Metro North Health's vision
Creating healthier futures together—where innovation and research meets compassionate care and community voices shape our services.

RBWH Cancer Care Services

Melanoma case based discussion

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Metro North Health | Queensland Government

Metro North Health acknowledges the Traditional Custodians of the land upon which we live, work and walk, and pay our respects to Elders past and present.

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Melanoma –Australian Stats

- Australia and NZ have the highest rates of melanoma in the world
- 4180 new cases in Qld each year
- 1 Australian Dx every 30 minutes
- 2nd most common cancer in men and women

SUPERFICIAL SPREADING MELANOMA	NODULAR MELANOMA	LENTIGO MALIGNA MELANOMA	ACRAL LENTIGINOUS MELANOMA
55-60% of cases age < 40 yrs Can start as new brown/black spot or an existing spot that demonstrates change Trunk, slow growing	10-15% of cases age > 65 yrs Round, raised firm lump that is pink /red / brown / black. Can have crusty surface w/ tendency to bleed Head and neck, fast growing	10-15 % of cases age > 40 yrs Large coloured spot in sun-damaged skin. Face, ears, neck, head. Can grow slowly and superficially	1-2% of cases age > 40 yrs Palms, soles, fingernails/toenails. Colourless or lightly coloured, long streak of pigment in nails.

Metastatic melanoma

up to 10% have unknown 1^0

M1a: mets to distant skin, subcutaneous or LN sites

M1b: lung mets

M1c: non-CNS visceral mets

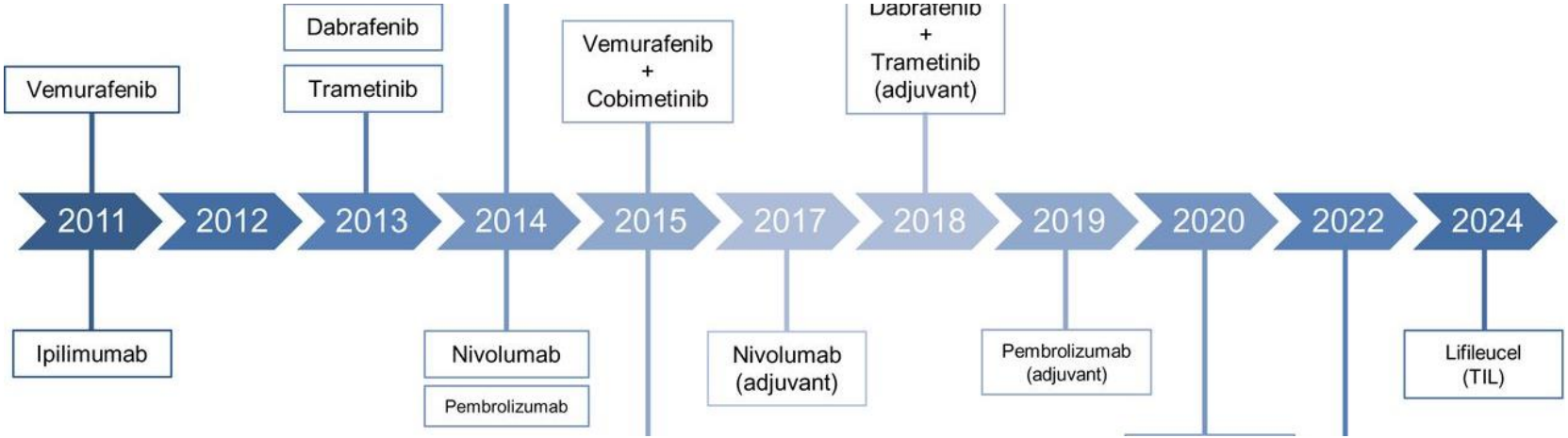
M1d: CNS mets with/without other sites involved

Prognosis:

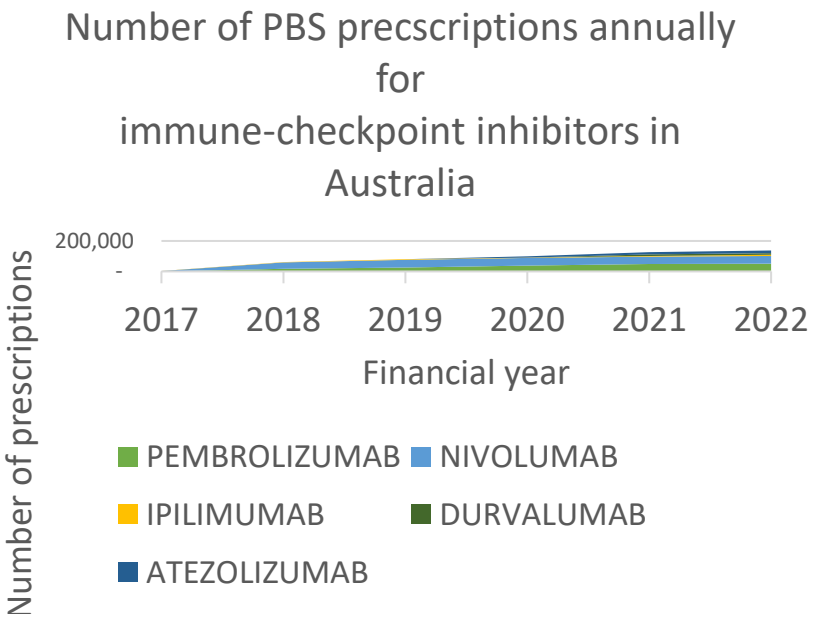
- mOS of untreated stage IV melanoma: <12 mo, 5yr OS: 10%
- M1a Prognosis: up to 15 mo
- M1c Prognosis: 6-9 mo
- M1d Prognosis: ~ 3 months
- Poor prognostic features: high tumour burden, elevated LDH, poor PS

