Replimune®

NEXT-GENERATION ONCOLYTIC IMMUNOTHERAPY

VIRTUAL INVESTOR DAY

March 2022

Safe Harbor

Any statements contained herein that are not statements of historical facts may be deemed to be forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, including statements regarding the advancement, timing and sufficiency of our clinical trials, patient enrollments in our existing and planned clinical trials and the timing thereof, the results of our clinical trials, the timing and release of our clinical data, statements regarding our expectations about our cash runway, our goals to develop and commercialize our product candidates, our expectations regarding the size of the patient populations for our product candidates if approved for commercial use and other statements identified by words such as “could,” “expects,” “intends,” “may,” “plans,” “potential,” “should,” “will,” “would,” or similar expressions and the negatives of those terms. Forward-looking statements are not promises or guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, and which could cause actual results to differ materially from those contemplated in such forward-looking statements. These factors include risks related to our limited operating history, our ability to generate positive clinical trial results for our product candidates, the costs and timing of operating our in-house manufacturing facility, the timing and scope of regulatory approvals, changes in laws and regulations to which we are subject, competitive pressures, our ability to identify additional product candidates, political and global macro factors including the impact of the SARS-COV-2 coronavirus as a global pandemic and related public health issues, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, and other reports we file with the Securities and Exchange Commission. Our actual results could differ materially from the results described in or implied by such forward-looking statements. Forward-looking statements speak only as of the date hereof, and, except as required by law, we undertake no obligation to update or revise these forward-looking statements.

Today's speakers

PHILIP ASTLEY-SPARKE
Chief Executive Officer
Replimune

ROBERT COFFIN
Founder, President & Chief Research & Development Officer,
Replimune

SUSHIL PATEL
Chief Commercial Officer
Replimune

KEVIN HARRINGTON
Professor
Biological Cancer Studies at Institute of Cancer Research, London

NIKHIL KUSHALANI, MD
Vice Chair
Cutaneous Oncology at Moffitt Cancer Center

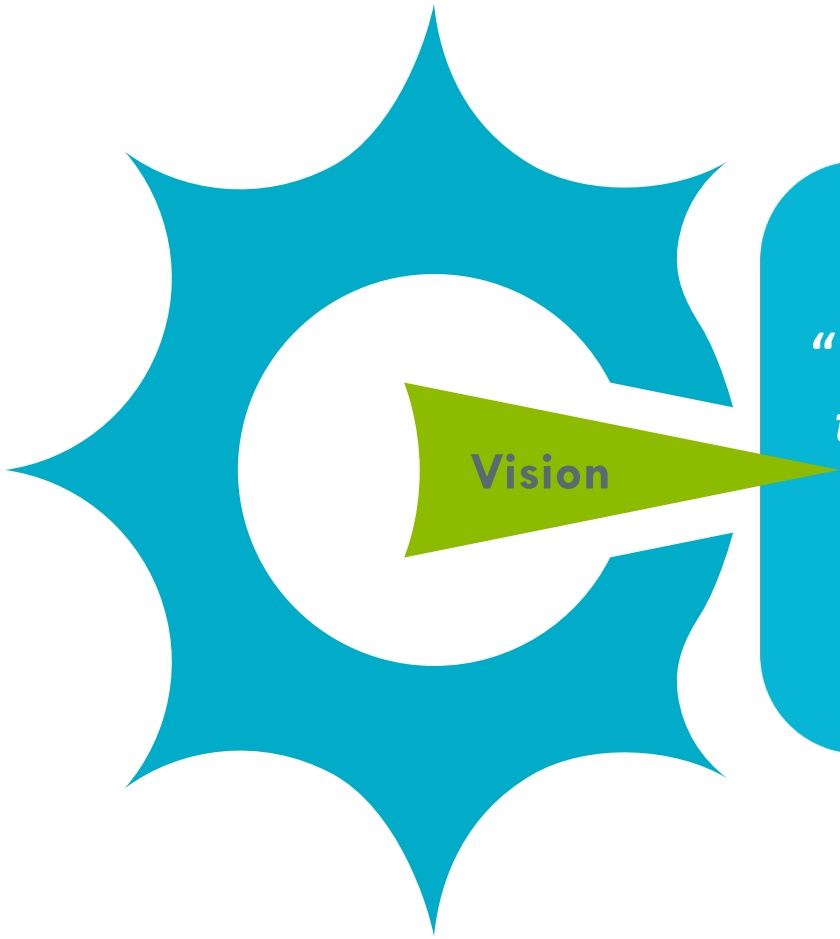
MUNEEB AHMED, MD
Interventional Radiologist, Division Chief
Beth Israel Deaconess Medical Center

TANIOS BEKAII-SAAB, MD
Leader, Gastrointestinal Cancer Program
Mayo Clinic Cancer Center

Agenda

March 30th, 2022 - ET Time Zone (8 am – 11:00) - Virtual	
TITLE	PRESENTER
Welcome and Introductions	Philip
Section 1: RP1 in skin cancer • Updated data: RP1 in melanoma (anti-PD1-failed) and NMSC (anti-PD1 naïve) • New data: RP1 in NMSC (anti-PD1-failed) and monotherapy in solid organ transplant CSCC • KOL perspective on CSCC • Skin franchise and RP1 commercialization in CSCC	Rob Coffin Kevin Harrington Nikhil Khushalani Sushil Patel
Section 2: Deep injections • Deep injections commercial feasibility & strategy • KOL perspective on deep injections for liver cancer/liver mets	Sushil Patel Muneeb Ahmed
Section 3: RP2/3 and our next wave of development • RP2/3 background • RP2/3 phase 2 development strategy • KOL perspectives on H&N, HCC/GI and development plans • Next wave implementation & timelines	Rob Coffin Kevin Harrington Tony Saab
Closing Remarks and Q&A	Philip

Ambition: To enable tumor directed oncolytic immunotherapy (TDOI) to become a cornerstone in the treatment of cancer

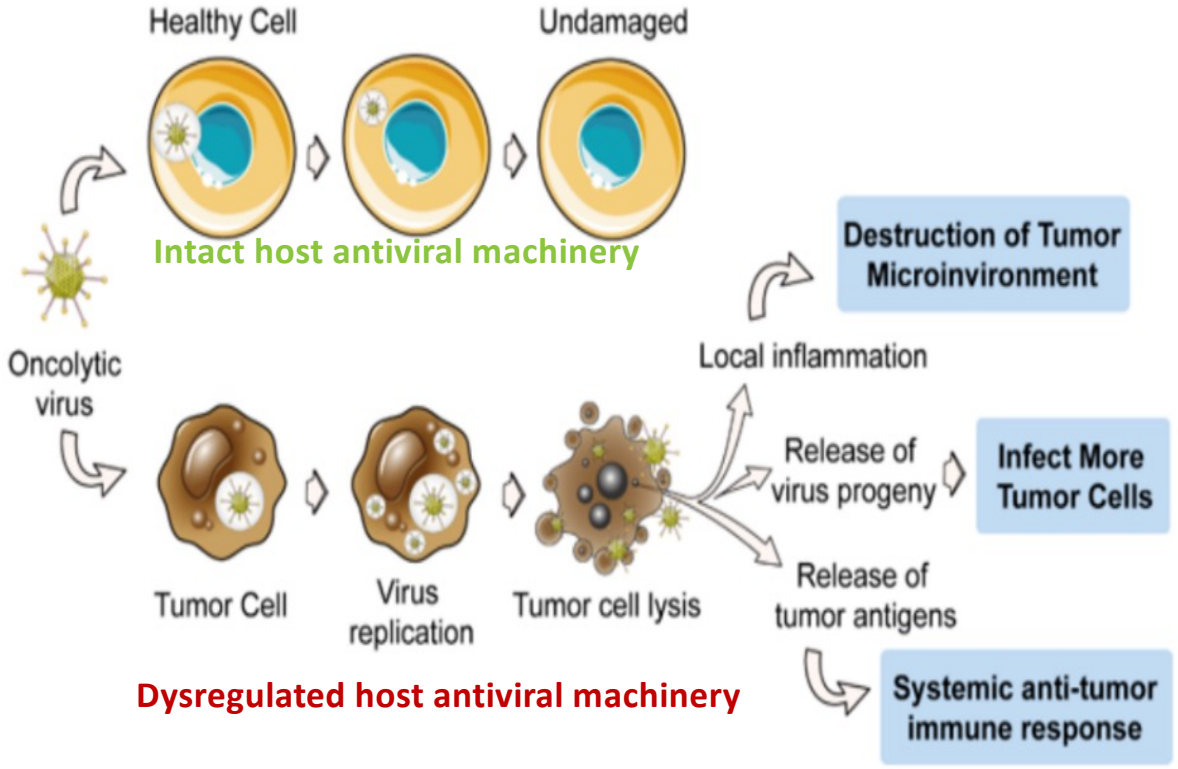


"To deliver transformational results for patients across cancers using tumor directed oncolytic immunotherapy to induce a powerful and durable systemic anti-tumor immune response resulting in quality survival and a chance for cure"

Replimune overview

- Industry leader in tumor directed oncolytic immunotherapy (TDOI) field
- Potential to be a cornerstone treatment in immuno-oncology; 3 wholly owned programs (RP1-3)
- Major skin cancer franchise planned with RP1
  - Data from two RP1 registrational clinical trials in >12 months
- Broad mid-stage development planned with RP2/3
- Potential for the portfolio to deliver substantial commercial revenue in 2025-2030
- Capitalized to build a fully integrated global biotech company
  - US commercial infrastructure, in-house manufacturing
  - $420M as of Dec 2021

Tumor directed oncolytic immunotherapy provides a unique dual mechanism by which to kill tumors



1. Direct local killing of the tumor & altering the TME
2. Release of tumor antigens igniting a strong systemic anti-tumor immune response
3. Flexibility to combine with multiple modalities due to minimal additive side effects
4. Designed to deliver transformational results across tumor types

Bommareddy PK et al AJCD. 2016

RPx positioning: Platform designed to address a range of tumor types with an optimal balance of potency & safety

CRITERIA	RP1	RP2	RP3
Payloads	GALV-GP R-, GM-CSF	GALV-GP R-, anti-CTLA-4, GM-CSF	GALV-GP R-, anti-CTLA-4, CD40L, 4-1BBL
Target	Immunologically responsive tumor types, including anti-PD1 failed	Less immunologically responsive tumor types	Less immunologically responsive tumor types (anticipated further improved compared to RP2)
Intended indication(s)	Skin cancers (CSCC, ant-PD1 failed melanoma, anti-PD1 failed CSCC, other NMSCs, etc)	Various solid tumor including primary liver cancers and/or those with a high prevalence of liver mets e.g. HCC, CRC Early disease (neoadjuvant/LA opportunities) e.g. SCCHN	
Clinical activity in anti-PD1 failed patients demonstrated	✓	✓	Ongoing
Safety & good tolerability demonstrated	✓	✓	Ongoing
Injection location	Superficial, nodal & visceral		
Systemic activity	Clear systemic effects seen in responding patients – uninjected tumors responding, responses generally highly durable		Ongoing
Other considerations	Optimally design for more I-O sensitive tumors with excellent safety in combination	Increased I-O systemic activity with good safety in combination	Maximized for systemic I-O activation & potency

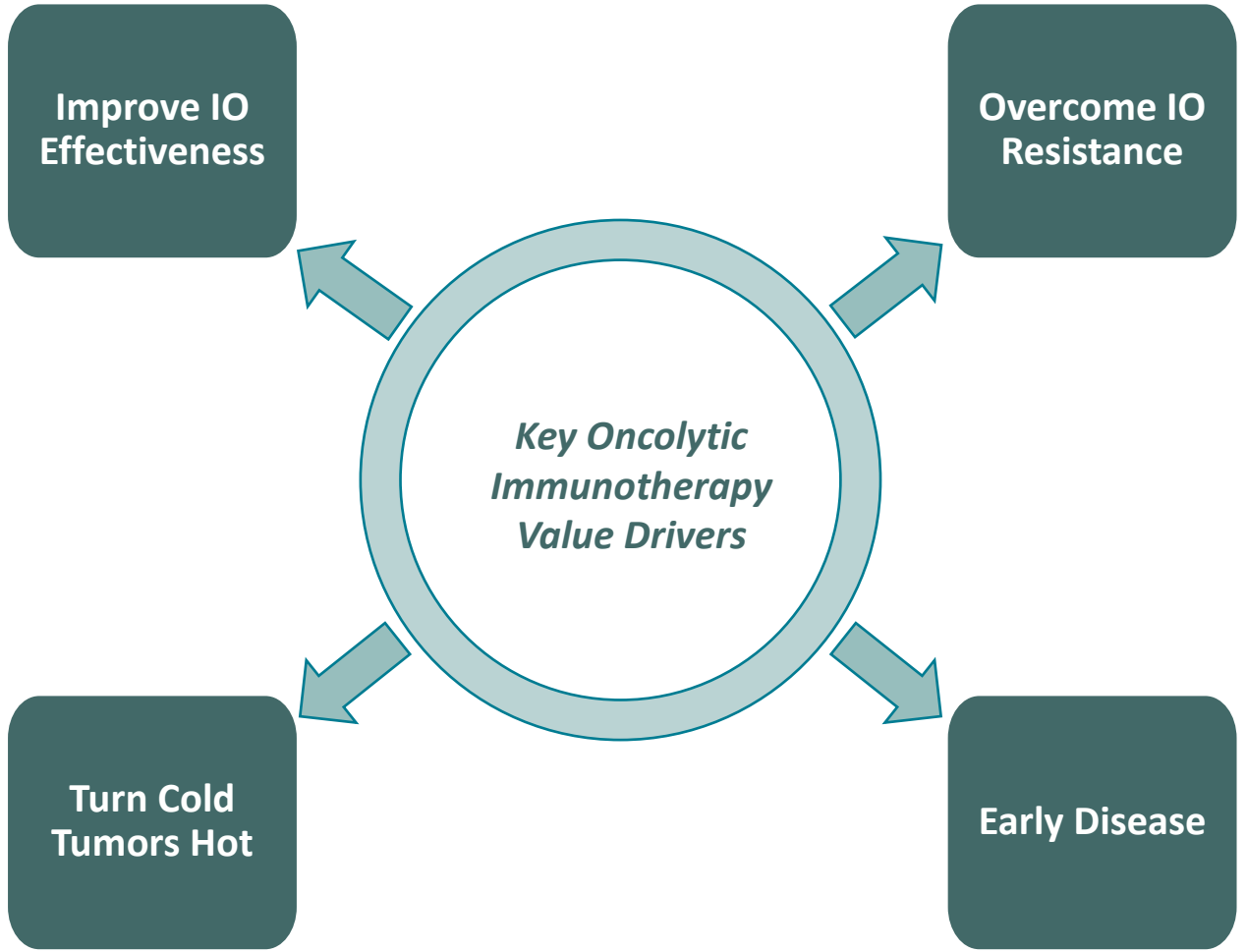
Oncolytic immunotherapy (O-I) enables multiple value drivers

Build on IO to establish new combination SOC

- *Value: Gain/defend share in large, but increasingly competitive, markets with differentiated combination*
- *Example:* ***RP1 + cemiplimab in 1L aCSCC (registrational study ongoing)***

Expand IO into new tumor types

- *Value: Extend the value of IO to large underserved patient populations*



Reverse IO resistance in pts who have failed anti-PD-(L)1 or have low PD-L1

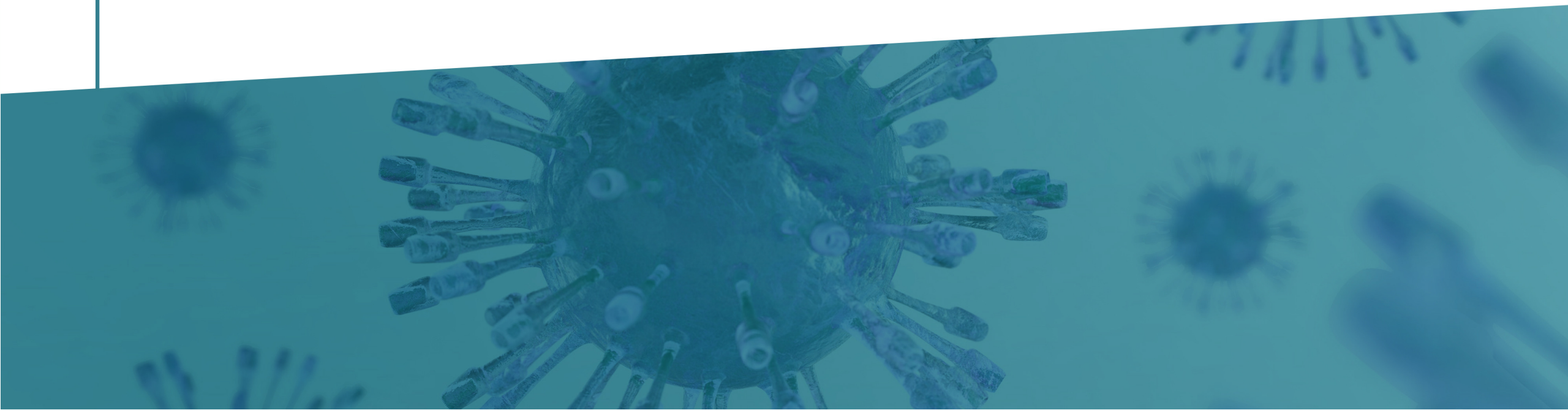
- *Value: Address large (and growing) patient populations with high unmet need*
- *Example:* ***RP1 + nivo in CPI-experienced melanoma (registrational study ongoing)***

Ultimate Goal: Achieve Cure

- *Value: Provide a differentiated/better combination partner in an emerging and competitive space*

RP1: Skin Cancer Updates

Professor Kevin Harrington



Kevin Harrington, Professor, The Royal Marsden Hospital

Professor Kevin Harrington specializes in treating patients with head and neck cancer, salivary gland, and skin cancers.

He is currently a Professor of Biological Cancer Therapies at The Institute of Cancer Research, London, and Consultant Clinical Oncologist at The Royal Marsden, He Leads the Targeted Therapy Team which focuses on two main areas:

i. The use of viruses as anti-cancer agents
ii. The development of new drugs that sensitize cancer cells to radiation.

He studied medicine at St Bartholomew's Hospital, London, and completed post-doctoral research in molecular medicine at the Mayo Clinic, Minnesota, before joining The Royal Marsden. He has published more then 500 articles on cancer treatment and his work has been featured in newspaper and television reports.

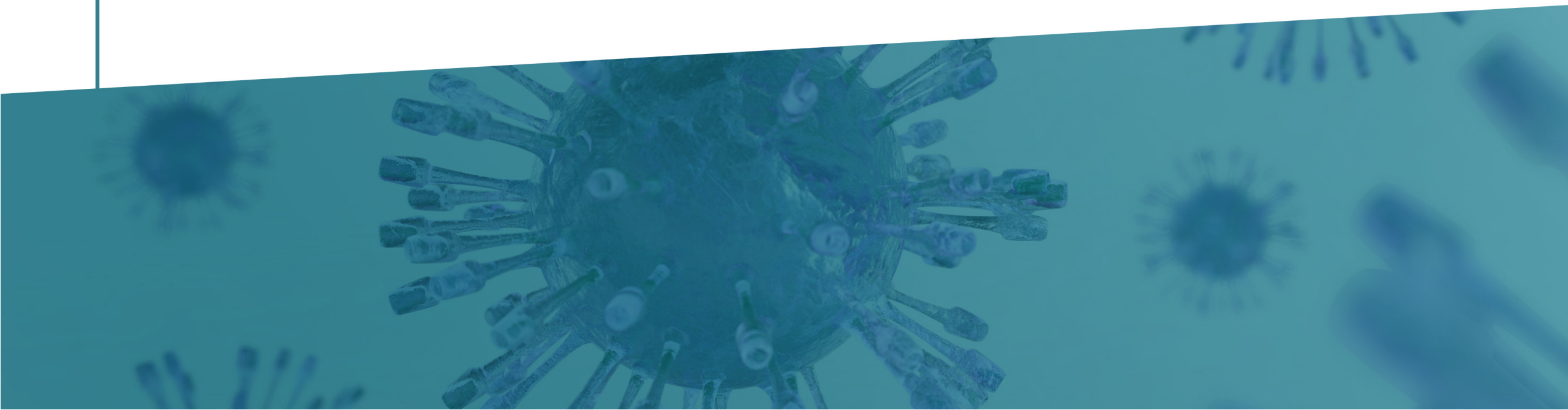
Updated safety data for patients treated with RP1 combined with nivolumab in patients with skin cancer

	N=84			
Preferred Term	Grade 1-2 (>10%)	Grade 3 (all)	Grade 4/5 (all)	Total
Chills	25 (29.8)	0	0	25 (29.8)
Pyrexia	24 (28.6)	1 (1.2)	0	25 (29.8)
Fatigue	19 (22.6)	5 (6.0)	0	24 (28.6)
Pruritus	19 (22.6)	2 (2.4)	0	21 (25.0)
Influenza like illness	18 (21.4)	0	0	18 (21.4)
Nausea	17 (20.2)	0	0	17 (20.2)
Diarrhoea	9 (10.7)	1 (1.2)	0	10 (11.9)
Injection site pain	9 (10.7)	0	0	9 (10.7)
Decreased appetite, Rash	7 (8.3)	1 (1.2)	0	8 (9.5)
Rash maculo-papular	3 (3.6)	2 (2.4)	0	5 (6.0)
Immune-mediated arthritis	3 (3.6)	1 (1.2)	0	4 (4.8)
Lipase increased	2 (2.4)	2 (2.4)	0	4 (4.8)
Dyspnoea, hypotension	1 (1.2)	2 (2.4)	0	3 (3.6)
Eczema	2 (2.4)	1 (1.2)	0	3 (3.6)
Amylase increased, aspartate aminotransferase increased, hyponatraemia, vertigo	1 (1.2)	1 (1.2)	0	2 (2.4)
Immune-mediated hepatitis	0	2 (2.4)	0	2 (2.4)
Alanine aminotransferase increased, cancer pain, confusional state, delirium, hypovolaemic shock, immune-mediated enterocolitis, injection site necrosis, liver function test increased, localized oedema, lymph node pain, oedema, oral candidiasis, prostate cancer, uveitis	0	1 (1.2)	0	1 (1.2)
Immune-mediated myocarditis	0	0	1 (1.2) Gr5	1 (1.2)

- RP1 combined with nivolumab continues to be well tolerated, irrespective of injection route
- Highlights the potential for combination with other anti-cancer therapies

Data snapshot date: 11th March 2022

RP1: Melanoma



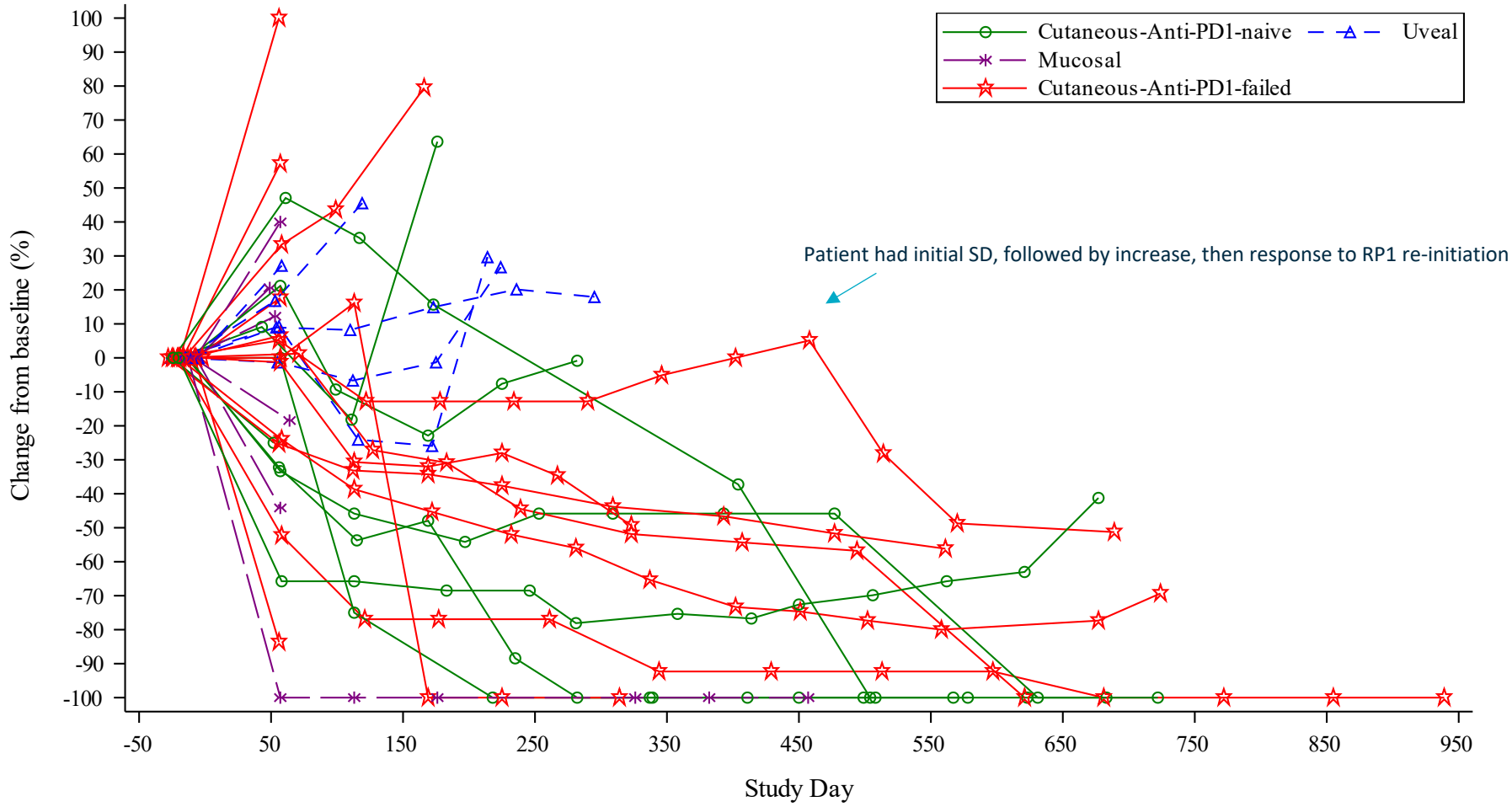
Updated melanoma response table

	Cutaneous: Anti-PD1 naïve	Cutaneous: PD1-failed	Mucosal: Anti-PD1 naïve	Mucosal: Anti-PD1-failed	Uveal: Anti-PD1 naïve	Uveal: Anti-PD1-failed
# of pts	8	16	1	5	3	3
Best overall response # (%)						
CR	3 (37.5)	2 (12.5)	1 (100)	1 (20.0)	0	0
PR	2 (25)	4 (25.0)	0	0	0	0
SD	2 (25)	1 (6.3)	0	0	1 (33.3)	3 (100.0)
PD	1 (12.5)	8 (50.0)	0	4 (80.0)	2 (66.7)	0
ORR	5 (62.5)	6 (37.5)	1 (100)	1 (20.0)	0	0
CR+PR+SD	7 (87.5)	7 (43.8)	1 (100)	1 (20.0)	1 (33.3)	3 (100.0)

- Incremental improvement in anti-PD1 failed cutaneous melanoma since the last data cut
  - ORR in anti-PD1-failed cutaneous melanoma increased from 31.3% to 37.5%
    - CR rate increased from 6.3% to 12.5%
- New CR in mucosal melanoma (previously PR)

Data snapshot date: 11th March 2022

Change in sum of tumor diameters from baseline – Melanoma

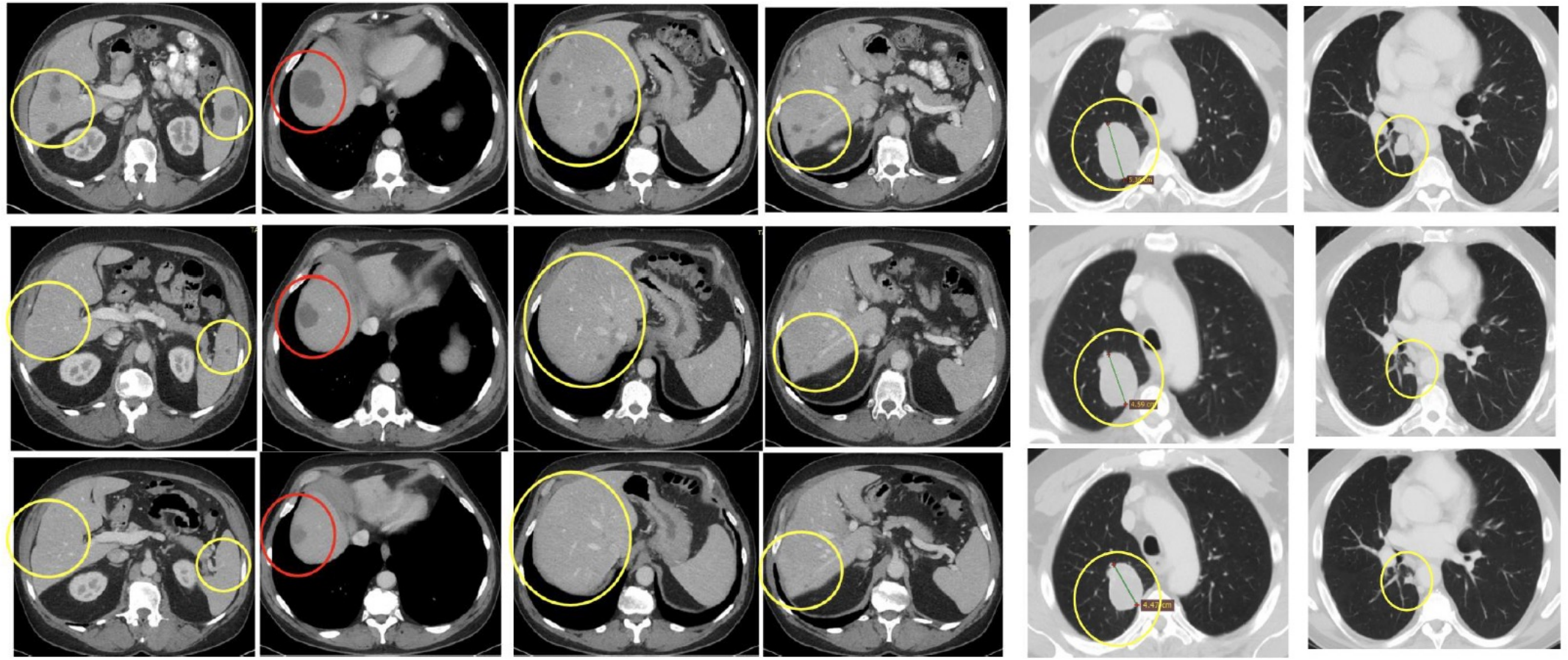


- Durability maintained, with general deepening of response over time

Data snapshot date: 11th March 2022

Patient example: systemic response in anti-PD1/anti-CTLA-4-failed melanoma

Pt 1122-2007 – PR (ongoing at 19 months from first RP1 dose)



Injected

Not injected

All lesions show no evidence of metabolic activity by PET scan

Conclusions – Melanoma (naïve and anti-PD1-failed)

- Incremental improvements in the data since the last data cut, with additional responses observed, deepening of response over time, and durability continuing to be demonstrated
- The response rate in anti-PD1-failed cutaneous melanoma has increased to 37%, further highlighting the potential for these patients

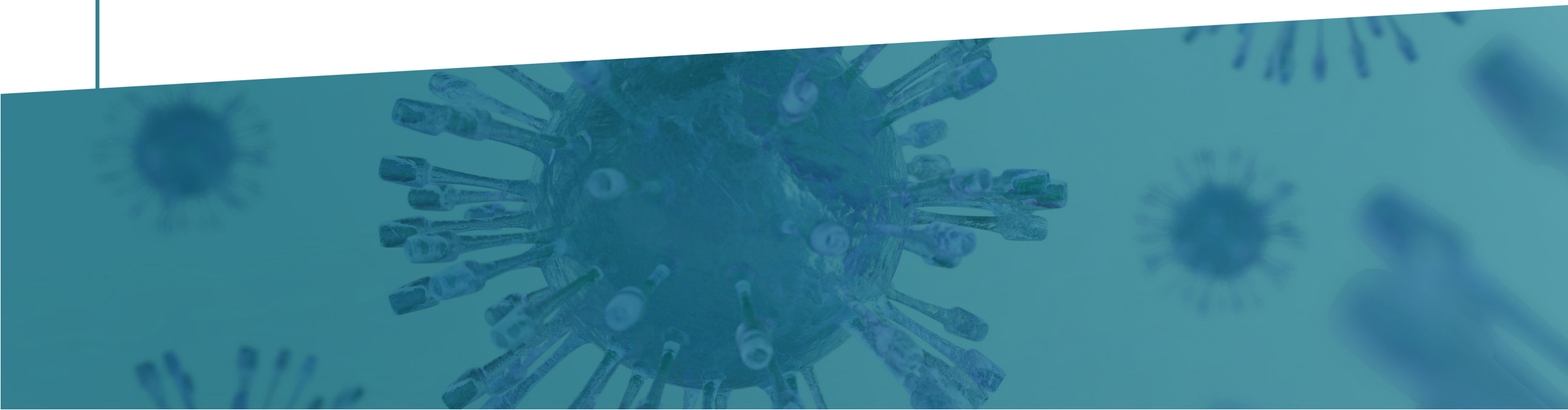
Anti-PD1 failed melanoma registration directed study
Directional data in < 12 months

- Approximately half of advanced melanoma patients still die of their disease
  - Approximately 7,230 US deaths annually[1]
  - 40-65% of all metastatic melanoma are refractory to initial anti-PD1 therapy[3]
- Expected response to anti-PD1 therapy following confirmed progression on single agent anti-PD1 is 6-7%[4,5]

- Ongoing registration-directed single arm 125 patient Phase 2 cohort of RP1 combined with Opdivo
  - Confirmed disease progression required while on prior anti-PD1 therapy
  - Primary endpoint: ORR by independent central review

[1]https://seer.cancer.gov (2019 data); [2]Global Burden of Disease Cancer Collaboration *JAMA Oncol* 2019 (12); [3]Gide et al *Clin. Cancer Res* 2018 (24)
[4]Ribas et al *Lancet Oncology* 2018 (19); [5]Hodi et al *JCO* 2016 (34); [6]Pires de Sliva et al *J Clin Onc* 2020 (38)

RP1: Non-melanoma skin cancers (NMSC)



Updated anti-PD1 naïve NMSC response table (with changes since June 2021)

	CSCC June	CSCC now	BCC June	BCC now	MCC June	MCC now	Angiosarcoma June	Angio now
# of patients*	15	17	4	4	4	4	5	6
Best overall response n (%)								
CR	7 (46.6)	8 (47.1)	0	1 (25.0)	0	2 (50.0)	0	1 (16.7)
PR	2 (13.2)	3 (17.6)	1 (25)	0	3 (75)	1 (25.0)	3 (60)	3 (50.0)
SD	1 (6.7)	1 (5.9)	2 (50)	2 (50.0)	0	0	1 (20)	1 (16.7)
PD	4(26.7)	4 (23.5)	1 (25)	1 (25.0)	1(25)	1 (25.0)	1 (20)	1 (16.7)
OR	9 (60)	11 (64.7)	1 (25)	1 (25.0)	3 (75)	3 (75.0)	3 (60)	4 (66.7)
CR+PR+SD	10 (66.7)	12 (70.6)	3 (75)	3 (75.0)	3 (75)	3 (75.0)	4 (80)	5 (83.3)

- Incremental improvement in each of CSCC, BCC, MCC & angiosarcoma

* Patients with follow up assessments (n=31), on study with no follow up currently for the other patient (MCC)

