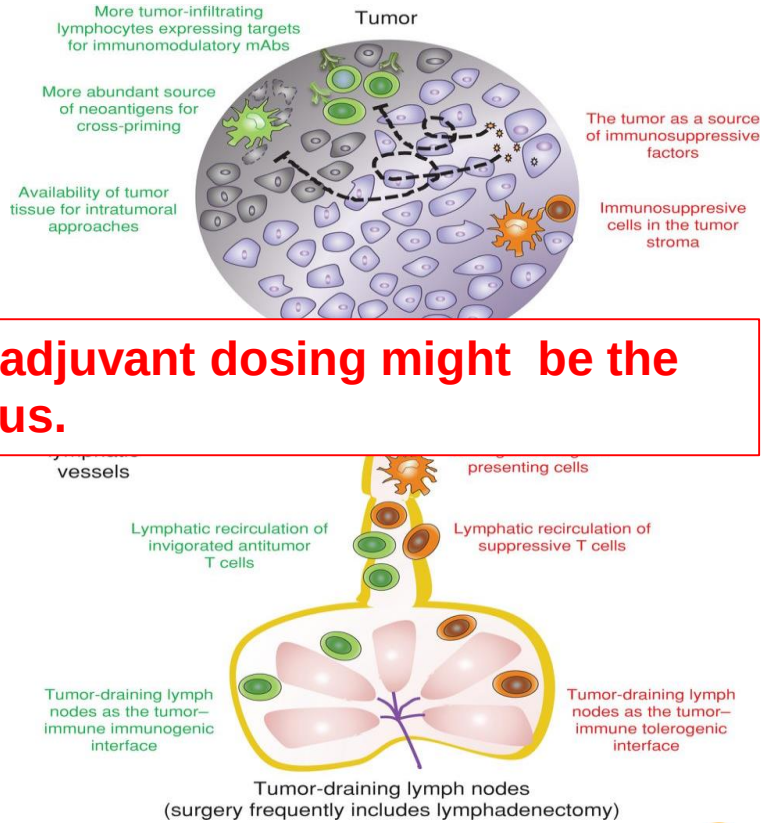
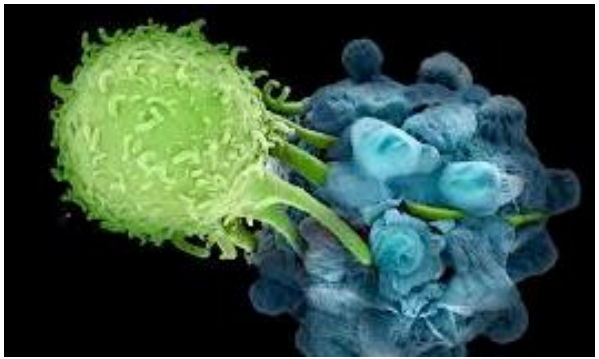


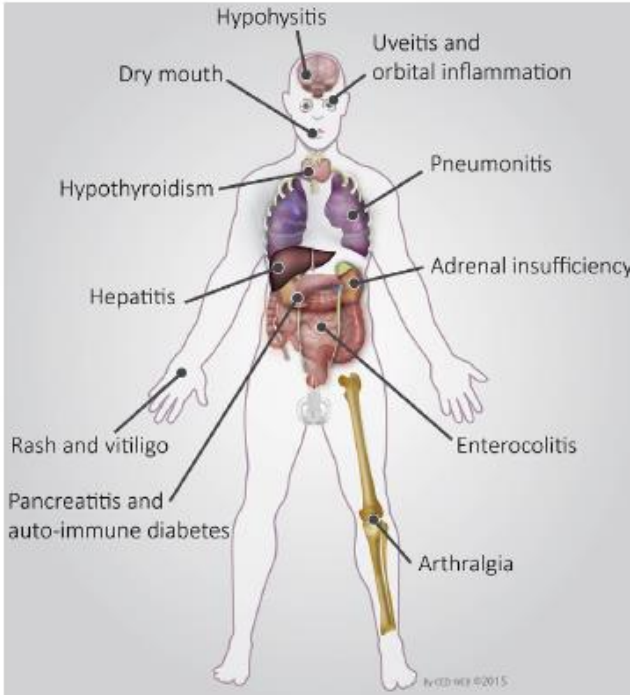
Strategies combining both neoadjuvant and adjuvant dosing might be the most efficacious.

Ignacio Melero et al. Cancer Discov 2016;6:1312-1314

How to best combine CPIs with surgery to reduce disease recurrence ?



What is the acceptable degree of toxicity in a curative setting ?



Michot JM et al., EJC 2015

OUTLINE

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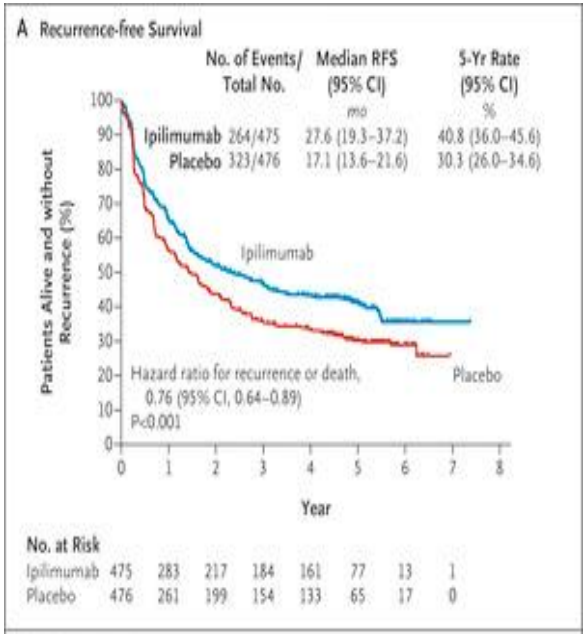
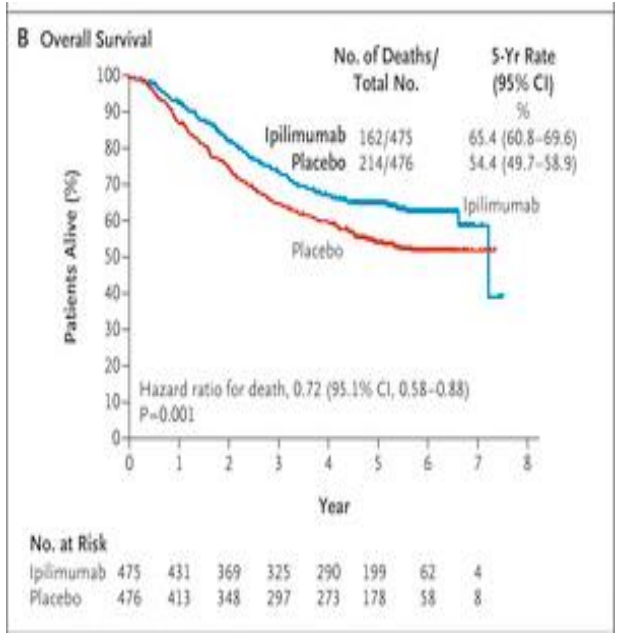
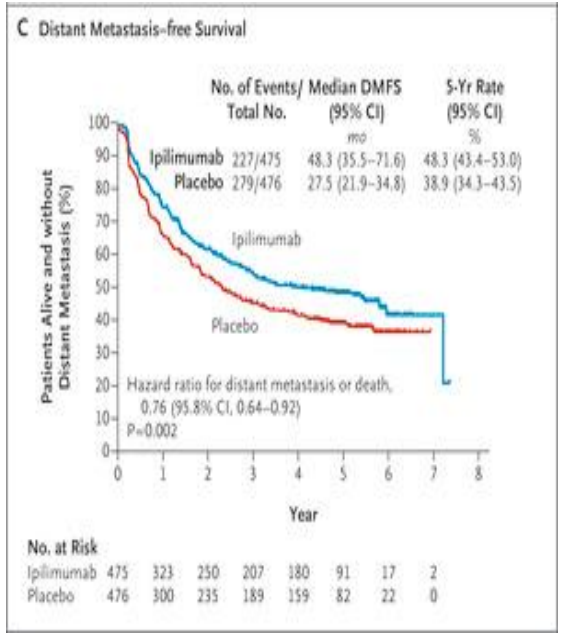
Melanoma: NCT00636168