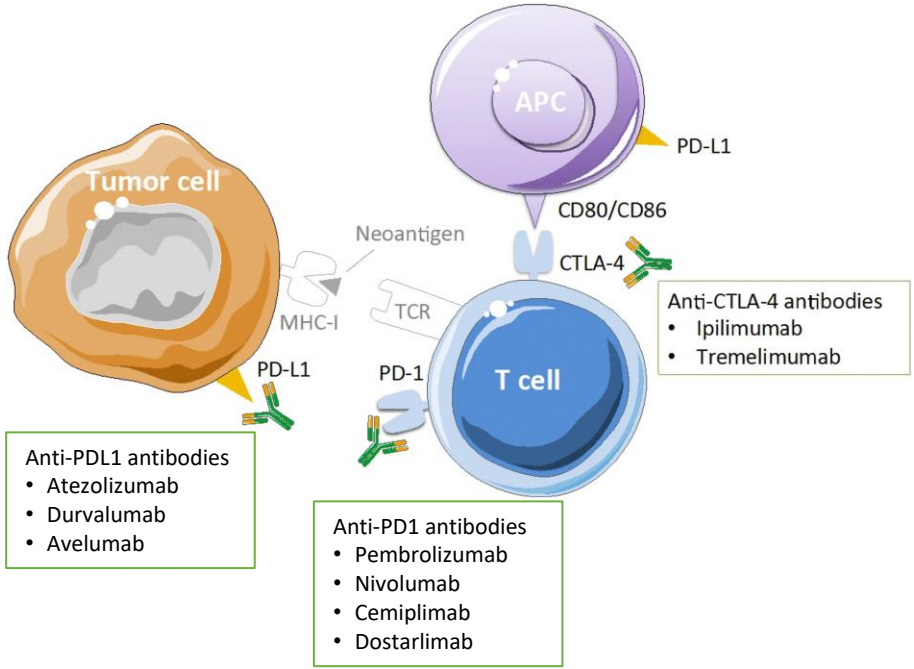
1. DeVita et al
2. Davies et al. Prognostic factors for survival in melanoma patients with brain mets. Cancer 2011; 117(8):1678-96
3. Vecchio et al. The treatment of melanoma brain mets before the advent of targeted therapies. Melanoma Res. 2014;24(1):61-7.

Metastatic melanoma treatments



Immune checkpoint inhibitors

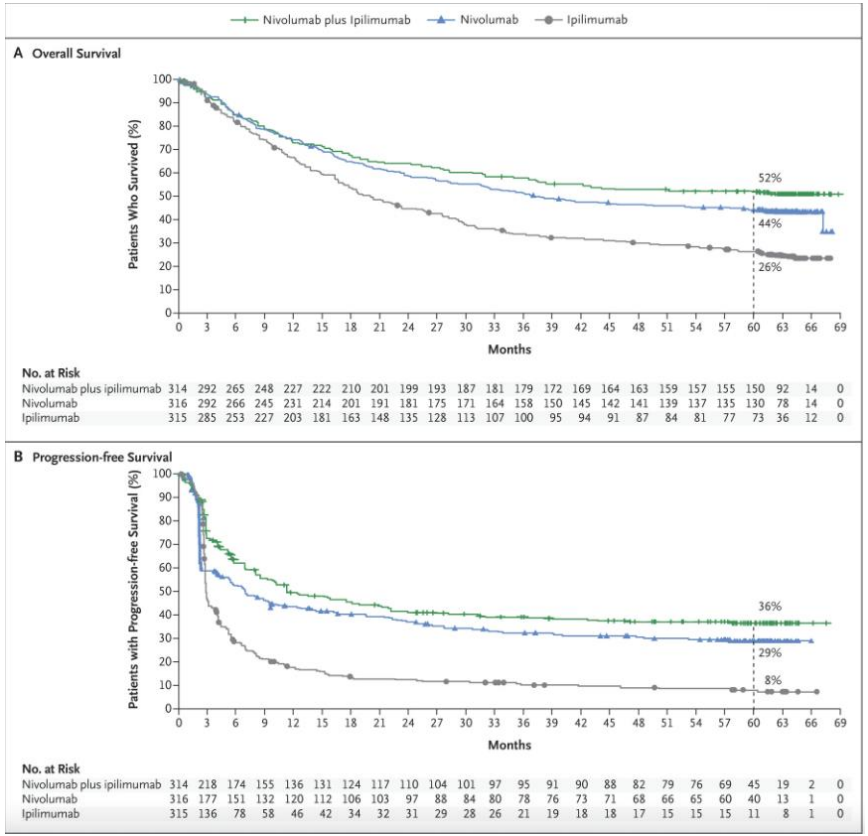




Rouanne et al, *World J Urology*, 2018

Checkmate 067 (2017, 2022) - Efficacy

	Ipi + Nivo	Nivo	Ipi
mOS (mo)	72.1	36.9	19.9
PFS (mo)	11.5	6.9	2.9
5yr OS	52%	44%	26%
6.5yr MSS	NR	58.7	21.9
ORR	58%	45%	19%
CR	23%	19%	6%
PR	36%	26%	13%
SD	12%	9%	22%
PD	24%	38%	50%
mDOR (mo)	NR (61.9-NR)	NR (45.7 –NR)	19.2 (8.8 – 47.4)