Data snapshot date: 11th March 2022

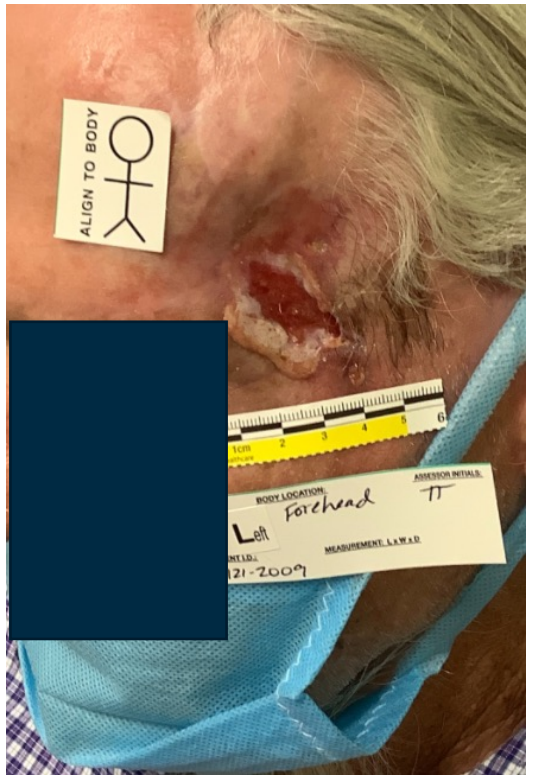
Patient example- anti-PD1 naïve CSCC

Pt. 101-1121-2009 – new ongoing PR

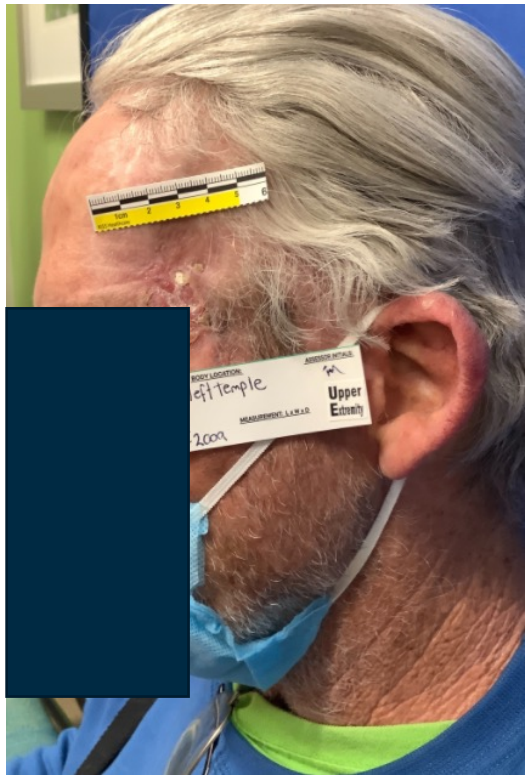
Baseline

1 month

4 months

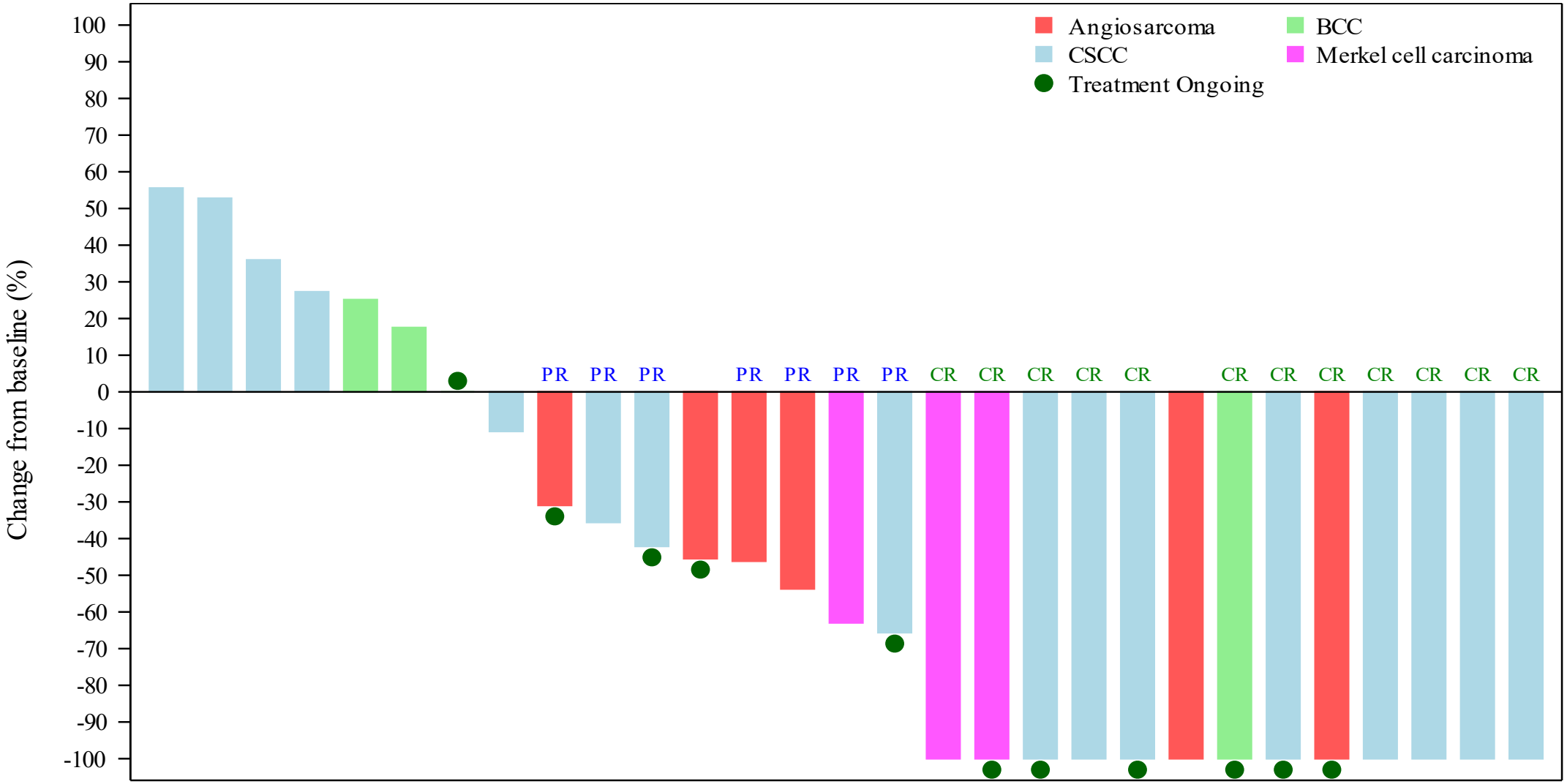


5 months



**Last CSCC pt enrolled into anti-PD1 naïve CSCC cohort – ie new from last data cut*

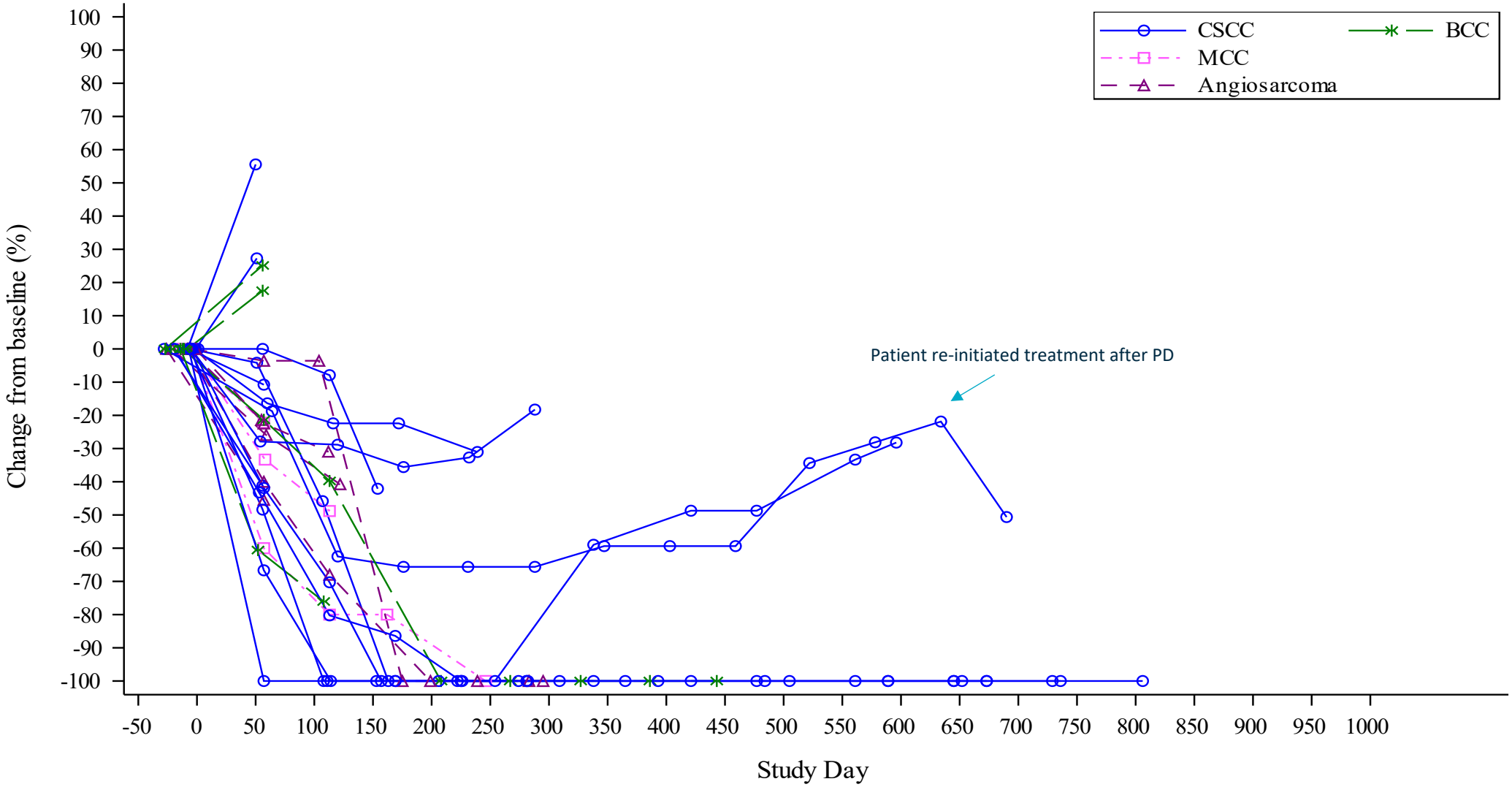
Maximum percent tumor reduction – anti-PD1 naïve NMSC



Data snapshot date: 11th March 2022

- A high frequency of deep responses continues to be observed

Anti-PD1 naïve NMSC: Deep & durable responses



Data snapshot date: 11th March 2022

- A high frequency of durable responses continues to be observed

Conclusions – anti-PD1 naïve NMSC

- As for melanoma, there have been incremental improvements in the data since the last data cut, with additional responses observed, deepening of response over time, and durability continuing to be demonstrated
- In CSCC, the ORR has increased to 64%, with the CR rate remaining at 47%
- Improving activity continues to be demonstrated in the other skin cancer types enrolled (MCC, BCC & angiosarcoma)
- The data highlights the potential for RP1 across skin cancer settings generally

Randomized controlled Phase 2 study in CSCC (CERPASS)

Key Eligibility Criteria:

- Locally-advanced/metastatic CSCC
- ECOG PS 0 or 1
- No active autoimmune disease
- No prior treatment with a PD-1/PD-L1 inhibitor
- No prior treatment with other immune modulating agents (incl CTLA-4)
- No untreated brain metastases

2:1
N=180

RP1 IT Q3W x 8 doses†
($1x10^6$ PFU/mL for one dose followed by $1x10^7$ PFU/mL for 7 doses)
+
Cemiplimab 350mg Q3W IV

Cemiplimab 350mg Q3W IV

57 weeks treatment‡

3-year survival follow up

Key Endpoints

Dual primary endpoints: CR& ORR (RECIST v1.1)
To win on both: An approximate 17% & 15% improvement for ORR & CRR, respectively, is required
To win on ORR only: An approximate 19% improvement is required
To win on CRR only: An approximate 17% improvement is required
Secondary: DOR, PFS, OS, Disease-Specific Survival, safety/tolerability

†First dose of RP1 to be given as monotherapy with cemiplimab to be given with second dose of RP1
‡57 weeks treatment for the combination arm; treatment duration for cemiplimab-only arm is 54 weeks

- Top level primary analysis data expected in Q1 2023

RP1: anti-PD1-failed* NMSC response table – first look

	All	CSCC	BCC	MCC	Angio-sarcoma
# of patients**	12	7	1	2	2
CR	1 (8.3)	0	0	1 (50.0)	0
PR	3 (25.0)	1 (14.3)	0	1 (50.0)	1 (50.0)
SD	5 (41.6)	4 (57.1)	1 (100)	0	0
PD	3 (25.)	2 (28.6)	0	0	1 (50.0)
OR	4 (33.3)	1 (14.3)	0	2 (100)	1 (50.0)
CR+PR+SD	9 (75.0)	5 (71.4)	1 (100)	2 (100)	1 (50.0)

- Initial data shows responses across each anti-PD1-failed tumor type
- Other SD patients, including with CSCC, with only short follow up are also responding to treatment

* Progressed while on anti-PD1 therapy as the patients last treatment before the clinical trial

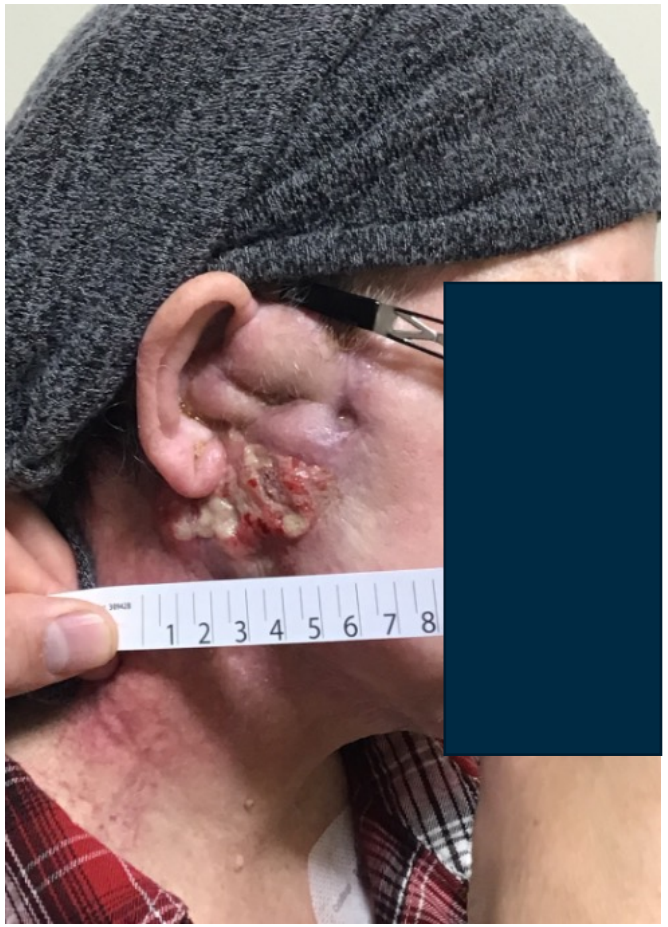
** Patients with follow up assessments (n=12), on study with no follow up as yet for the other two patients enrolled

Data snapshot date: 11th March 2022

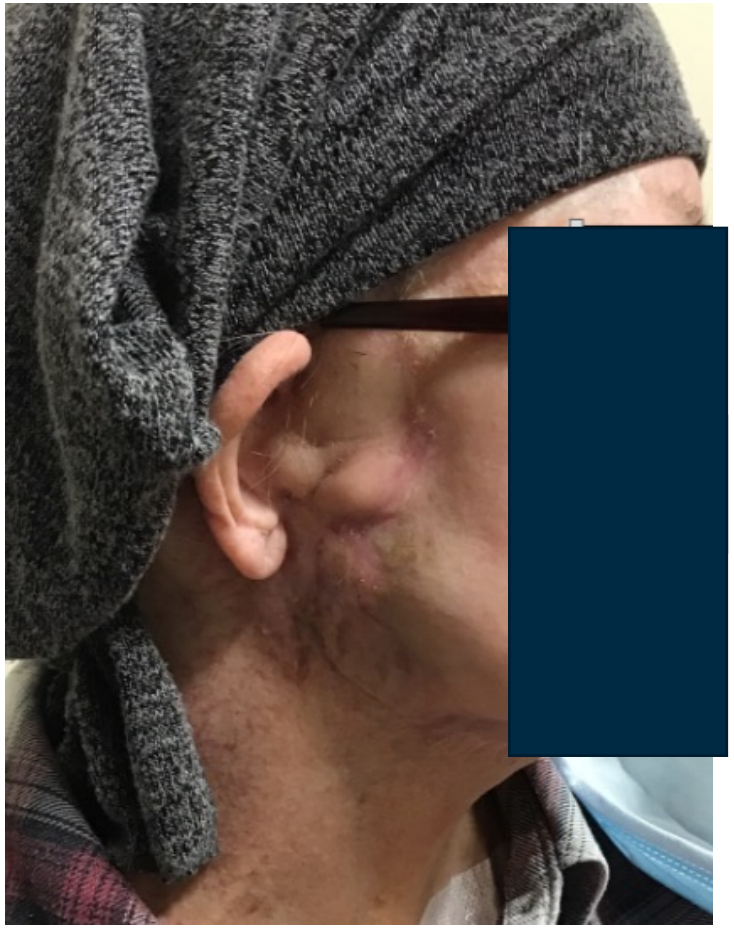
Patient Example-anti-PD1 failed CSCC (ongoing PR)

Pt. 101-1122-2029 – Anti-PD1-failed CSCC (ongoing PR)

Baseline



6 months



CD8+ T cells

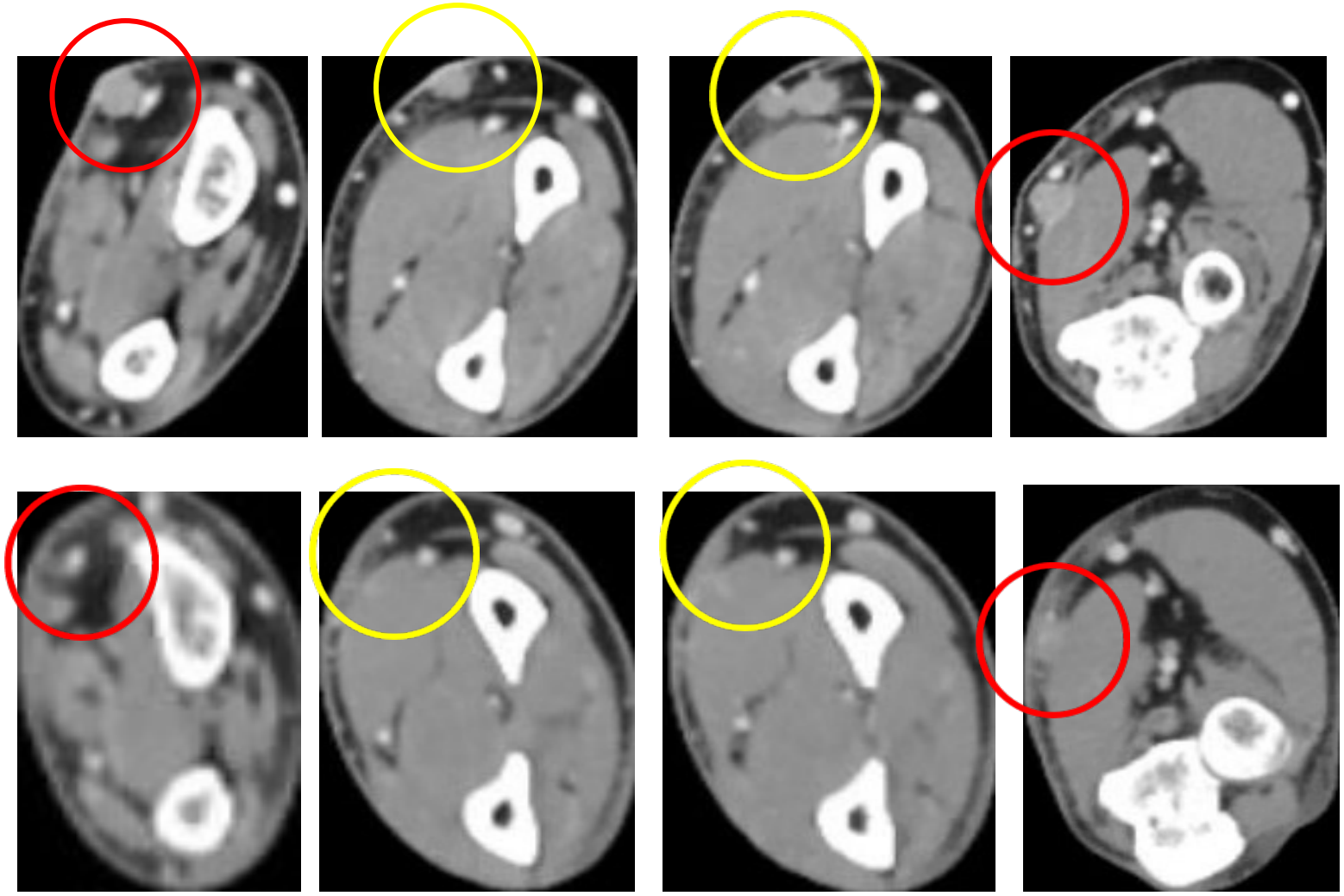
Screening

Day 43

Patient example– anti-PD1 failed MCC (ongoing PR)

Baseline

3 months



Injected

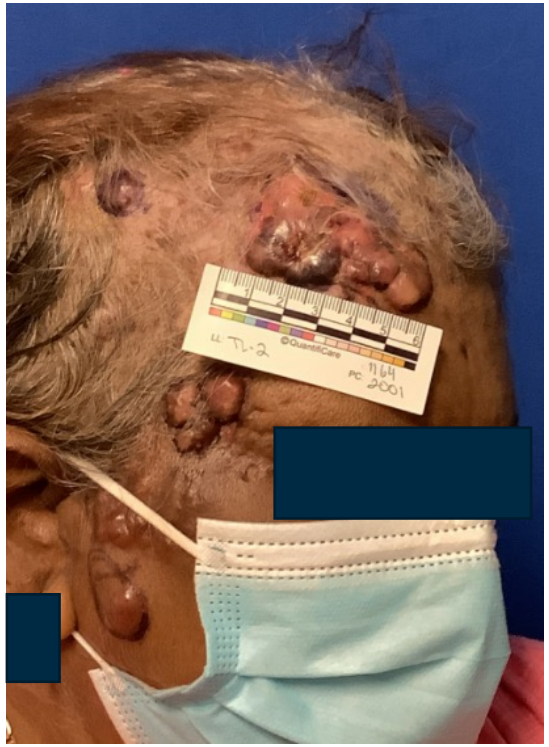
Uninjected

Pt. 101-1121-2012 – multiple forearm subcutaneous MCC lesions

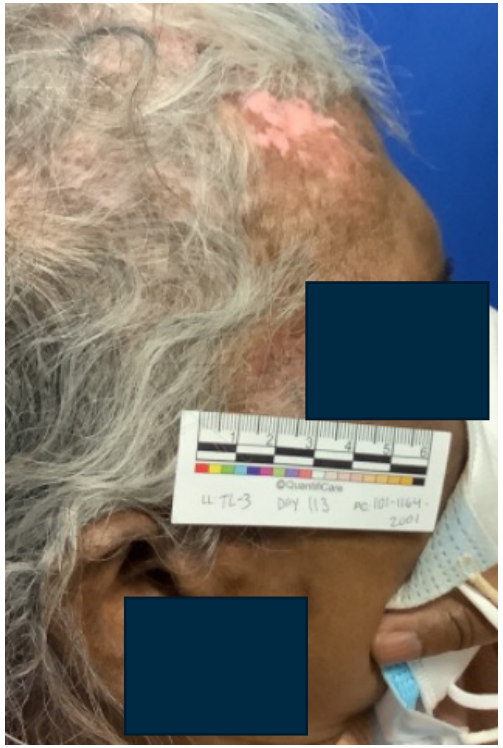
Patient example: anti-PD1-failed angiosarcoma (ongoing PR)

Pt. 101-1164-2001 - Anti-PD1-failed angiosarcoma (ongoing PR)

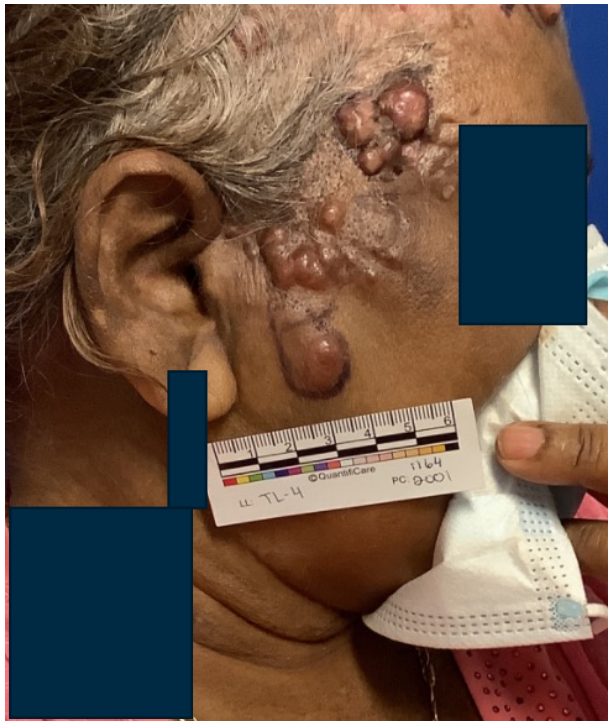
Baseline



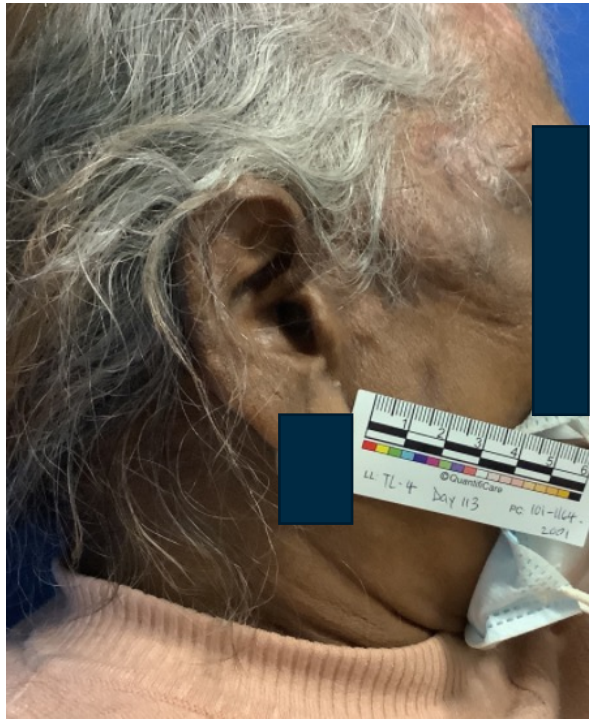
4 months



Baseline

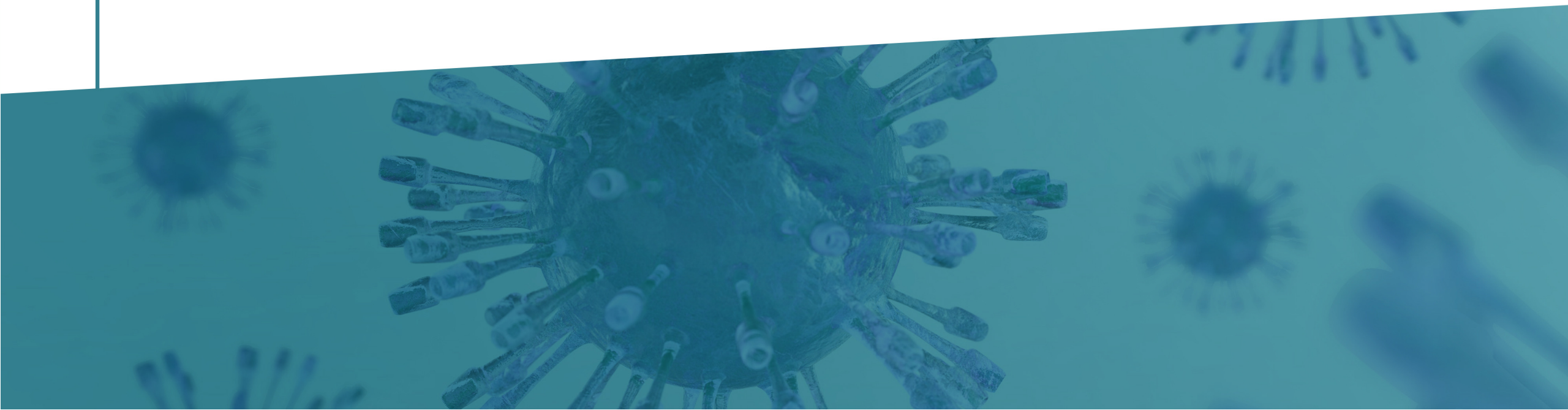


4 months



RP1 Monotherapy: ARTACUS (Solid Organ Transplant Recipients with Skin Cancer)

Replimune®



Response to treatment: RP1 monotherapy in solid organ transplant recipients (ARTACUS) – First Look

	Total (#/%)
Tumor type	CSCC
# of patients	6
CR	1 (16.6)
PR	1 (16.6)
SD	0
NE	1 (16.6)
PD	3 (50)
ORR	2 (33.3)

All enrolled patients have CSCC & kidney transplants so far

- Three patients had PD & one patient died of COVID-19 before the first response assessment

- Initial data shows that one third of the patients enrolled to date have responded to treatment, with all responses maintained to date
- May provide a potential new treatment option for these patients

Data snapshot date: 11th March 2022

Related TEAEs for patients treated with RP1 monotherapy in organ transplant patients with skin cancer (ARTACUS)

Preferred Term	Grade 1-2 (all) (%)	Grade 3 (all) (%)	Grade 4 (all) (%)	Grade 5 (all) (%)	Total (all) (%)
Chills	1 (16.7%)	1 (16.7%)	0	0	2 (33.3%)
Fatigue	2 (33.3%)	0	0	0	2 (33.3%)
Dry mouth	1 (16.7%)	0	0	0	1 (16.7%)
Eyelid oedema	1 (16.7%)	0	0	0	1 (16.7%)
Influenza like illness	1 (16.7%)	0	0	0	1 (16.7%)
Injection site pain	0	1 (16.7%)	0	0	1 (16.7%)
Injection site paraesthesia	0	1 (16.7%)	0	0	1 (16.7%)
Nausea	1 (16.7%)	0	0	0	1 (16.7%)
Pyrexia	1 (16.7%)	0	0	0	1 (16.7%)
Tumour haemorrhage	1 (16.7%)	0	0	0	1 (16.7%)
Vomiting	1 (16.7%)	0	0	0	1 (16.7%)

- RP1 monotherapy has been well tolerated in patients with solid organ transplants
  - These patients are significantly immune-compromised
  - No evidence of organ rejection so far
- While the number of patients is small, no evidence of difference as compared to other clinical trials with RP1

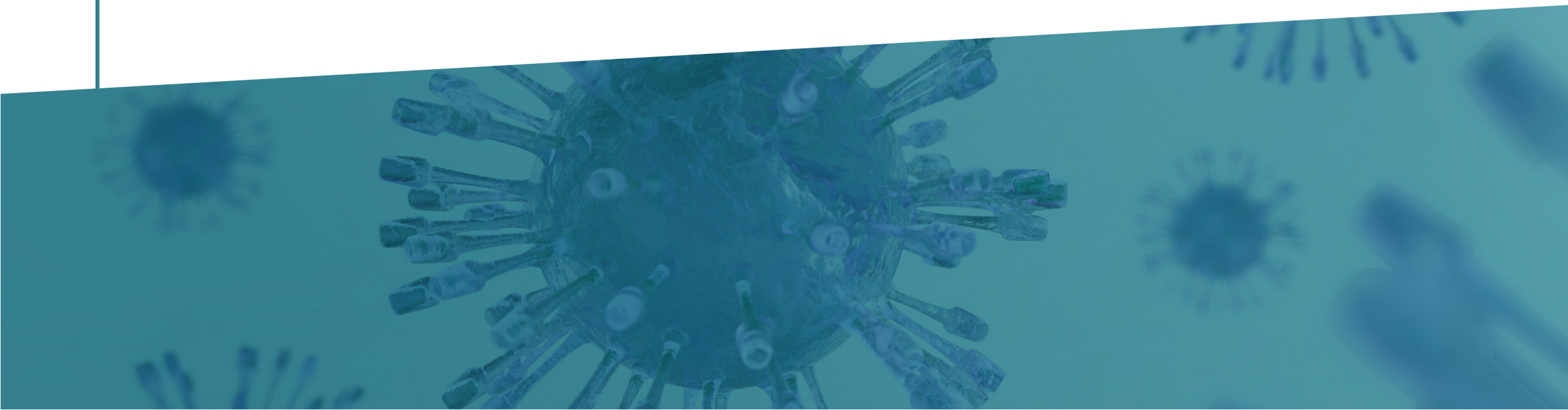
Data snapshot date: 11th March 2022

Conclusions – anti-PD1 failed NMSC & ARTACUS

- Initial data in both anti-PD1-failed NMSC treated with RP1 combined with Opdivo & RP1 monotherapy in solid organ transplant recipients with CSCC shows clinical activity, with responses observed in 33% of patients
- Further highlights the potential for RP1 to treat patients with anti-PD1-failed and other difficult-to-treat disease
- Further demonstration of the monotherapy activity of RP1

RP1: Summary

Rob Coffin



Establishing a broad skin cancer franchise

Full accrual expected mid-2022, primary data trigger expected YE 2022; Initial approval in anti-PD1 naïve CSCC

Interim data expected in late 2022, primary data expected mid-2023; Rapid follow-on label in anti-PD1-failed melanoma

Established high OR & CR rate in CSCC, demonstrated activity in other NMSCs; Commercialization in MCC, BCC, angiosarcoma likely to be based on compendia listing

With signal can expand for registrational purposes; label expansion

Potential registration or compendia listing

Study being planned: enables capture of significant high-risk patient population

CERPASS – first-line CSCC randomized controlled pivotal trial N=180

IGNYTE anti-PD1-failed melanoma registrational cohort N=125

IGNYTE initial NMSC cohort (anti-PD1 naïve) N=30 (fully accrued)

IGNYTE anti-PD1-failed NMSC cohort N=30

ARTACUS skin cancers in solid organ transplant recipients N=65

Neoadjuvant CSCC

RP1 establishes confidence in easy-to-administer settings

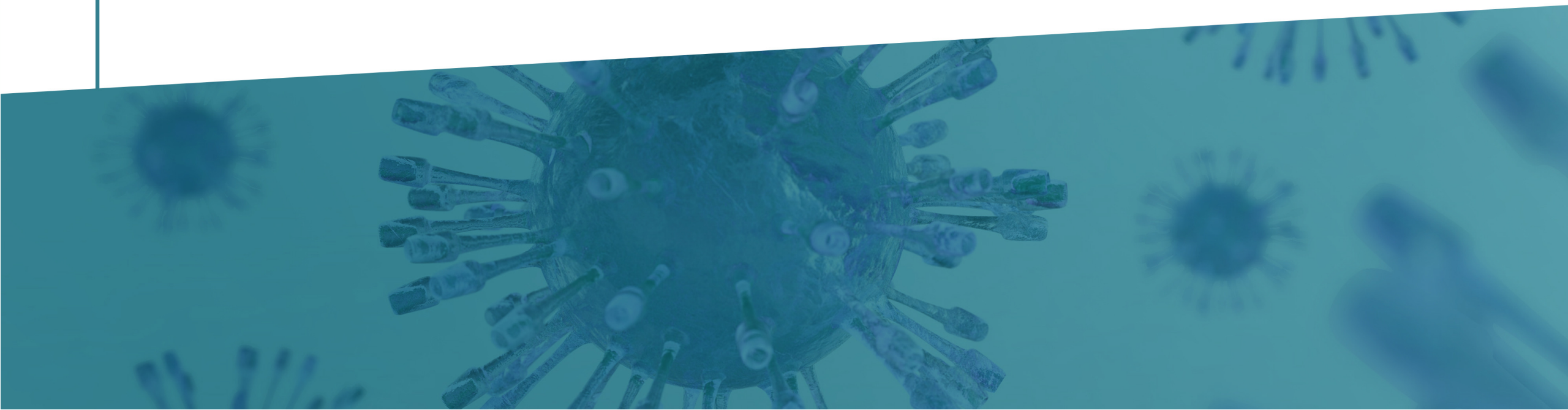
Deep and durable responses across multiple settings in skin cancer, including high CRs in 1L CSCC

Responses in anti-PD1-failed patients with melanoma & a range of NMSCs

Development to provide proof-of-concept in neoadjuvant setting

RP1: CSCC Overview

Nikhil Khushalani, M.D.



Nikhil Khushalani, M.D, Moffitt Cancer Center

Dr. Khushalani is the Vice Chair and Senior Member for the Department of Cutaneous Oncology at Moffitt Cancer Center.

His clinical interest is the development of novel therapeutics for people diagnosed with melanoma and other skin cancers.

Dr. Khushalani was an Associate Professor of Oncology at Roswell Park Cancer Institute and, prior to joining the Moffitt team, was Associate Professor of Medicine at SUNY, Buffalo, where he was the Section Chief of Soft Tissue and Melanoma Medicine, and Director of the IL-2 Program.

He earned his MD from Topiwala National Medical College, University of Bombay, in Maharashtra, India. He completed a Medical Oncology Fellowship at Roswell Park Cancer Institute in 2002.

Going Beyond the Classic Management of Cutaneous Squamous Cell Carcinoma

Nikhil I. Khushalani, MD
Assistant Center Director, Clinical Research Review and Partnerships
Vice-Chair and Senior Member, Cutaneous Oncology
Chief, Medical Oncology Service
Moffitt Cancer Center

Disclosures

- Dr. Khushalani is a compensated consultant for BMS, Jounce, Iovance, Merck, Immunocore, Regeneron, Sanofi, Novartis, Incyte, and AstraZeneca (Incyte, AZ-Data Safety Monitoring Committee); stock ownership in Bellicum, Asensus Surgical, Amarin; research support (all to institution) from BMS, Merck, Celgene, Novartis, GSK, HUYA, Amgen, Regeneron, Replimmune.

The content of this presentation has been entirely controlled and prepared by Dr. Khushalani, who is not acting as an agent or spokesperson for any company. No company had the right of final approval of the content and/or edits of this presentation

Agents that have not been FDA approved or are used for purposes other than the label indications may be discussed in this presentation.