ORIGINAL ARTICLE

Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy







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Eggermont et al. NEJM 2016

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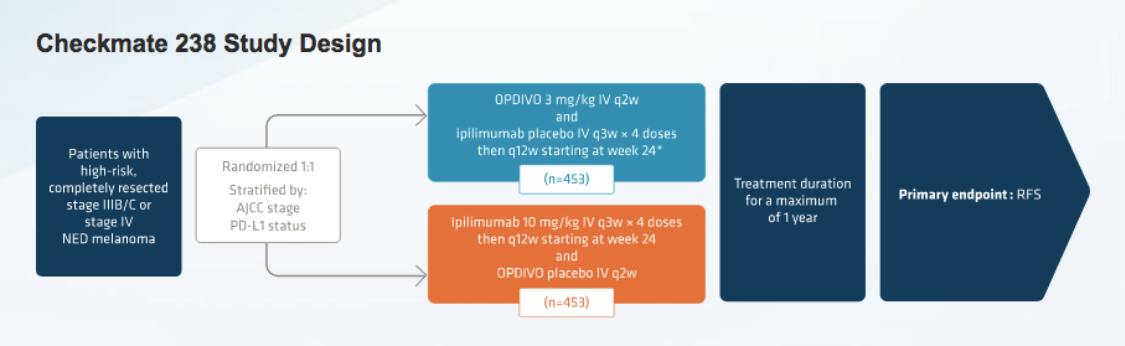
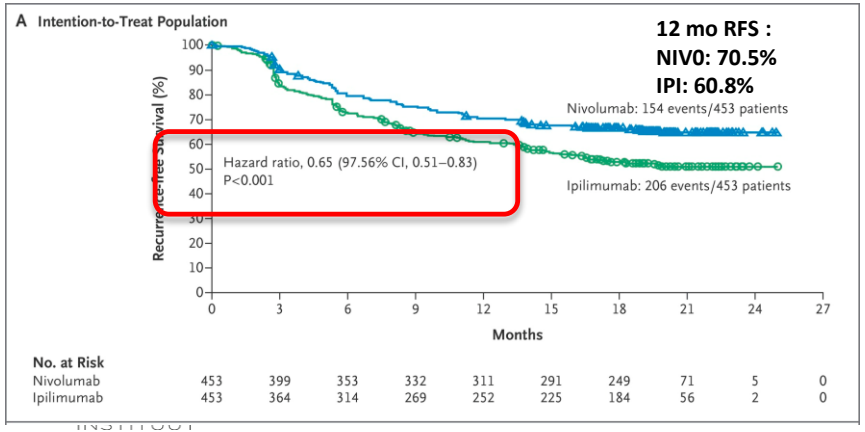
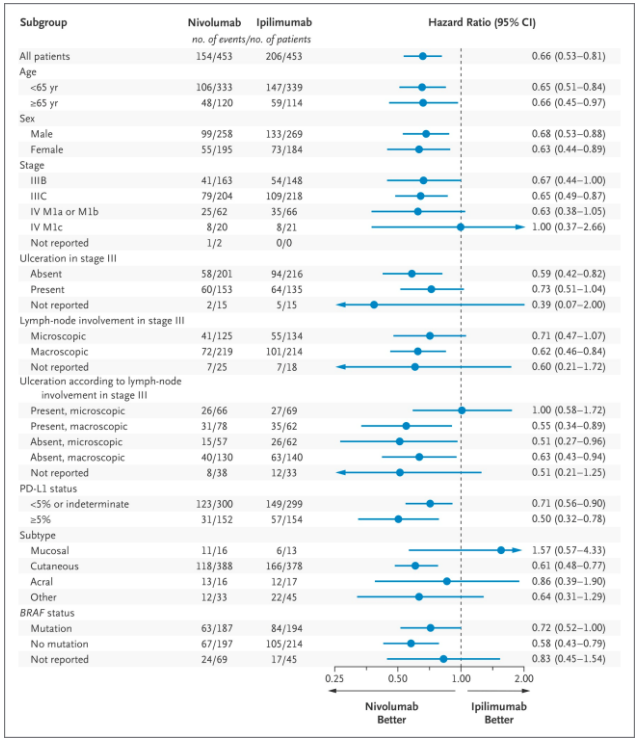
Melanoma: Checkmate 238







TRAES grade ¾
- NIVO: 14.4% (ttt discontinuation 9.7%)
- IPI: 45.9% (ttt discontinuation 42.6%)
-Two deaths (0.4%) related to ipilimumab

Weber et al. NEJM 2018

Melanoma: KEYNOTE 054

Phase III multicenter study

Median FU 15 months

Eligibility criteria

Cutaneous Melanoma Stage III (High risk) after surgery (n=1019)

1:1

R

Pembrolizumab 200mg IV Q3W for up to 12 months

Placebo IV Q3W for up to 12 months

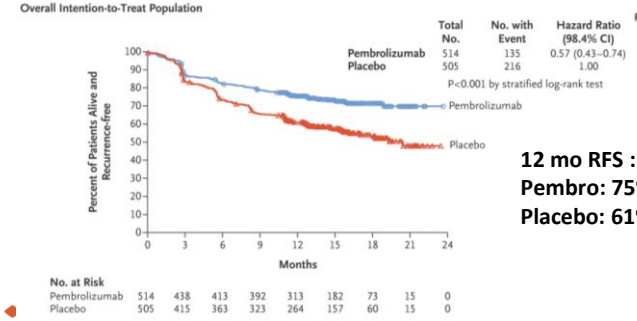
Relapse > 6 months

Pembrolizumab 200mg IV Q3W untill PD or relapse for up to 24 months

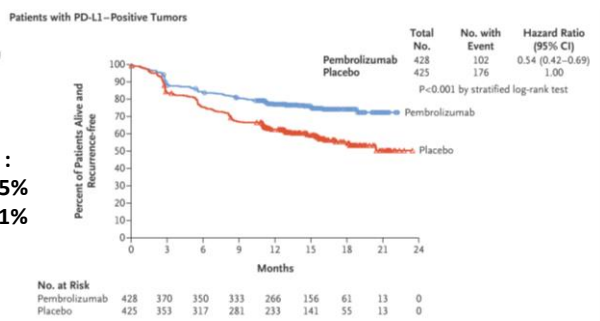
Primary endpoints: RFS all comers and in PDL1 + (n=853)

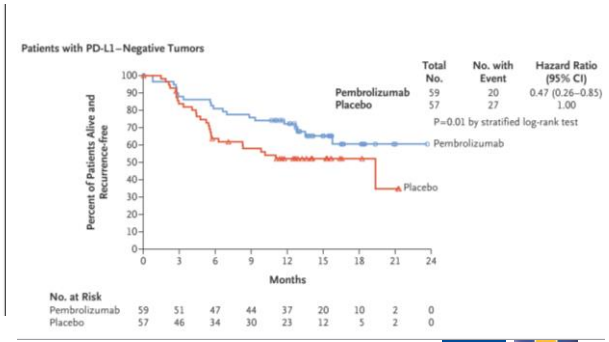
Secondary endpoints; Safety

TRAEs grade 3/5:
-14.7% pembrolizumab group
-3.4% in the placebo group.
-one pembrolizumab-related death due to myositis.