M1d Melanoma –Brain mets

- mOS of melanoma brain mets (MBM): 2.8-4 mo
- 2 trials: ABC (n=76) and CM 204 (n=94)
- ABC-X trial underway: Ipi/Nivo + SRT vs Ipi/Nivo

A: asymptomatic brain mets, no local Rx: Ipi/Nivo then Nivo
B: asymptomatic brain mets, no local Rx: Nivo
C: brain mets failed local Rx, neuro Sx, leptomeningeal disease: Nivo

	A (ipi+nivo)	B (nivo)	C (nivo)
All patients	n=35	n=25	n=16
ICR	51%	20%	6%
5-yr IC PFS	46%	15%	6%
5-yr OS	51%	34%	13%
Rx naïve	n=27	n=19	n=4
ICR (Rx naïve)	59%	21%	25%
5-yr IC PFS (Rx naïve)	52%	14%	.
5-yr OS (Rx naïve)	55%	40%	25%
TRAE G3/4	63%	20%	13%

CM 204 schema

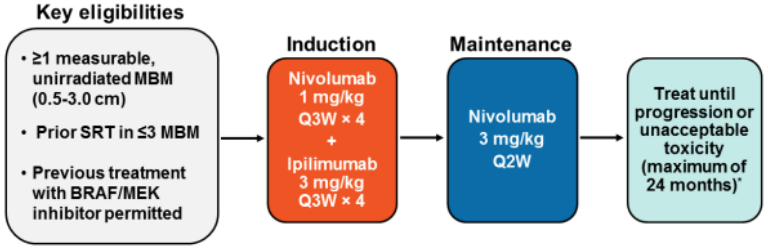


Table 2. Response to Treatment.

Variable	Intracranial (N=94)	Extracranial (N=94)	Global (N=94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)

ABC trial: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30139-6/abstract

Stage 3 melanoma

Survival Endpoints at 5 Years of Follow-Up

Endpoint	COMBI-AD[1]	KEYNOTE-054[2]	CHECKMATE-238[3]
Population	Dabrafenib + trametinib (n=438) vs placebo (n=432) *BRAF* V600E/K only	Pembrolizumab (n=514) vs placebo (n=505)	Nivolumab (n=453) vs ipilimumab (n=453)
Melanoma stage	AJCC 7th edition Stage IIIA-C	AJCC 7th edition Stage IIIA-C	AJCC 7th edition Stage IIIB-C/IV
RFS	52% vs 36% HR: 0.51 95% CI: 0.42, 0.61	55% vs 38% HR: 0.61 95% CI: 0.51, 0.72	50% vs 39% HR: 0.72 95% CI: 0.60, 0.86
DMFS	65% vs 54% HR: 0.55 95% CI: 0.44, 0.70	61% vs 44% HR: 0.62 95% CI: 0.52, 0.75	58%[a] vs 51%[b] HR: 0.79 95% CI: 0.63, 0.99
OS	Not analyzed[c]	Not analyzed	76% vs 72% HR: 0.86 95% CI: 0.66, 1.12

[a]n=370; [b]n=366; [c]Inadequate number of events to trigger the final analysis.

1. Dummer R, et al. *N Engl J Med*. 2020;383:1139-1148. 2. Eggermont A, et al. *NEJM Evidence*. 2022;1:EVIDoa2200214. 3. Larkin J, et al. *Clin Cancer Res*. 2023;29:3352-3361.

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Neoadjuvant therapy

ORIGINAL ARTICLE

Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

Authors: Sapna P. Patel, M.D., Megan Othus, Ph.D., Yuanbin Chen, M.D., Ph.D., G. Paul Wright, Jr., M.D., Kathleen J. Yost, M.D., John R. Hyngstrom, M.D., Siwen Hu-Lieskovan, M.D., Ph.D., +45, and Antoni Ribas, M.D., Ph.D. Author Info & Affiliations

Published March 1, 2023 | N Engl J Med 2023;388:813-823 | DOI: 10.1056/NEJMoa2211437 | VOL. 388 NO. 9