Epidemiology

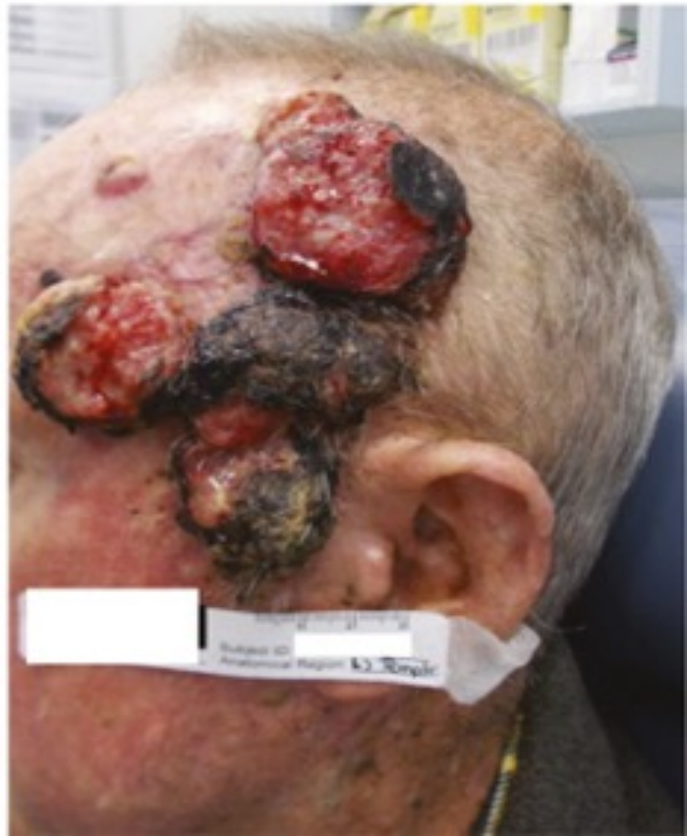
- The second most common skin cancer with ≈700,000 patients annually (>90% have excellent prognosis) in the U.S.[1]
- Caused by exposure to ultraviolet radiation
- 263% increase in incidence of CSCC between 1976–1984 and 2000–2010
- ~10% of CSCC patients are high risk (neo-adj opportunity)
- Approximately 7,000-15,000 US deaths annually[1-3]
  - 80% of patients die from locoregional progression, not metastatic disease[4,5]
- ~15-30% of patients have underlying immune deficiencies from solid organ transplant, RA, MS, CLL, HIV

[1]Rogers et al JAMA Dermatol **10** 2015
[2]Clayman et al JCO **23** 2005
[3]Mansouri et al J Am Acad Dermatol **153** 2017
[4]Schmults et al JAMA Dermatol **149** 2013
[5]Motaparthi et al Adv Anat Pathol **24** 2017

Alam M. NEJM. 2001;344:975; Karia PS. J Am Acad Dermatol. 2013;68:957; Rogers HW. JAMA Dermatol. 2015;151:1081; Nehal KS, NEJM. 2018;379:363.

Typical Patient Presentation

- Patients tend to be older, >60 yrs old
- Usually develops from precursor lesions (actinic keratosis) but may be *de novo; m*ajority (80–90%) occur on the head and neck
- Clinical presentation for recurrent or metastatic disease can be quite variable
- Locally advanced tumors can impact quality of life and contribute to social isolation
  - Disfiguring, painful
  - Foul smelling drainage
  - Delay in seeking medical care
- Given locoregional progression occurs in many patients with high-risk disease*, and ~70-90% CSCC have superficial tumors intra-tumoral approaches are of special interest



*Desiniottis et al. *JEADV 2022*;36:39-50.

The Question(s): Unmet Needs

- Anti-PD1 therapy is an effective option for many patients but room for improvement exists
  - Can we improve overall and complete response rates with combination therapy?
  - Is there an optimal 2nd line treatment post-aPD1?
  - Non-check-point inhibitor therapy for specific populations of high risk CSCC (e.g., transplant, auto-immune disease)?
  - Mimic advanced therapy success in earlier stage disease (e.g., neoadjuvant therapy)?

Cemiplimab: EMPOWER Study

Phase 1 (n = 26): adult patients with locally advanced or metastatic cSCC who are not candidates for surgery

Phase 2 (n = 59): cSCC with distant or regional metastasis

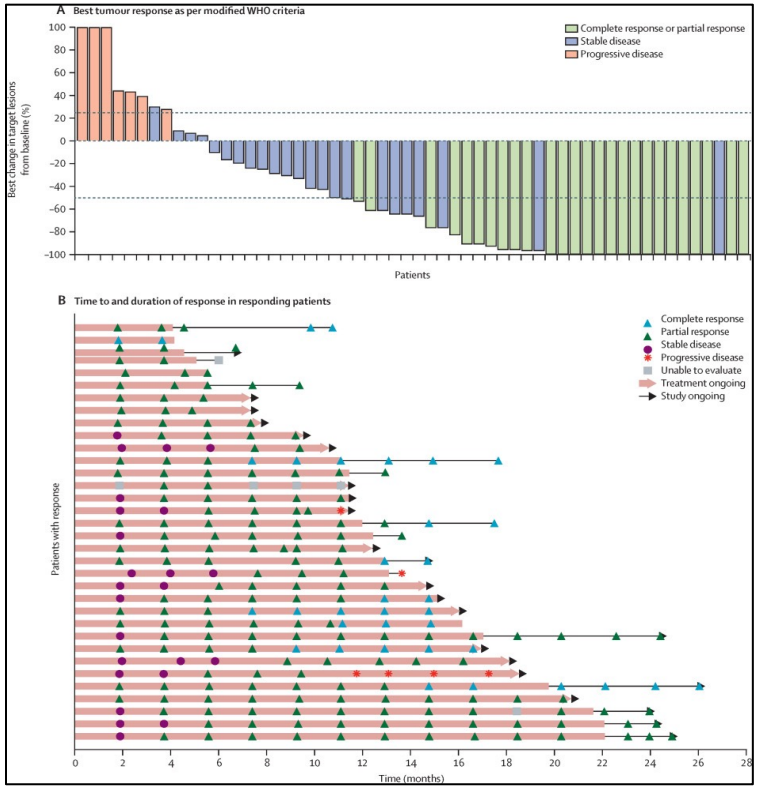
IV cemiplimab (3 mg/kg of body weight) Q2W for up to 48 weeks (phase 1) or up to 96 weeks (phase 2)

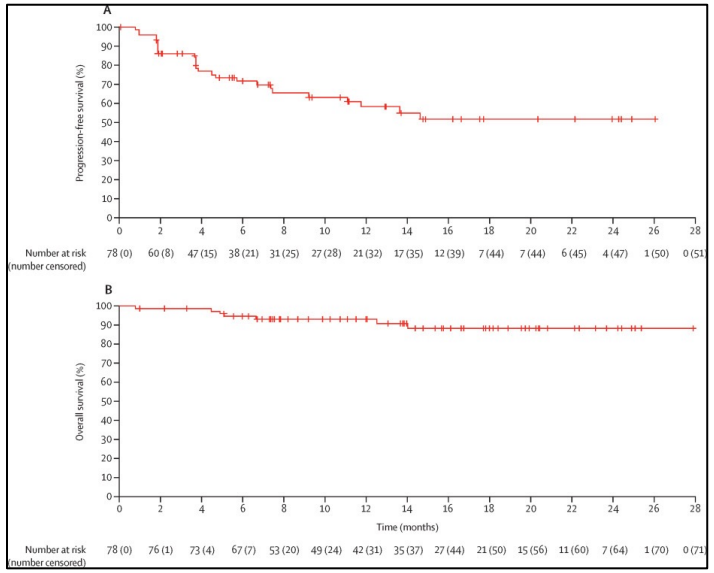
Inclusion criteria: ECOG of 0 or 1, adequate organ function, at least 1 lesion that could be measured (RECIST 1.1)

Exclusion criteria: Ongoing or recent autoimmune disease treated with systemic immunosuppressive therapy, previous treatment with anti-PD-1 or PD-L1 therapy, solid organ transplantation, concurrent cancer

Migden MR, et al. *N Engl J Med*. 2018;379:341

EMPOWER: Locally Advanced Cohort



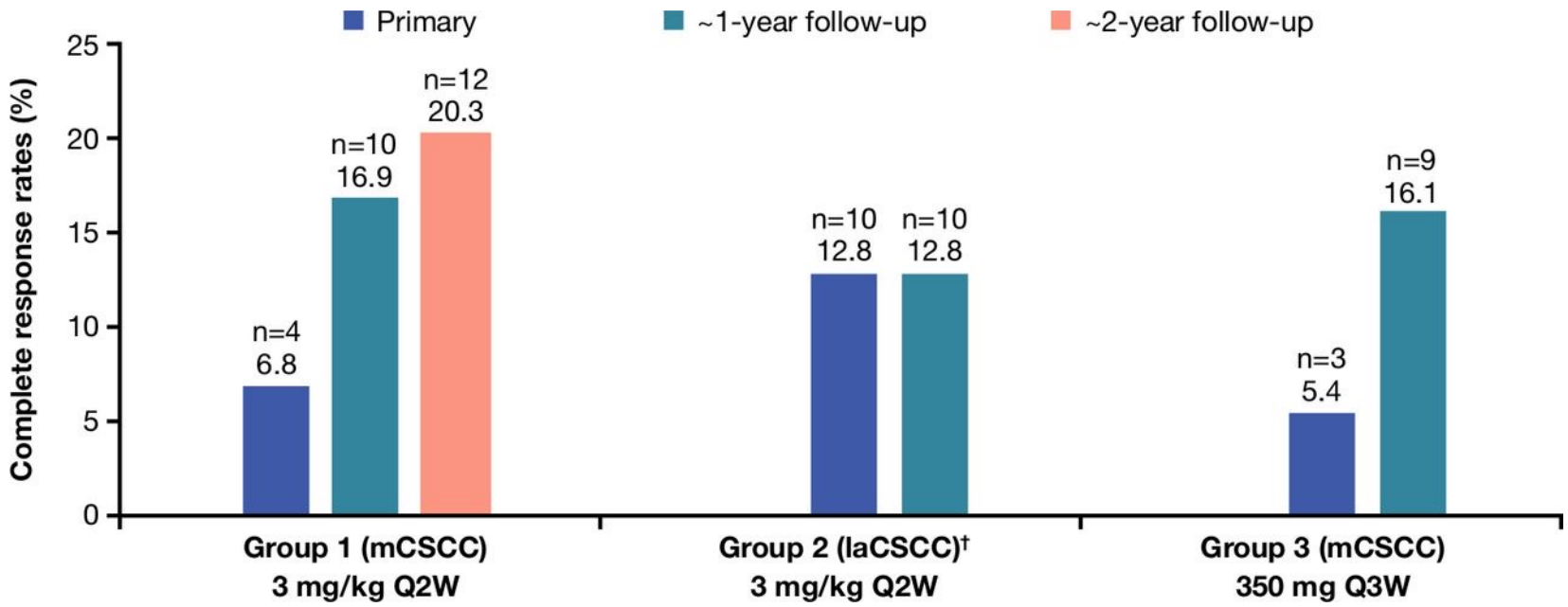


N=78; ORR **44%** (13% CR)

G3/4 treatment emergent adverse events: 44%

Migden MR, Khushalani NI, et. al *Lancet Oncol* 2020;21:294

Complete Response Rates (BIR)

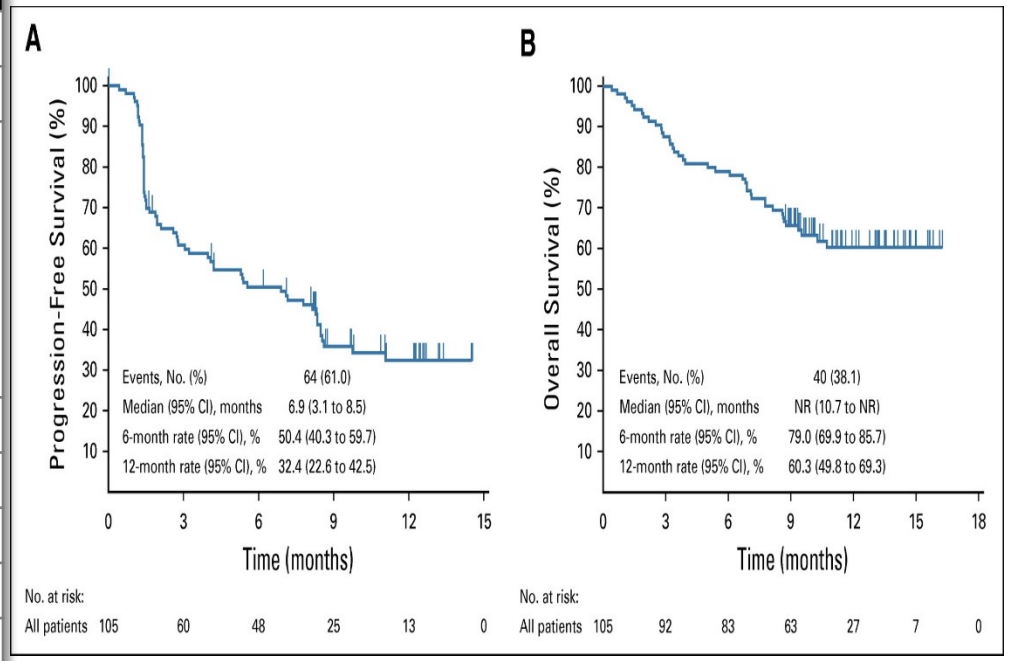


Rischin D, Khushalani NI, et al. J Immunother Cancer 2021;9:e002757

KEYNOTE 629

Pembrolizumab for Advanced CSCC

Endpoint	Patients (N = 105)
Median follow up	11.4 (0.4-16.3) months
Objective RR	**34.3%**
Best overall response • CR • PR • SD • Progressive disease • Not evaluable	 3.8% 30.5% 29.5% 26.7% 1.9%
Disease control (CR+PR+SD)	52.4%
SD ≥12 weeks	18.1%
Median time to response	1.5 months
Median DoR	NR
Estimated 12-month PFS/OS	32.4%/60.3%



Grob. J Clin Oncol 2020;38:2916

Post aPD1 Treatment

- Nothing FDA approved for patients who have failed anti-PD1 treatment
  - Chemotherapy, cetuximab or a combination of these agents are used for some patients
    - Efficacy
    - Toxicity
  - New options are need for patients
    - Less toxicity
    - Higher ORR/CRs and/or durable benefit?

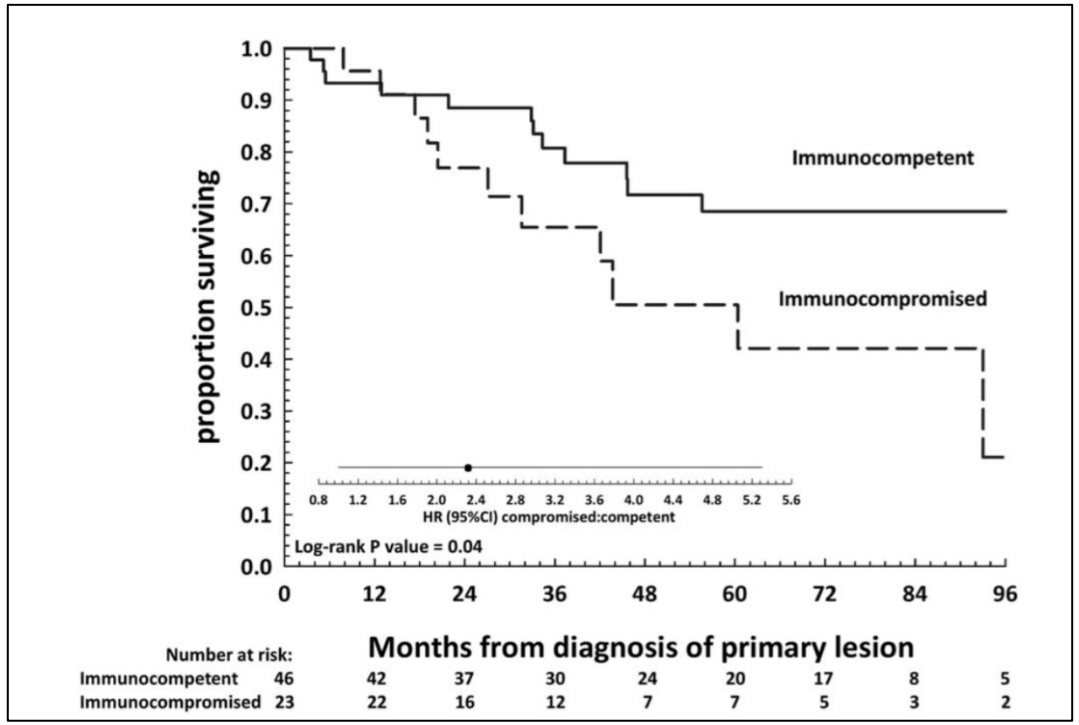
Immunosuppression and Skin Cancer

	BCC	CSCC	Melanoma	MCC	KS
Transplant	10	65-250	2-5	5-50	80-500
CLL	8*	8*	2-4	-	-
HIV	2	5	1	2-10	100,000

- Skin is the most common site of malignancy post solid organ transplant
- Incidence rate: 1437/100,000 person-years
  - CSCC: 812/100,000 person-years
  - Male, white race, increased age and thoracic organ transplant conferred higher risk

Garrett, Blanc, et al. *JAMA Dermatol* 2017;153:296; Collins, Quinn, et al. *Dermatol Clin.* 2019;37-83

Immunosuppressed (IS) do much worse



- 23 IS vs 46 IC (OTR or hematologic malignancy) with nodal metastases
- 5 year disease-specific survival 42% vs 68% *(26% ↓ in survival when IS)*

Lam JKS, et al. *Head Neck*. 2018;40:985-992.

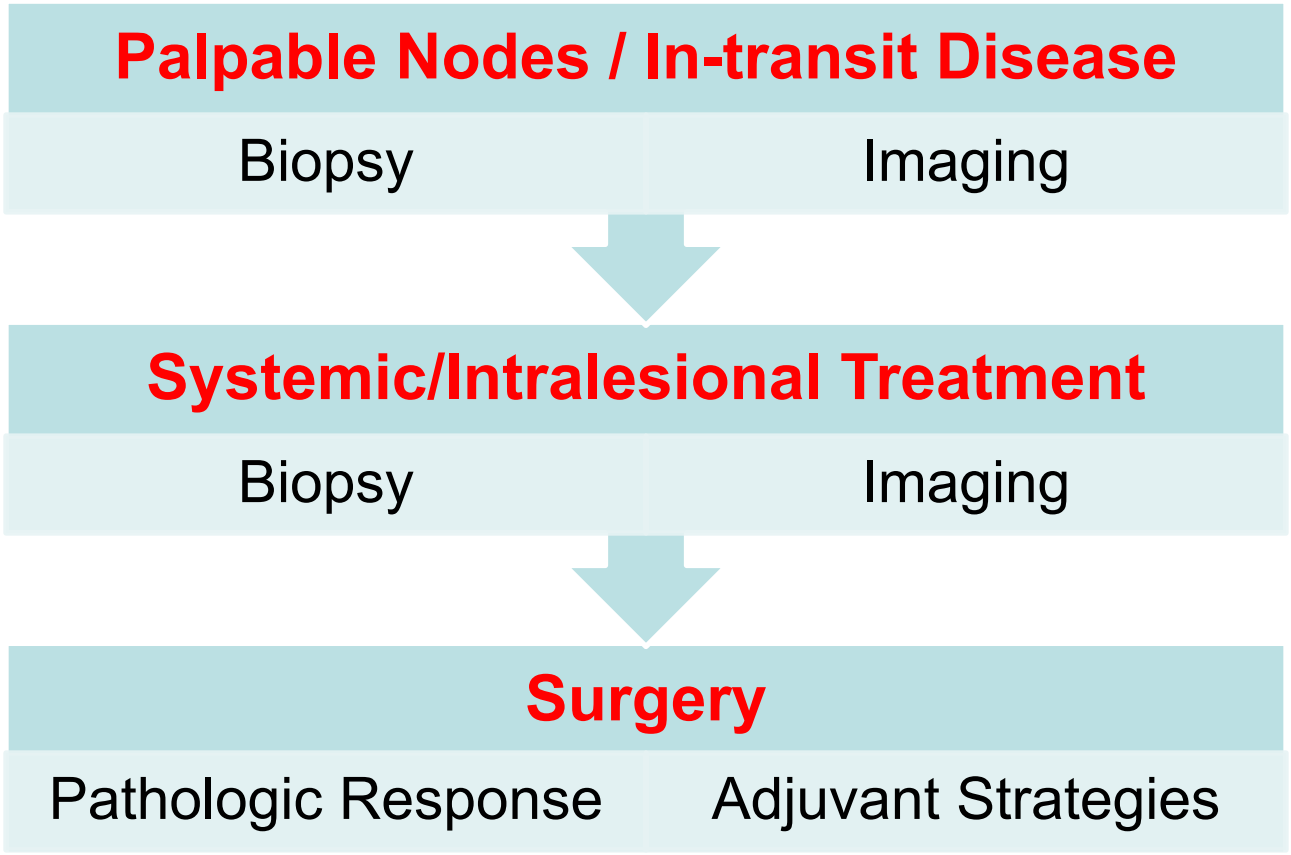
Treatment of Solid Organ Transplant (SOT)/Immunocompromised Pts

- Use of anti-PD1 is limited for SOT
  - contraindicated due to risk of organ rejection
- Use of anti-PD1s in other immunocompromised patients?
  - These patients were excluded from registration trials of approved aPD1 agents
  - Use can be considered on a case-by-case basis

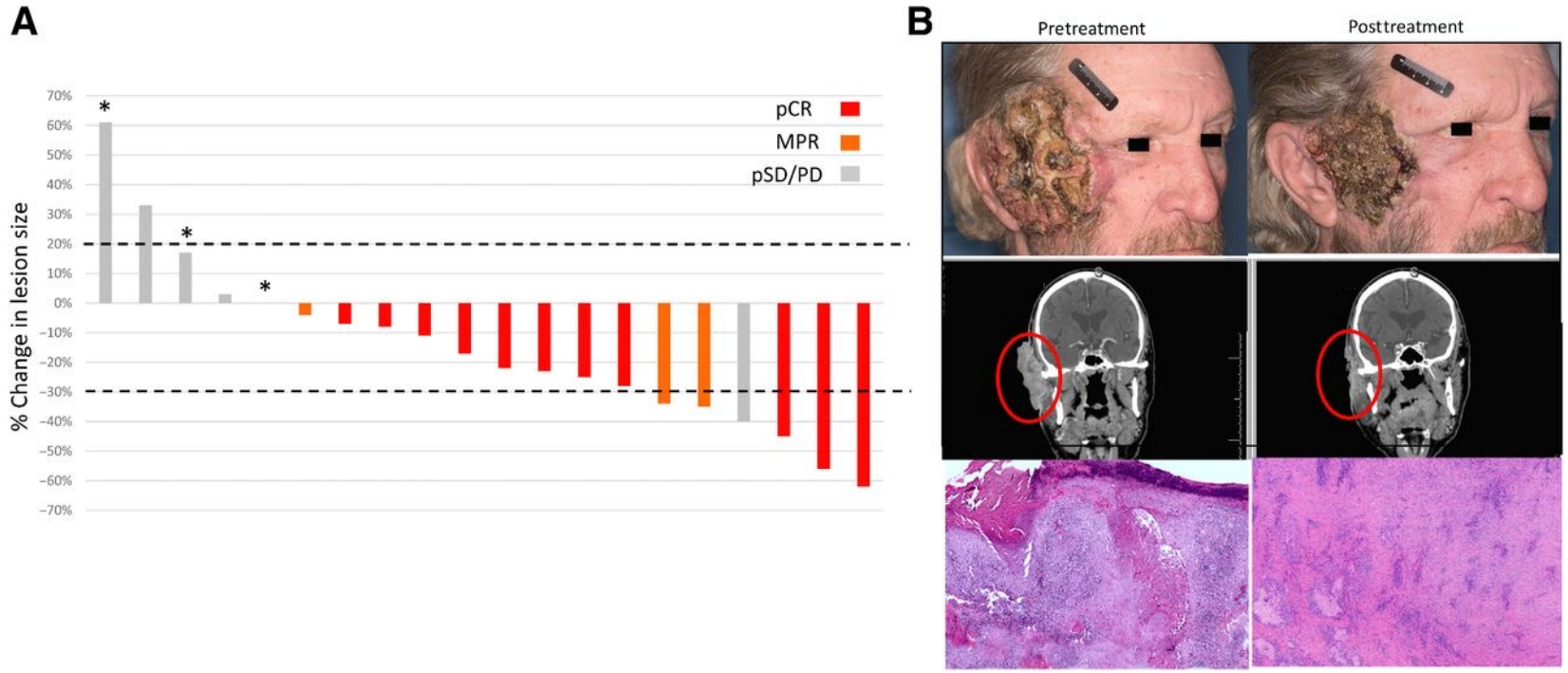
Neoadjuvant Therapy: Terminology

- Neoadjuvant therapy is the administration of systemic therapy prior to surgery in patients with assessable regionally advanced or metastatic disease, with a ***plan to carry out resection*** of the tumor after a defined period of time
  - The response of the tumor to neoadjuvant therapy can be assessed radiographically (CT - RECIST), metabolically (PET) and histologically
  - Postoperative adjuvant therapy may or may not be used, and its use may be mandated or considered based on response to neoadjuvant therapy

Neoadjuvant Therapy:
Paradigm to Study Tumor Biology

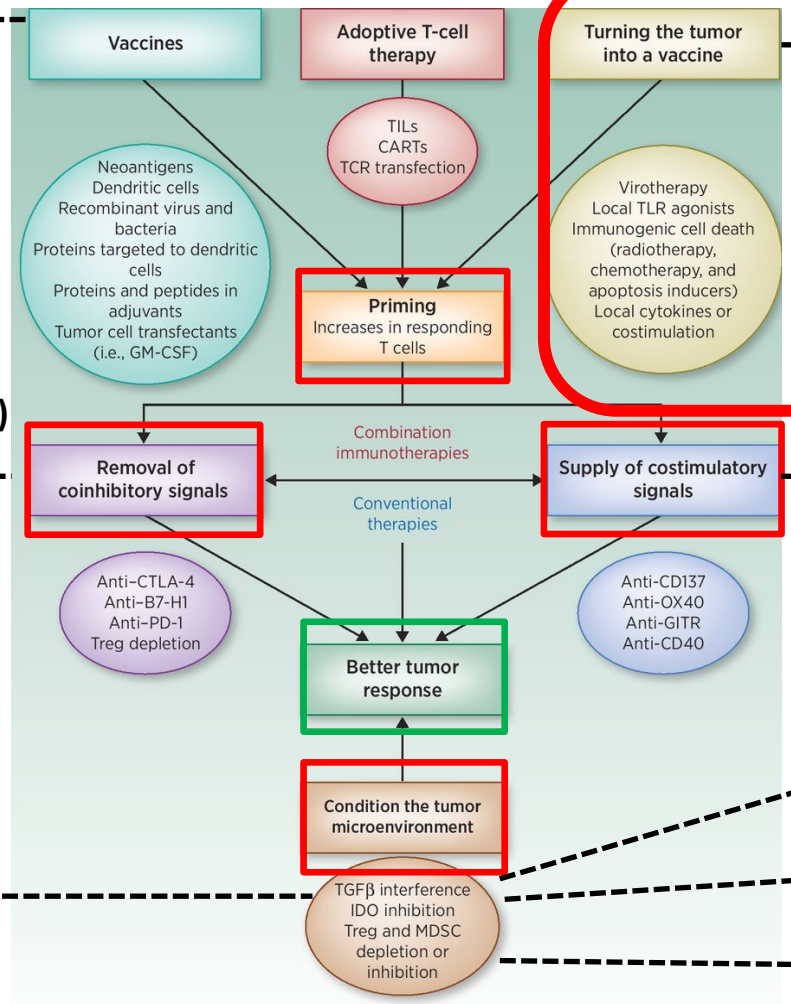


Neoadjuvant Cemiplimab in CSCC



Renata Ferrarotto et al. Clin Cancer Res 2021;27:4557-4565

Treatments Beyond aPD1



TiTAN-1
NCT04596033

Ipi+nivo (neoadjuvant)
NCT04620200

Cetuximab
Plus pembrolizumab
NCT03666325

Oncolytic

RPx
TVEC
HVS-1

NCT03714828

CAVATAK
Coxsackievirus A21

NCT02565992

rIL-7+atezolizumab
NCT03901573

Treg targeting therapies
Lai C et al, Clin Cancer Res 2016

Anti-CD47
NCT04502888

SL-172154 (SIRPa/CD40L)
NCT04502888

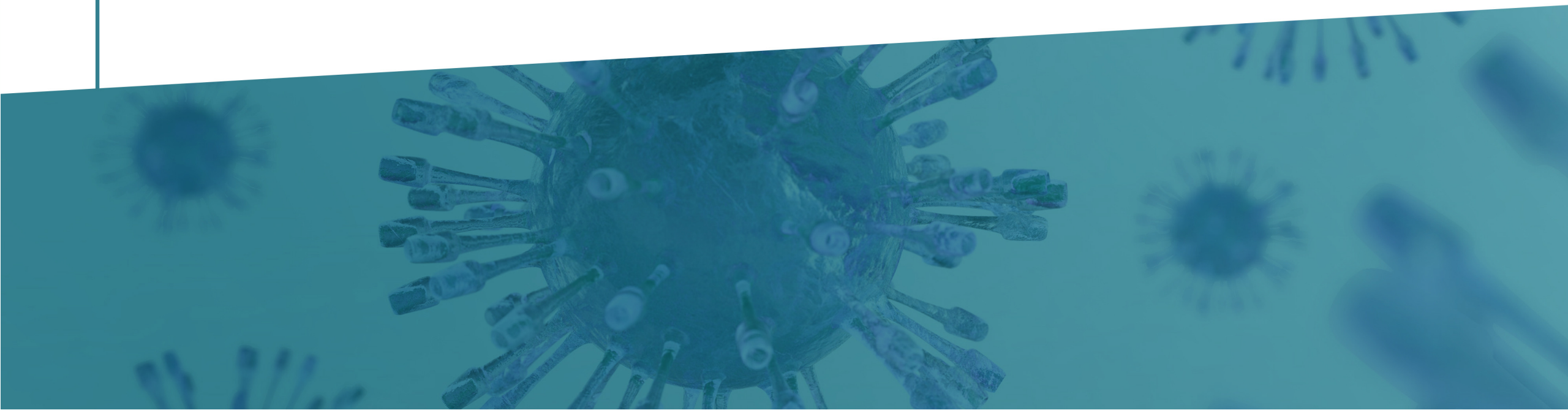
Whiteside TL et al, Clin Cancer Res 2016

Conclusions

- Rising incidence = ↑ public health burden = greater urgency in prevention and treatment
- While anti-PD1 is effective for the treatment of CSCC, roughly 70% of treated patients still ultimately progress
- Oncolytic immunotherapy provides a promising option to help a broader group of CSCC patients
- Molecular understanding of CSCC = therapeutic advances
  - This sets the stage for investigation into combination therapy and adjuvant/neoadjuvant therapy; trials have been initiated

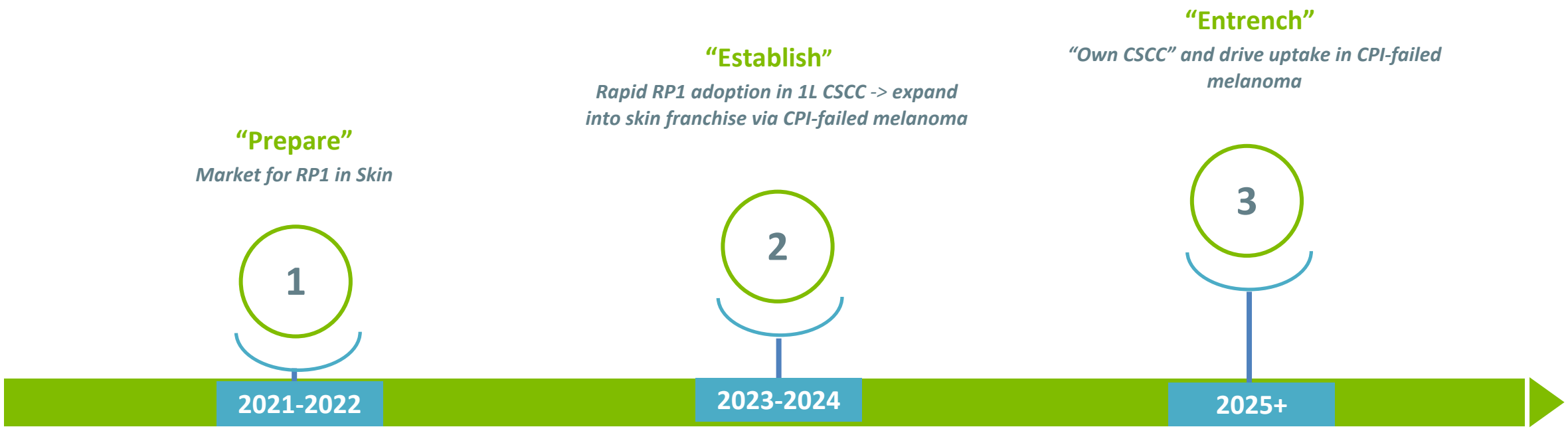
RP1: Skin
Commercial Plans

Sushil Patel



Establishing an RP1 “Skin Cancer Franchise”

Vision: *“To deliver transformational results for patients across cancers using tumor directed oncolytic immunotherapy to induce a powerful and durable systemic anti-tumor immune response resulting in quality survival and a chance for cure”*



- LPI in 1L CSCC
- LPI in CPI-failed Melanoma

- Approval in 1L CSCC
- Approval in CPI-failed melanoma

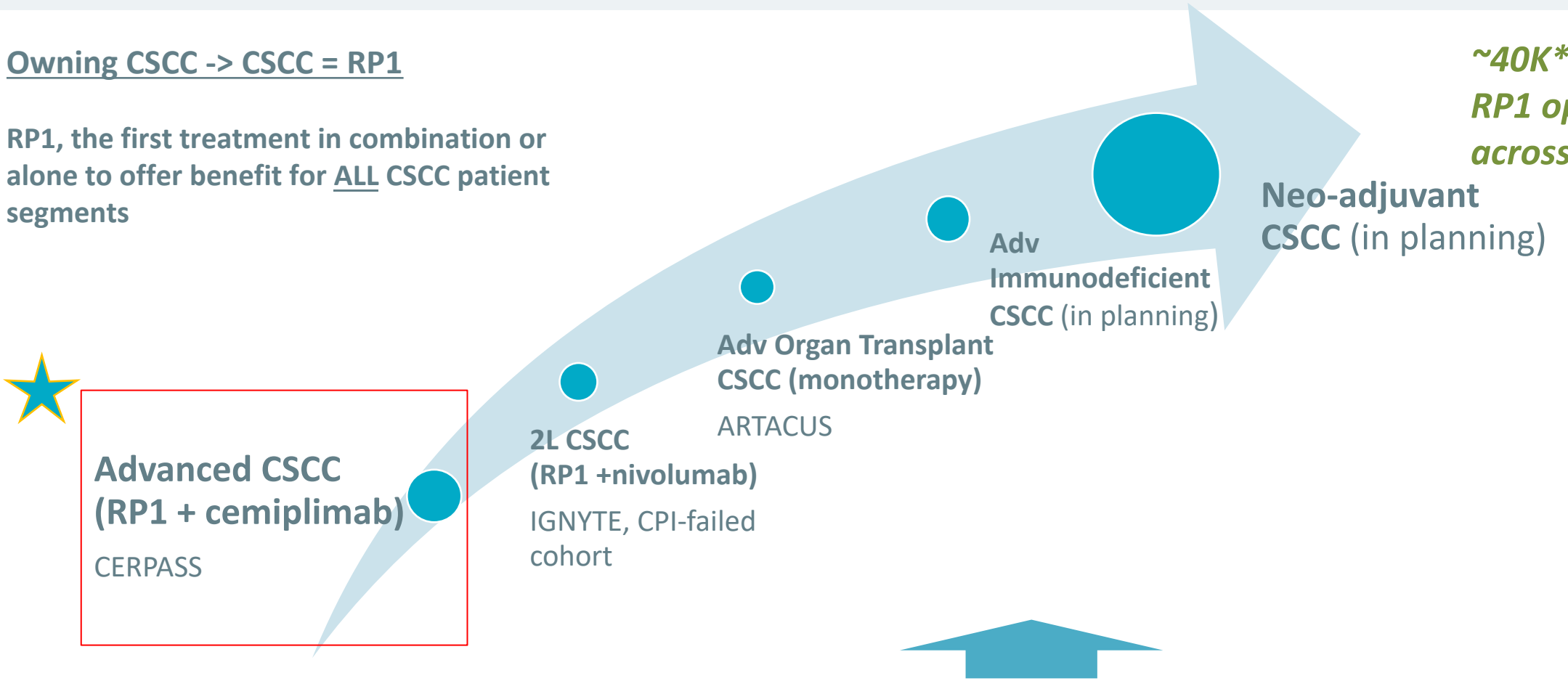
- Neoadjuvant CSCC
- Broaden to other CSCC patient segments/skin cancers via compendia listing

Building a skin cancer franchise starts with a successful RP1 launch in advanced CSCC

Owning CSCC -> CSCC = RP1

RP1, the first treatment in combination or alone to offer benefit for ALL CSCC patient segments