12 mo RFS :
Pembro: 75%
Placebo: 61%





Eggermont et al. NEJM 2018

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NSCLC: PACIFIC trial

Eligibility criteria

Unresecable Stage III NSCLC after definitive platinium-based cCRT (≥2 cycles)
All comers (n=713)

2:1

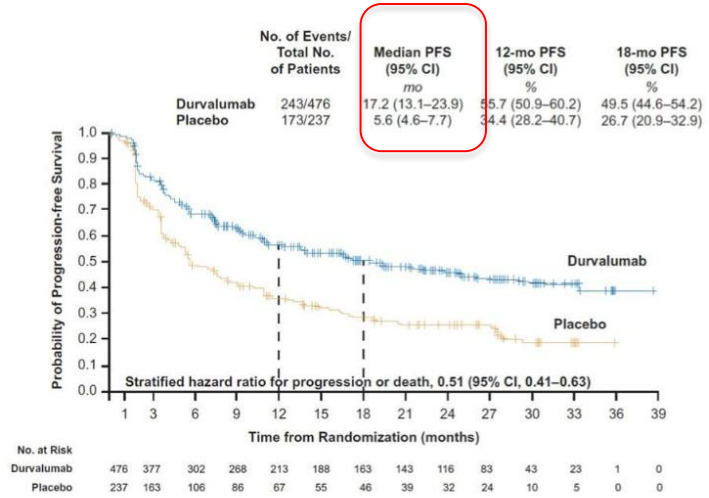
R

Durvalumab 10mg/kg Q2W for up to 12 months

Placebo Q2W for up to 12 months

1-42 days

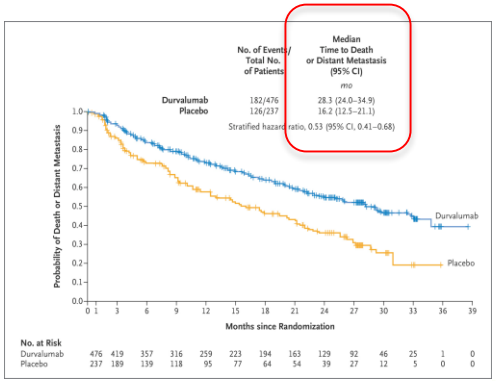
Phase III multicenter study



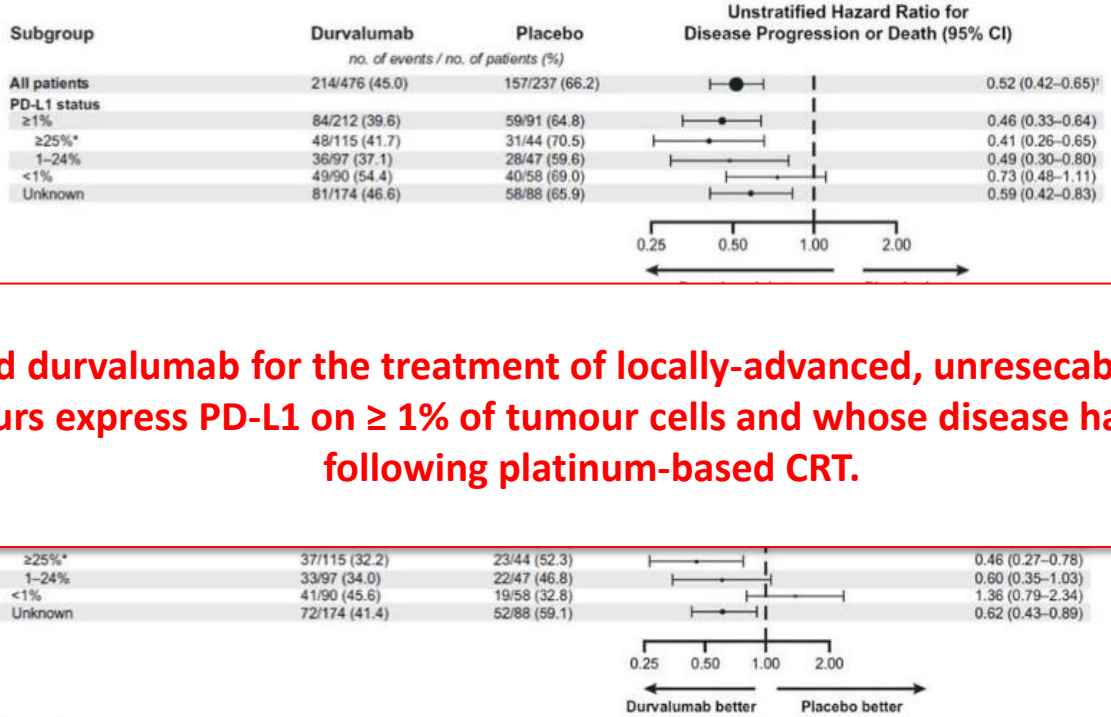
Primary endpoints: PFS, OS

Secondary endpoints; ORR, DoR and TTDM, PFS2 by investigator, safety, PROs

	All patients[1]		PD-L1 TC ≥1%		PD-L1 TC <1%	
AE category n (%)	Durvalumab (N=475)	Placebo (N=234)	Durvalumab (N=213)	Placebo (N=90)	Durvalumab (N=91)	Placebo (N=57)
Any-grade all-causality AEs, n (%)	460 (96.8)	222 (94.9)	205 (96.2)	83 (92.2)	88 (96.7)	54 (94.7)
Grade 3/4	145 (30.5)	61 (26.1)	67 (31.5)	21 (23.3)	26 (28.6)	12 (21.1)
Outcome of death	21 (4.4)	15 (6.4)	8 (3.8)	4 (4.4)	3 (3.3)	4 (7.0)
Leading to discontinuation	73 (15.4)	23 (9.8)	36 (16.9)	5 (5.6)	10 (11.0)	10 (17.5)
SAEs	138 (29.1)	54 (23.1)	64 (30.0)	18 (20.0)	20 (22.0)	11 (19.3)
AESIs	317 (66.7)	115 (49.1)	146 (68.5)	39 (43.3)	62 (68.1)	30 (52.6)