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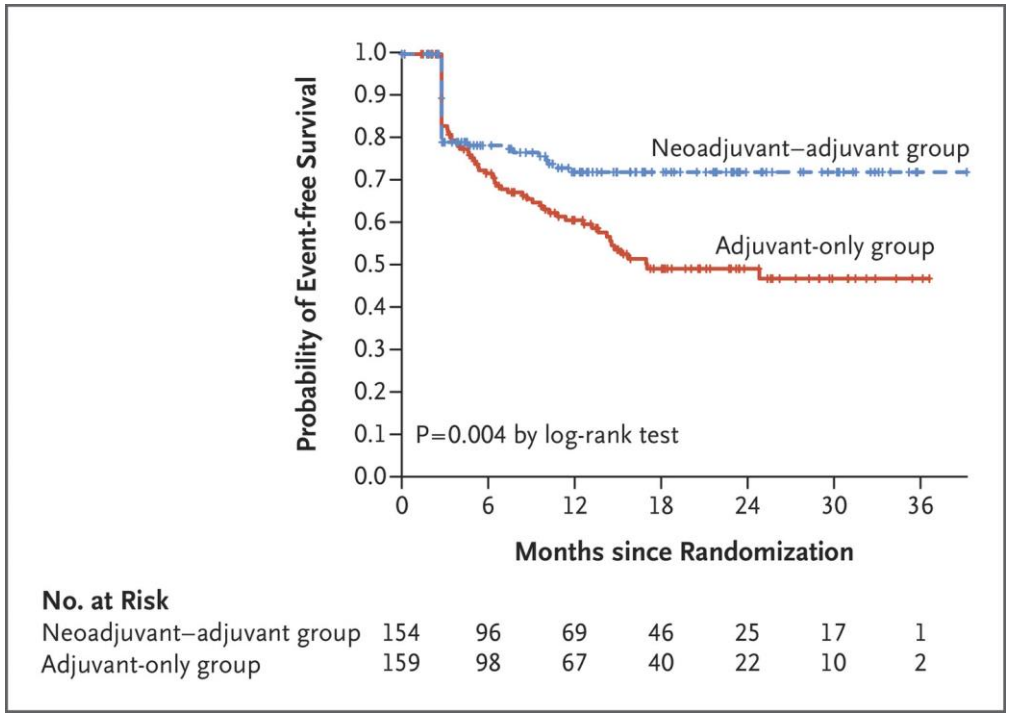
Neoadjuvant therapy



2024 ASCO ANNUAL MEETING

Neoadjuvant Nivolumab Plus Ipilimumab Versus Adjuvant Nivolumab in Macroscopic, Resectable Stage III Melanoma: The Phase 3 NADINA Trial

Christian U. Blank, M.W. Lucas, R.A. Scolyer, B.A. van de Wiel, A.M. Menzies, M. Lopez-Yurda, A.C.J. van Akkooi, W.J. van Houdt, R.P.M. Saw, A. Torres-Acosta, S.N. Lo, G.A.P. Hospers, M.S. Carlino, J.W.B. de Groot, E. Kapiteijn, K.P.M. Suijkerbuijk, P. Rutkowski, S. Sandhu, A.A.M. van der Veldt, G.V. Long

lay abstract

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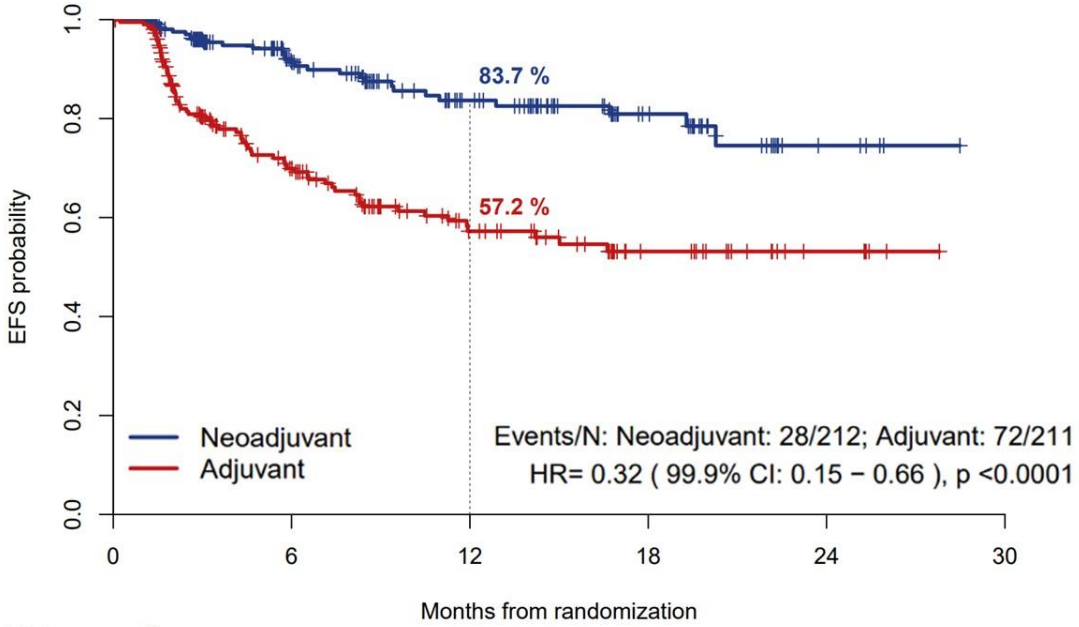
NADINA – Primary Endpoint: Event-Free Survival (EFS)



# at risk (censored)										
Neoadjuvant	212	(0)	126	(71)	77	(111)	34	(152)	5	(179)
Adjuvant	211	(0)	100	(57)	53	(89)	23	(116)	6	(133)