~40K* US patient RP1 opportunity across segments



Unmet Needs

- **Better 1L/neoadjuvant therapy : higher/faster CR rates and improved durability**
- **Better 2L therapy post-CPI**
- **Immunodeficient pts who can't get a CPI and/or don't benefit from them**

*Est. US treated population (Kantar epidemiology data)

Critical success factors for RP1

Replimune®

Key Product Attributes:

- **High CRs**
- **Compelling duration of response**
- **Improve quality of life**
- **Safety and tolerability**
- CSCC are characteristically **large superficial tumors** -> ideal first launch due to method of delivery and MOA

Note: RP1 is in addition to SOC, not a replacement

1. Establish Strong HCP Confidence

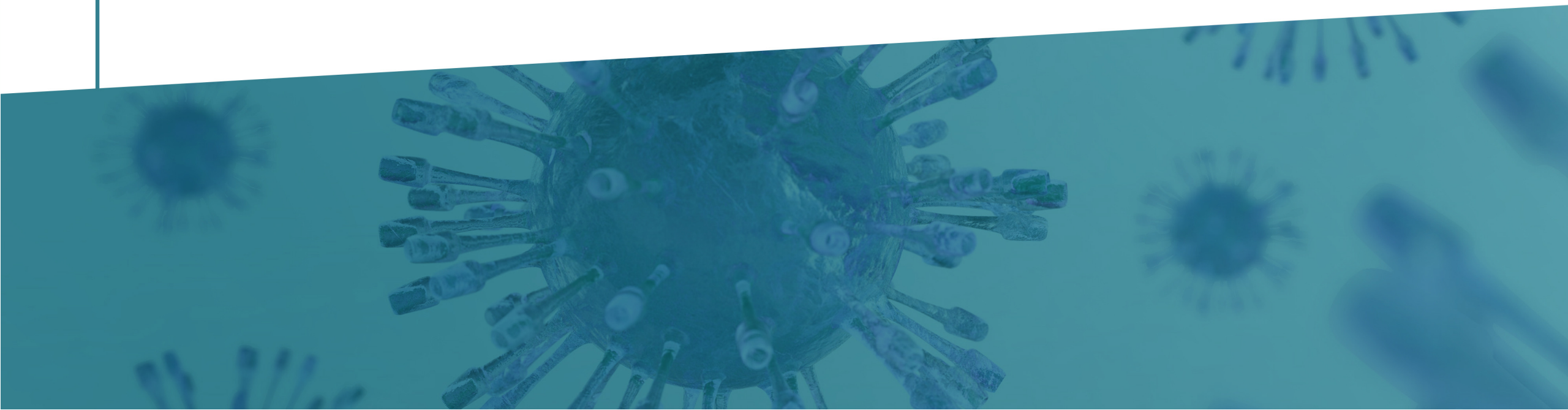
- **Narrative focused on local and systemic effects**
  - Differentiate on potent HSV backbone /GALV transgene
- Maximize awareness of compelling efficacy
- **Establish trained injector champions at every major hospital**

2. Deliver a Positive Experience

- **Simplified dosing & logistics**
  - Flexible schedule (Q2w, Q3w, Q4w), easy clean up/disinfection
- Partner with patient advocacy groups/patient ambassadors
- **HCPs and patients visibly see life-changing shrinking tumors**

Deep Injections (RP2/3): Commercial Considerations

Sushil Patel



Strategic tumor/setting selection will enable commercial success

Replimune®

"Focus for today"

1 **Accessible tumors**

Indications where delivery can be easy and routine: *Superficial/palpable lesions e.g., skin cancers*

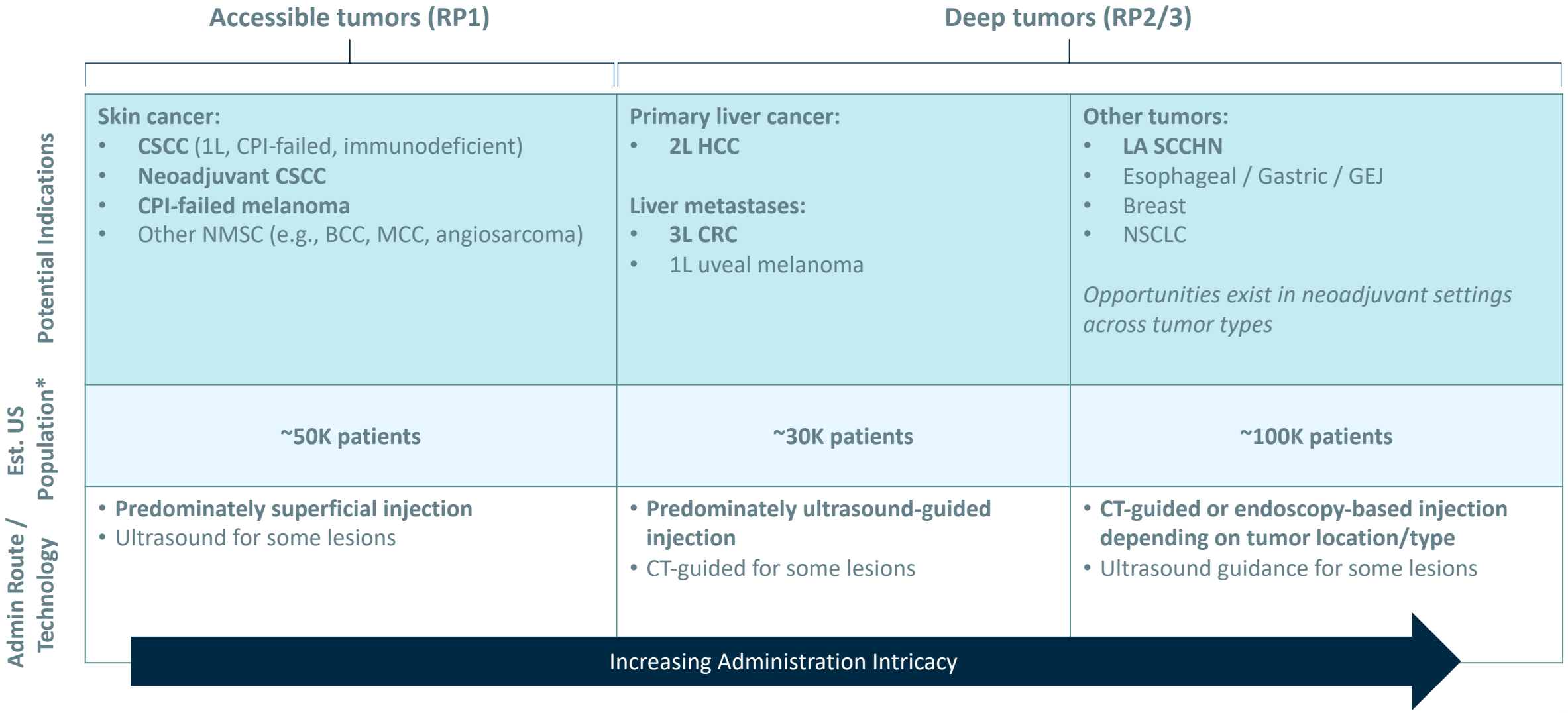
2 **Deep tumors (liver enriched)**

Indications where delivery is part of routine medical practice or can be easily adopted: *e.g., primary liver cancer or liver metastases*

3 **Deep tumors (other organs)**

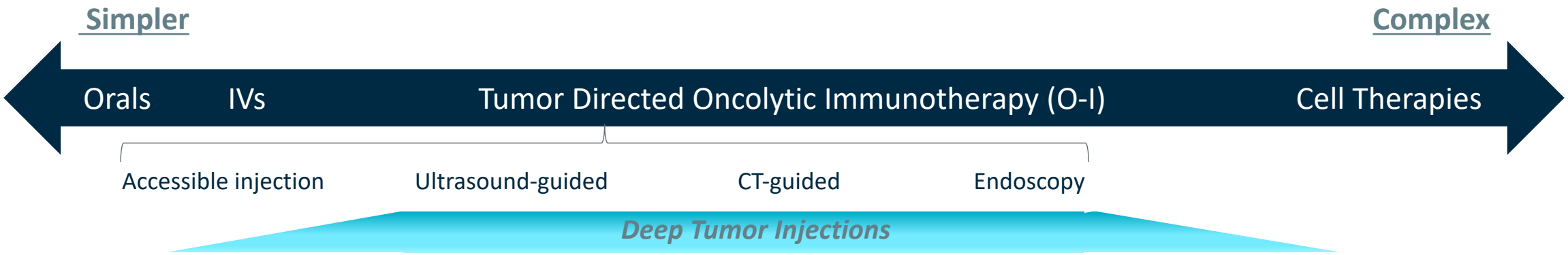
Indications where routine adoption poses a higher barrier*: Tumors where strong data is required to justify injections e.g., neoadjuvant lung or breast*

Indication prioritization via means of administration (commercial adoptability)



Bold = indications where pivotal studies labeling enabling studies are ongoing/planned or are new prioritized Ph2 signal-seeking opportunities. Others listed include additional signal-seeking opportunities *US treated population (Kantar epidemiology data)

Deep injections utilize existing expertise and logistics, enabling adoption in most settings



Potential Hurdles	Findings
Scheduling, Coordination & Logistics	• **Most injections are routine for IRs/Rads** • Similar logistics to other IR/Rad oncology procedures • Collaboration already exists between Oncs & Rads in most settings
Economics and Reimbursement	• **Value position / unmet need key to driving adoption by IRs/Rads** • Can make IR/Rad an essential part of transformative therapy/immuno-oncology • Opportunities to mitigate or improve reimbursement
Oncolytic Virus Biosafety	• **HCP training/education will increase confidence and help address misperceptions** • Can leverage extensive T-VEC (Imlygic) safety data

IRs= interventional radiologists, Rads= radiologists

Transformative data and sequence will enable broad RPx adoption and achievement of the vision

RP2/3: Liver as a "gateway"

Facilitates adoption of deeper injections in solid tumors "beyond skin" with RP2/RP3

#3

RP1: Building belief with CPI-exp melanoma

- High unmet need/presence of liver mets lowers deep injection barrier -> demonstrates feasibility
- Ability to leverage uveal data -> hard to treat "cold" tumor creates a positive halo effect

#2

- Durable benefit in high unmet-need population further establishes RP1 as transformational
- Opportunity to showcase the benefits of injecting deeper lesions (e.g. lymph nodes)

RP1: "Owning CSCC"

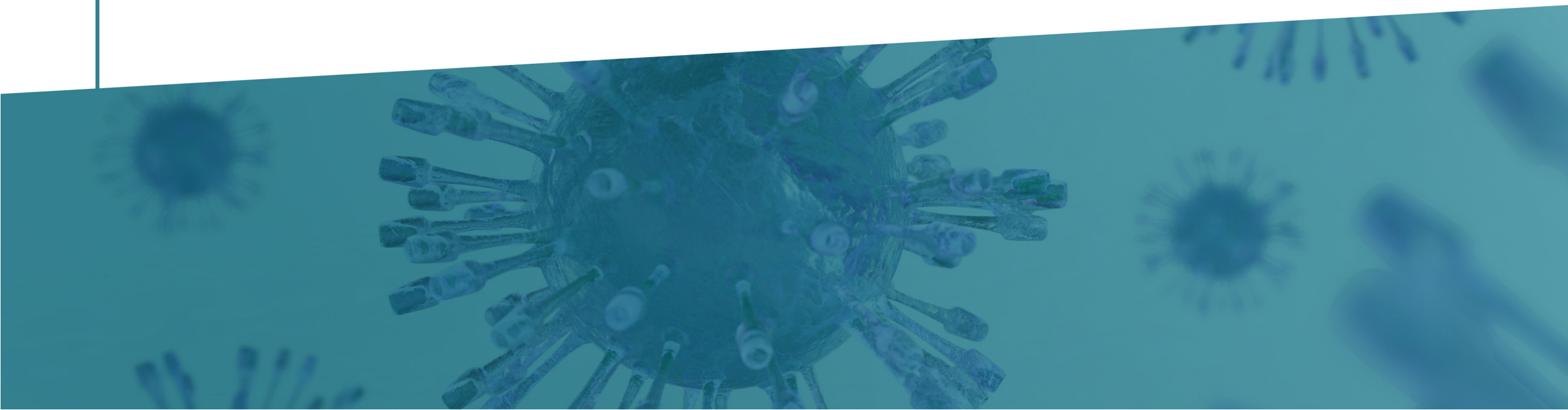
#1

The First launch sets the trajectory of the portfolio and company

- Addressing the key unmet needs in CSCC by improving CR rates, etc.
- "Hands on" superficial injection by HCPs with visible tumor shrinkage leads to positive first experience

RP2/3: Deep Injections, Technical/Clinical Considerations

Muneeb Ahmed, M.D.



Muneeb Ahmed, M.D, Beth Israel Deaconess Medical Center

Dr. Ahmed is a physician leader, Division Chief, and Vice Chair for Interventional Radiology at Beth Israel Deaconess Medical Center.

Dr. Ahmed's research focus includes NIH-funded studies in cancer biology, medical device development, clinical outcomes, and health services research. He serves national and international specialty societies through Board membership, committee service, and medical journal Editorial Board membership.

Following radiology and interventional radiology training at BIDMC/Harvard and Johns Hopkins Hospital, he joined the faculty at BIDMC. He is a nationally-recognized expert in the minimally-invasive treatment of cancer and currently serves as President-elect of the Society of Interventional Oncology.

Deep/visceral tumor injections

- **Definition**:
  - Tumors that cannot be injected with direct visualization or palpation
  - Require imaging guidance in order to be injected
    - **LIVER**, Lung, other solid organs
    - Lymph nodes – deep locations (e.g. retroperitoneal, pelvic, thoracic)

- **Why LIVER tumors first?**
  - Rising incidence of liver metastases
  - Liver metastases determine outcome regardless of primary cancer (50% higher risk of death)
  - Liver metastases are very resistant to current treatment options
  - Unique immune-resistant landscape
  - Direct injection concept for liver tumors has been around for decades
  - ***Targeting liver metastases = opportunity to treat multiple cancers types***

Horn SR. Cancer Epidemiology 2020; 67(101760)
Tsilimigras DI. Nat Rev Dis Primers. 2021 Apr 15;7(1):27.

Deep ‘tumor directed’ RPx injections

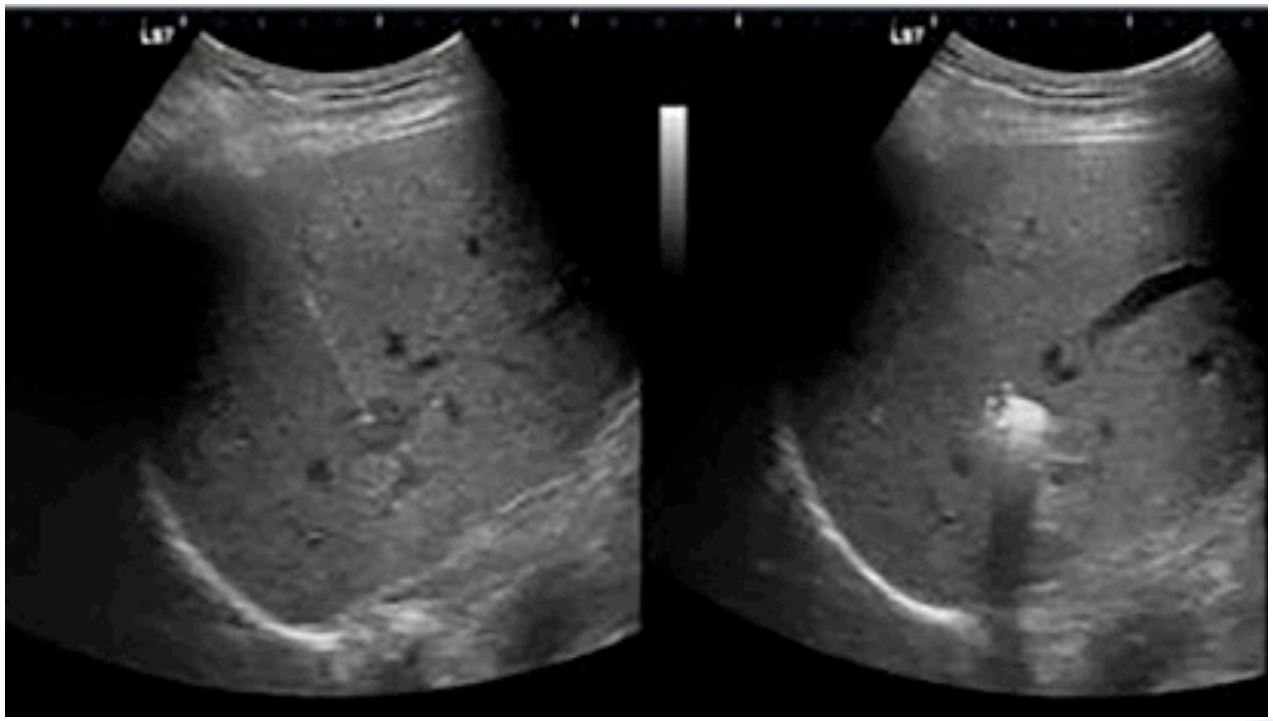
- **Ultrasound or CT guidance**
  - Approx. 80% of liver tumors can be injected with ultrasound guidance
  - Needle placed in target lesion
  - Up to 10 mL RPx can be injected
  - Agent distributed across the tumor(s)

- **Can be done by any radiologist (either diagnostic or interventional)**
  - Outpatient procedures usually with conscious sedation
  - Logistics similar to FNA or biopsy (infrastructure and processes in place)
  - 20 min procedure; monitoring for 2-4h

***Formal injection protocol for RPx has been developed with KOL input*

Ultrasound image with needle placed in tumor

Immediate post injection image



Tselikas L. Clin Canc Res 2021;27:2698–705.
Sheth RA. JAMA Network Open. 2020;3(7):e207911.

All grade treatment-emergent adverse events (TEAE) >15% following intra-tumoral injection into liver metastasis

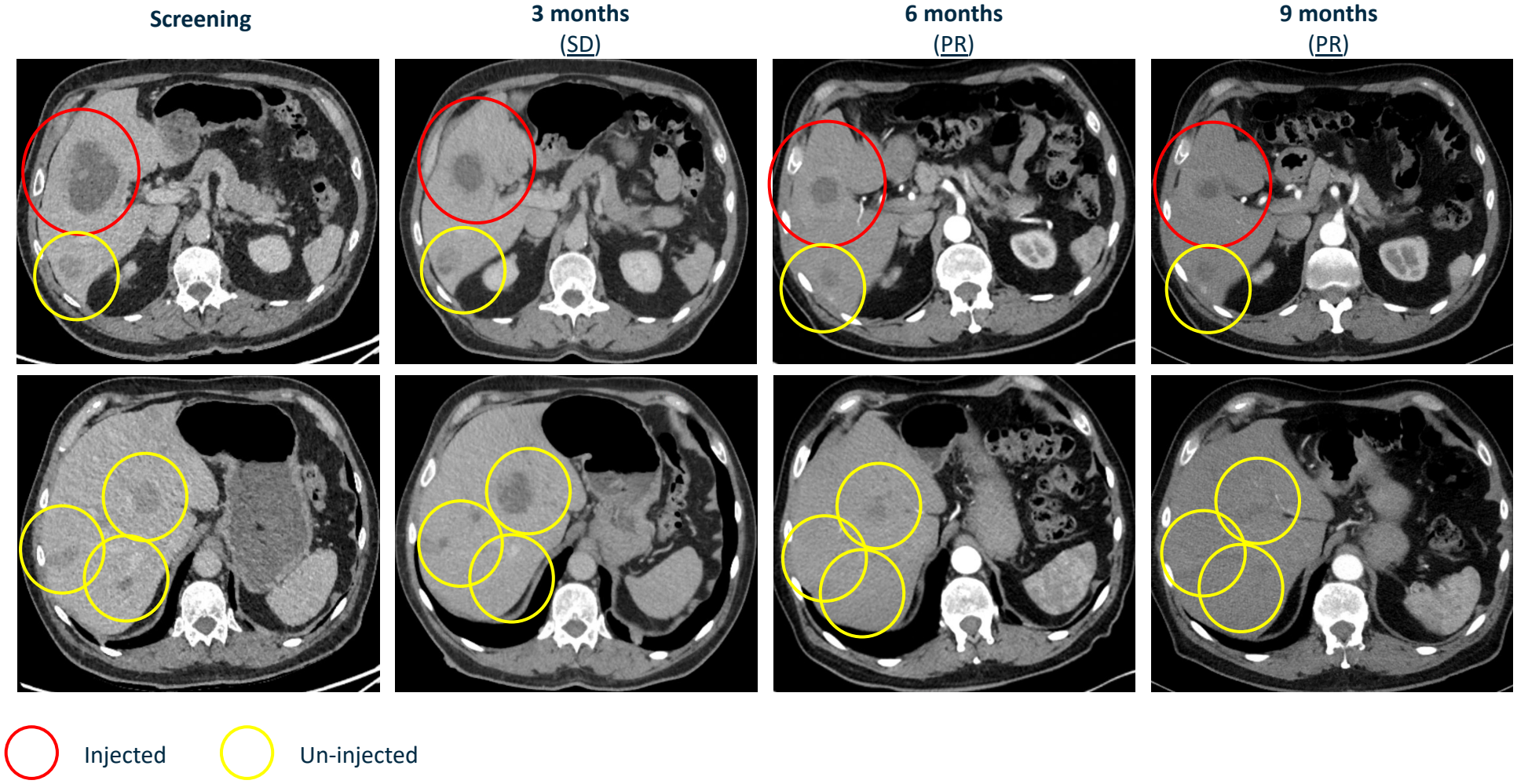
	RP1			RP2		
	Liver Mets Injected	Liver Mets Not Injected	All Liver Mets	Liver Mets Injected	Liver Mets Not Injected	All Liver Mets
N	26	19	45	10	5	15
Pyrexia	17 (65.4)	5 (26.3)	22 (48.9)	7 (70.0)	3 (60.0)	10 (66.7)
Nausea	14 (53.8)	7 (36.8)	21 (46.7)	2 (20.0)	3 (60.0)	5 (33.3)
Chills	16 (61.5)	4 (21.1)	20 (44.4)	2 (20.0)	4 (80.0)	6 (40.0)
Hypotension	-	-	-	3 (30.0)	2 (40.0)	5 (33.3)
Fatigue	12 (46.2)	8 (42.1)	20 (44.4)	2 (20.0)	2 (40.0)	4 (26.7)
Back pain				2 (20.0)	2 (40.0)	4 (26.7)
Constipation	7 (26.9)	7 (36.8)	14 (31.1)	0	2 (40.0)	2 (13.3)
Vomiting	10 (38.5)	4 (21.1)	14 (31.1)	0	3 (60.0)	3 (20.0)
Influenza like illness	8 (30.8)	5 (26.3)	13 (28.9)	1 (10.0)	1 (20.0)	2 (13.3)
Abdominal pain	8 (30.8)	4 (21.1)	12 (26.7)	2 (20.0)	2 (40.0)	4 (26.7)
Pruritus				2 (20.0)	1 (20.0)	3 (20.0)
Arthralgia	6 (23.1)	5 (26.3)	11 (24.4)	0	2 (40.0)	2 (13.3)
Cough	4 (15.4)	5 (26.3)	9 (20.0)	3 (30.0)	0	3 (20.0)
Diarrhoea	6 (23.1)	3 (15.8)	9 (20.0)	-	-	-
Decreased appetite	3 (11.5)	5 (26.3)	8 (17.8)	-	-	-
Injection site pain	7 (26.9)	1 (5.3)	8 (17.8)	2 (20.0)	0	2 (13.3)

≥Grade 3 TEAEs in all patients with liver mets (injected or not injected)
RP1 – Abdominal pain (n=4); Lipase increased (n=4); Anaemia (n=3) (Injected only (2 events each): ALT increased, Pyrexia, Urinary tract infection; Not injected only (2 events each): Diarrhoea, Disease progression)
RP2 – Injected only (1 event each): Hepatic pain, Infusion related reaction, Syncope; Not injected only (1 event each) : Abscess limb, Acute myeloid leukaemia, Anaemia, Arthralgia, Haemorrhage, Pain, Pancytopenia

Example patient with liver metastases treated with RP2 monotherapy

Pt 4401-0003 – PR

- Uveal melanoma
- Extensive liver metastases (others not shown)
- Prior therapies: Ipilimumab/ nivolumab
- Patient progressed at 15 months



Importance of stakeholder engagement

- **Tumor directed therapy success depends on key stakeholder engagement**

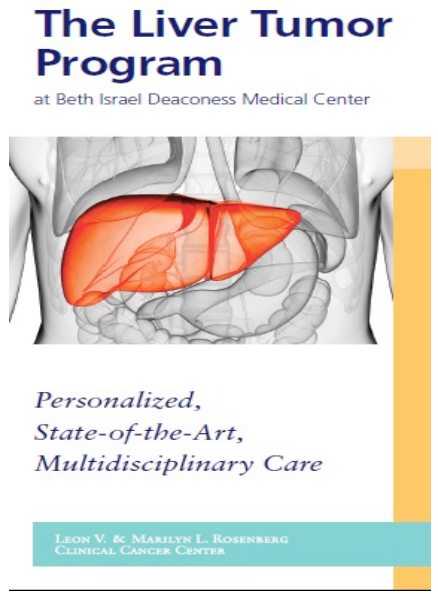
- **Patients receive treatment from multiple physicians, in particular:**
  - **Medical oncologists**
    - General or specialized
    - Patient point of contact
  - **Interventional Radiologists**
    - Primary treatment of liver cancers – tumor ablation; embolization (TACE/TARE)
    - Gateway for all image-guided procedures, in particular deep injections

- **At many institutions, virtual or formal multidisciplinary tumor boards or clinics**
  - Central point of referral for patients with primary and metastatic liver tumors
  - Brings key specialties together (medical oncology, radiation oncology, surgery, interventional radiology)
  - Opportunity/gateway for clinical trials

- **Successful early clinical trial success depends on engagement of both groups**

Cancer Center

Beth Israel Deaconess Medical Center

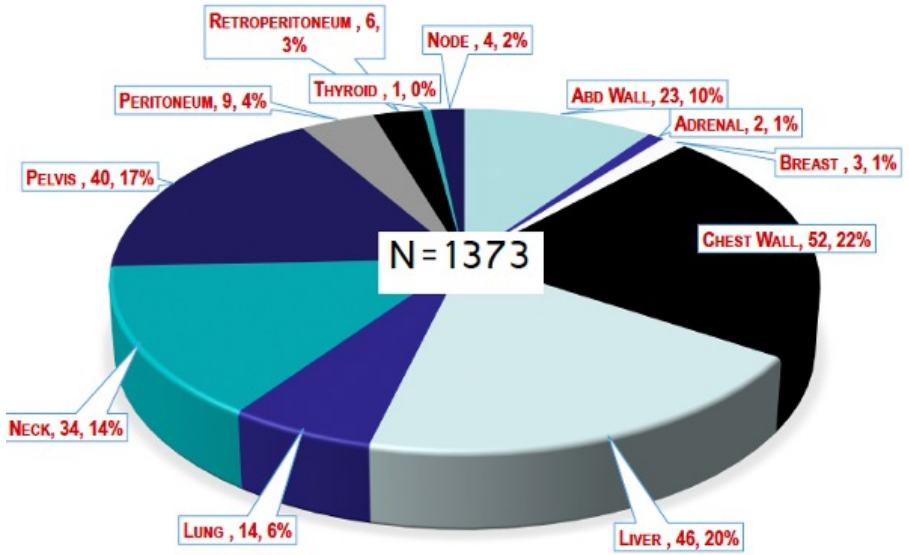


@BIDMC –
Liver Tumor Program has
5 specialties led by Interventional Radiology

SIO Society of Interventional Oncology

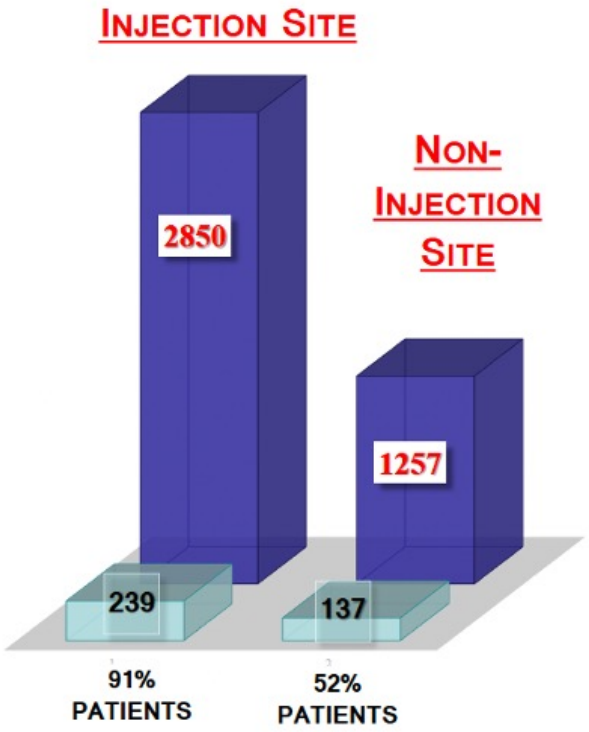
Significant clinical trial experience at MDACC demonstrates feasibility, safety and scalability of intra-tumoral injection across tumors

Intra-Tumor Therapy Injection



- 4 injections MDN/pt
- Target Dimensions 32 mm MDN (8-230mm)
- Parietal169 / Visceral 93; subset 'Nodal' 83
- 68% US guided; 65% 'subcutaneous'
- 2ml Injectate volume MDN (1-6.9ml)

Core Biopsy



Serious Adverse Events

ITT I related 1.3% NCI CTC V3
Biopsy related 0.5%
No deaths

Conclusion

Technicaly safe; variety agents
Side effects managable
Scalable - use of ultrasound

*262 patients in 29 immunotherapy trials (TLR/STING agonists, Gene therapy, Anti-CD40, viral/bacterial/metabolic Oncolytics)
Data extracted from Murthy et al, MDACC, SITC Poster #397, 2020

Tumor directed oncolytic immunotherapy: RPx injection summary

- Intra-tumoral immunotherapy injection for liver metastases is a compelling proposition

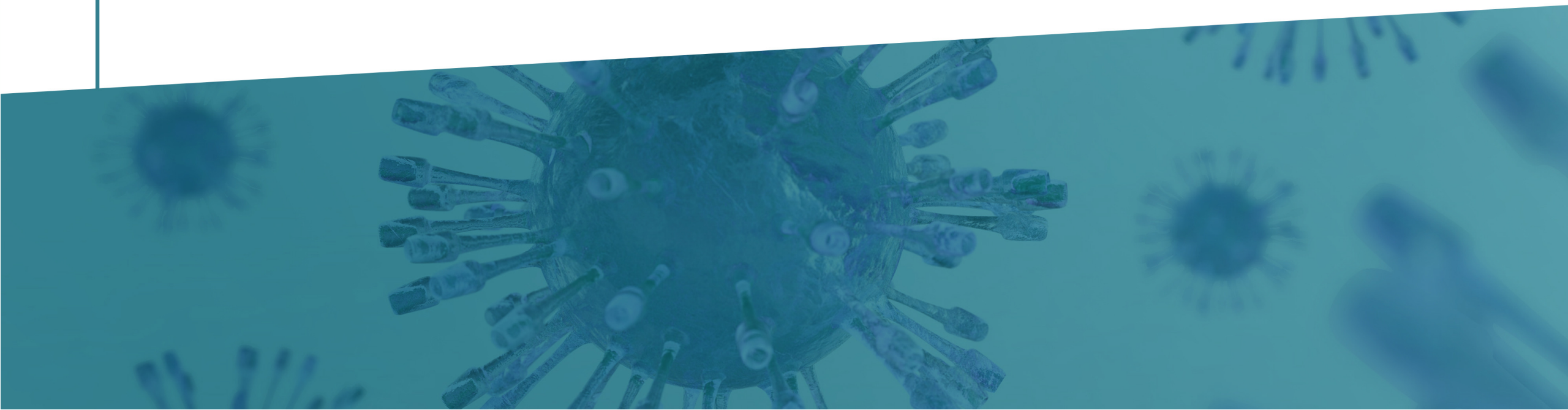
- Liver is a frequent site of metastasis across multiple tumor types -- approx. 50% patients of various cancer types develop liver mets (Tsilimigras et al Nat Rev Apr 2021)
  - Poor prognostic indicator, agnostic of primary tumor type
  - Disproportionately reduces the activity of I-O when compared to metastases in other organs
  - Hepatic mets have the ability to siphon and functionally inactivate tumor-specific CD8+ T cells

- RP1 & RP2 can be safely administered repeatedly to hepatic metastases and have demonstrated activity both locally and systemically

- Intra-tumoral immunotherapy injection of other deep organs beyond primary liver cancer/HCC and liver mets can be safely done

RP2/3 Next Wave Development

Rob Coffin



RP2 & RP3 leverage Replimune's platform to express additional potent immune stimulators

- Focus on the delivery of molecules which function at the time & place of immune activation, i.e. in tumors & draining lymph nodes
- Delivered mechanisms are clinically validated
  - Anti-CTLA-4 – ipilimumab, tremelimumab
  - CD40L, 4-1BBL – agonistic antibodies against CD40 & 4-1BB (CD137) have shown clinical activity

- The RP1 backbone maximizes antigen presentation & T cell activation to kickstart an immune response
  - CTLA-4 inhibits the effectiveness of antigen presentation and T cell activation (immunogenic 'Signal 1' & 'Signal 2')
  - CD40L & 4-1BBL provide immune co-stimulation (immunogenic 'Signal 2') needed for full immune activation
    - Leads to the expression of inflammatory cytokines – immunogenic 'Signal 3'

- **Local expression of each of anti-CTLA-4, CD40L & 4-1BBL optimal**, both mechanistically, and to reduce systemic toxicity

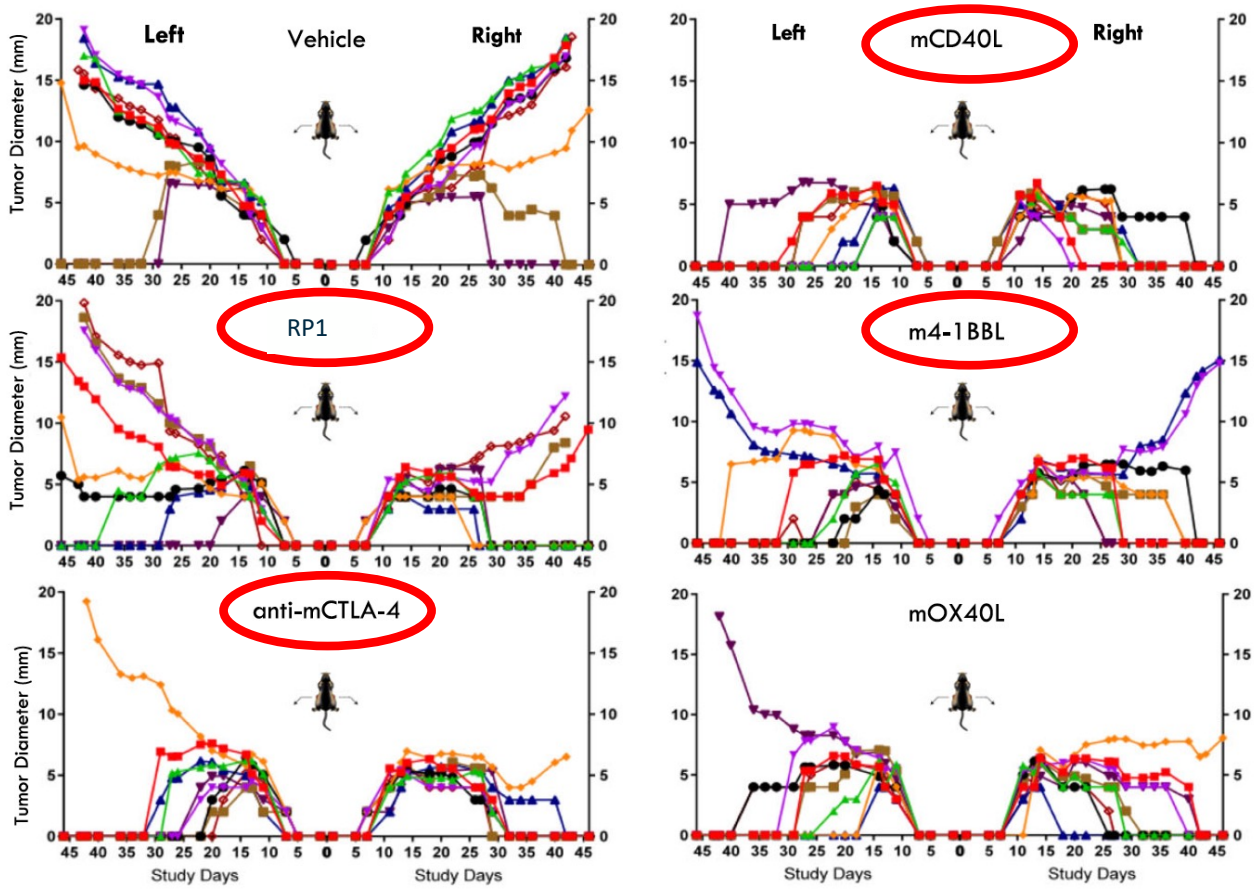
RP2 & RP3 Rationale for additional payloads: increased tumor killing and systemic activity in immune-competent mice