NSCLC: PACIFIC - Survival data by PDL1 status



Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events / no. of patients (%)		
All patients	214/476 (45.0)	157/237 (66.2)	0.52 (0.42–0.65)†
PD-L1 status			
≥1%	84/212 (39.6)	59/91 (64.8)	0.46 (0.33–0.64)
≥25%*	48/115 (41.7)	31/44 (70.5)	0.41 (0.26–0.65)
1–24%	36/97 (37.1)	28/47 (59.6)	0.49 (0.30–0.80)
<1%	49/90 (54.4)	40/58 (69.0)	0.73 (0.48–1.11)
Unknown	81/174 (46.6)	58/88 (65.9)	0.59 (0.42–0.83)
≥25%*	37/115 (32.2)	23/44 (52.3)	0.46 (0.27–0.78)
1–24%	33/97 (34.0)	22/47 (46.8)	0.60 (0.35–1.03)
<1%	41/90 (45.6)	19/58 (32.8)	1.36 (0.79–2.34)
Unknown	72/174 (41.4)	52/88 (59.1)	0.62 (0.43–0.89)

0.25 0.50 1.00 2.00

Durvalumab better Placebo better

*Pre-specified subgroup.

EMA approved durvalumab for the treatment of locally-advanced, unresecable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based CRT.

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Early Evidence of Neoadjuvant PD-1 Blockade in NSCLC

Study name	Phase	IMP	n=	Primary Endpoint(s)	TRAEs grade 3-5 n=	Delay / No surgery n=	mCR	Potential Biomarkers
NCT 02259621	Pilot study	Nivolumab	21	Safety and feasibility.	1 (4%)	0	mPR 45%	TMB Neoantigen-specific T-cell clones
NEOSTAR	II randomized	Nivolumab/Ipilimumab	36	mPR	3 (8%)	5	N/NI 26% N 25% NI 27%	T cell infiltration
LCMC 3	II single-arm	Atezolizumab	45	mPR	6 (3%)	0	22% (10%) 3 pCR	No mPR in PDL1- TC0/IC0
NADIM STUDY-SLCG	II single-arm open-label randomized	Nivolumab 360mg IV Carbo AUC6/Taxol 200mg/m2 Q3W 12mo adjuvant Nivolumab	46	24mo-PFS	Related to CT +++	0 (20)	80% pCR 65% (13)	/

NSCLC: NCT02259621

Pilot Study bicenter trial

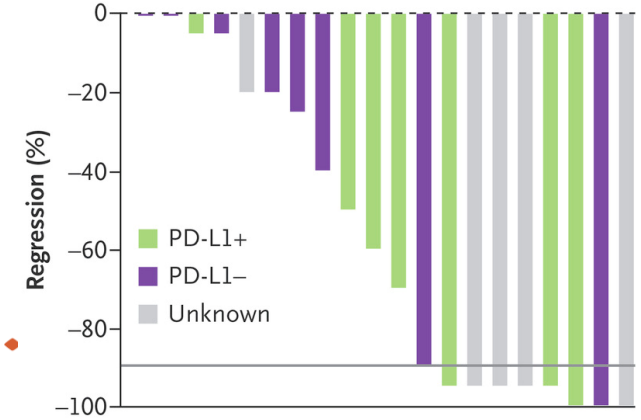
Eligibility criteria

Newly diagnosed surgically resectable early (stage I, II, or IIIA) NSCLC n=21

→ Nivolumab 3mg/kg IV D-28 / D-14 → Surgery (D0) → *SOC FU*

Primary endpoints: Safety and feasibility.

Secondary and exploratory endpoints: Radiologic and pR and correlates of response in blood and tumor

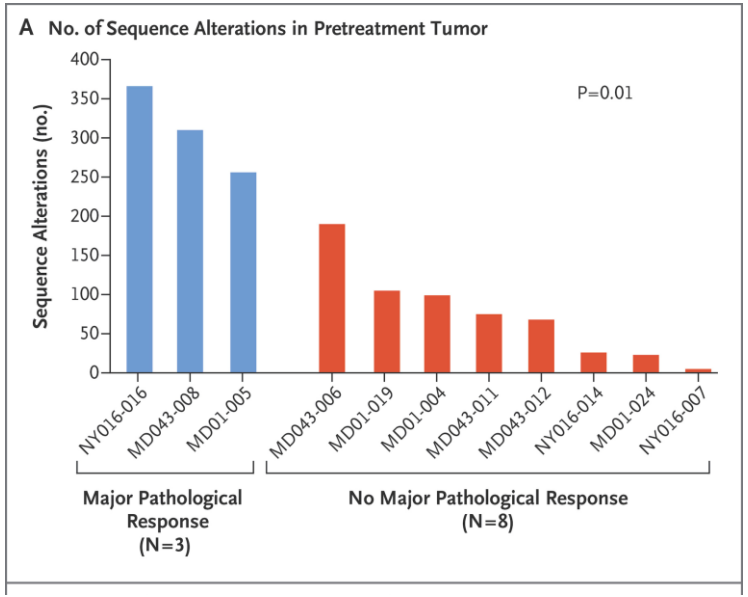


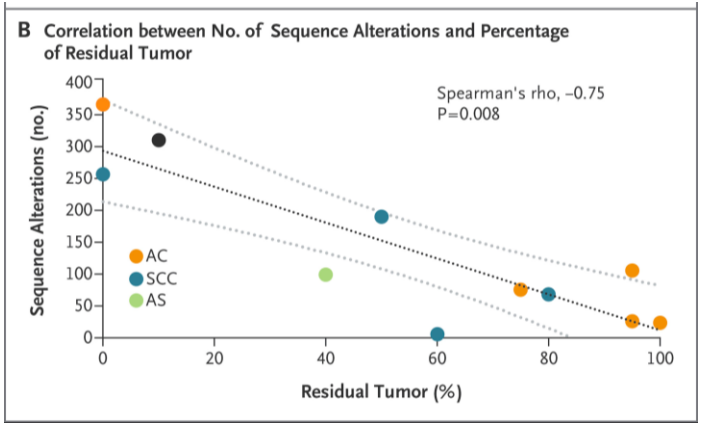
mCR rate: 45%

TRAEs:
Any grade: 23%
Grade 3: 1 pneumonitis
with no delay to surgery

Forde et al. NEJM 2018

Association between Mutational Burden and Pathological Response to PD-1 Blockade.