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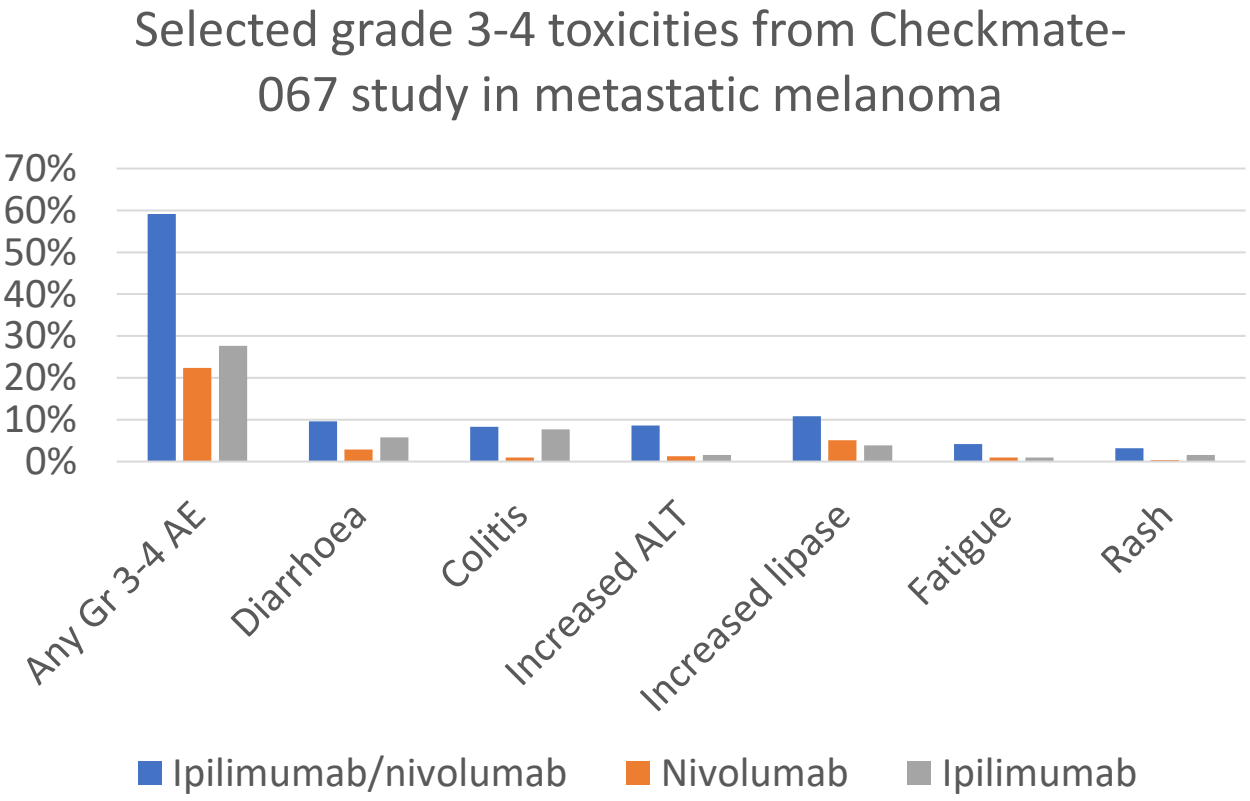
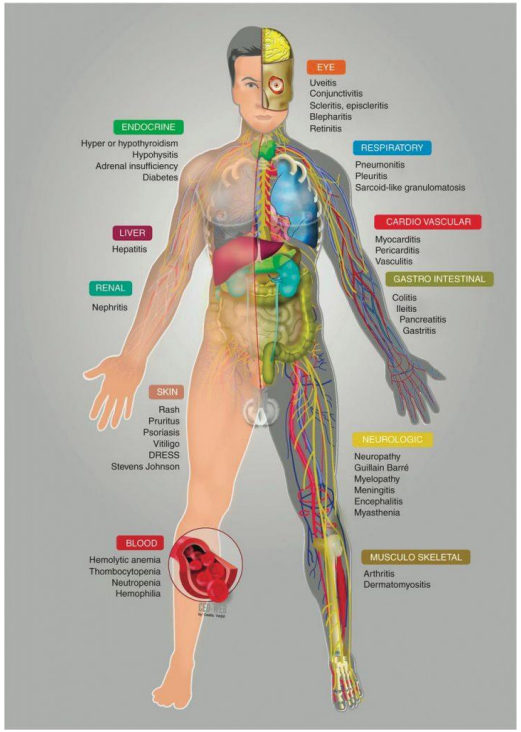
Immune checkpoint inhibitors



Immunotherapy toxicity



Champiat et al, Ann Oncol, 2016

Gastrointestinal toxicity

- Lower GI toxicity most common – diarrhea/colitis
- Upper GI toxicity uncommon but does occur
  - Symptoms include:
  - Nausea/vomiting (50-100%)
  - Abdominal pain (30-75%)
  - Dyspepsia (38%)
  - Bleeding (18% in one case series)
  - Concomitant lower GI symptoms eg. diarrhoea up to 50%
- Management steroids and anti-TNF-α agents in refractory cases

Endocrinopathies

- Clinically significant endocrinopathies in up to 10% patients
  - Most commonly hypothyroidism
  - Can include: hypoadrenalism, hypopituitarism / hypophysitis, diabetes
  - Incidence of ICI-associated diabetes <1%
- Irreversible
- Steroids rarely indicated
- Do not preclude further immunotherapy

Fever and systemic inflammatory syndromes

- Fever and systemic inflammatory complications of immunotherapy can occur including cytokine release syndrome (CRS) and haemophagocytic lymphohistiocytosis (HLH)
- Requires usual workup to exclude infectious causes
- Limited data to guide management but can be steroid responsive

Metastasectomy

- For palliation of symptoms
- May be associated with improved long-term survival following complete curative resection
- Generally, best outcomes in pts with indolent disease, fewer metastatic sites and metasatatic disease that can be completely resected
- In pts with major response to systemic therapy, complete resection of residual mets may contribute to improved DFS and potential for cure
- Lung: 22% 5 yr survival, 16% 10 yr survival cf 0% after incomplete resection, SBRT is an option
- Liver: mOS 24.8mo vs 8mo (highly selected group, n= 58/1078)