RP2

Engineered HSV backbone + GM-CSF + **GALV-GP R- + anti-CTLA-4**

RP3

Engineered HSV backbone + **GALV-GP R- + anti-CTLA-4 + 4-1BBL + CD40L**

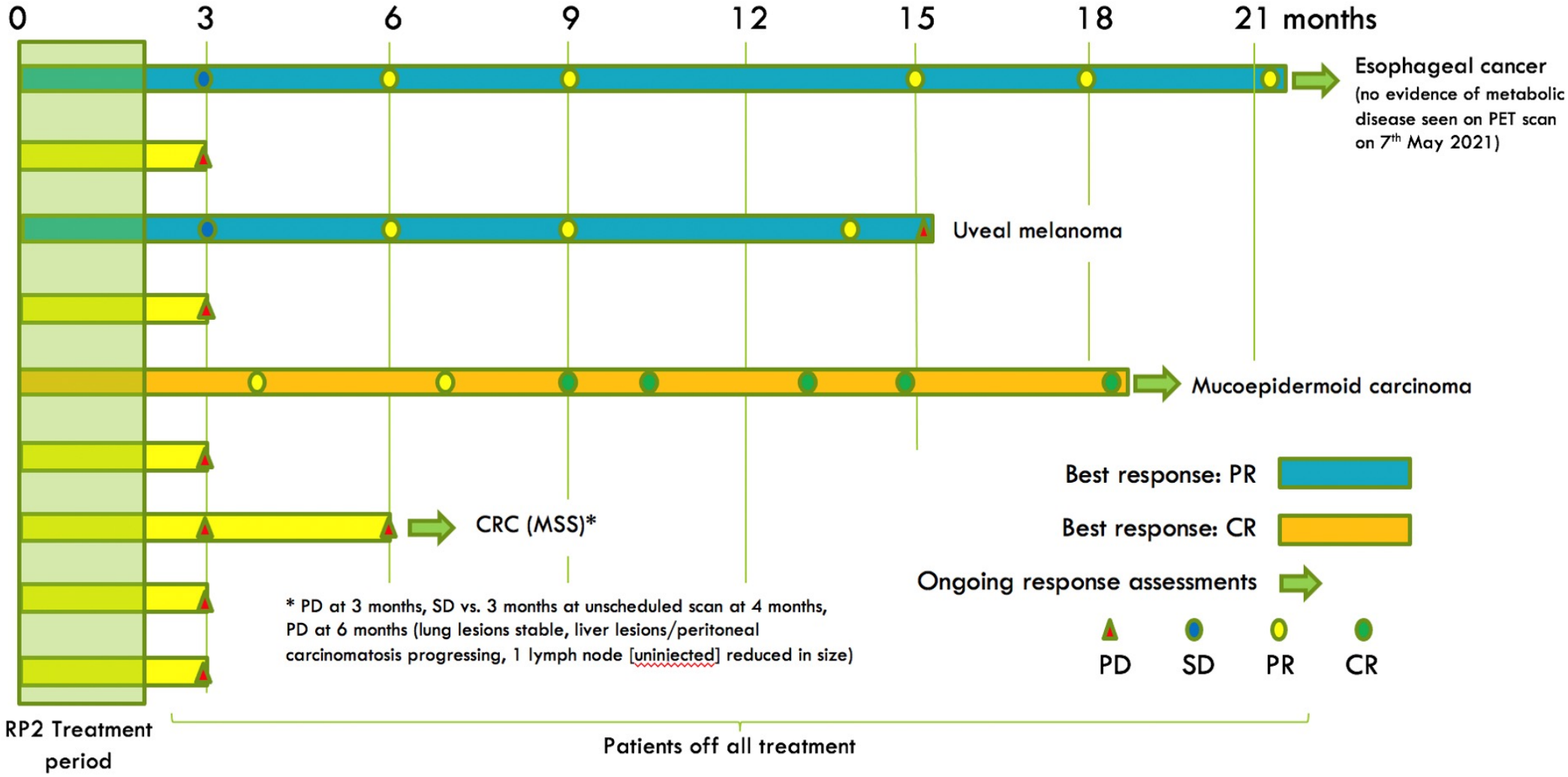


A20 lymphoma mice (immune competent) model

Thomas et al JITC. 2019

Single agent activity demonstrated in traditionally 'cold' tumor types

Kinetics of response following treatment with single agent RP2



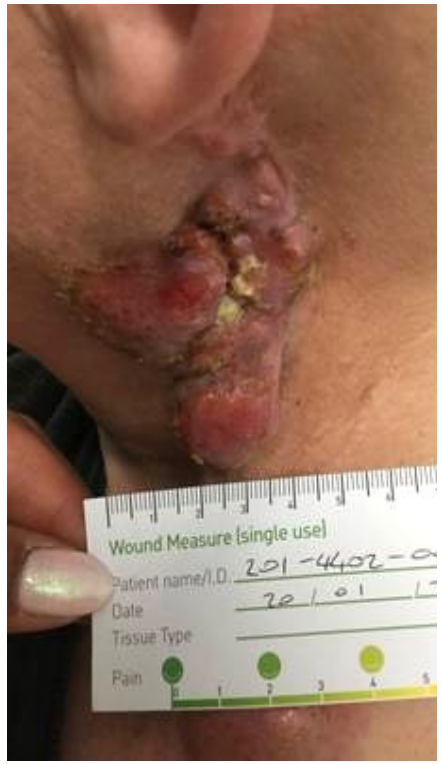
Data as of Oct 12th 2021

Ongoing CR in mucoepidermoid carcinoma following monotherapy RP2

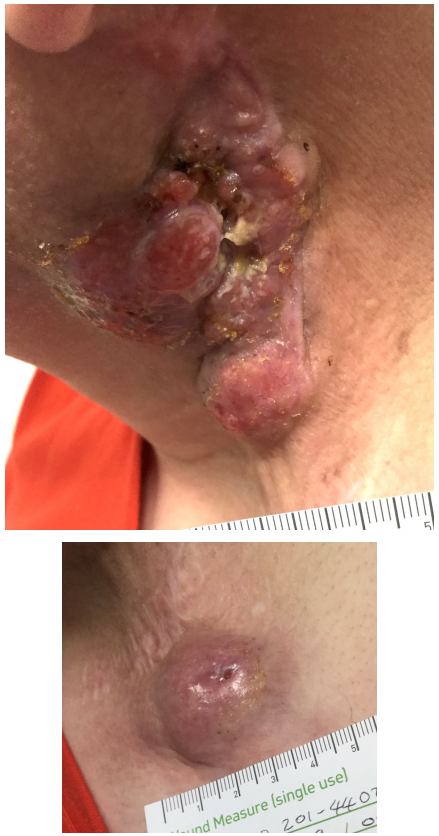
Pt 4402-0001 - ongoing CR

- Mucoepidermoid carcinoma of the parotid gland
- Prior therapies: carboplatin/ paclitaxel, bicalutamide, ceralasertib
- Cervical lymph node & supraclavicular fossa lesions injected

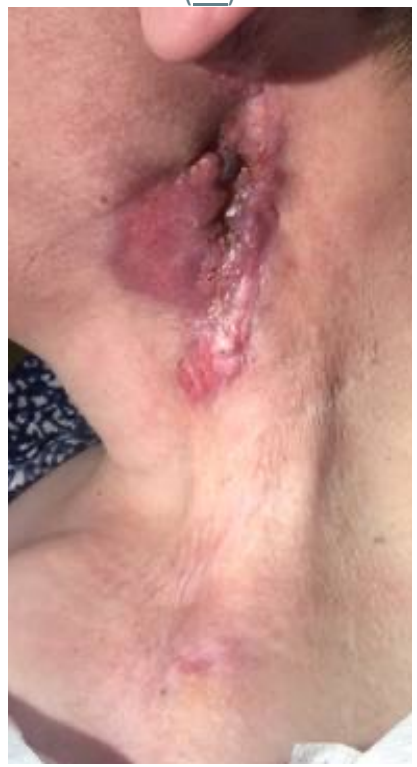
Baseline



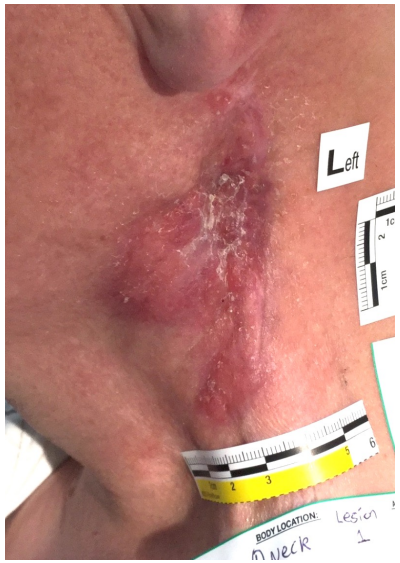
1 month

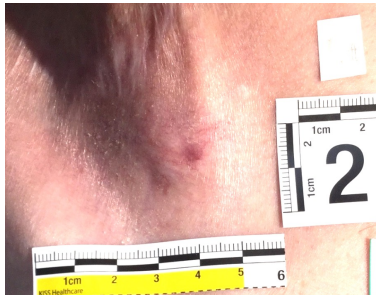


3 months
(PR)



4 months

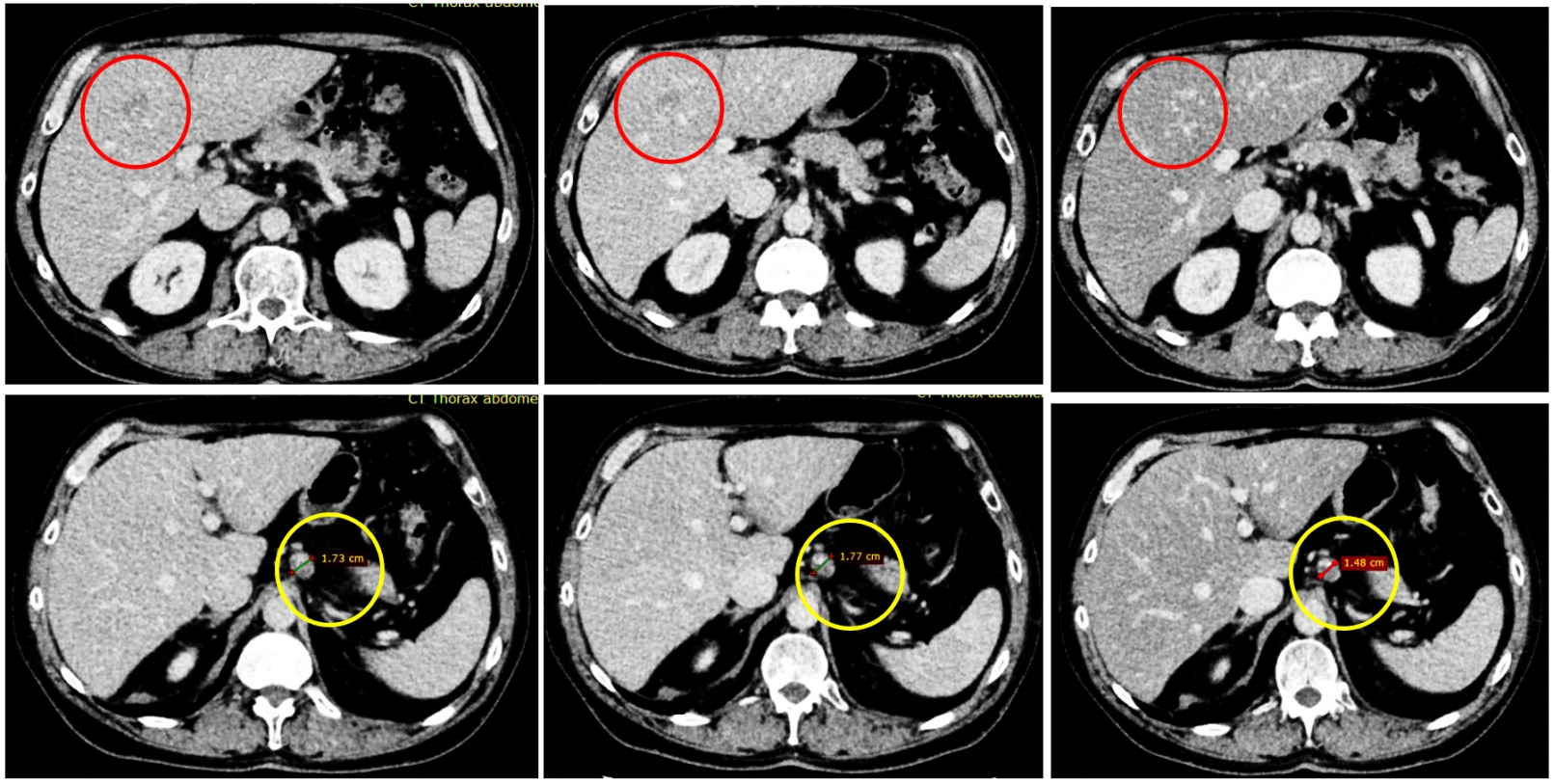




Ongoing PR in anti-PD-L1 failed esophageal cancer following single agent RP2

Pt 4401-0001 - ongoing PR

- Esophageal cancer
- Liver & abdominal lymph node metastases
- Prior therapies: Durvalumab (anti-PD-L1), M6620 (ATR kinase inhibitor), capecitabine, oxaliplatin, cisplatin, chemoradiation
- Liver lesion injected

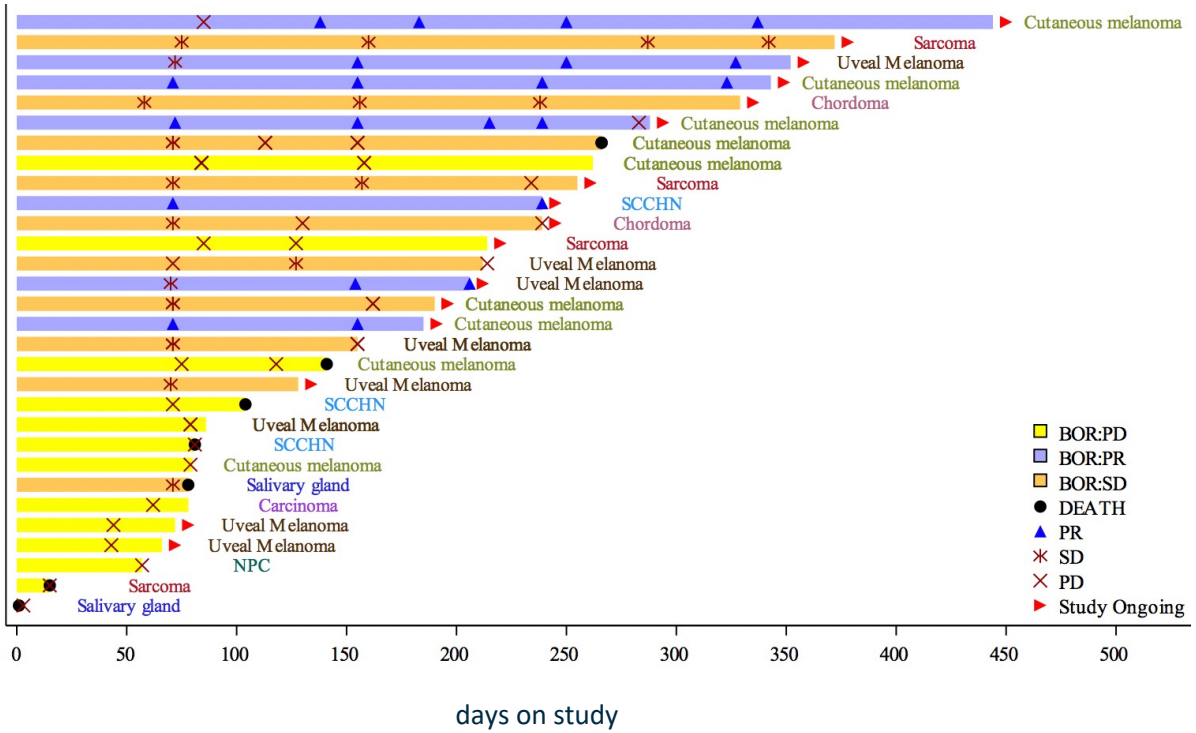


Injected Un-injected

RP2 + nivolumab shows deep and durable responses

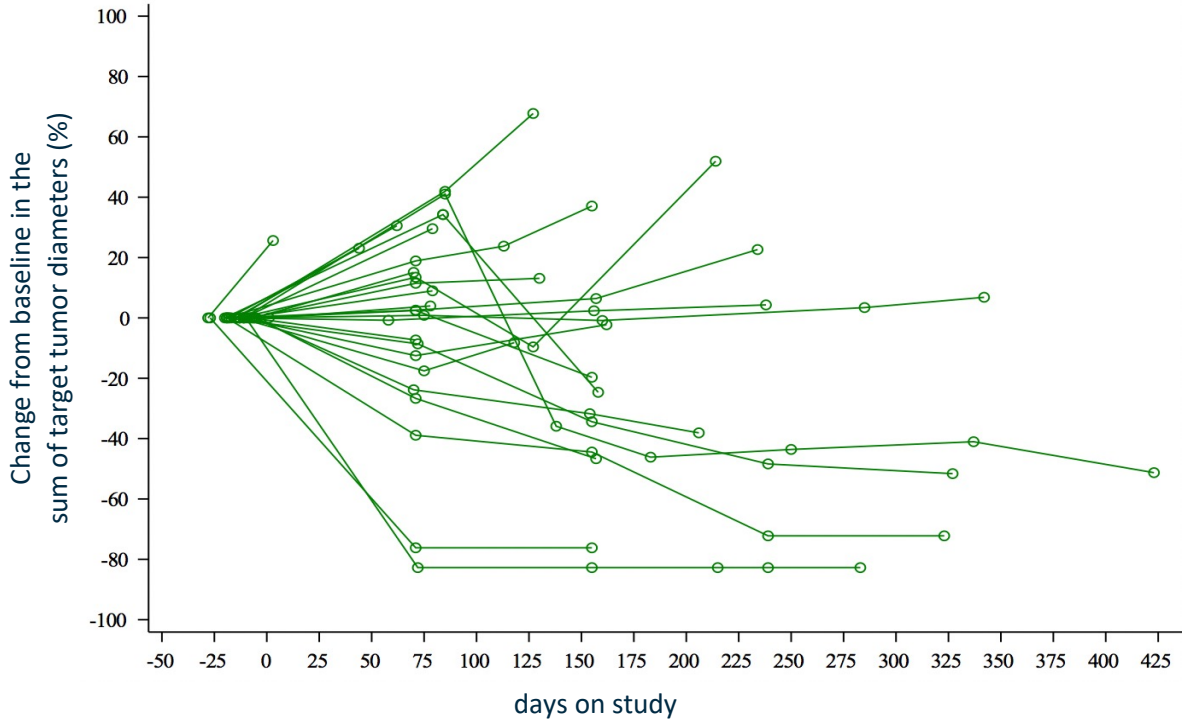
Duration of best response

Patients with a best response of at least SD



Change in tumor size

Patients with at least one follow up assessment

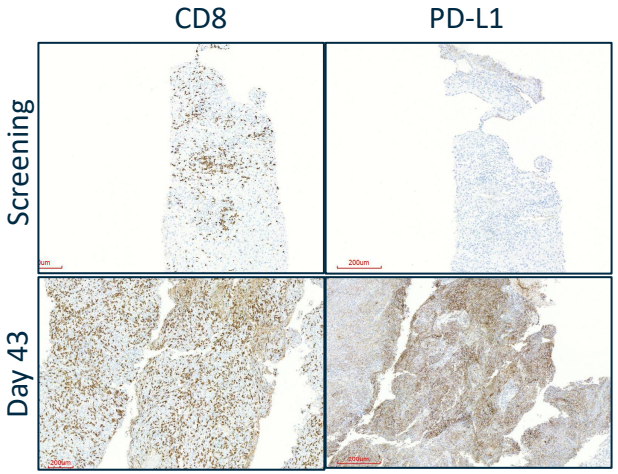


- 30 advanced, heavily-pretreated Phase 1 patients treated with RP2 combined with Opdivo
- Seven responses as of last data cut; all patients having failed prior anti-PD1
  - 2x uveal melanoma; 4x cutaneous melanoma; 1x SCCHN
- All but one response durable to date at out to >425 days

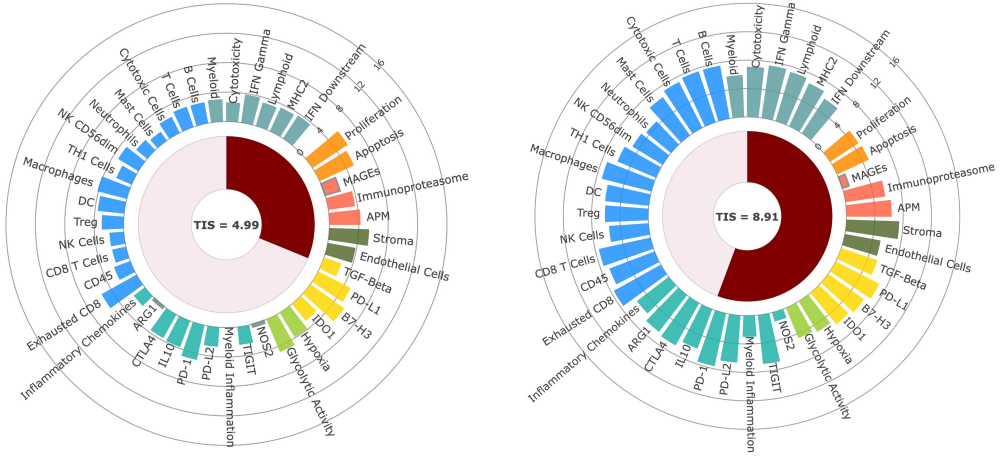
Data as of Oct 12th 2021

Broad immune activation with RP2: Response is independent of baseline PD-L1 status & CD8+ T cell density

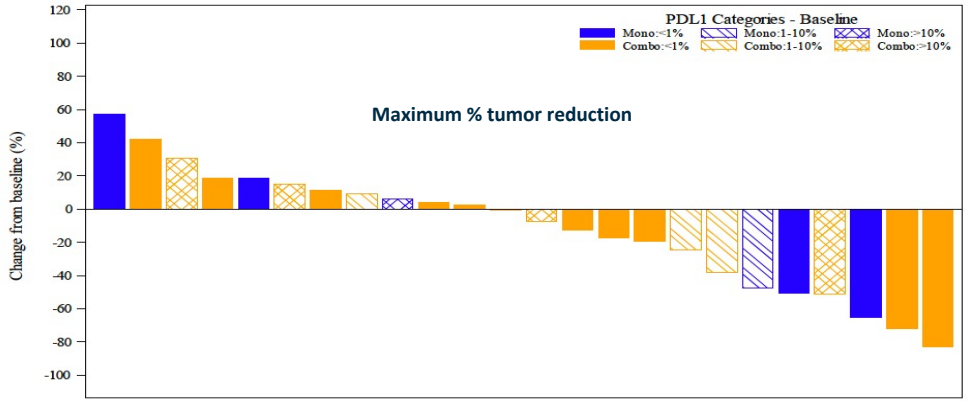
Substantial increases in in CD8+ T cell infiltration and PD-L1 expression are seen (Example: pt 4403-0015, uveal melanoma)



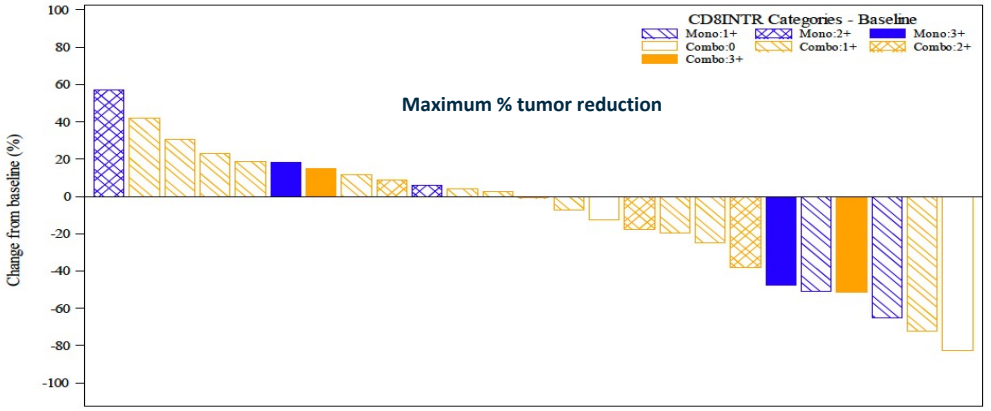
Changes in gene expression signature indicate broad immune activation (Example: pt 4401-0016 ipi/nivo-failed melanoma)



No correlation of clinical response with baseline tumor PD-L1 expression status

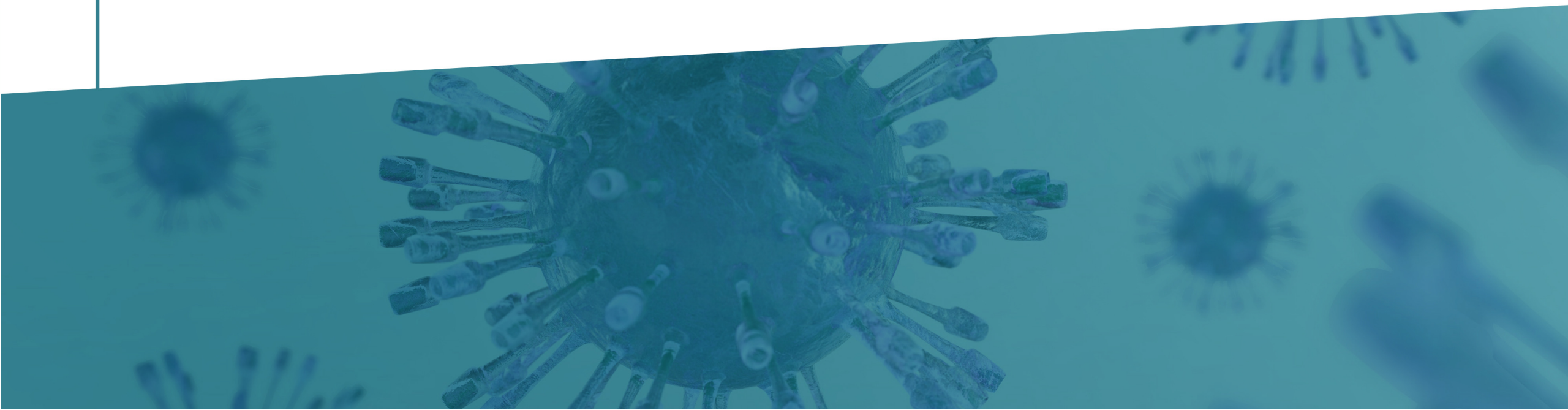


No correlation of clinical response with baseline intra-tumoral CD8+ T cell density



RP3 Update

Professor Kevin Harrington



RP3 Phase 1 clinical trial design

- Typical all-comers Phase 1 patients having exhausted all standard of care
  - Three patients treated at low dose (10^5 pfu/mL followed by four doses of 10^6 pfu/mL, up to 10mL)
  - Three patients treated at high dose (10^6 pfu/mL followed by four doses of 10^7 pfu/mL, up to 10mL)
  - Expand either group to 6 if dose-limiting toxicity (DLT) seen
- Assess safety, scans at one month & three months post-last dose
- Determine RP2D, add additional HSV-seronegative patients if <3 dosed at the RP2D
- Open combination cohort with nivolumab
  - Initially 30 ‘all-comers’ patients
  - Protocol amendment about to open focusing on patients with SCCHN, GI cancers, breast cancer and lung cancer, with additional monotherapy & biomarker patients too

RP3 Phase 1 clinical trial status

- Three patients enrolled at low dose
- Three patients enrolled at high dose
  - No DLTs seen
  - RP2D declared as a first dose of 10^6 pfu/mL followed by multiple doses of 10^7 pfu/mL, up to 10mL
- Additional HSV-seronegative monotherapy patients enrolled to make up to three
  - No DLTs seen
  - RP2D confirmed in seronegative patients
- Combination therapy with nivolumab recently opened for enrollment
  - The protocol is being expanded from the UK also into the US & EU
  - Initial data from the combination phase expected during 2022
- Data is currently available for the first 6 patients dosed as monotherapy

Treatment related TEAEs for patients treated with RP3

	N=6				
Preferred Term	Grade 1-2 (all)	Grade 3 (all)(%)	Grade 4 (all)(%)	Grade 5 (all)(%)	Total (all)(%)
Chills	2 (33.3%)	0	0	0	2 (33.3%)
Pyrexia	2 (33.3%)	0	0	0	2 (33.3%)
Abdominal wall mass	1 (16.7%)	0	0	0	1 (16.7%)
Blood alkaline phosphatase increased	1 (16.7%)	0	0	0	1 (16.7%)
Fatigue	1 (16.7%)	0	0	0	1 (16.7%)
Gamma-glutamyltransferase increased	1 (16.7%)	0	0	0	1 (16.7%)
Headache	1 (16.7%)	0	0	0	1 (16.7%)
Influenza like illness	1 (16.7%)	0	0	0	1 (16.7%)
Injection site pain	1 (16.7%)	1 (16.7%)	0	0	1 (16.7%)
Injection site swelling	1 (16.7%)	0	0	0	1 (16.7%)
Lethargy	1 (16.7%)	0	0	0	1 (16.7%)

- RP3 monotherapy has been well tolerated with so far a safety profile similar to RP1 & RP2

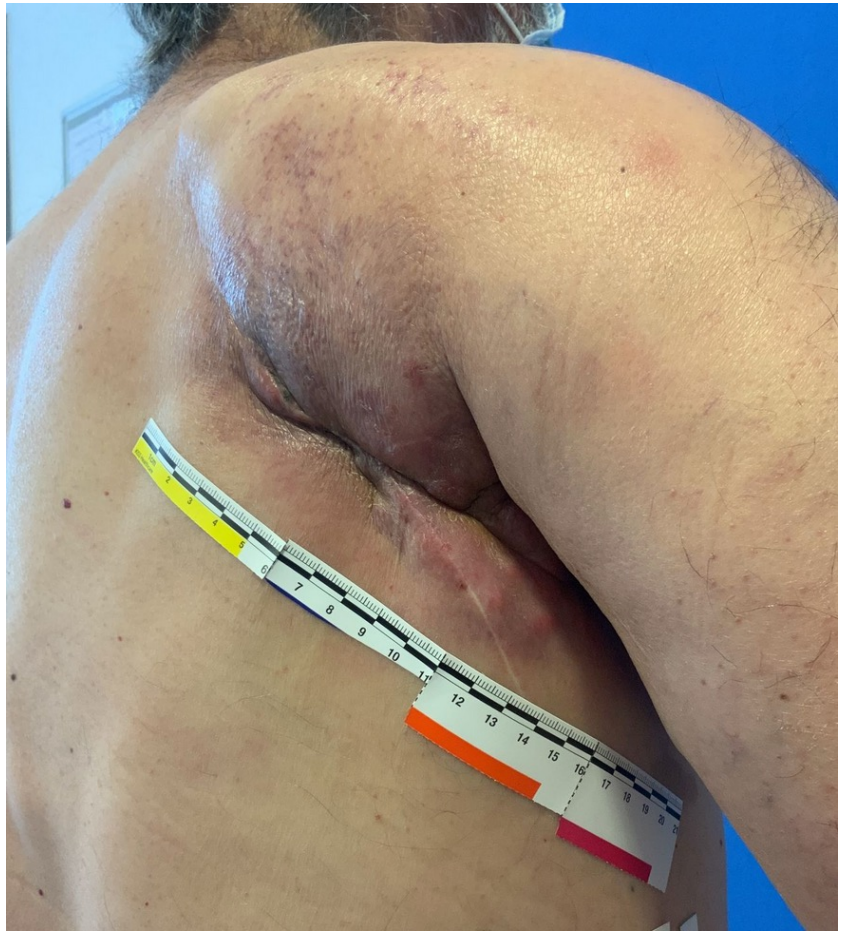
Data snapshot date: 11th March 2022

Marked inflammation seen with RP3

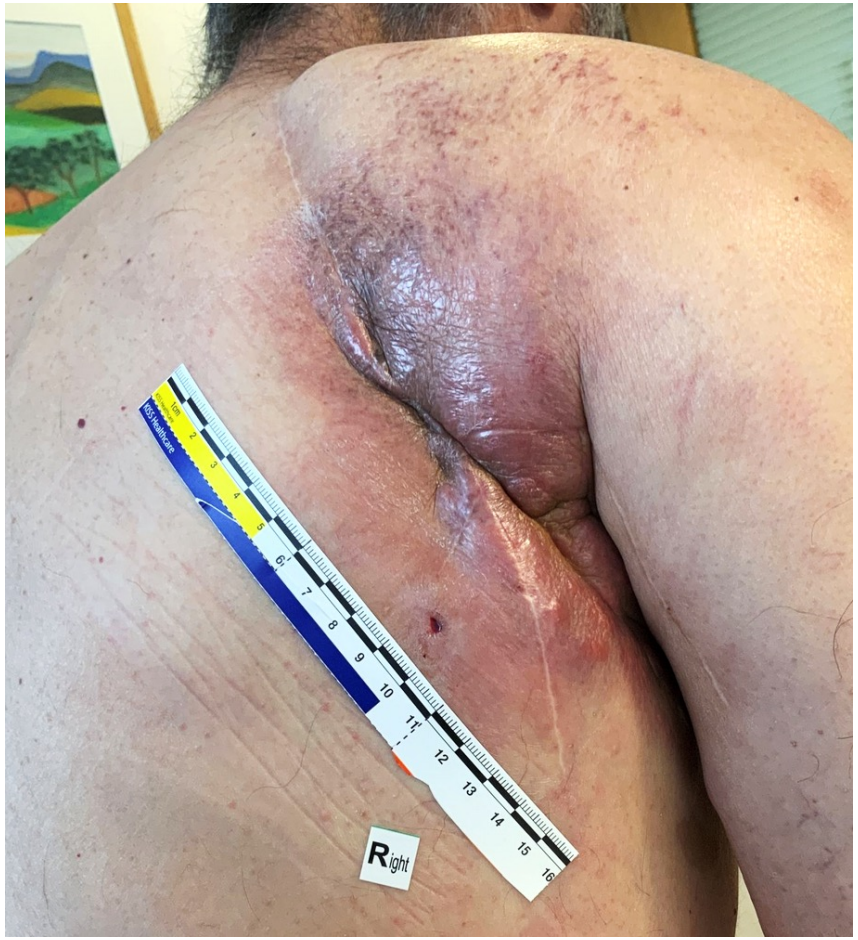
Pt 4401-0001

- Pleomorphic sarcoma

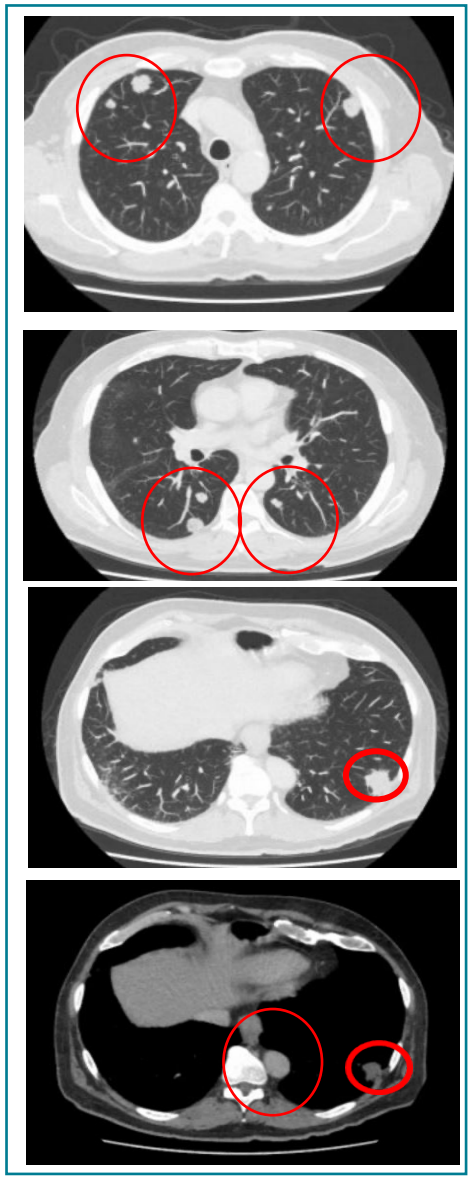
Baseline

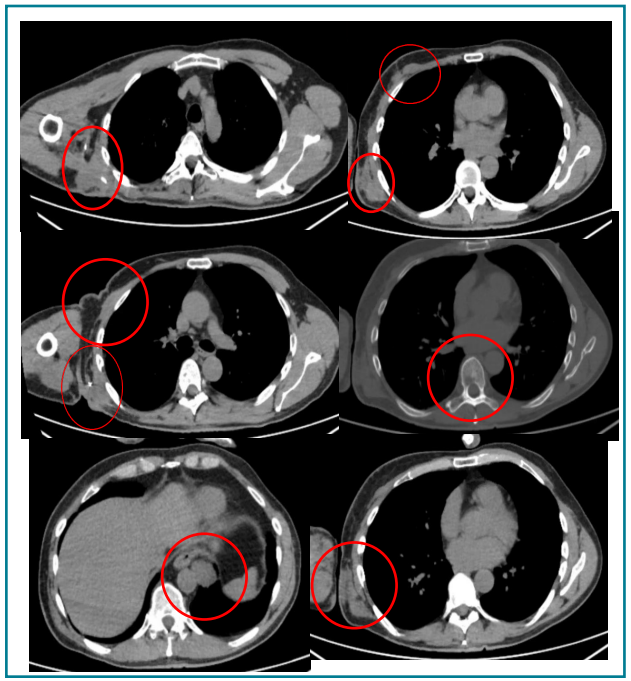


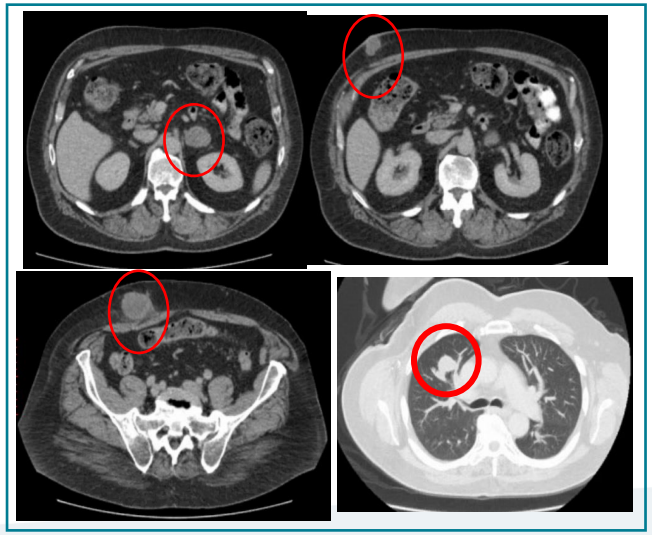
Day 3

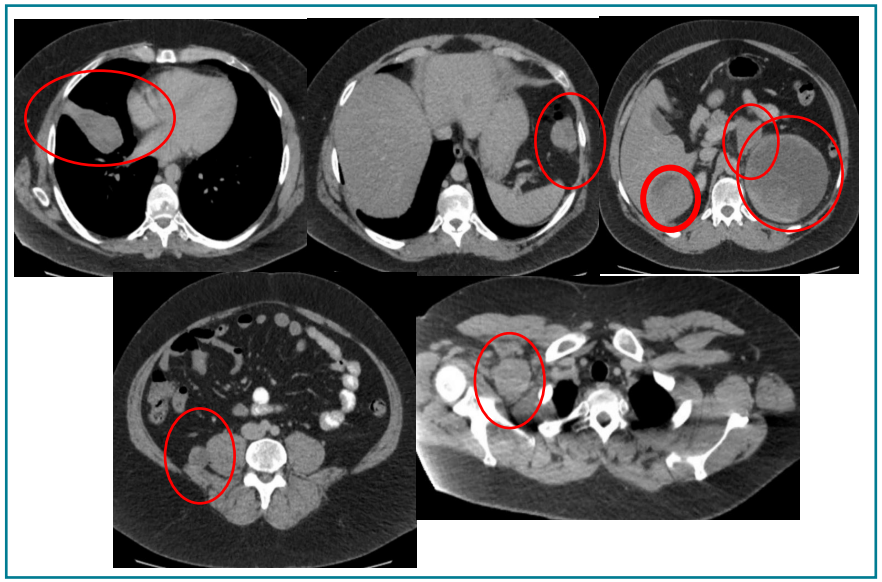


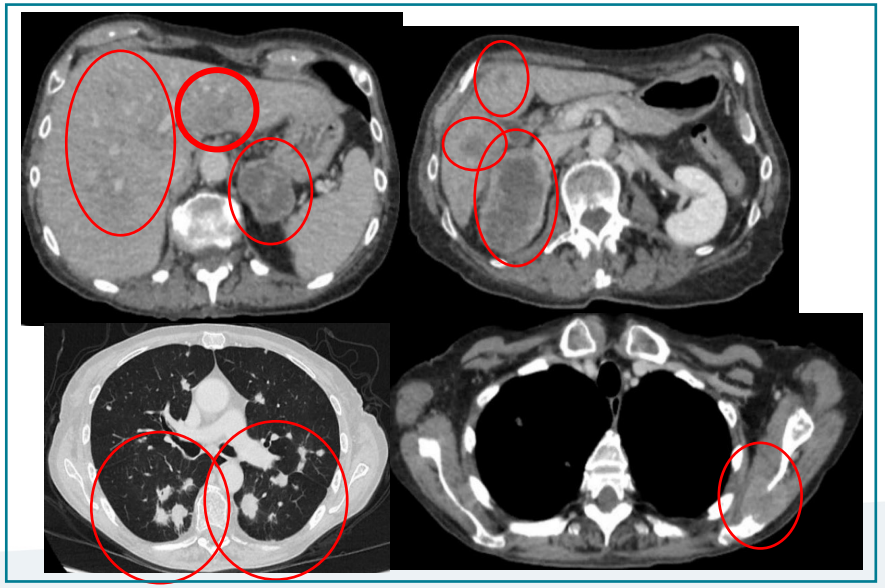
The patients enrolled have had widespread, advanced disease