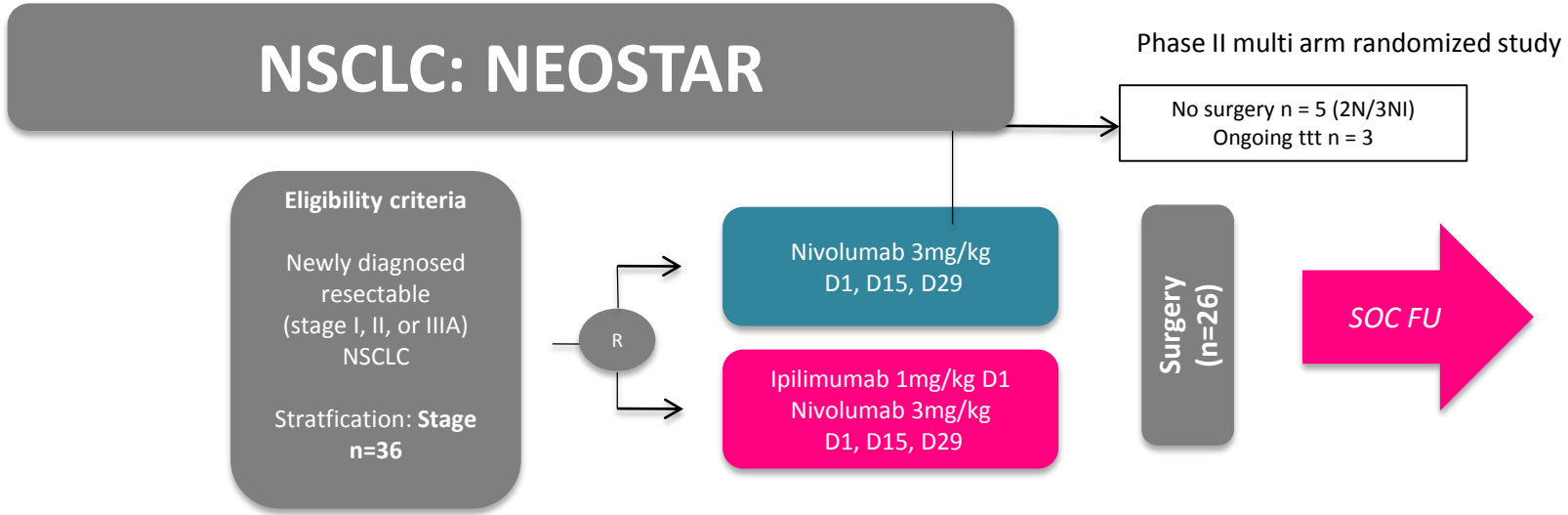




Forde et al. NEJM 2018

NSCLC: NEOSTAR

Phase II multi arm randomized study



Primary Endpoint : MPR ≥ 40% in both arms
Secondary Endpoints; Safety, ORR, RFS, OS, correlates MPR/RECIST with OS/RFS, complete resction rate, pCR, CD8 Tils, tissue, blood and stools biomarkers

Overall** Resected + unresectable	n=31	N n=16	NI n=15
MPR + pCR	8 (26%)	4 (25%)	4 (27%)
0% viable tumor cells (pCR)	5 (16%)	2 (13%)	3 (20%)
1-10% viable tumor cells	3 (10%)	2 (13%)	1 (7%)
Path response pending	5**	2	3

**5 pending (2 N, 3 NI)

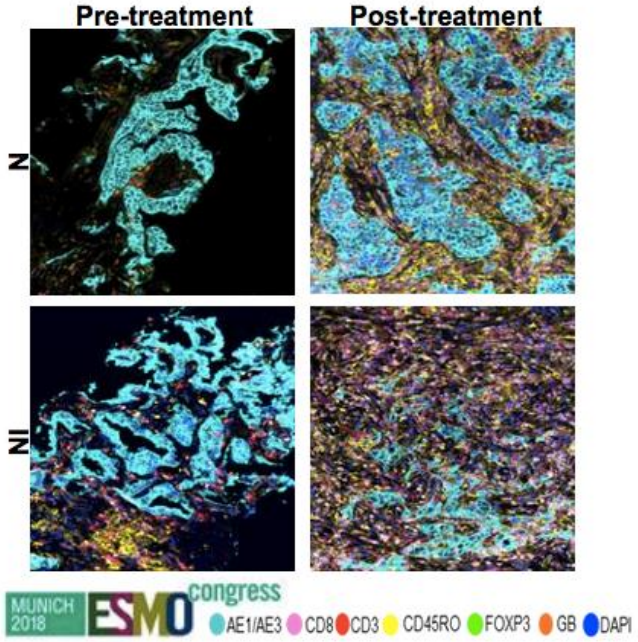
ORR (CR+PR): 22%(7/32)

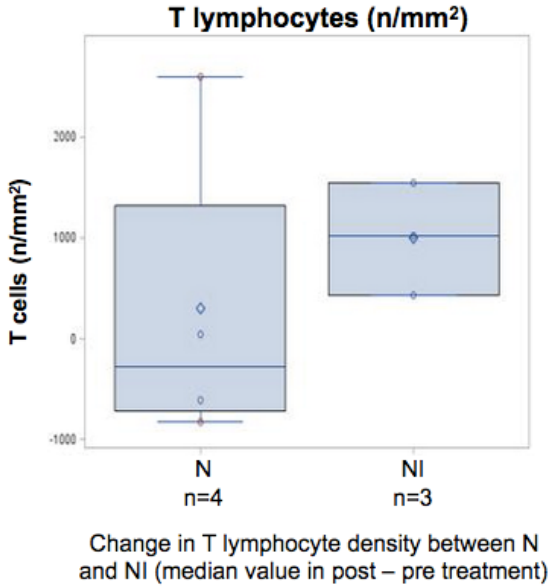
ORR by Arm:
N: 31% (5/16)
NI: 12% (2/16)

TRAEs: NI > N
grade ½ : Cough, Fatigue, Nausea, Rash n = 59
Grade 3/5: pneumonitis, hypoxia n = 3
Surgical complications; : *pneumonitis, pneumonia, bron*
fistula(same pt), air leak > 5 days

Cascone T. LBA49 ESMO 2018

Tumors treated with neoadjuvant NI are characterized by greater T cell infiltration





Change in T lymphocyte density between N and NI (median value in post – pre treatment)

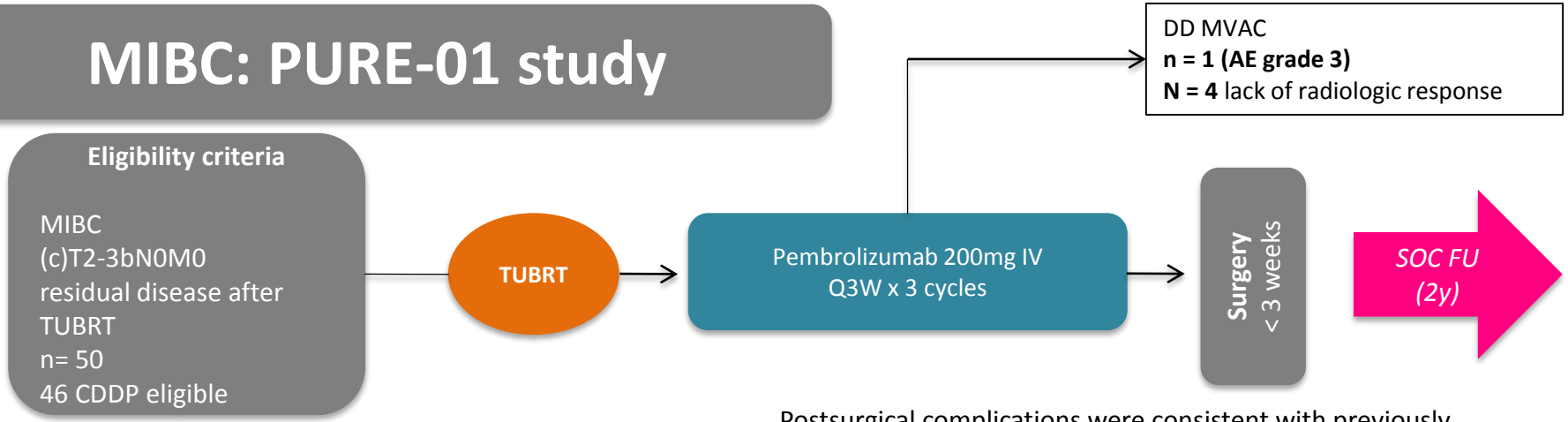
Preliminary results suggest neoadjuvant CPIs induce higher TIL proliferation and activation vs. untreated tumors.