Summary

- Metastatic Melanoma outcomes have vastly improved since IO + TT became available
- BRAF WT Melanoma:
  - Ipi / Nivo
  - Relatlimab / Nivo –available on PBS
  - Nivo
- BRAF MT Melanoma
  - IO then TT > TT then IO (Dream-Seq, SECOMBIT)
  - ? Ipi /Nivo over Relat/Nivo
  - D+T; Enco / Bini; Vemurafinib + Cobimetinib
- Brain mets
- Metastasectomy
- Questions:
  - Ipi / Nivo vs Rela / Nivo
  - Does Ipi / Nivo still have activity following PD on Relat/Nivo (currently not allowed on PBS)

Summary

- Systemic therapies are moving further forward in the patient journey

Clinical cases

Case 1

66 F

November 2020 – Chest wall melanoma excised 1.3mm, T2a
Sept 2023 – Presented to GP with L axilla pain, USS showed pathologically enlarged LN
L axillary LN dissection – 50mm nodal deposit
PET no metastatic disease
Feb 24 – Stage 3B melanoma resected, BRAF mutant
Started adjuvant nivolumab 15/2/24

Saw GP 4/3/24 – itchy skin, pale stools, dark urine
What would you do next?

Case 1 cont’d

Bloods done – Bilirubin 84

What would you do next?

ISTRY

06/02/23	10/11/23	04/03/24		
07:20	08:12	12:28		
72220811	74517234	74519449		
FASTING	RANDOM	RANDOM		RANDOM
140	141	139	mmol/L	(137-147)
4.6	4.9	4.6	mmol/L	(3.5-5.0)
103	105	105	mmol/L	(96-109)
30	29	26	mmol/L	(25-33)
12	12	13	mmol/L	(4-17)
5.4	5.2	5.8	mmol/L	(3.0-7.7)
5.8	4.9	5.2	mmol/L	(2.5-7.5)
66	68	79	umol/L	(50-120)
84	81	68	mL/min	(over 59)
0.38	0.37	0.41	mmol/L	(0.14-0.35)
8	12	84	umol/L	(2-20)
		64	umol/L	(0-8)
81	76	516	U/L	(30-115)
29	16	440	U/L	(0-45)
20	20	655	U/L	(0-45)
19	21	346	U/L	(0-41)
156	223	360	U/L	(80-250)
2.37	2.47	2.41	mmol/L	(2.15-2.60)
2.33	2.40	2.37	mmol/L	(2.15-2.60)

Case 1 cont’d

- Repeat bloods a week later
  - Bili 177
- CT liver NAD

10/11/23	04/03/24	11/03/24	11/03/24
08:12	12:28	10:10	10:10
74517234	74519449	75735534	75735533
RANDOM	RANDOM	FASTING	FASTING
141	139	140	138
4.9	4.6	4.2	4.0
105	105	105	103
29	26	25	25
12	13	14	14
5.2	5.8	5.2	4.8
4.9	5.2	3.4	3.3
68	79	68	58
81	68	81	> 90
0.37	0.41	0.32	0.33
12	84	177	181
	64	140	138
76	516	561	558
16	440	417	422
20	655	378	382
21	346	197	197
223	360	256	254
2.47	2.41	2.44	2.37
2.40	2.37	2.34	2.33
1.1	1.1	1.0	1.0
68	70	72	71
45	44	46	44
23	26	26	27
	6.0	7.8	
	2.1	2.7	

Case 1 cont’d

- Started oral pred as an outpatient
- Admitted to hospital
- High dose steroids – IV methylpred then 90 mg pred daily
- USS nad

Date	Alanine Transaminase U/L	Albumin g/L	Alkaline Phosphatase U/L	Anion Gap mmol/L	Aspartate Transaminase U/L	Bicarbonate mmol/L	Bilirubin (Conj.) µmol/L	Bilirubin (Total) µmol/L	C n
11-Jun-2024	**598**	36	**538**	7	**377**	28	**6**	15	
28-May-2024	**98**	35	**357**	6	**63**	29	< 4	9	
30-Apr-2024	**219**	**34**	**583**	5	**118**	28	**7**	17	
18-Apr-2024	**232**	**33**	**382**	4	**93**	30	**11**	**23**	
04-Apr-2024	**328**	**34**	**254**	7	**85**	30	**31**	**48**	
18-Mar-2024	**299**	**29**	**393**	9	**129**	26	**124**	**162**	
16-Mar-2024	**283**	**33**	**412**	9	**172**	26	**131**	**169**	
14-Mar-2024	**226**	36	**496**	9	**109**	**21**	**139**	**182**	
07-Feb-2024	22	36	95	6	19	28	< 4	9	

Case 2

72F

Metastatic clear cell renal cell carcinoma

- Ipilimumab/nivolumab x4 from June 2021
- Complicated by gr 2 hepatitis post C4
  - Responded to prednisone
- Maintenance nivolumab from Oct 21
- Complicated by rash
  - Responded to further low dose prednisone
- Treatment continued with stable disease radiologically
- Distal pancreatectomy Nov 2022 for presumed pNET
  - Histology, met RCC
  - Loose BM post – on Creon