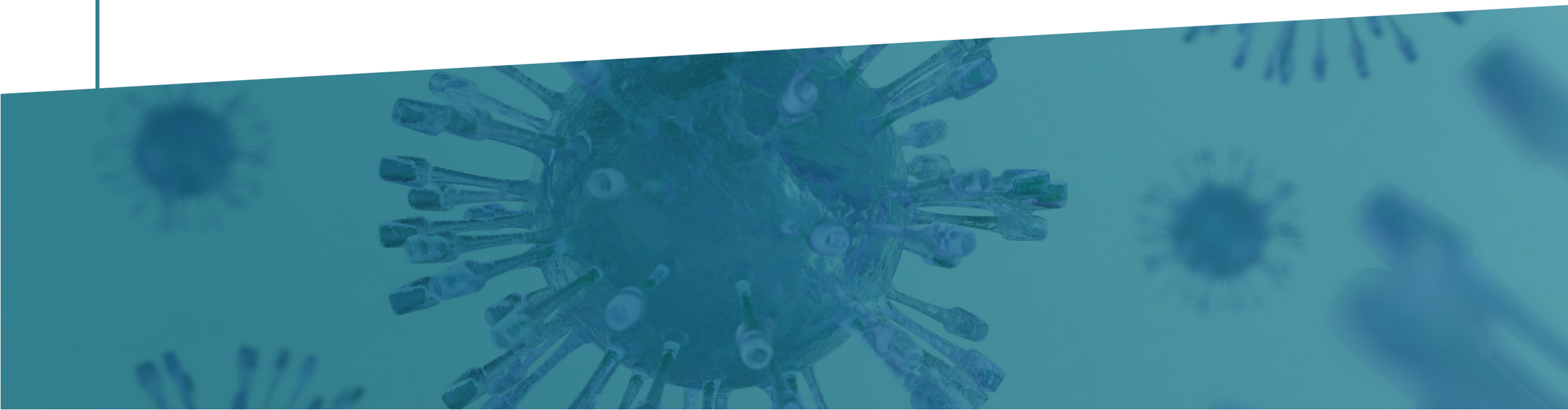
RP3 Patient Summary

Patient	Tumor Type	Prior Anticancer Therapies (Preferred Term)	Sites of recorded disease (injection site underlined)	Response Status on study (Day on Study)	Current status
4401-0001	SARCOMA	1. DOXORUBICIN, IFOSFAMIDE 2. DOCETAXEL, GEMCITABINE	Chest wall, shoulder, bone, para-aortic	PD (87)	In survival follow up
4401-0006	OESOPHAGEAL CANCER	1. CAPECITABINE, CISPLATIN, TRASTUZUMAB 2. TRASTUZUMAB 3. DOCETAXEL	Multiple bi-lateral lung, esophagus	SD (88) SD (176)	SD until PD of lung and liver lesions 7th Jan 2022 (356)
4401-0008	MELANOMA	1. IPILIMUMAB, NIVOLUMAB	Multiple lung, adrenal, abdominal	PD (43) Death (79)	NA
4401-0010	MELANOMA	1. PEMBROLIZUMAB 2. IPILIMUMAB, NIVOLUMAB	Adrenal, lung, esophagus, liver, abdominal	Death (121)	NA
4401-0014	COLORECTAL CANCER	1. FLUOROURACIL;FOLINIC ACID;OXALIPLATIN 2. FLUOROURACIL;FOLINIC ACID;OXALIPLATIN 3. CALCIUM FOLINATE;FLUOROURACIL;IRINOTECAN HYDROCHLORIDE 4. BEVACIZUMAB 5. TIPIRACIL HYDROCHLORIDE;TRIFLURIDINE	Lung, kidney, adrenal, scapula, liver, rectum, bone	PD (36) Death (88)	NA
4402-0001	HEAD AND NECK CANCER	1. NIVOLUMAB 2. CISPLATIN;FLUOROURACIL 3. DOCETAXEL	Chest wall, subcarinal & hilar nodes, multiple lung, sub-pleural, pretracheal	PD (85) PD (169)	In survival follow up

- Advanced, heavily pre-treated patients with extensive disease were enrolled
  - Four of six patients did not receive the full treatment course due to early PD
  - Three of six patients died due to disease progression by approx 3-4 months
- One patient had extended stable disease out to approximately 1 year (esophageal cancer)
- The patients enrolled were appropriate to assess safety and to determine the RP2D, but it is too early to draw any conclusions as to efficacy based on the population enrolled

RP2/3
Phase 2 Development

Rob Coffin



RP2/3 conclusions

- **RP2 and RP3 are well tolerated (including injections into lung & liver)**
  - Vast majority of AEs are mild (90% grade 1-2)
    - Most commonly fever, chills, fatigue, influenza-like illness & injection site reaction
    - Quickly resolving: vast majority within 72 hours
  - Indicates the potential for combination across the spectrum of anti-cancer modalities
- **RP2 has shown durable clinical activity in difficult-to-treat & anti-PD1-failed all-comers Phase 1 patients**
  - Warrants progression into Phase 2 development - including in earlier patients in combination with the SOC
    - Clear signal in uveal melanoma (3 responses), in addition to activity in other tumor types
    - Additional cohort of patients with GI, lung, breast cancer, SCCHN & uveal melanoma being enrolled
- **RP3 has shown good tolerability, & expected to provide enhanced efficacy as compared to RP1 and RP2, although based on the patients enrolled so far with RP3 it is too early to draw conclusions as to efficacy**
  - Focused cohort of patients with GI, lung, breast cancer & SCCHN being enrolled, together with further monotherapy patients to be enrolled
- **Appropriate to keep options open regarding which of RP2 or RP3 to develop in particular indications, i.e. as the data for RP3 catches up**

RP2/3 development plan: Overarching principles

- Opportunity to show signal in single-arm setting compared to combination drug(s) alone
- Unmet need without near term confounding new drug approvals expected
- Feasibility of injection
- Risk-balanced portfolio of indications
  - Immunologically cold–prevalent tumor types where IO doesn't work
  - High unmet-need populations in somewhat IO-sensitive tumor types
    - Patients with low/no PD-L1 where anti-PD1 is active for high PD-L1
    - Anti-PD1-failed patients
  - Neoadjuvant/locoregionally advanced
- Combine with other SOC to move beyond salvage therapy with the potential for synergy
  - This is generally chemotherapy in IO-failed/IO non-responsive patients
- Prioritize indications with highest conviction & potential for cure, where the objective should be to generate randomized controlled data ASAP

1. Liver cancer/liver mets

Unmet Need[1]

- Liver is a common site of metastasis across tumor types
- Patients with liver mets have a poor prognosis
- IO has a particularly poor outcome in pts with liver mets
- Liver mets are often the primary driver of mortality

Scientific Rationale[2]

- Liver metastases are associated with the antigen-specific elimination of T cells from the circulation by macrophages
  - Leads to systemic loss of T cells and diminished immunotherapy efficacy

"OI" Rationale/ Feasibility

- RPx MOA - powerful direct tumor killing & systemic immune activation
  - Relief of organ (liver) symptoms & systemic disease control
- Liver/liver mets are routinely injected by ultrasound and IR/Rads already play a key role in patient management

Development path

✓ 1. **Primary liver cancer - 1L combined with SOC immunotherapy/2L combined with anti-PD1 HCC** (Ph2 planned)

Improve IO Effectiveness

Overcome IO Resistance

✓ 2. **Cancers with high prevalence of liver mets - 3L CRC combined with anti-PD1** (Ph2 planned)

Turn Cold Tumors Hot

[1]SEER 2021 Estimated Deaths. From SEER Cancer Stat Facts by indication; Riihimaki et al Cancer Med 2018
[2]Yu et al Nat Med Jan 2021; IR=interventional radiologists, Rads=radiologists

Replimune has a clinical trial collaboration & supply agreement with BMS for the supply of Opdivo in its clinical trial program with RP2/3

2. Treating early disease

"OI" Rationale/ Feasibility

- Early disease (neoadjuvant/LA) provides a unique opportunity for OI to maximize patient outcomes:
  - Tumors easily accessible
  - Locoregional progression optimally addressed by OI
  - OI safety profile including ability to combine with multiple modalities allows opportunity to maximize CRs & long-term benefit
  - Feasibility of pre- and post- biopsies in this setting allows understanding of biologic effects and biomarker analysis
  - Objective: To increase the chance for cure

Development path

1. **Neoadjuvant CSCC** (study being planned with RP1)
2. **Locoregional disease, i.e. LA SCCHN combined with SOC chemoradiation** (Ph 2 study planned)
3. **Signal-seeking ISS* studies** (planned) **include:**
   - Neoadj breast cancer
   - Neoadj CSCC
   - Neoadj immunosuppressed CSCC
   - Neoadj BCC

*ISS=investigator sponsored studies

3. Overcoming IO resistance

"OI" Rationale/ Feasibility

- RPx increase PD-L1 and CD8+ T cells in tumors to turn cold tumors hot, generating responses irrespective of baseline PD-L1/CD8+ levels:
  - Potential to treat tumor types which do not respond to immunotherapy or which respond poorly to immunotherapy, for which PD-L1 levels are important for efficacy
  - Potential to treat patients who have failed immunotherapy
  - 1L/2L patients often have less widespread & more injectable disease than later-line patients
  - Synergy with SOC may increase the clinical benefit achieved

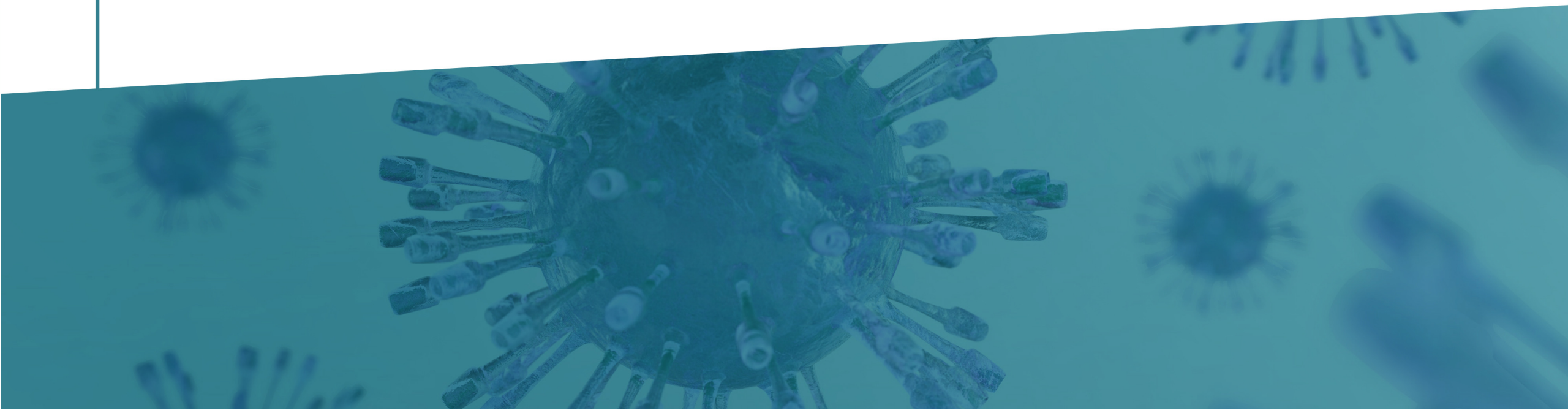
Development path

- 1. **1L recurrent SCCHN combined with SOC chemotherapy & anti-PD1** (CPS<20; Ph2 study planned)
- 2. **2L HCC combined with anti-PD1** (Ph 2 study planned)
- 3. **Additional signal-seeking e.g., esophageal cancer and breast cancer**

Replimune has a clinical trial collaboration & supply agreement with BMS for the supply of Opdivo in its clinical trial program with RP2/3

Background & Unmet Need in SCCHN

Professor Kevin Harrington

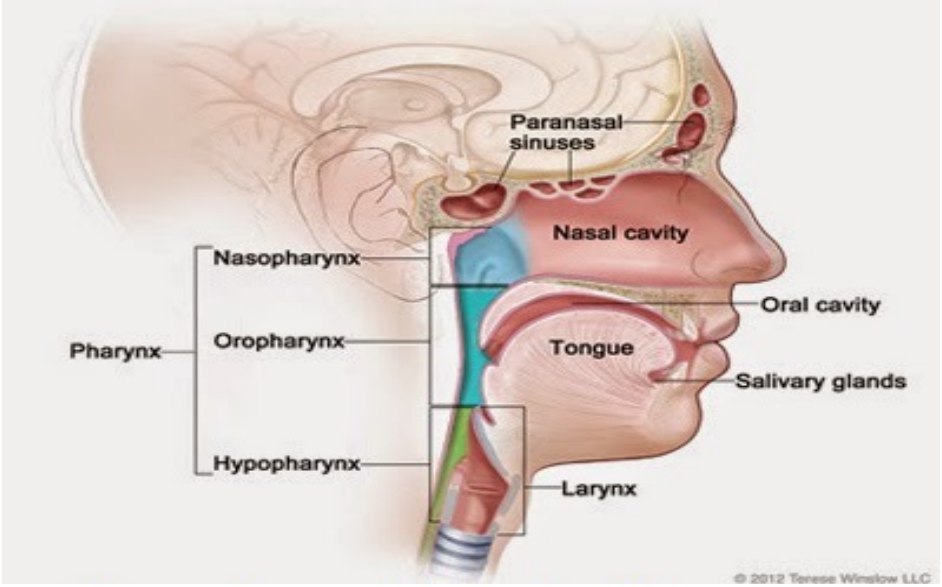


Unmet Need in the Treatment of Squamous Cell Cancer of the Head and Neck

Kevin Harrington

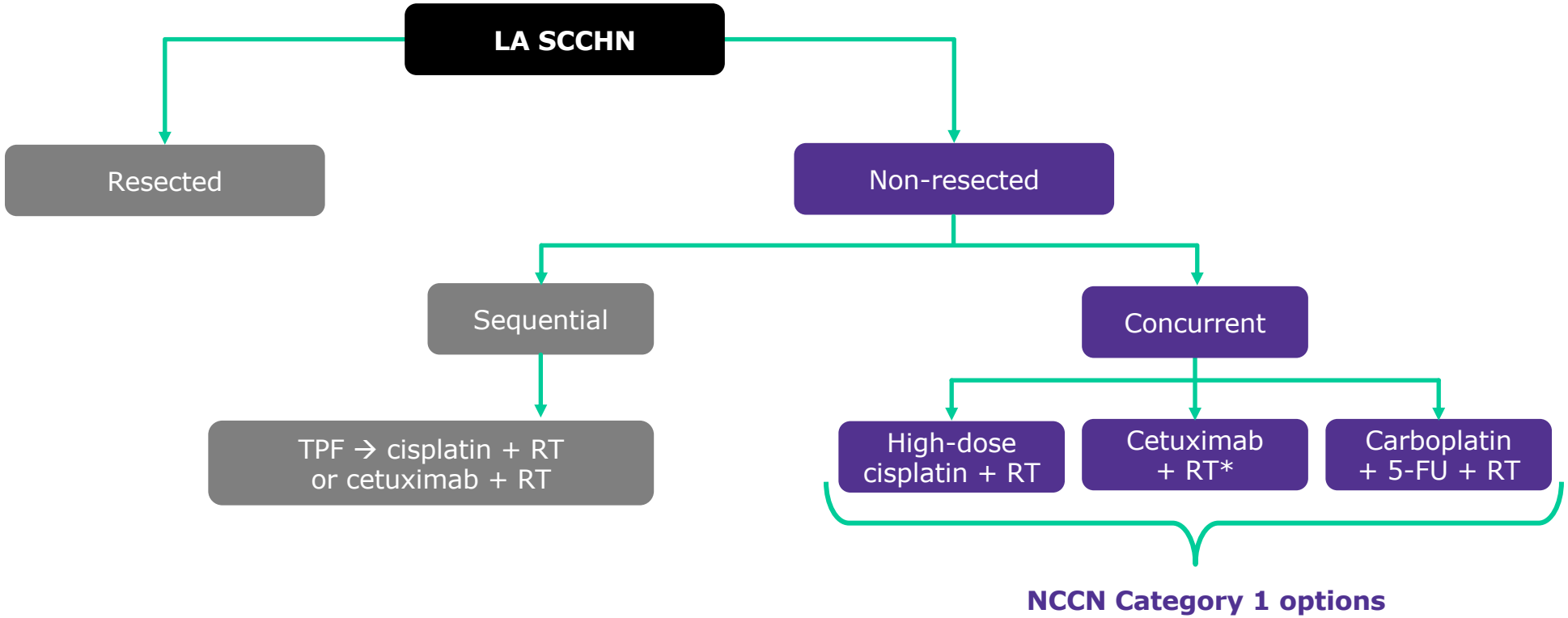
The Institute of Cancer Research, London

Background



- One of the most frequently diagnosed cancers worldwide:
  - 1 000 000 cases per year by 2030
- Alcohol and tobacco consumption[1]
- Human papillomavirus (HPV) types 16 and 18, particularly oropharyngeal cancers
- 90% Squamous cell carcinoma (HNSCC)

Treatment options in LA SCCHN



*Category 1 option for oropharyngeal, hypopharyngeal and laryngeal SCCHN; Category 2B option for lip, oral cavity, ethmoid sinus, maxillary sinus, occult primary SCCHN; NCCN, National Comprehensive Cancer Network; TPF, taxane, cisplatin + 5-FU.

NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers V1.2018.

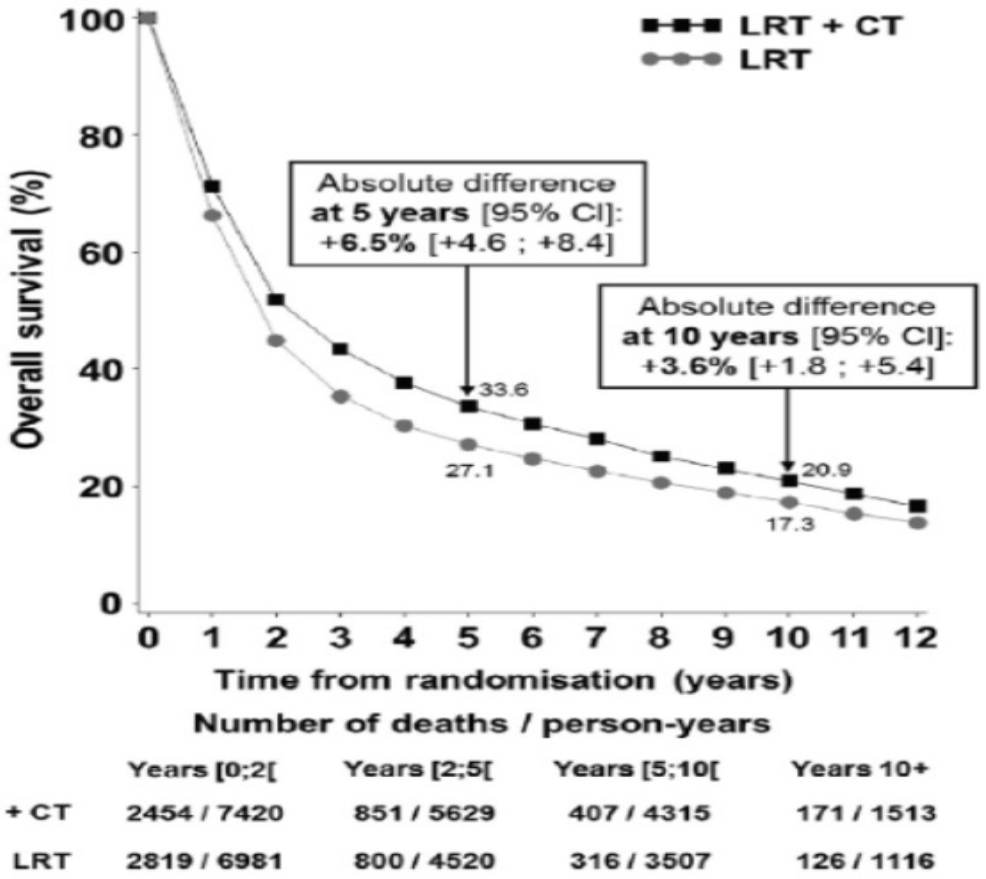
Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group



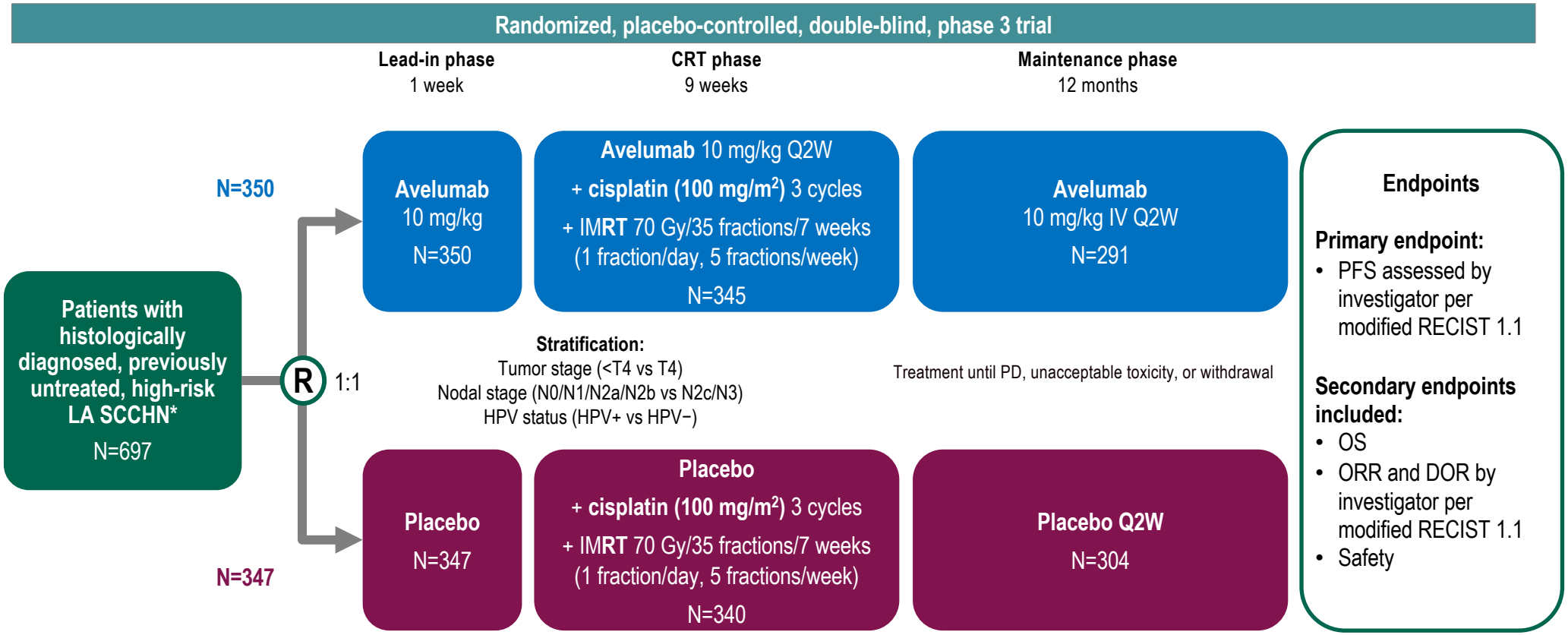
Number of deaths / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
LRT + CT	2454 / 7420	851 / 5629	407 / 4315	171 / 1513
LRT	2819 / 6981	800 / 4520	316 / 3507	126 / 1116

Chemotherapy improves survival compared to RT alone, but huge unmet need remains

Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial

Nancy Y Lee, Robert L Ferris*, Amanda Psyrri, Robert I Haddad, Makoto Tahara, Jean Bourhis, Kevin Harrington, Peter Mu-Hsin Chang, Jin-Ching Lin, Mohammad Abdul Razaq, Maria Margarida Teixeira, József Lövey, Jerome Chamois, Antonio Rueda, Chaosu Hu, Lara A Dunn, Mikhail Vladimirovich Dvorkin, Steven De Beukelaer, Dmitri Pavlov, Holger Thurm, Ezra Cohen**

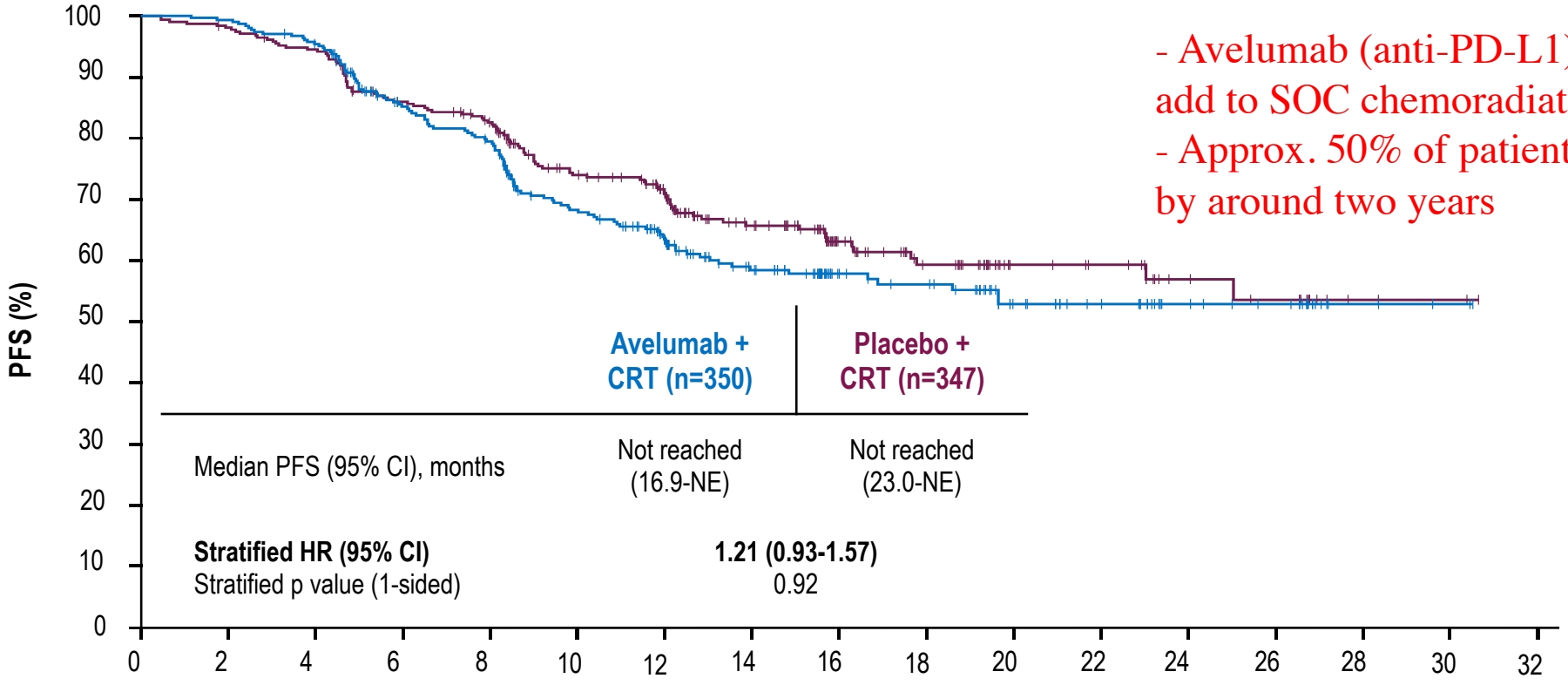


DOR, duration of response; **HPV**, human papillomavirus; **IMRT**, intensity-modulated radiation therapy; **IV**, intravenously; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomized; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1.

* High-risk LA SCCHN (oral cavity, oropharynx, larynx, or hypopharynx): HPV-negative disease stage III, IVa, IVb; nonoropharyngeal HPV-positive disease stage III, IVa, IVb; HPV-positive oropharyngeal disease T4 or N2c or N3 (TNM staging per AJCC, 7th edition).

Lancet Oncol 2021; 22: 450–62

Primary endpoint: PFS per modified RECIST 1.1



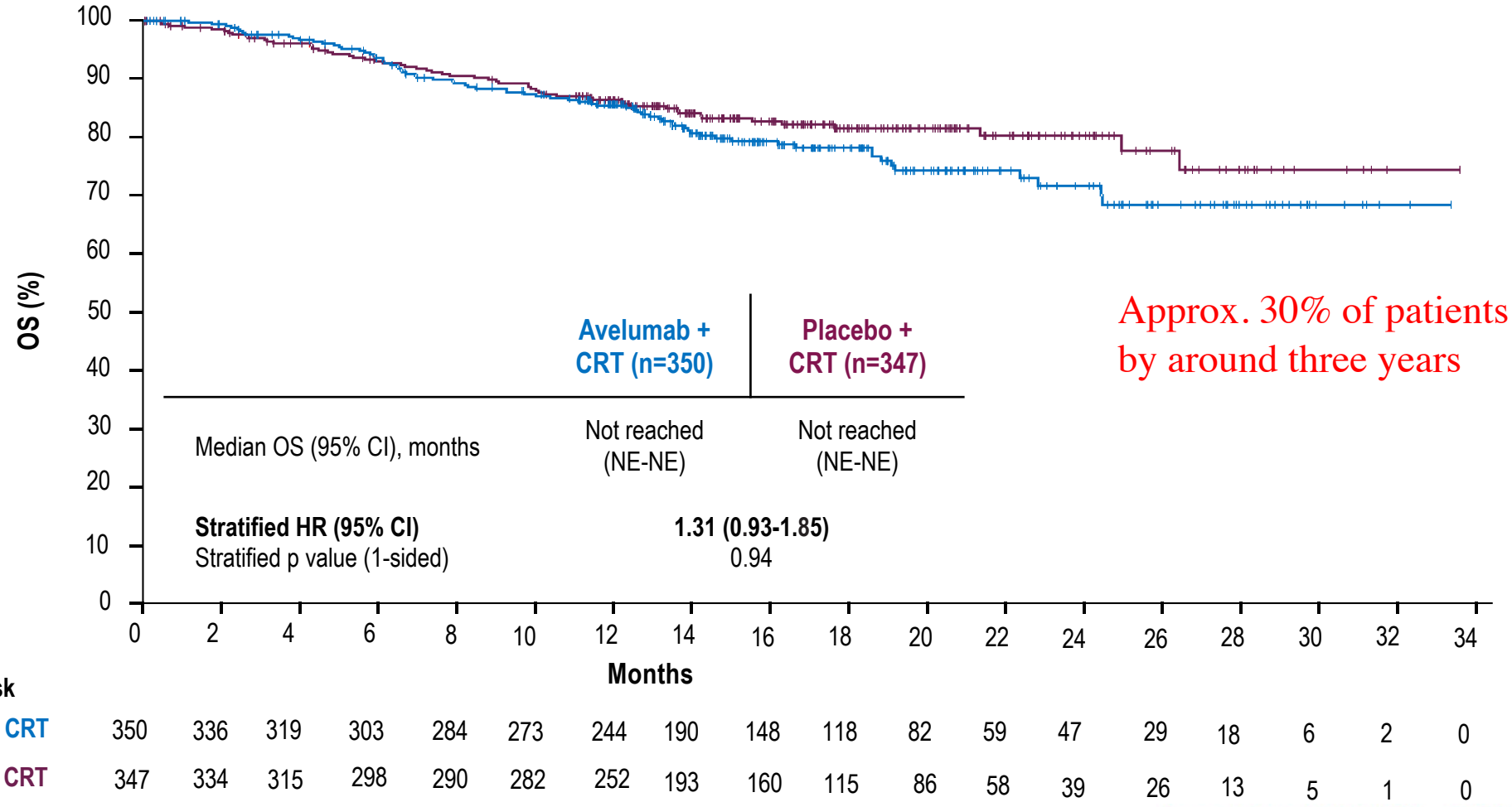
At risk																	
Avelumab + CRT	350	303	289	239	222	176	143	107	69	63	41	33	22	18	4	2	0
Placebo + CRT	347	303	291	257	241	200	172	121	75	56	31	28	18	15	3	2	0

NE, not estimable.