Cascone T. LBA49 ESMO 2018

Early Evidence of Neoadjuvant PD-1 Blockade in MIBC

Study name	Phase	IMP	n=	Primary Endpoint(s)	TRAEs grade 3-5 n=	Delay / No surgery n=	pCR	Potential Biomarkers
PURE-01	II single-arm	Pembrolizumab 200mg x 3 Q3W	50	pCR	3 (6%)	0	21 (42%)	PD-L1 CPS ≥ 10%. Higher tumor mutation burden
ABACUS	II single-arm	Atezolizumab 1200mg x 2 Q3W	74	pCR (> 20%) / increase in CD8 count	< 5%	7	29% PDL1 + (> 5%) 40% PDL1 – 16%	PD-L1 CD8 expression

MIBC: PURE-01 study



Primary endpoint: pCR
Secondary endpoints: Pathologic downstaging pT < 2, safety

Postsurgical complications were consistent with previously reported findings
No post operative death related to surgery

Response	All treated patients (n=50)	PDL1 CPS ≥ 10% (n=35)	PDL1 CPS < 10% (n=15)
pCR (n%)	21 (42) [28.2-56.8]	19 (54.3)	2 (13.3)
Pathologic downstaging (n%)	27 (54) [39.3-68.2]	23 (65.7)	4 (26.7)
Treatment failure (n%)			
Additional MVACx4	5 (10)		
RECIST v1.1 PD	0		

Grade ¾ AEs 6% (3pts):
- Diarrhea
- Hyperkaliemia
- ASAT/ALAT increase (>> Pembro discontinuation)

Necchi et al. JCO 2018

MIBC: ABACUS study

Eligibility criteria

T2-T4aN0M0 MIBC
Transitional histology
Residual disease post TUBTR
Cisplatin ineligible

TUBRT

Atezolizumab IV
Week 1 / Week 3
n = 74 (2 cycles n = 59)

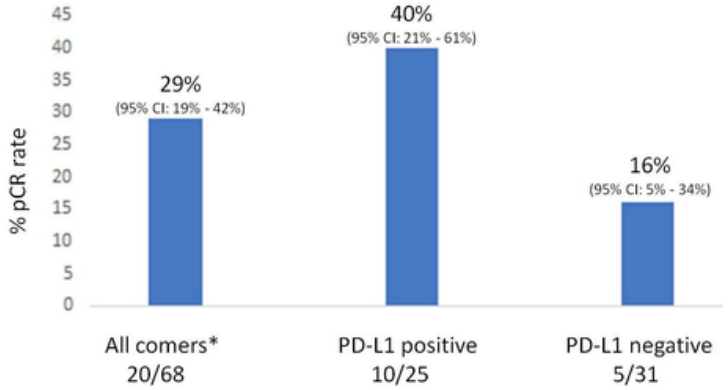
7 did not have cystectomy
Patient decision = 1
Clinical deterioration = 3
Death = 2 (1TR PE)
Disease progression = 1

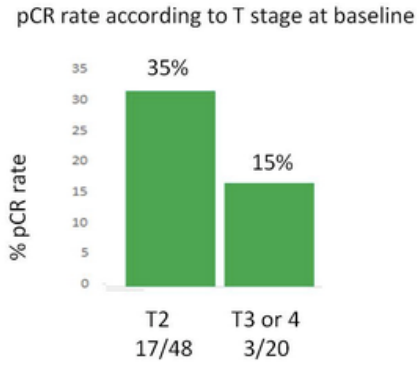
Surgery n = 67

SOC FU

Primary endpoints: pCR (> 20%) / increase in CD8 count
Secondary endpoints: safety and radiological response

No post operative death related to surgery





Grade ¾ AEs < 5%:
Fatigue
transaminitis
Anorexia
Pyrexia

Powles T et al , ASCO 2018c

Early Evidence of Neoadjuvant PD-1 Blockade in other tumor types

MCC: Checkmate 358

Phase I/II

Eligibility criteria

Resecable RXnaive MCC
AJCC stage IIA-IV
n= 29

Nivolumab 240mg Q2W x 2 doses (D1/D15)

AE and/or withdrawn consent N=2

Median FU after 1st dose of NIVO : 67.1 weeks (2.3-106.3)

Surgery (D29)

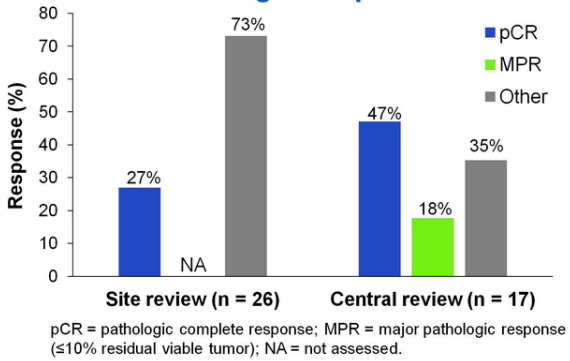
n=27

FU ≥ 12 weeks / Optional SOC Rx – Resume Nivo if PD within 12 mo

Primary endpoint: Safety and tolerability of neoadjuvvant NIVO
Secondary: Immunologic changes in blood and tumor
Exploratory: RECIST, Pathologic response, PFS, OS, Association with MCPyV status and PDL1 expression with efficacy

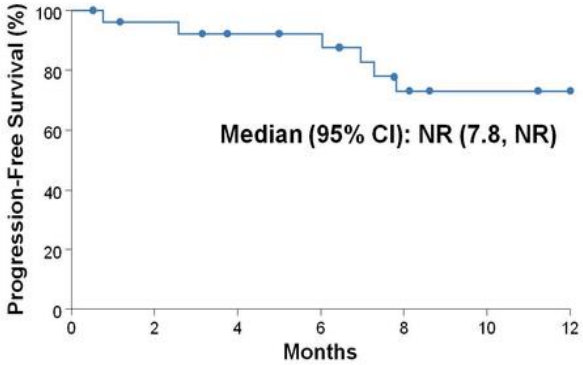
TRAEs grade ¾: 2 pts
Rash >> leading to ttt discontinuation
Lipase increased)
No surgery 2pts (AE/withdrawn consent)
No delay in surgery

Pathologic Response



pCR = pathologic complete response; MPR = major pathologic response (≤10% residual viable tumor); NA = not assessed.