Case 2 cont’d

- Presented to ED 4.1.23 with:
  - Abdominal and ‘burning’ chest pain worsening over weeks
  - Nausea and vomiting
  - 3 loose bowel motions / day stable over months
- CT: multiple new enlarged abdominal lymph nodes and mesenteric stranding. Suggestive of nodal metastases from RCC. Enteritis with reactive lymphadenopathy is thought less likely. Fluid in pancreatic bed
- Admitted 48 hours, analgesia and antiemetics

for symptomatic management

Sample Appearance	Clear		
Sodium	137	mmol/L	(135 - 145)
Potassium	3.7	mmol/L	(3.5 - 5.2)
Chloride	103	mmol/L	(95 - 110)
Bicarbonate	28	mmol/L	(22 - 32)
Anion Gap	6	mmol/L	(4 - 13)
Glucose	8.1	mmol/L	(3.0 - 7.8)
		(Fasting	3.0 - 6.0)
Urea	5.2	mmol/L	(2.9 - 8.2)
Creatinine	76	umol/L	(36 - 73)
Urea/Creat	68		(40 - 100)
GFR (estimated)	68	mL/min/1.73m^2	(> 90)
Urate	0.31	mmol/L	(0.15 - 0.45)
Protein (Total)	56	g/L	(60 - 80)
Albumin	30	g/L	(35 - 50)
Globulin	26	g/L	(25 - 45)
Bilirubin (Total)	7	umol/L	(< 20)
Bilirubin (Conj.)	< 4	umol/L	(< 4)
Alkaline Phosphatase	114	U/L	(30 - 110)
Gamma-GT	82	U/L	(< 38)
Alanine Transaminase	37	U/L	(< 34)
Aspartate Transaminase	30	U/L	(< 31)

Case 2 cont’d

- Re-presented 48 hours after discharge; family frustrated
- Ongoing nausea, vomiting and abdominal pain

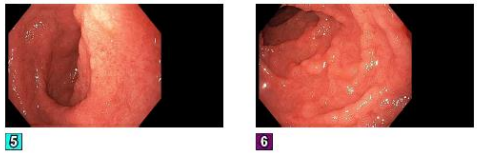
What next?

- CT Brain with contrast
- Endoscopy
- Palliative care consult to manage refractory nausea
- Psychology input

Case 2 cont'd

- Symptoms escalated during hospital stay with worsening vomiting and minimal oral intake. Now 20 bowel motions/24 hours

Sample Appearance	Clear	Clear		
Sodium	135	137	mmol/L	(135 - 145)
Potassium	3.1	2.8	mmol/L	(3.5 - 5.2)
Chloride	96	100	mmol/L	(95 - 110)
Bicarbonate	26	23	mmol/L	(22 - 32)
Anion Gap	13	14	mmol/L	(4 - 13)
Glucose	7.1	6.1	mmol/L	(3.0 - 7.8)
			(Fasting	3.0 - 6.0)
Urea	7.4	6.3	mmol/L	(2.9 - 8.2)
Creatinine	74	73	umol/L	(36 - 73)
Urea/Creat	100	87		(40 - 100)
GFR (estimated)	70	71	mL/min/1.73m^2	(> 90)
Urate	0.32	0.31	mmol/L	(0.15 - 0.45)
Protein (Total)	60	51	g/L	(60 - 80)
Albumin	28	23	g/L	(35 - 50)
Globulin	32	27	g/L	(25 - 45)
Bilirubin (Total)	9	8	umol/L	(< 20)
Bilirubin (Conj.)	< 4	< 4	umol/L	(< 4)
Alkaline Phosphatase	133	100	U/L	(30 - 110)
Gamma-GT	79	61	U/L	(< 38)
Alanine Transaminase	31	23	U/L	(< 34)
Aspartate Transamina	18	13	U/L	(< 31)
Lactate Dehydrogenas	214	187	U/L	(120 - 250)
Calcium	2.23	2.01	mmol/L	(2.10 - 2.60)
Calcium (Alb. Corr.)	2.47	2.34	mmol/L	(2.10 - 2.60)
Phosphate	1.28	1.25	mmol/L	(0.75 - 1.50)
Lipase (Serum)	26		U/L	(< 60)
Magnesium	0.68	0.91	mmol/L	(0.70 - 1.10)
Osmolality (Calculated	290	293	mmol/L	(275 - 295)



Reduced folds in duodenum, flattening
Colon macroscopically normal appearance

1. Duodenum 1: This specimen shows mild villous blunting. There is diffuse hypercellularity of the lamina propria with increased plasma cells and neutrophils. There is also surface epithelial injury with increased intraepithelial neutrophils and lymphocytes. Viral cytopathic changes and parasites have not been identified.

SUMMARY

1. Duodenum 1: Moderate active duodenitis.
2. Duodenum 2: Moderate active duodenitis.
3. Colon random colon: Mild active inflammation with epithelial lymphocytosis and increased apoptosis.

COMMENT

Given the clinical history, the inflammatory changes in the duodenum and random colonic biopsies are highly suspicious for immune checkpoint inhibitor enterocolitis. Severe coeliac disease could conceivably cause the duodenal changes, but the histological features are atypical for that diagnosis.

Case 2 cont’d

- IV methylpred 2mg/kg commenced
- Improvement but not resolution of symptoms
- Infliximab 5mg/kg on D5 of methylpred with ongoing resolution of symptoms

Case 3

69M

- Resected stage IIIC (pT3bN2bM0) melanoma
- BG: AF with prior tachycardia induced CMP, asthma
- Treated with adjuvant nivolumab from June 2022
- Presented for cycle 9 treatment, reporting:
  - Fatigue/lethargy
  - Postural dizziness
  - Anorexia, abdominal pain, nausea/vomiting
  - No diarrhoea

Case 3 cont’d

What do you think this is likely to be?