- Avelumab (anti-PD-L1) did not add to SOC chemoradiation
- Approx. 50% of patients relapse by around two years

Lancet Oncol 2021; 22: 450–62

OS: overall patient population



Approx. 30% of patients die by around three years

Lancet Oncol 2021; 22: 450–62

Primary endpoint

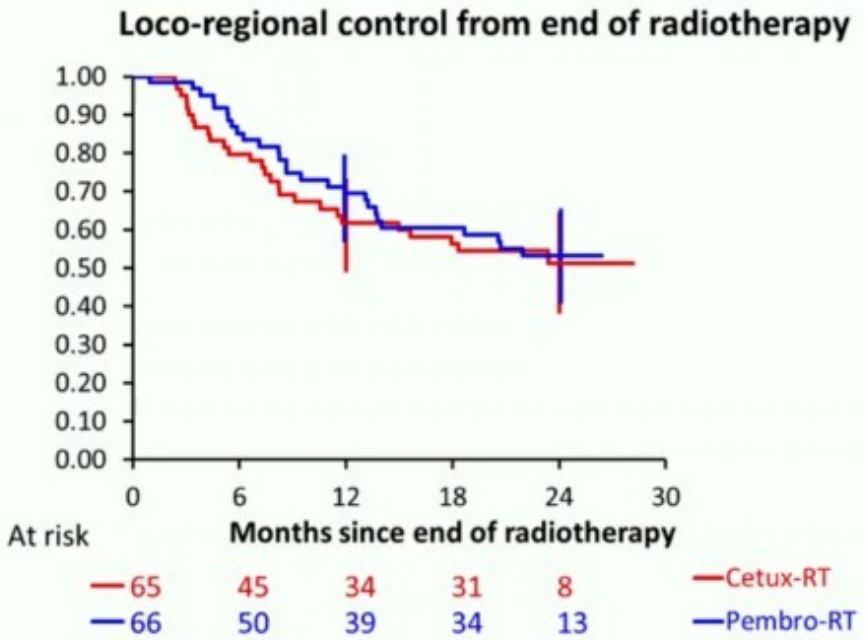
Loco-regional control at 15 months after radiotherapy

- **Median Follow-up: 25.6** months (9.0-30.2 months)
- **LRC at 15 months after RT:**

Cetux-RT : 59% (95%CI 45%-72%)

Pembro-RT : 60% (95%CI 46%-72%)

OR = 1.05, (95%CI 0.43-2.59); **p = 0.91**

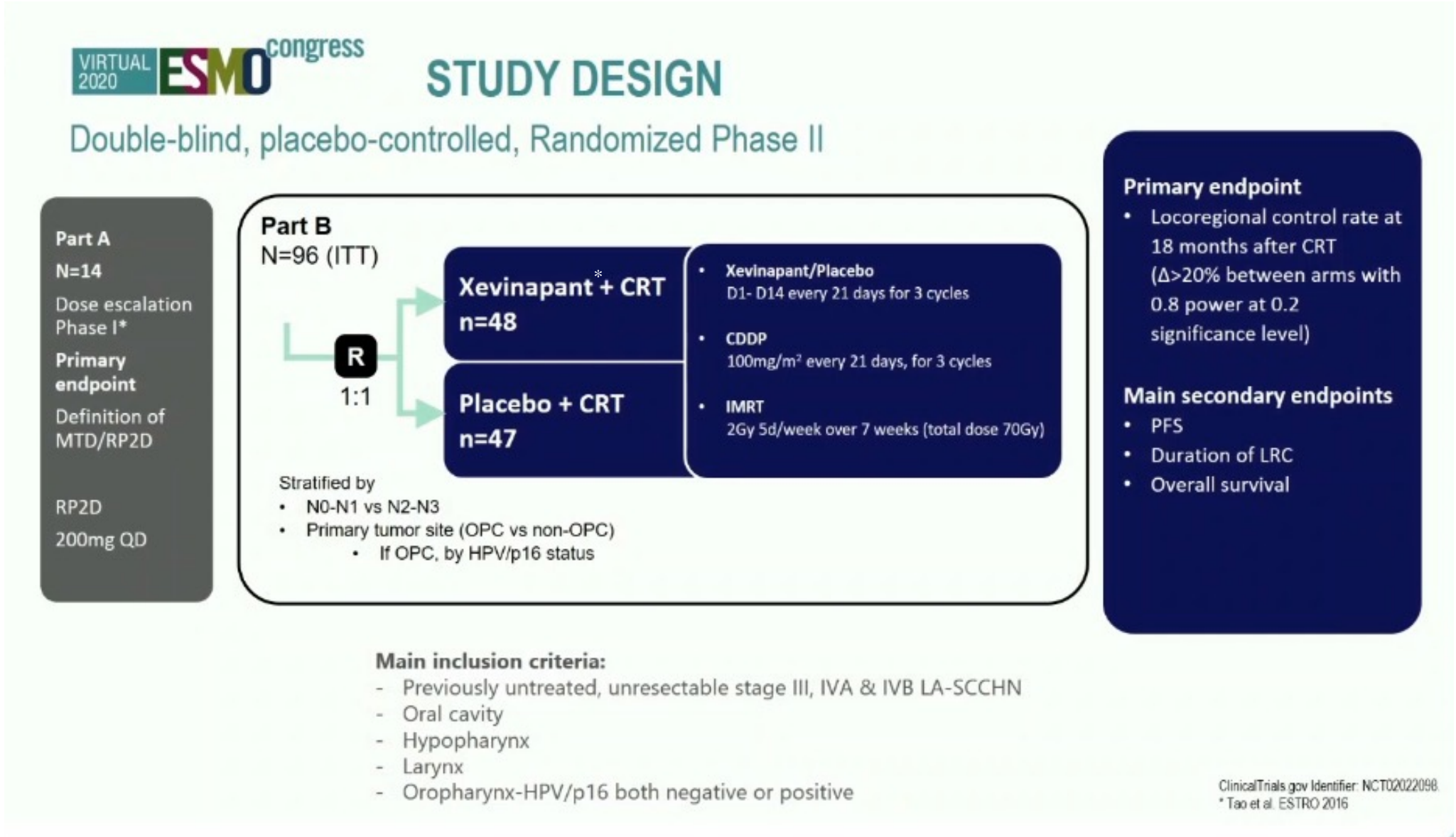


Pembrolizumab has also been tested in LA SCCHN, here compared to cetuximab as an alternative to chemotherapy

As for avelumab pembrolizumab did not improve PFS in LA SCCHN

Other studies also show no benefit of anti-PD1/L1 in LA SCCHN

Tao et al. ESMO 2020

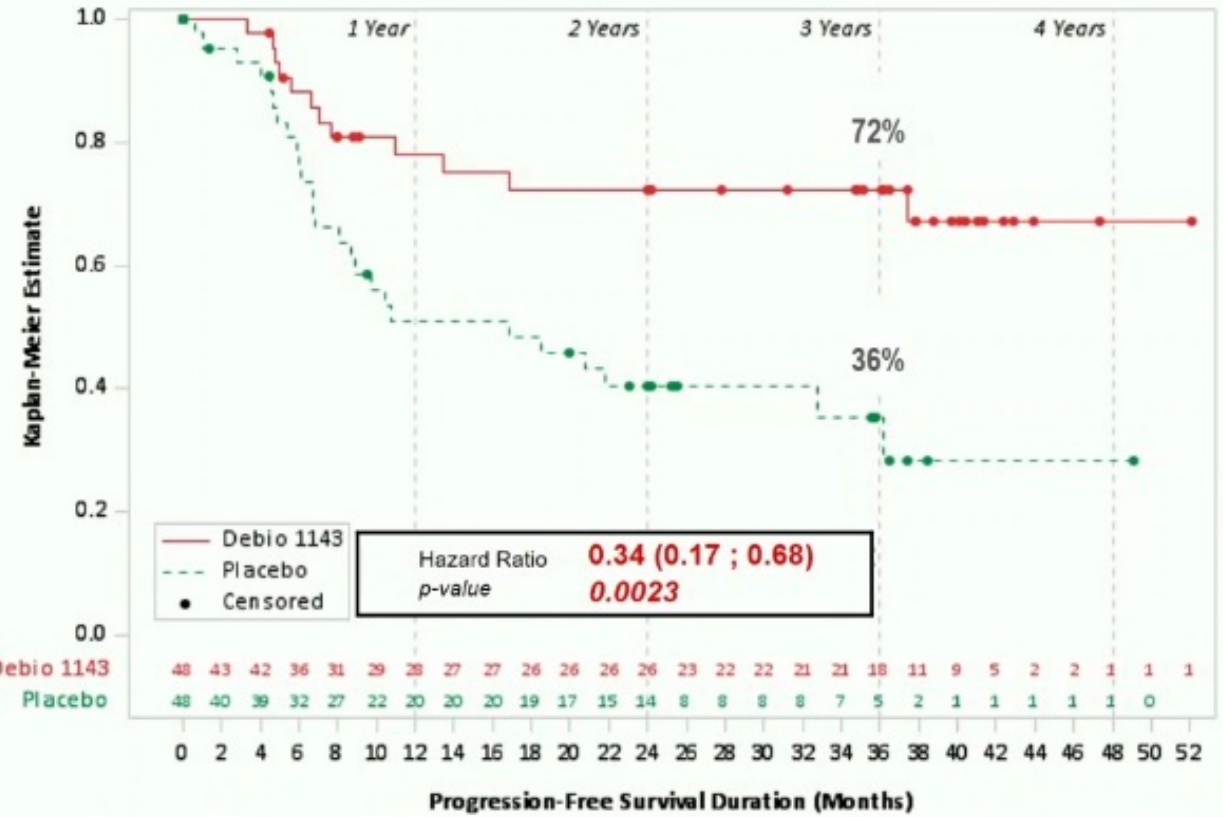


*Inhibitor of apoptosis proteins/radiation sensitizer

VIRTUAL 2020 ESMO congress

Duration of PFS - 3-year follow up

As per investigator, with censoring for late events* – ITT



Median PFS

- Placebo: 16.9 months (95%CI: 6.8 - 36.1)
- Xevinapant: Not reached (95%CI: 37.4- NR)

Statistically significant, clinically compelling PFS improvement

* Late events: those occurring after missed assessments: censored to avoid assumption of non-PD for long periods before PD identified (FDA guidance)

Promising phase 2 data

Ongoing Phase 3 trial

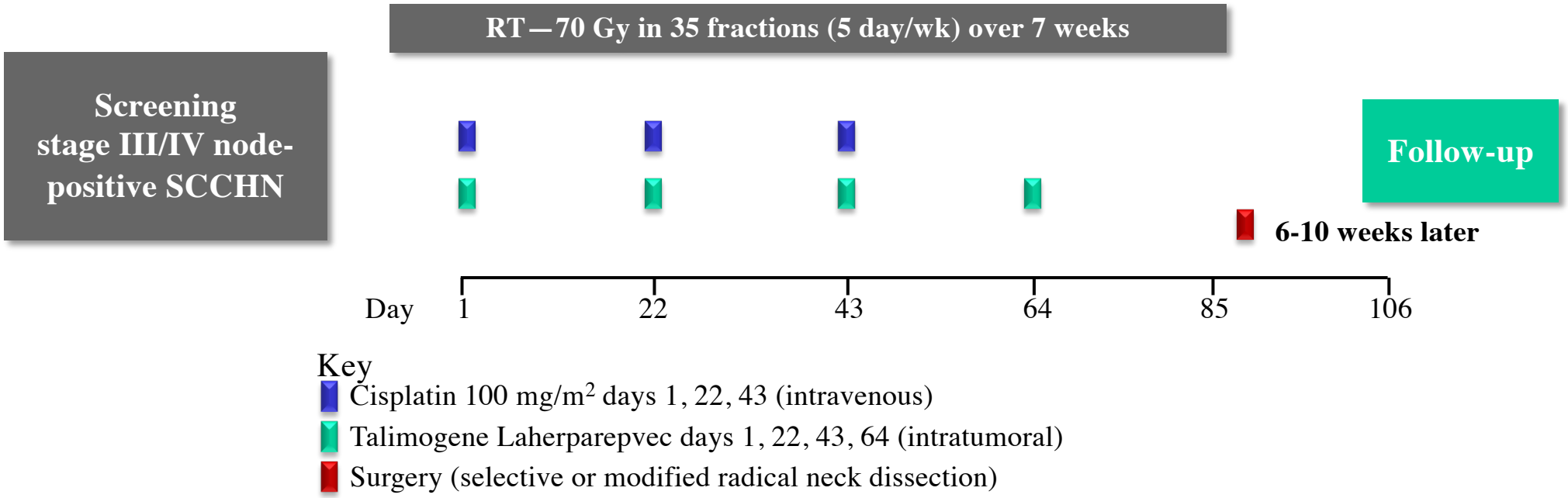
- Small patient numbers
- Control arm PFS worse than other trials (e.g. 12 month PFS approx. 50% vs. approx. 70% in other trials, 40% vs. 60% at two years)

Cancer Therapy: Clinical

Clinical Cancer Research

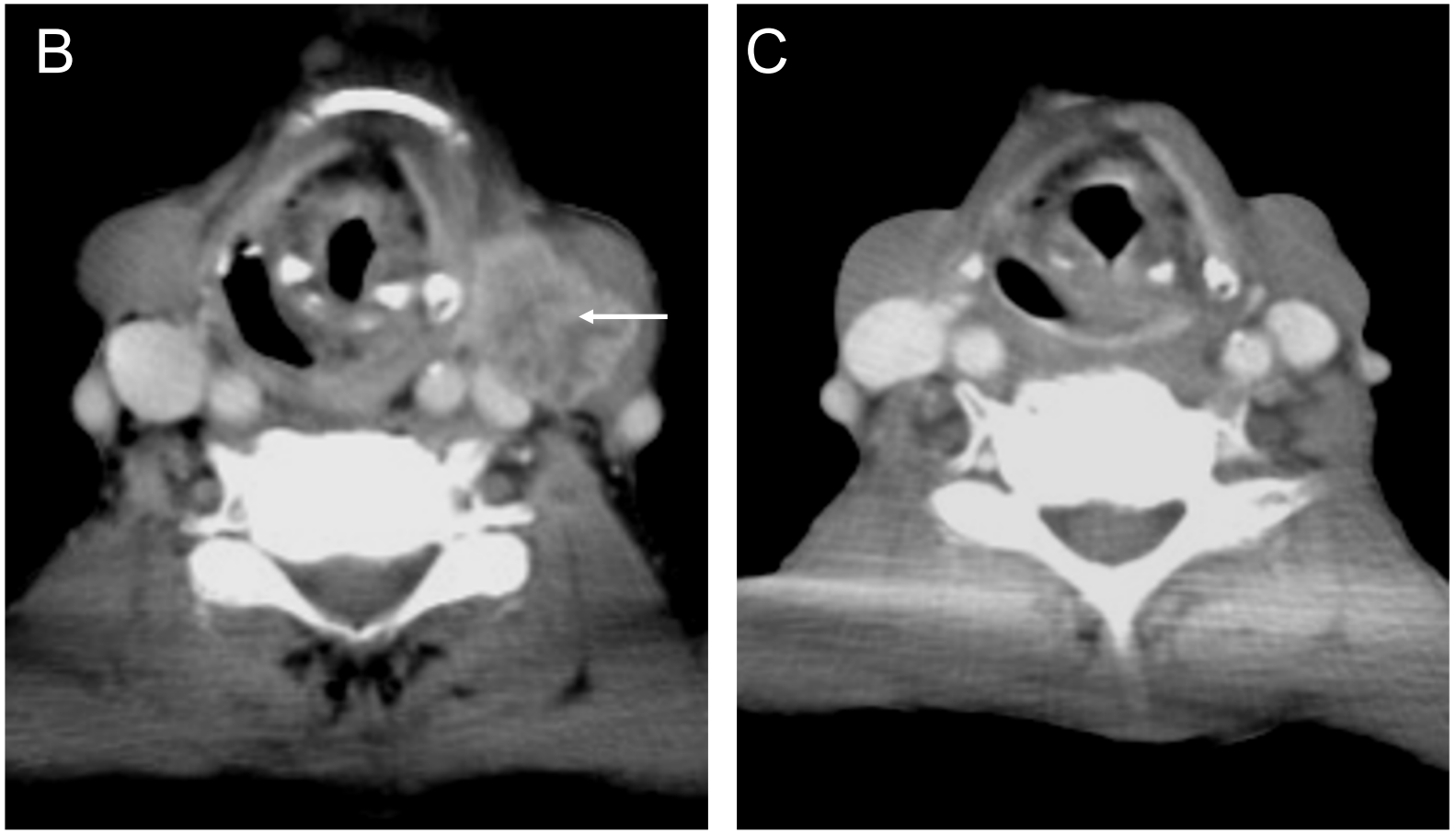
Phase I/II Study of Oncolytic HSV$^{GM\text{-}CSF}$ in Combination with Radiotherapy and Cisplatin in Untreated Stage III/IV Squamous Cell Cancer of the Head and Neck

Kevin J. Harrington[1,2], Mohan Hingorani[1], Mary Anne Tanay[2], Jennifer Hickey[2], Shreerang A. Bhide[2], Peter M. Clarke[2], Louise C. Renouf[2], Khin Thway[1,2], Amen Sibtain[3], Iain A. McNeish[3,4], Kate L. Newbold[2], Howard Goldsweig[5], Robert Coffin[5], and Christopher M. Nutting[2]



Harrington KJ, et al. *Clin Cancer Res*. 2010;16:4005-4015.

Phase I/II SCCHN Study: Response Data



Example of complete response

Harrington KJ, et al. Clin Cancer Res. 2010;16:4005–15 and supplementary figures.

Phase I/II SCCHN Study: Results

- Well tolerated (86% grade 2 AEs, no grade 3-5)
- 14 patients (82.3%) showed response by RECIST at post-treatment CT scans
- pCR confirmed in 93% of patients at neck dissection
- HSV detected in injected and adjacent uninjected nodes at levels higher than the input dose, indicating viral replication
- Disease-specific survival was 82.4% and OS 70.5% at a median follow-up of 29 months (range, 19-40 months)
- Locoregional control was achieved in all patients, with a 76.5% relapse-free rate
- >50% of patients remain in remission on long-term follow-up

Harrington KJ et al. Clin Cancer Res; 16(15); 4005–15, 2010

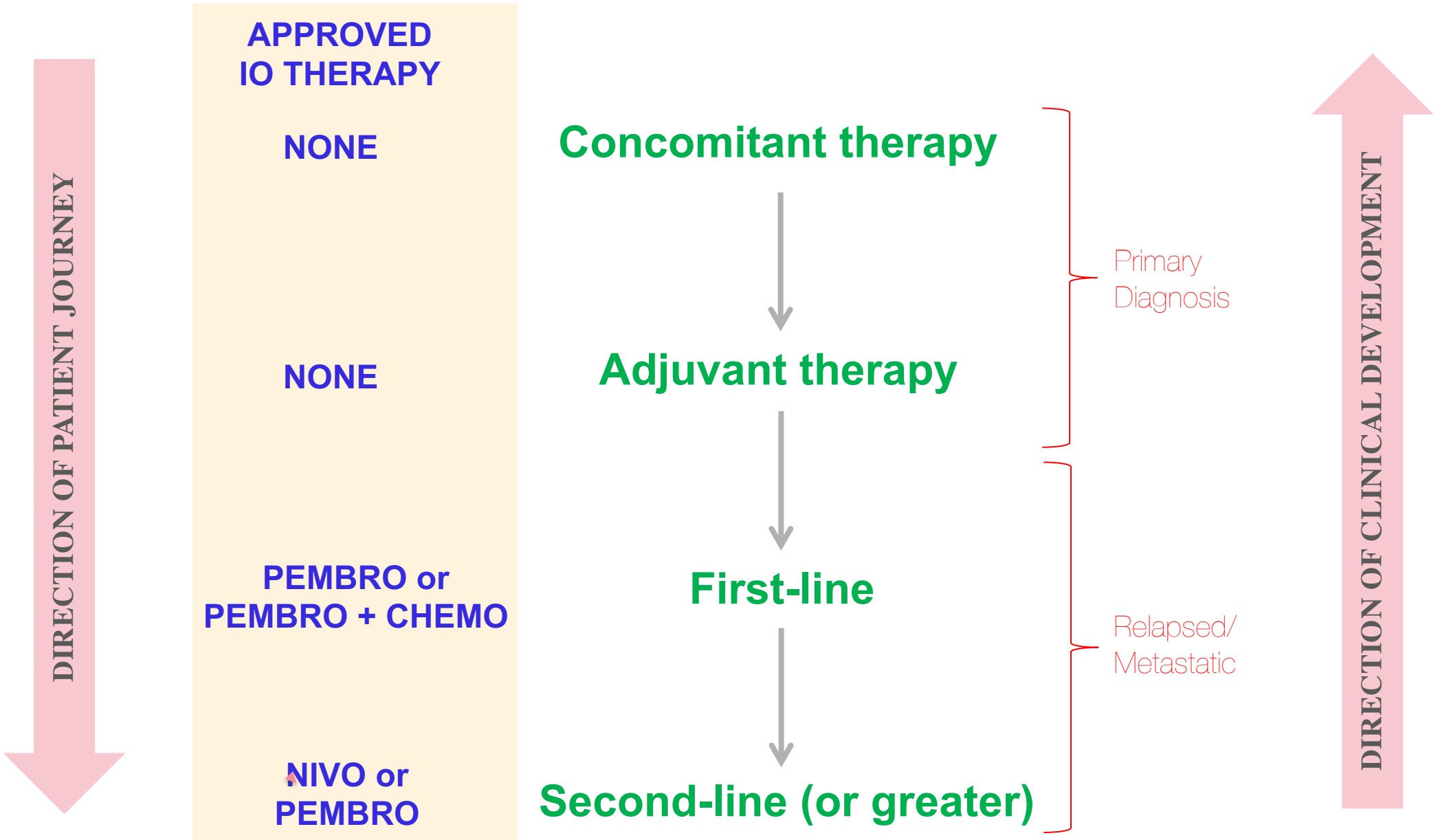
Summary/Conclusions for LA disease

- Primary therapy is highly effective, but still 40% of pts relapse by 18-24 months
- Particularly the case for patients with high-risk disease
- Recently tested approaches (including anti-PD1/L1) have not met with success
- The field is wide open and in urgent need of better therapy
- Oncolytic immunotherapy may be useful in achieving a high rate of initial sterilization through both the oncolytic and immune effects, and the immune effects protect against relapse
- Synergy with both chemotherapy and radiation would be expected
- Adding in adjuvant nivolumab may further potentiate benefit (by analogy to PACIFIC study in non-small-cell lung cancer)[1]

[1]Antonia et al N Engl J Med. 2017;377:1919-1929

Un-met Need in Relapsed/Metastatic Head and Neck Cancer

Treatment Landscape in SCCHN



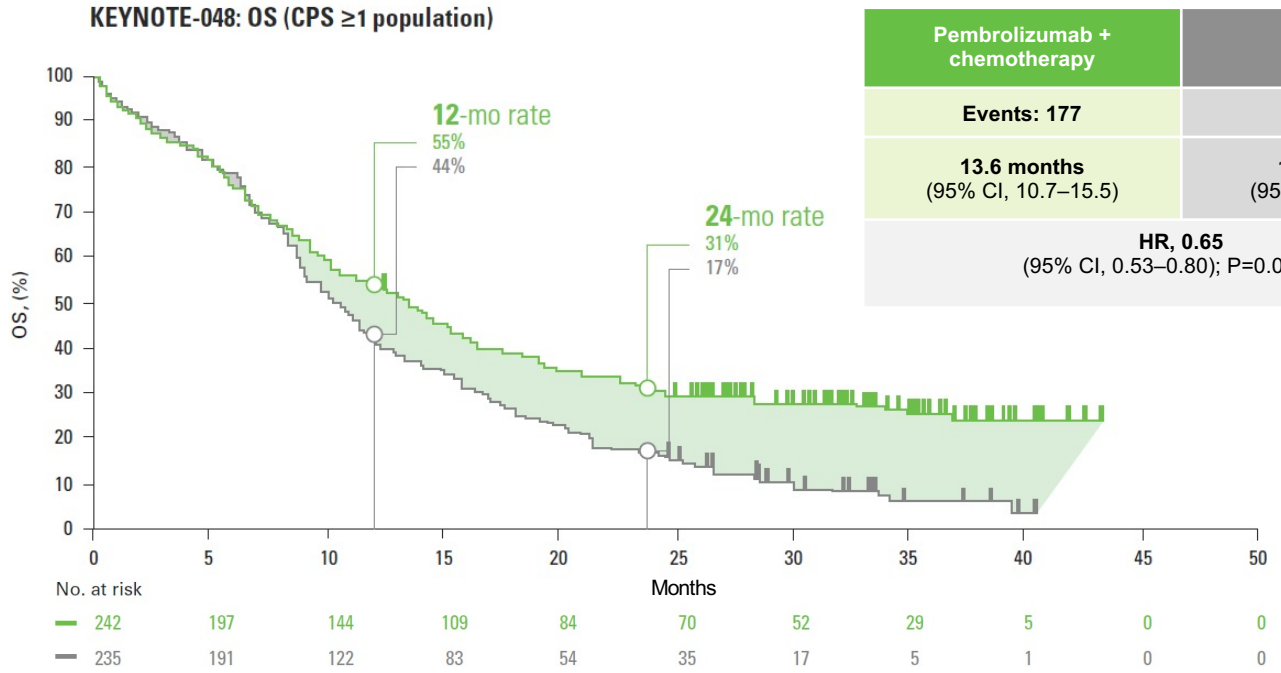
OS: Pembro-chemo vs EXTREME (PD-L1 CPS ≥1)

FIRST-LINE

Pembro + chemo vs EXTREME

OS

CPS ≥1



Median OS in CPS ≥1 population[1]

Pembrolizumab + chemotherapy	EXTREME
Events: 177	**Events: 213**
13.6 months (95% CI, 10.7–15.5)	**10.4 months** (95% CI, 9.1–11.7)
HR, 0.65 (95% CI, 0.53–0.80); P=0.00002[a]	

- Pembrolizumab combined with chemotherapy moderately improved benefit compared to pembro alone (in patients with CPS>1)

Figure adapted from KEYTRUDA (pembrolizumab) SmPC. [a]Statistically significant at the superiority of P=0.0026[2]. FA data cutoff date: February 25, 2019
CI, confidence interval; CPS, combined positive score; FA, final analysis; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1

1. KEYTRUDA (pembrolizumab) SmPC. Available at: https://www.medicines.org.uk/emc/product/6947/smpc. Accessed December 2019. 2. Burtness B et al. Lancet. 2019:394;1915–28

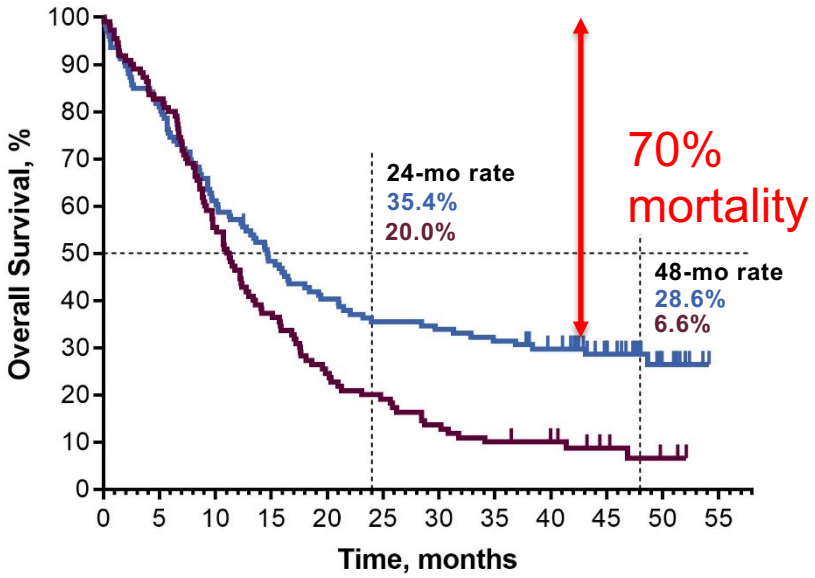
Burtness B et al. Lancet. 2019:394;1915–28

LONG-TERM FOLLOW-UP DATA [ESMO 2020]

FIRST-LINE

PD-L1 CPS ≥20

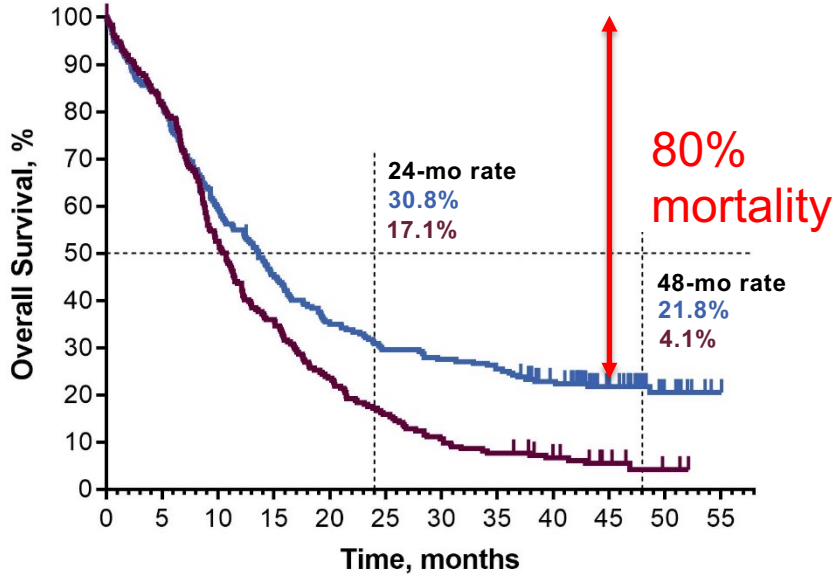
	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembro + Chemo	71.4%	14.7 (10.3-19.3)	0.62 (0.46-0.84)	0.00082
EXTREME	91.8%	11.1 (9.2-13.0)		



No. at Risk												
Pembro + Chemo	126	102	77	60	50	44	42	39	33	22	7	0
EXTREME	110	91	61	41	27	21	15	11	9	5	2	0

PD-L1 CPS ≥1

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembro + Chemo	78.1%	13.6 (10.7-15.5)	0.64 (0.53-0.78)	0.00001
EXTREME	94.0%	10.6 (9.1-11.7)		



No. at Risk												
Pembro + Chemo	242	197	144	109	84	71	66	61	48	29	9	1
EXTREME	235	191	123	84	55	37	25	18	12	6	2	0

But vast majority of the benefit is in patients with CPS ≥20

Greil R et al. ESMO 2020

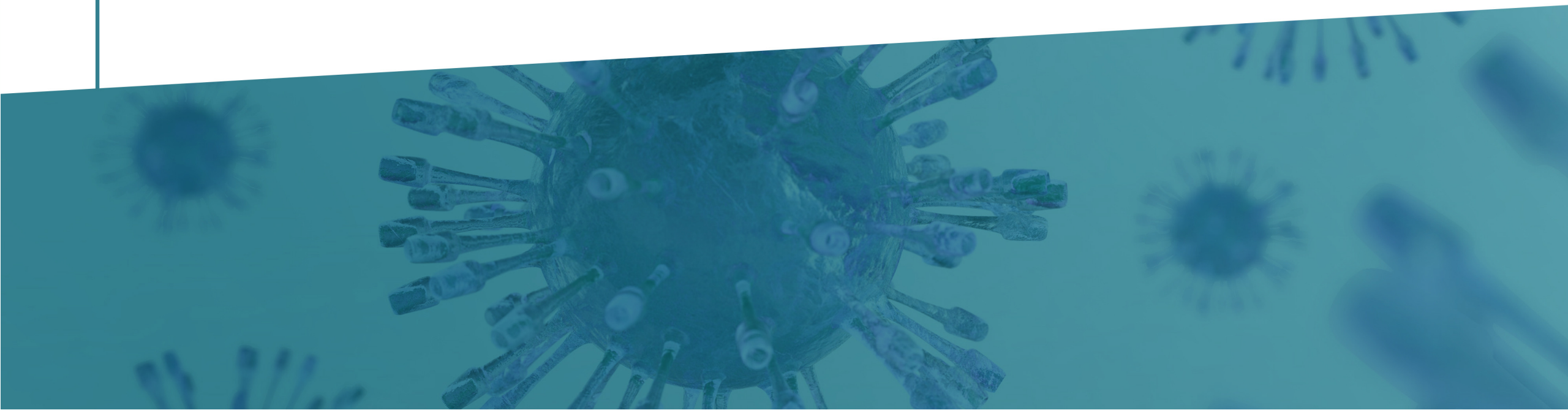
[a]Nominal, unadjusted one-sided p-value based on log-rank test. Data cutoff: February 18, 2020.

CONCLUSIONS: CHALLENGES & OPPORTUNITIES IN FIRST-LINE THERAPY FOR RECURRENT & METASTATIC DISEASE

- Although there are 2 new standards-of-care in 1st-line setting, most patients die of R/M SCCHN
- Long-term benefit is greatest with pembro-chemo combinations
- Addition of chemotherapy reduces the rate of early progressive disease
- Unmet need persists, especially in CPS <20
- Intratumoral RPx directly kills tumors, turning cold (i.e. low PD-L1) tumors hot, and inducing systemic anti-tumor immune responses
    - Expected to be potentiated by anti-PD1
    - Synergy with taxane-based chemotherapy also expected
- New opportunities for intratumoural RPx platform viruses, with chemotherapy and immune checkpoint blockade, particularly in CPS <20

Unmet Need in HCC and CRC

Tanios Bekaii-Saab, M.D.



Tanios Bekaii-Saab, M.D, F.A.C.P, Mayo Clinic Cancer Center

Tanios Bekaii-Saab, MD, FACP is a Professor of Medicine at the Mayo Clinic College of Medicine and Science, Leader of the Gastrointestinal Cancer Program and Director of the Clinical Cancer Research Office for the Enterprise-wide Mayo Clinic Cancer Center.

Dr. Bekaii-Saab's research includes a large focus on the incorporation of agents that target the multiple facets of cancer, including genetic and epigenetic drivers, as well as the feeding microenvironment and the immune milieu.

Dr. Bekaii-Saab conducts clinical and translational research focused on developing anticancer agents for patients with gastrointestinal cancers. He collaborates extensively with various scientists and industry partners to design and execute innovative clinical trials, including many first-in-human studies.

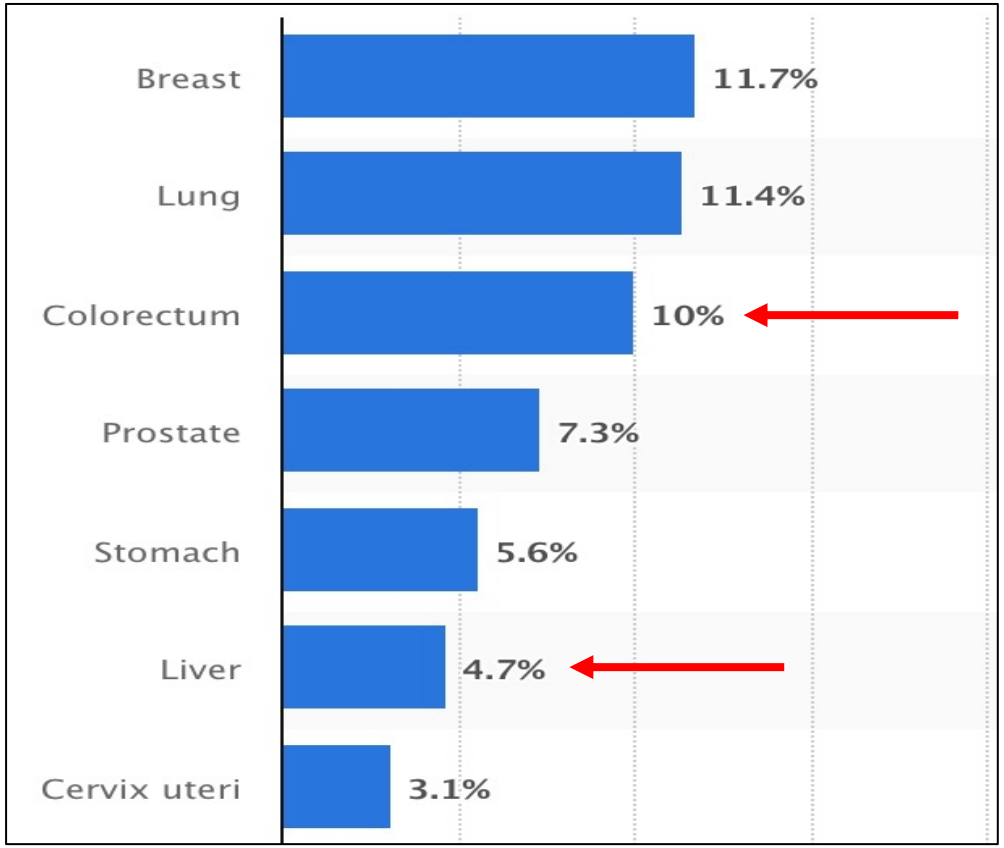
Dr. Bekaii-Saab earned his medical degree from the American University of Beirut in Lebanon and completed a residency in internal medicine at Indiana University Medical Center in Indianapolis, Indiana, USA. He then completed fellowships in clinical pharmacology and experimental therapeutics and hematology/oncology at Tufts University/New England Medical Center in Boston, Massachusetts, USA.