Progression-Free Survival

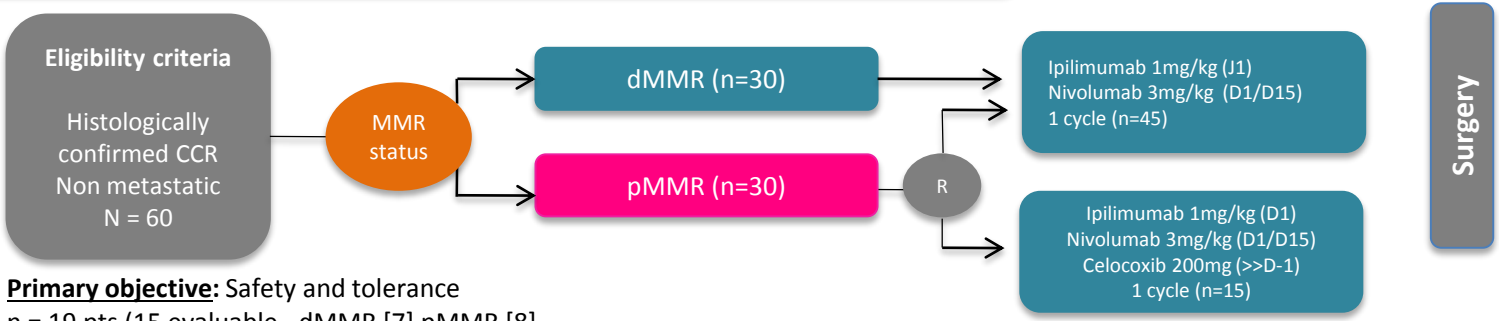


Postop interval, months	PFS rate, % (95% CI)
3	92.1 (72.1, 98.0)
6	92.1 (72.1, 98.0)
9	72.6 (48.6, 86.8)
12	72.6 (48.6, 86.8)

Topalian et al. ASCO 2018

CRC MSI-H: The NICHE study

Chalabi et al. ESMO 2018



Primary objective: Safety and tolerance
n = 19 pts (15 evaluable -dMMR [7] pMMR [8]
Median duration between D1 and surgery = 32 days

No new safety signals
Treatment was well tolerated

dMMR n=7

cTNM	ypTNM	Residual tumor cells (%)
cT2N2a	ypT0N0	0
cT2N0	ypT0N0	0
cT3N0	ypT0N0	0
cT3N2a	ypT1N0	1
cT4aN2a	ypT2N0	2
cT4aN1a	ypT3N1	2

pMMR n=8

cTNM	ypTNM	Residual tumor cells (%)
cT3N1a	ypT3N2	85
cT3N0	ypT3N0	90
cT2N0	ypT3N1	90
cT2N0	ypT3N0	90
cT3aN1b	ypT3N1	90
cT3aN1b	ypT3N2	95
cT3N0	ypT3N0	100
cT2N0	ypT3N0	100

OUTLINE

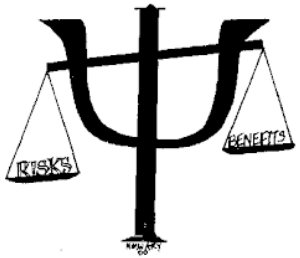
- Rationale for immunotherapy use in the early setting
- Adjuvant checkpoint blockade
- Neoadjuvant checkpoint blockade
- **Perspectives for development of CPIs in the early setting**
- Conclusions

Perspectives

- **≥ 75 ongoing trials investigating IO in the early setting in various tumor types**
  - Various CPIs
  - Combination with either chemotherapy/radiotherapy
  - Innovative immunotherapies and/or approaches
  - Combining neoadj/adj approaches

- High potential for translational research and identification of clinical utility
  - PDL1, TiLs, TMB, CD8 expression

- Moving to an much more earlier setting ?
  - (e.g Pembrolizumab IV in NMBIC)

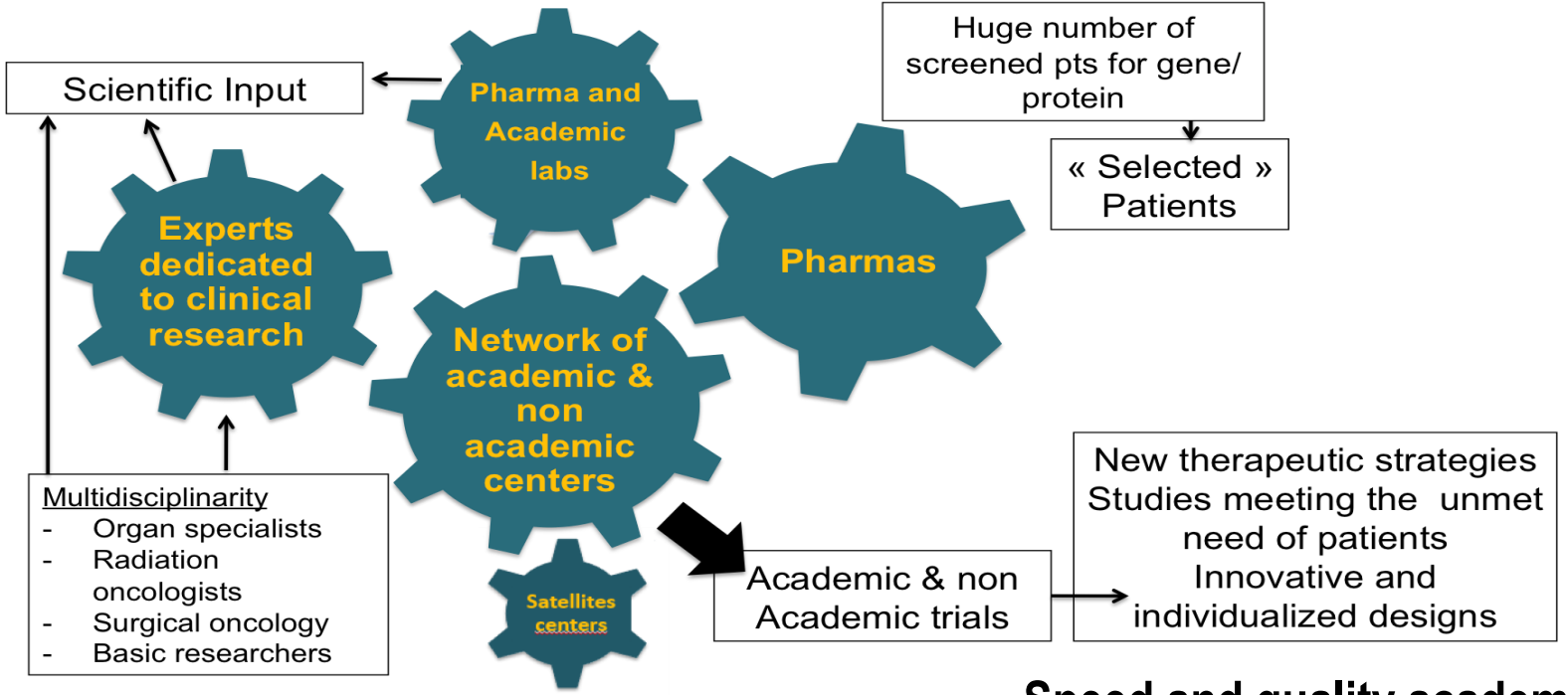


Challenges for moving Immunotherapies from salvage therapy to earlier disease treatments

The use of ICPis in the adjuvant/neoadjuvant setting raises a number of questions:

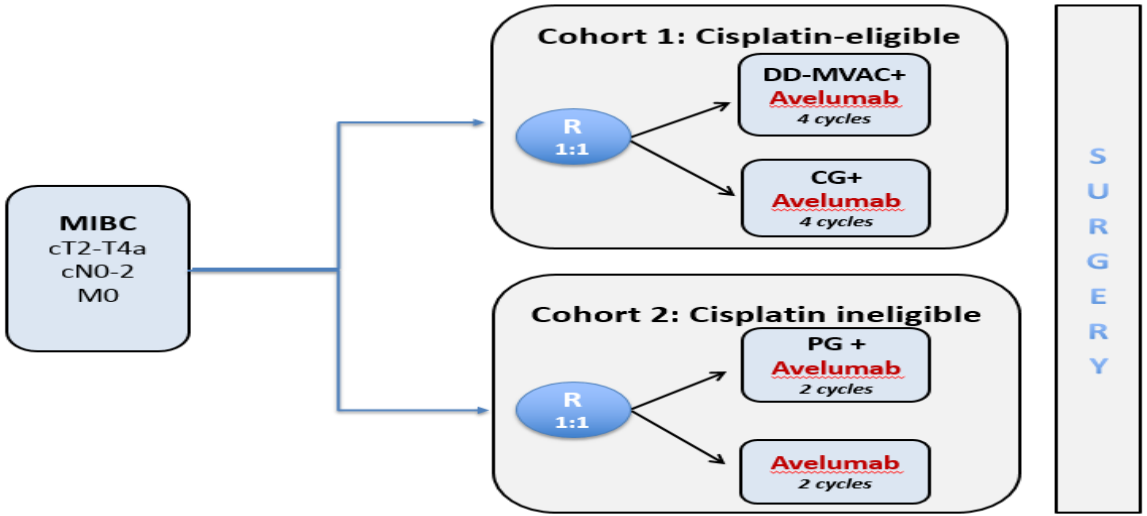
- Acceptable degree of toxicity in a potentially curative setting
- Duration of treatment
- Best treatment shedule (intermittent vs continuous)
- Choosing appropriate comparators
- Combinations with others types of neoadjuvant treatments

A NEW ACADEMIC MODEL OF CLINICAL RESEARCH COLLABORATION BASED ON THE PROGRESS ON MOLECULAR BIOLOGY AND METHODOLOGICAL ISSUES



Speed and quality academic and non academic trials

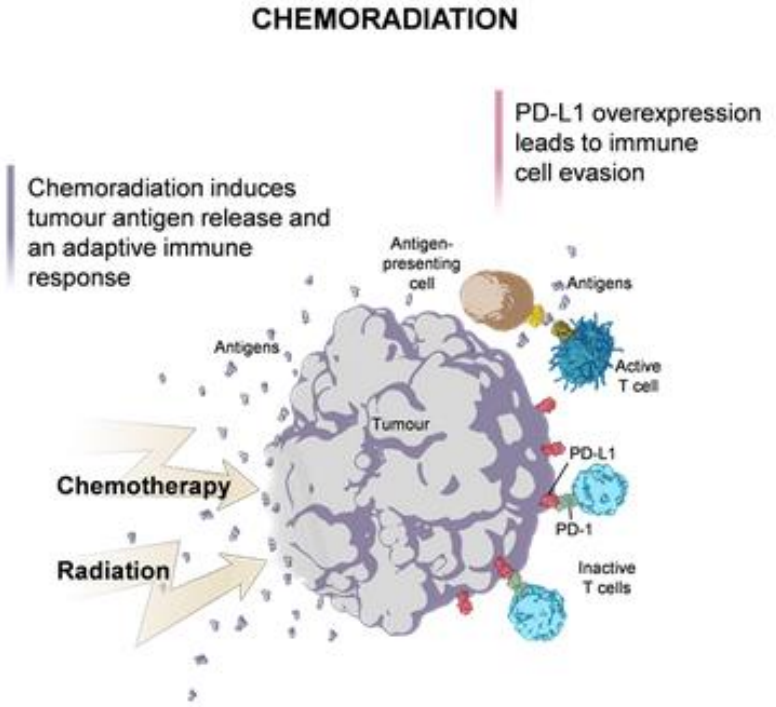
Oncodistinct 004: AURA trial



Primary endpoint:
PCR rate (ypT0ypN0)

Number of pts
150 evaluable patients

RATIONAL FOR COMBINING RADIATION & IMMUNOTHERAPY



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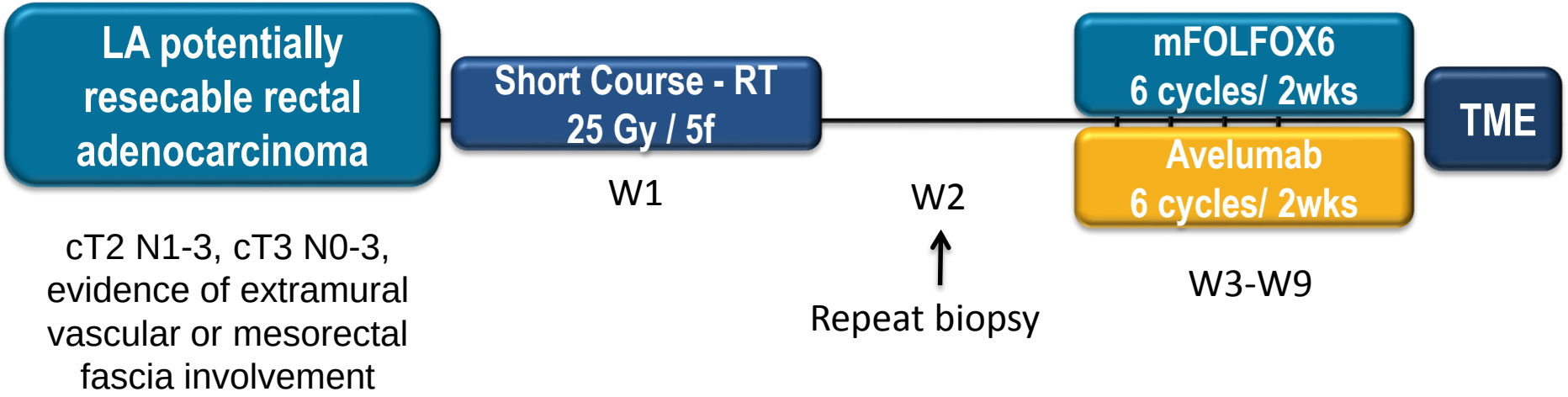
Oncodistinct 005 - Short-course RT followed by mFOLFOX6 + Avelumab agent for LA rectal ADK



Primary objective: pCR rate
Secondary objectives: 3-year DFS, Safety and tolerability, QoL, explore changes in PD-L1 expression and T-cell infiltration

OUTLINE

- Rationale for immunotherapy use in the early setting
- Adjuvant checkpoint blockade
- Neoadjuvant checkpoint blockade
- Perspectives for development of CPis in the early setting
- **Conclusions**

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Conclusions

- Early use of CPis seems feasible and safe with very few delay to surgery
- **Encompassing both neoadjuvant and adjuvant dosing might be the most efficacious**.
- **Implement TR** as much as possible using the possiblity of WOO trials in this setting to discover biomarker of clinical activity
- Try to select patients who will need neoadjuvant/adjuvant CPis
- In the NA setting does pCR benefit = overall survival benefit ?
- Many questions remains open and results needs to be confirmed
- >> Many trials ongoing

Thank you.

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