Non specific immunotherapy toxicity

Gastritis/duodenitis

Brain metastasis

New onset diabetes

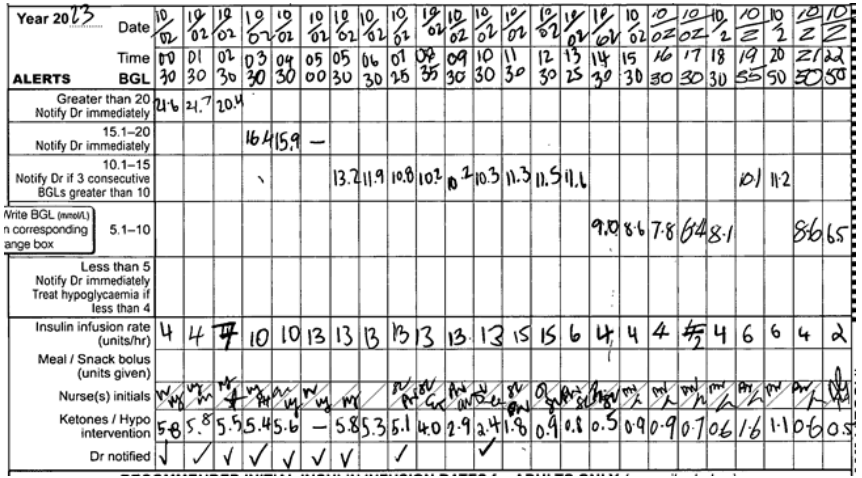
Pituitary dysfunction

Case 3

Sample Appearance	Clear		
Sample Integrity			
Status	Fasting		
Sodium	130	mmol/L	(135 - 145)
Potassium	5.5	mmol/L	(3.5 - 5.2)
Chloride	99	mmol/L	(95 - 110)
Bicarbonate	15	mmol/L	(22 - 32)
Anion Gap	16	mmol/L	(4 - 13)
Glucose	19.1	mmol/L	(3.0 - 7.8)
		(Fasting	3.0 - 6.0)
Urea	4.7	mmol/L	(2.9 - 8.2)
Creatinine	98	umol/L	(64 - 108)
Urea/Creat	48		(40 - 100)
GFR (estimated)	68	mL/min/1.73m^2	(> 90)
Urate	0.44	mmol/L	(0.15 - 0.50)
Protein (Total)	77	g/L	(60 - 80)
Albumin	39	g/L	(35 - 50)
Globulin	38	g/L	(25 - 45)
Bilirubin (Total)	6	umol/L	(< 20)
Bilirubin (Conj.)	< 4	umol/L	(< 4)
Alkaline Phosphatase	72	U/L	(30 - 110)
Gamma-GT	90	U/L	(< 55)
Alanine Transaminase	22	U/L	(< 45)
Aspartate Transaminase	16	U/L	(< 35)
Lactate Dehydrogenase	179	U/L	(120 - 250)
Calcium	2.30	mmol/L	(2.10 - 2.60)
Calcium (Alb. Corr.)	2.32	mmol/L	(2.10 - 2.60)
Phosphate	0.85	mmol/L	(0.75 - 1.50)
Lipase (Serum)		U/L	(< 60)
Magnesium	0.82	mmol/L	(0.70 - 1.10)
Osmolality (Calculated)	290	mmol/L	(275 - 295)

Case 3

- Diagnosed with immunotherapy related diabetes mellitus
- IV rehydration, IV insulin and IV dextrose
- Vomiting and abdominal pain resolved with correction of ketoacidosis



Year 2023	Date	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02	10/02
	Time	00	01	02	03	04	05	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22
ALERTS	BGL	30	30	30	30	30	00	30	30	25	35	30	30	30	30	25	30	30	30	30	30	55	50	50	50
Greater than 20 Notify Dr immediately		21.6	21.7	20.4																					
15.1–20 Notify Dr immediately					16.4	15.9	—																		
10.1–15 Notify Dr if 3 consecutive BGLs greater than 10								13.2	11.9	10.8	10.2	10.2	10.3	11.3	11.5	11.6						10.1	11.2		
Write BGL (mmol/L) in corresponding range box	5.1–10																9.0	8.6	7.8	6.4	8.1			8.6	6.5
Less than 5 Notify Dr immediately Treat hypoglycaemia if less than 4																									
Insulin infusion rate (units/hr)		4	4	4	10	10	13	13	13	13	13	13	13	15	15	6	4	4	4	4.5	4	6	6	4	2
Meal / Snack bolus (units given)																									
Nurse(s) initials		MW	MW	MW	MW	MW	MW	MW	MW	PW	PW	PW	PW	PW	PW	PW	MW	MW	MW	MW	MW	PW	PW	PW	PW
Ketones / Hypo intervention		5.8	5.8	5.5	5.4	5.6	—	5.8	5.3	5.1	4.0	2.9	2.4	1.8	0.9	0.8	0.5	0.9	0.9	0.7	0.6	1.6	1.1	0.6	0.5
Dr notified		✓	✓	✓	✓	✓	✓	✓		✓			✓												

OTHER TISSUE AUTOANTIBODIES

anti-Pancreatic Islet Cell	Negative
GAD Ab	< 5.0
IA2 Ab	<15.0
C-Peptide	<0.1