MAYO CLINIC

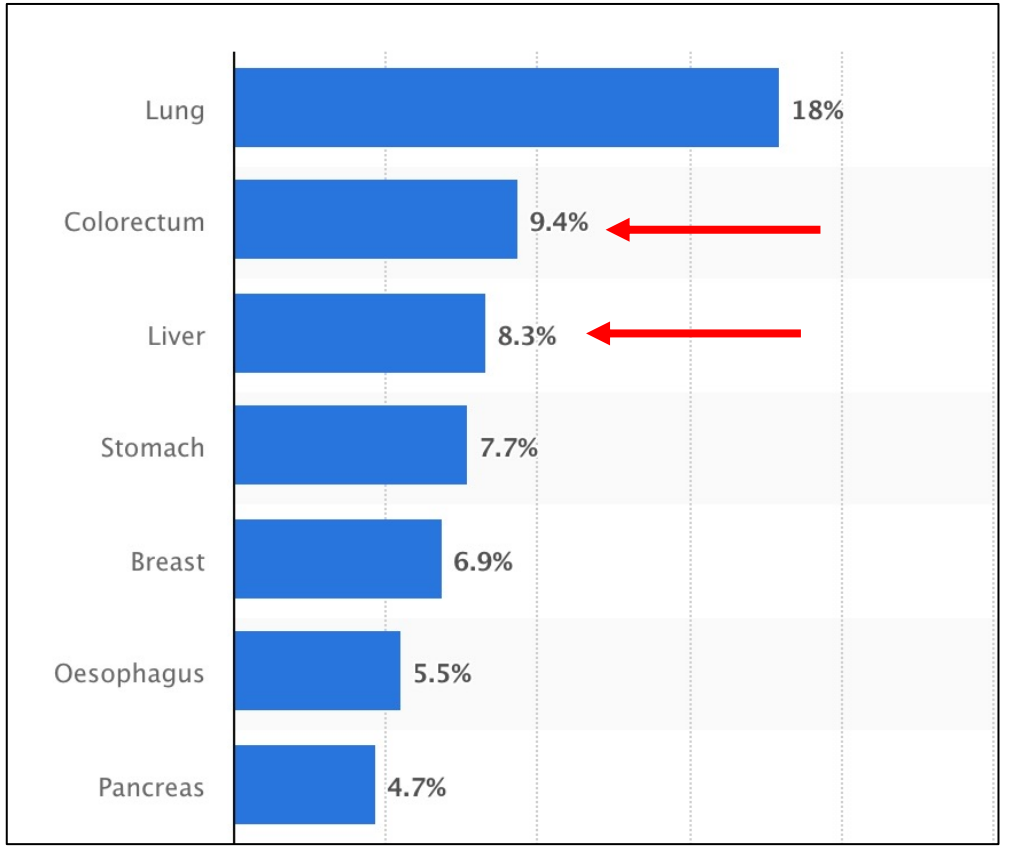
Updates and Unmet Needs in Hepatocellular Cancer (HCC) and Colorectal Cancers (CRC)

Tanios Bekaii-Saab, MD
Program Leader, GI Cancer, Mayo Clinic Cancer Center (AZ, FL and MN)
Professor , Mayo Clinic College of Medicine and Science
Consultant, Mayo Clinic AZ
Chair , ACCRU Consortium

Percentage of new cancer cases worldwide in 2020 (Top 7)



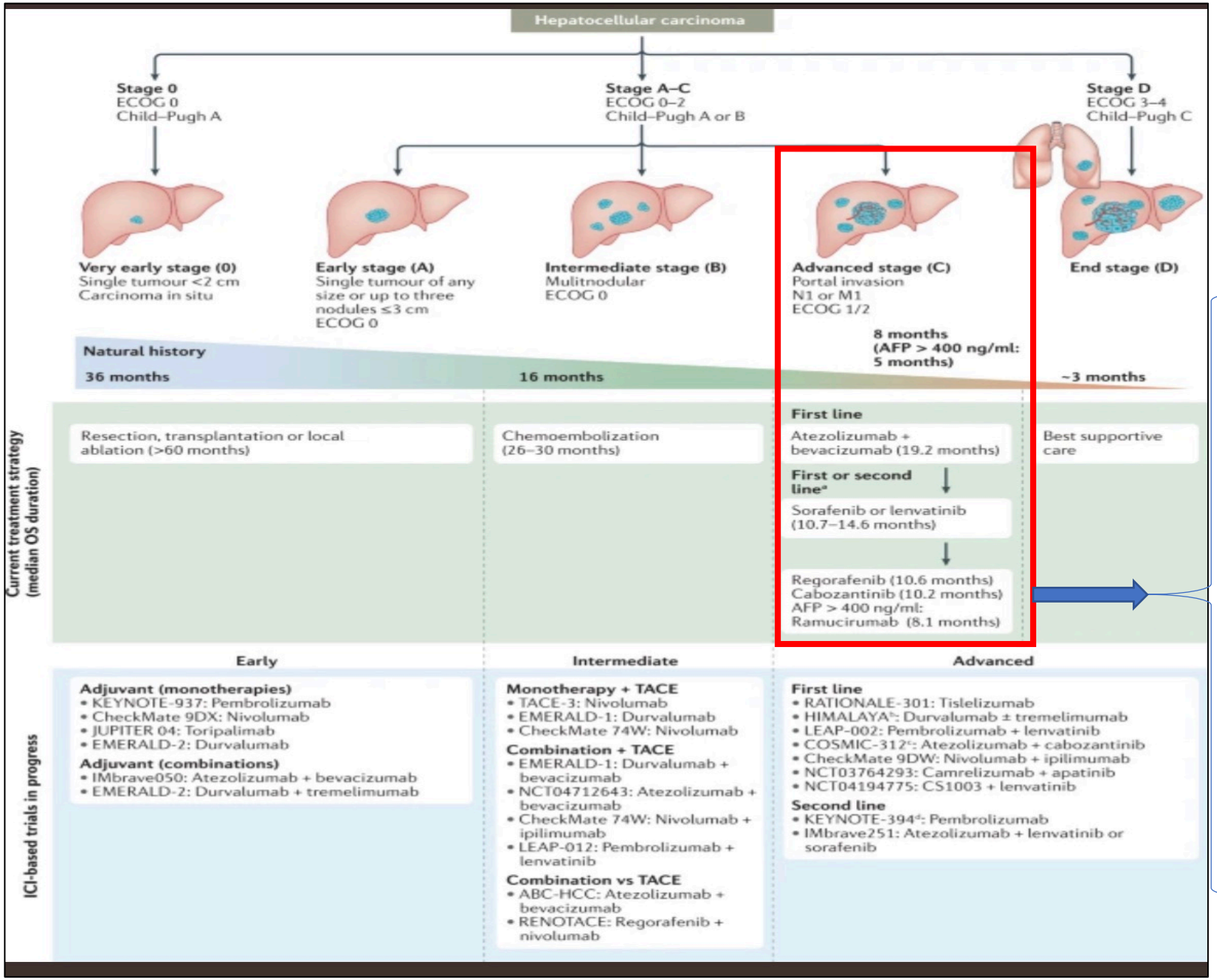
Percentage of cancer deaths worldwide in 2020 (Top 7)



Statistica 2022

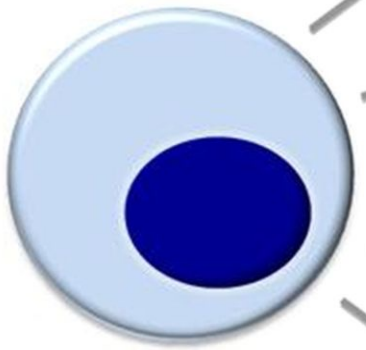
HCC

High Level Overview of the Treatment Landscape in HCC



- Therapy has advanced relatively well with Immunotherapy but opportunities exist for improvement
- Novel approaches such as direct interference with Local Immune Microenvironment have the potential to improve outcomes
- Unmet needs in 1L and 2L post CPI (lack of data)

How do we expand and improve the benefit of immunotherapy to more patients with hepatocellular carcinoma?



Tumour-specific → - Alter the TME and enhance tumor associated antigen exposure through Intra-tumoral Treatment

Intrinsic activity (CTLA4, PD1 blockade) → - Beyond PD-1: OX40, LAG-3
- IO/IO combinations

Extrinsic activity (immunosuppressive microenvironment) → - Anti VEGF combinations (TKI, Bevacizumab)

Migrate into the tumour → - Other ongoing preclinical and early clinical research

1. *Chen Y et al. Hepatology. 2015;61(5):1591-1602.*
2. *Greten et al. Rev Recent Clin Trial. 2008*
3. *Hedge PS, Semin Cancer Biol 2017*
4. *Tim F Greten et al. Gut 2015;64:842-848*

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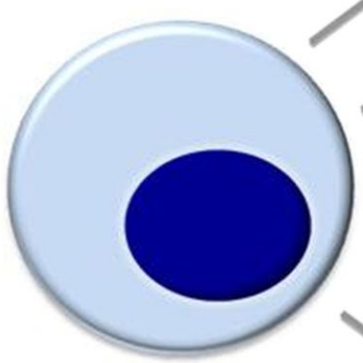

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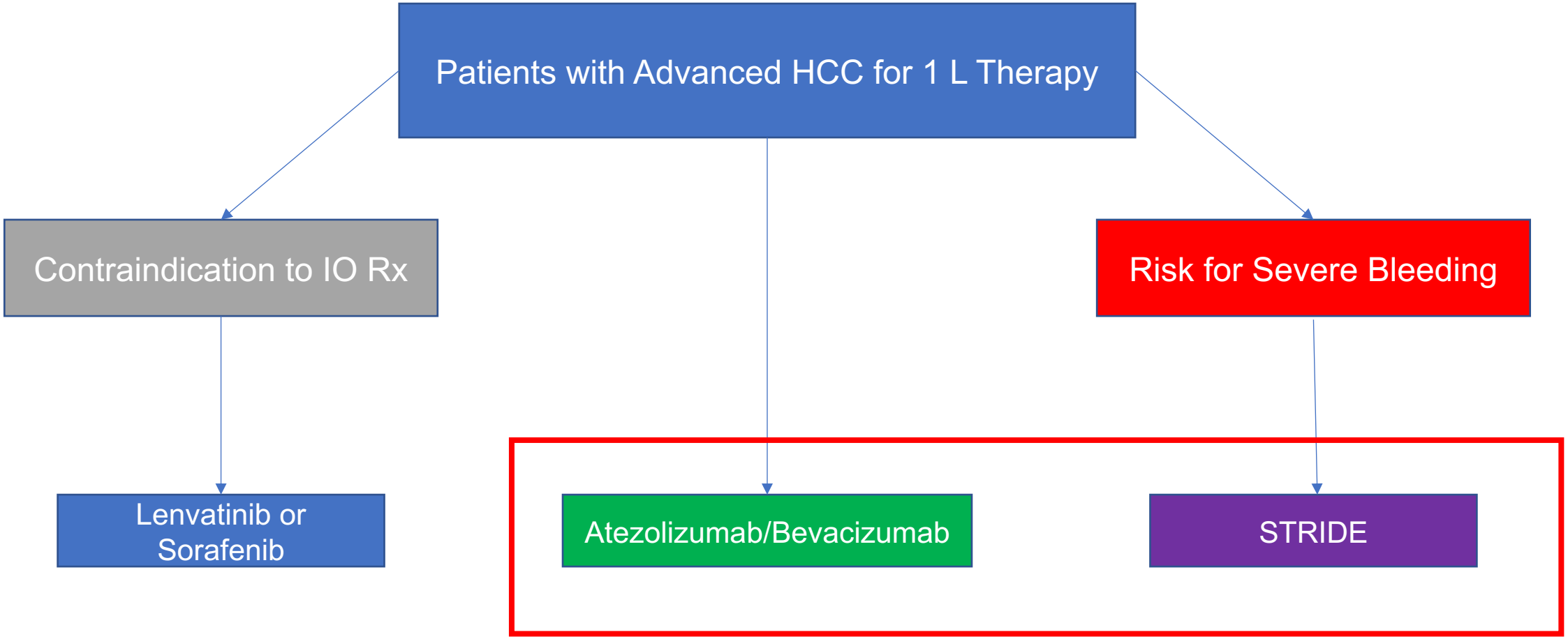
Patients with Advanced HCC for 1 L Therapy
Contraindication to IO Rx
Risk for Severe Bleeding
Lenvatinib or Sorafenib
Atezolizumab/Bevacizumab
STRIDE

Efficacy Plateau reached in IO Combination 1L HCC

	IMBRAVE 150		HIMALAYA		COSMIC 312	
	Atezo/Bev	Sorafenib	STRIDE	Sorafenib	Cabozantinib/Atezo	Sorafenib
mOS (mo)	19.2 HR 0.66 (0.52,0.85)	13.4	16.4 HR 0.78 (0.65-0.92)	13.8	15.4* HR 0.9 (96% CI 0.69–1.18)	15.5
mPFS (mo)	6.9 HR 0.65(0.53, 0.81)	4.3	3.78 HR 0.9 (0.77-1.05)	4.07	6.8 0.63 (99% CI 0.44–0.91)	4.2
ORR (RECIST 1.1)	30%	11%	20.1%	5.1%	11%	3.7%
CR	8%		3.1%		0.2%	
PD	19%		39.9%		14%	
Median DoR (months)	18.1	14.9	22.3	18.4	10.6	8.8
DCR	74%	55%	60.1%	60.7%	78%	65%

IMAEs requiring steroids	12.2%		20.1%	
All grade bleeding events	25%	17.3%	1.8%	4.8%
Grade 3/4 bleeding events	6.4%	5.8%	0.5%	1.6%

Kelley RK, ESMO ASIA 2021

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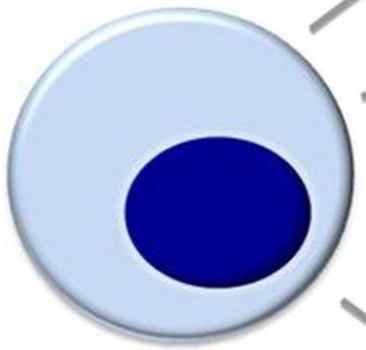
Large Unmet Need in 2L HCC*

Trial	CELESTIAL		RESORCE		REACH-2		KEYNOTE-224	CheckMate 040
	NCT01908426		NCT01774344		NCT02435433		NCT02702414	NCT01658878
Trial arms	carbozantinib	placebo	regorafenib	placebo	ramucirumab	placebo	pembrolizumab	nivolumab + ipilimumab (Arm A)‡
Sample size	470	237	379	194	197	95	104	50
Geography	U.S., EU5, ROW		U.S., EU5, JP, ROW		U.S., EU5, JP, ROW		U.S., EU5, JP, ROW	U.S., EU5, JP, ROW
Patient Segment	Child-Pugh A; prior sorafenib		Child-Pugh A or B; All BCLC; progressed on sorafenib		Child-Pugh A; BCLC stage B or C; AFP ≥400 ng/mL; prior sorafenib		Child-Pugh A or B; BCLC B or C; prior sorafenib	Child-Pugh A; All BCLC; progressed on sorafenib
Overall Response Rate	4%**	0.4%**	11%^; 7%**	4%^; 3%**	4.60%	1.20%	18.3%**	34%^; 32%**
	p=0.009		p=0.0047^; p = 0.02**		p=0.1697			
Progression-Free Survival	5.2 months	1.9 months	3.1 months^	1.5 months^	2.8 months	1.6 months	4.9 months	mDOR: 17.5 months
	HR, 0.44; p<0.001		HR, 0.46; p<0.0001		HR, 0.452; p<0.0001			
Overall Survival	10.2 months	8.0 months	10.6 months	7.8 months	8.5 months	7.3 months	13.2 months	22.8 months
	HR, 0.76; p=0.005		HR, 0.63; p<0.0001		HR, 0.710; p=0.0199			
Total Grade 3/4 AEs	68%	36%	66%	39%	35%^	29%^	26%	53%
AE-related discontinuation rate	16%	3%	10%	4%	18%	11%	5%	18%
Most common Grade 3/4 AEs*	palmar–plantar erythrodysesthesia (17%), hypertension (16%), increased AST (12%)	palmar–plantar erythrodysesthesia (0%), hypertension (2%), increased AST (7%)	hypertension (15%),	hypertension (5%),	hypertension (13%),	hypertension (5%),	increased AST (7%),	AST increase (16%), lipase increase (12%),
			hand-foot skin reaction (13%), fatigue (9%)	hand-foot skin reaction (1%),	hyponatremia (6%),	hyponatremia (0%),	increased ALT (4%),	ALT increase (8%)
				fatigue (5%)	increased AST (3%)	increased AST (5%)	fatigue (4%)	
Citation	Abou-Alfa, NEJM, 2018		Bruix, Lancet, 2017; Bruix, J of Hepatology, 2017		Zhu, Lancet Oncol, 2019		Zhu, Lancet Oncol, 2018; Kudo, J Clin Oncol, 2020	Yau, JAMA Oncol, 2020

*All 2L studies were following failure of sorafenib

How do we expand the benefit of immunotherapy to more patients with hepatocellular carcinoma?



Tumour-specific → - Enhance tumor associated antigen exposure through Intra-tumoral Treatment

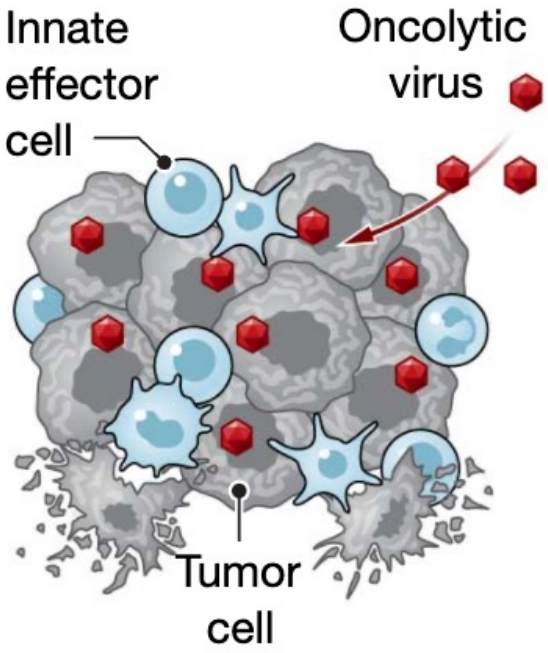
Intrinsic activity (CTLA4, PD1 blockade) → - Beyond PD-1: OX40, LAG-3
- IO/IO combinations

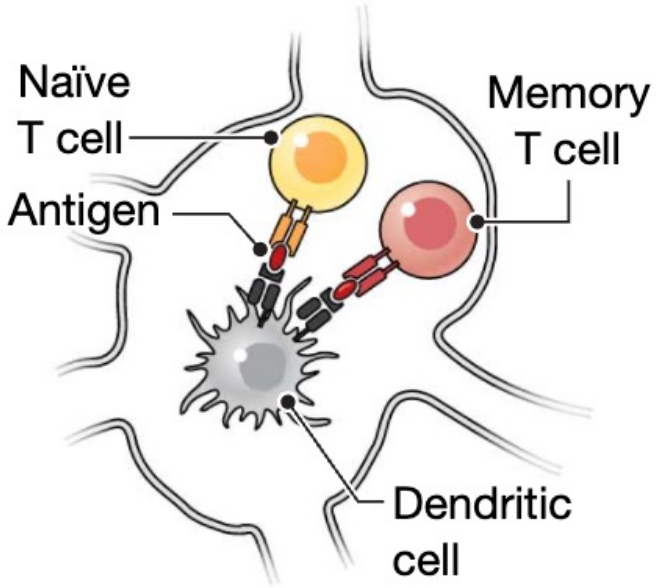
Extrinsic activity (immunosuppressive microenvironment) → - Anti VEGF combinations (TKI, Bevacizumab)

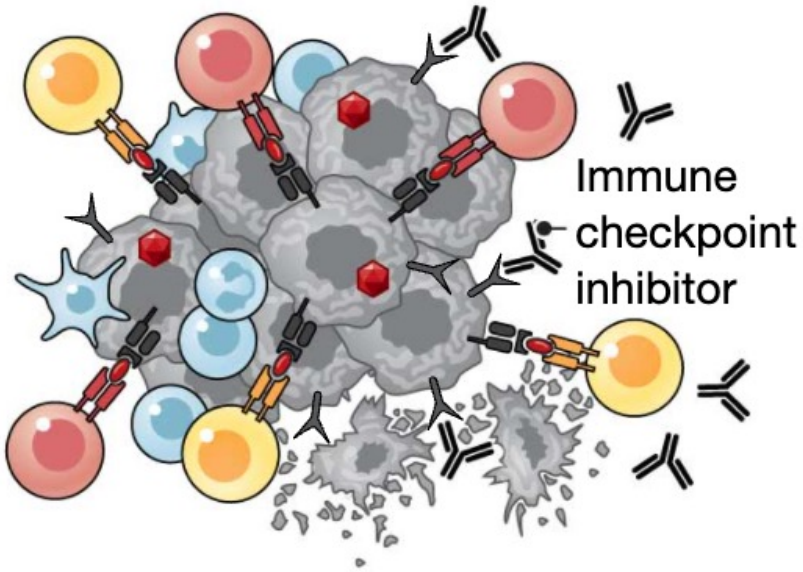
Migrate into the tumour → - Other ongoing preclinical and early clinical research

1. *Chen Y et al. Hepatology. 2015;61(5):1591-1602.*
2. *Greten et al. Rev Recent Clin Trial. 2008*
3. *Hedge PS, Semin Cancer Biol 2017*
4. *Tim F Greten et al. Gut 2015;64:842-848*

Oncolytic virus infection → **Immune checkpoint inhibition**







Oncolytic viral infection kills tumor cells, releasing antigens and recruiting innate effector cells.

At the **lymph node**, viral, self, and tumor antigens are presented to naïve and memory T cells, which, primed and expanded, travel to the tumor.

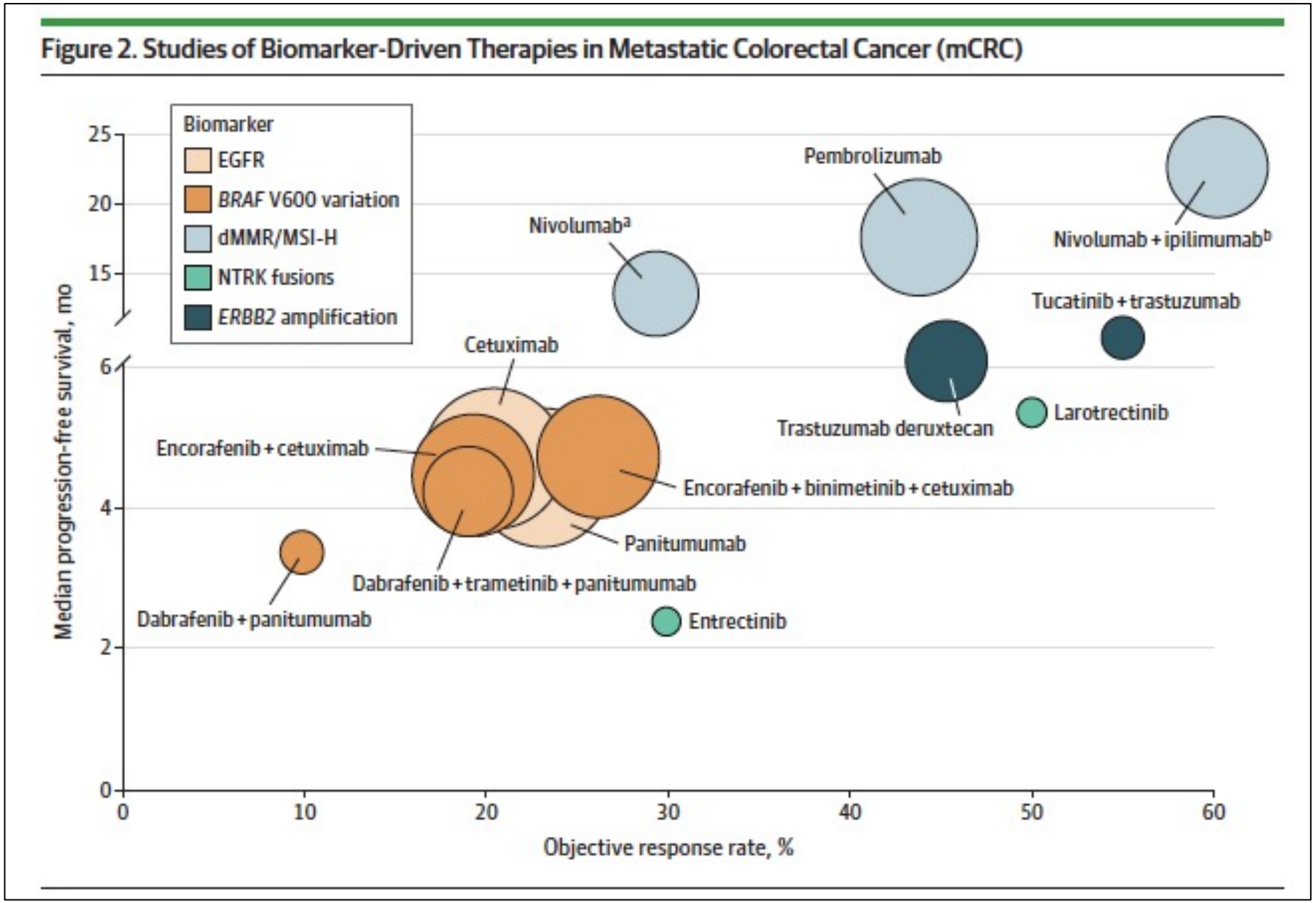
Activated T cells infiltrate the tumor, where they recognize antigens and kill tumor cells. This antitumor response can be boosted by immune checkpoint inhibitors.

Melcher A et al. Science 2021

Enhancing current IO platforms in HCC

- IO plateau reached in 1L HCC
- Beyond 1L , absence of data post-IO
- Tumor directed Oncolytic Immunotherapy has promise to improve IO effectiveness in 1L and overcome resistance in 2L
  - Liver procedures by IRs are routine in HCC (TACE, TARE)
- Explore in earlier disease stages
  - TACE combination and neoadjuvant setting

Refractory CRC



- 3L mCRC treatments offer modest efficacy
- ~70-80% of 3L pts have liver mets
- mCRC pts
- Patients commonly die from liver mets

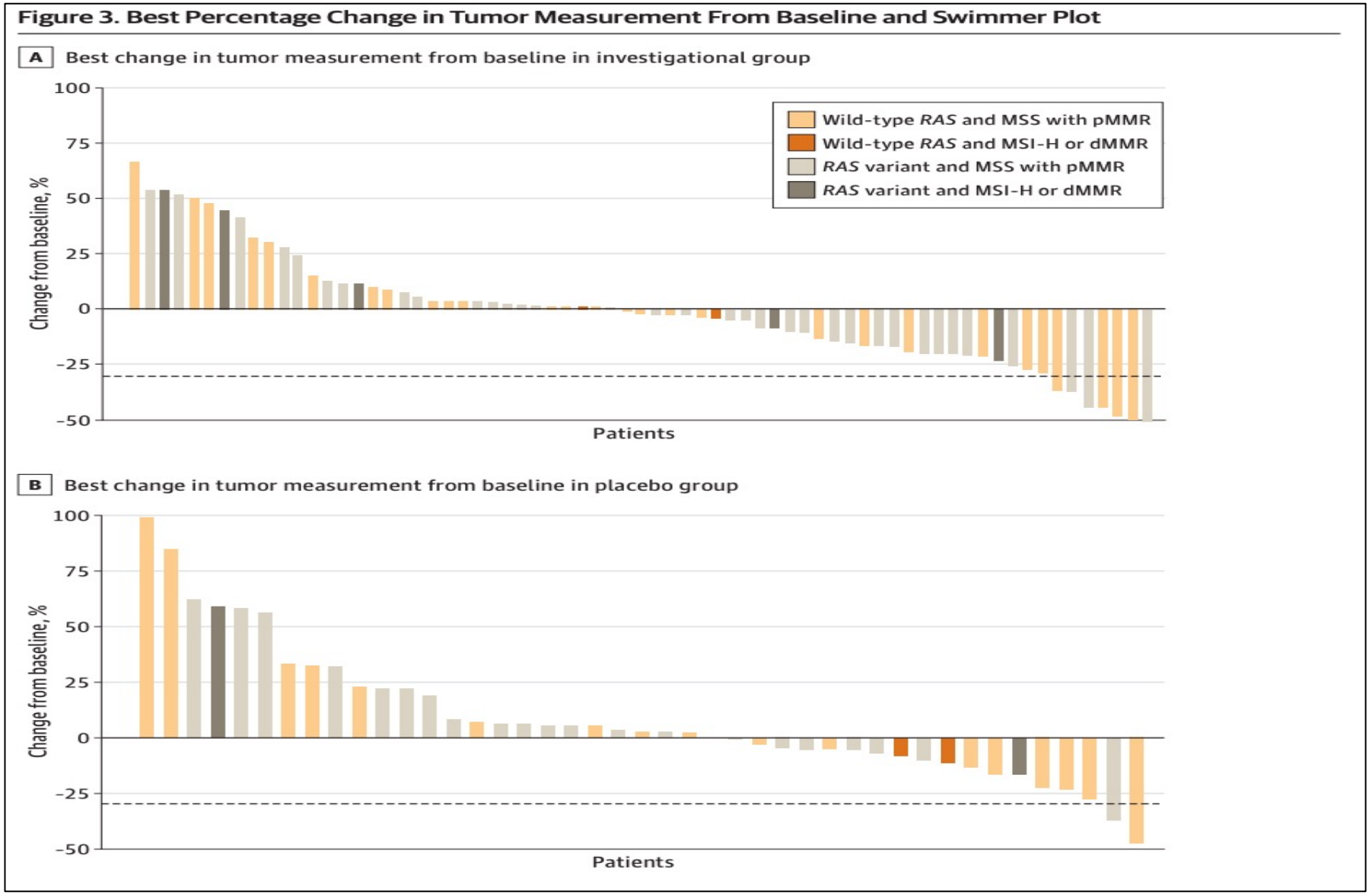
Strickler J , Bekaii-Saab T et al JAMA Onc 2022

Limited Efficacy and Significant Toxicity in 3L mCRC Treatments

Agent	Regorafenib				TAS-102			
Trial	**CORRECT[1]**		**CONCUR[2]**		**RECOURSE[3]**		**TERRA[4]**	
Prior biologics	100% BEV 100% EGFR mAbs		60%		100% BEV 53% EGFR mAbs 18% Prior REGO		20% BEV 18% EGFR mAbs	
	REGO (n = 505)	BSC + PL (n = 255)	REGO (n = 136)	BSC + PL (n = 68)	TAS-102 (n = 534)	BSC + PL (n = 266)	TAS-102 (n = 271)	BSC + PL (n = 135)
Prior lines ≤2 3 ≥4	 27% 25% 49%	 25% 28% 47%	 35% 24% 38%	 35% 25% 40%	 18% 22% 60%	 17% 20% 63%	 23% 27% 50%	 19% 27% 55%
Median OS, mo	**6.4**	**5.0**	**8.8**	**6.3**	**7.1**	**5.3**	**7.8**	**7.1**
	P = .0052		*P* = .0002		*P* <.0001		*P* = .0035	
Median PFS, mo	**1.9**	**1.7**	**3.2**	**1.7**	**2.0**	**1.7**	**2.0**	**1.8**
	P <.0001		*P* <.0001		*P* <.0001		*P* <.0001	
RR, %	1.0	0.4	4.4	0	1.6	0.4	1.1	0

1. Grothey A, et al. *Lancet*. 2013;381:303-312; 2. Li J, et al. *Lancet Oncol*. 2015;16:619-629; 3. Mayer RJ, et al. *N Engl J Med*. 2015;372:1909-1919; 4. Kim TW, et al. ESMO 2016. Abstract 465PD.

Assessment of Capecitabine and Bevacizumab With or Without Atezolizumab for the Treatment of Refractory Metastatic CRC

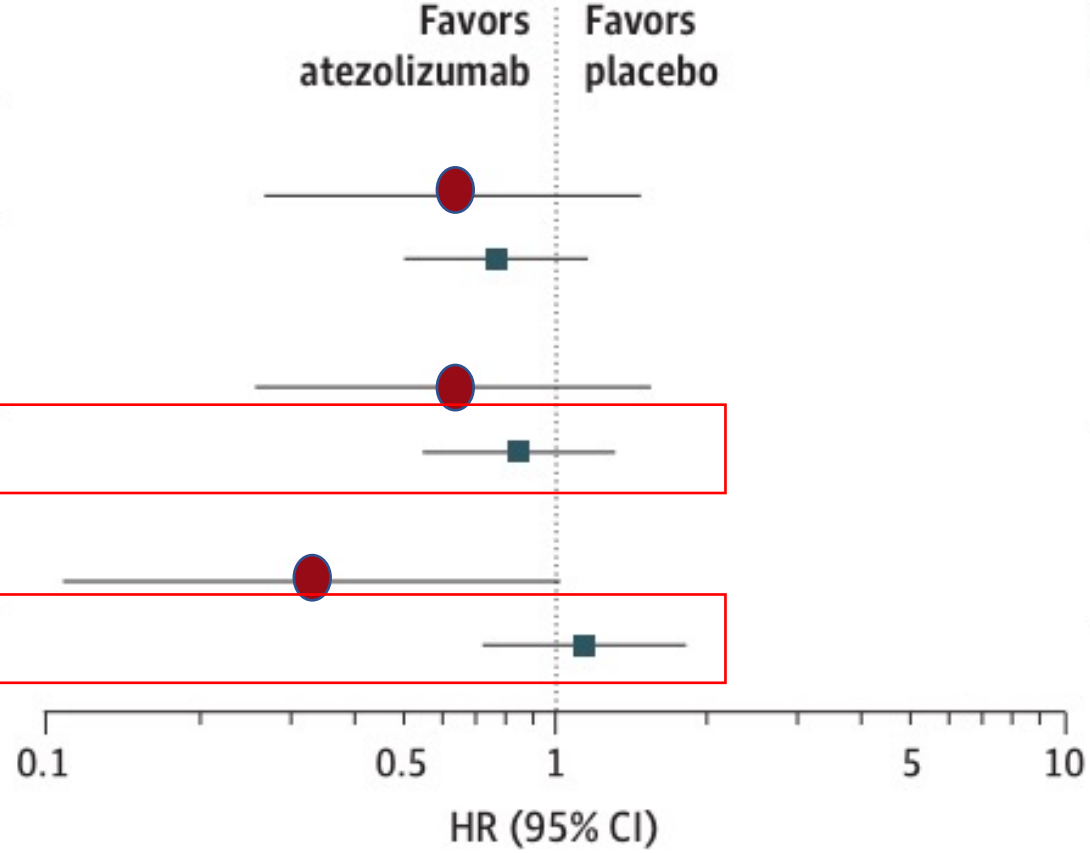


Mettu N and Bekaii-Saab T et al JAMA ON 2022.

IO Less Effective in Refractory Metastatic CRC with Liver Mets in Cape + Bev With or Without Atezo Trial

Figure 4. Survival End Points of Investigational vs Placebo Groups by Presence and Absence of Liver Metastasis

Presence or absence of metastatis	Events, No.	Total No.	HR (95% CI)	*P* for interaction
PFS				
No liver metastasis	22	23	0.63 (0.27-1.47)	.68
Liver metastasis	101	105	0.77 (0.51-1.17)	
PFS (sensitivity)				
No liver metastasis	20	23	0.63 (0.26-1.53)	.55
Liver metastasis	94	105	0.85 (0.56-1.31)	
OS				
No liver metastasis	13	23	0.33 (0.11-1.02)	.04
Liver metastasis	83	105	1.14 (0.72-1.81)	



In Atezo Group
ORR **23.1%** if No Liver mets
ORR **5.8%** if Liver Mets
P=0.04

Mettu N and Bekaii-Saab T et al JAMA ON 2022.

Turning MSS CRC “Cold” Tumors into “Hot” Tumors

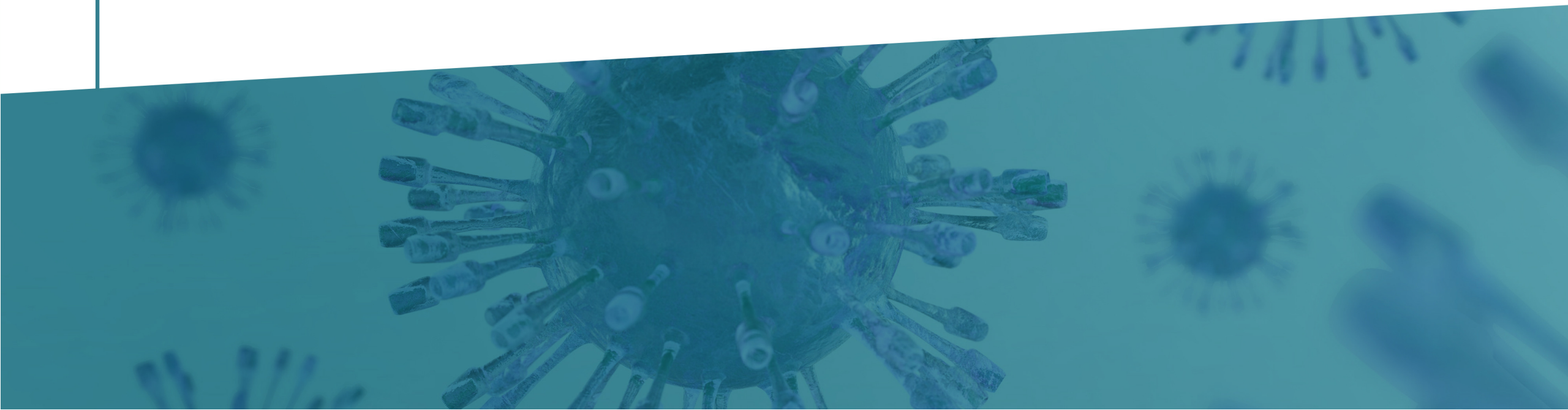
- 3L CRC remains a significant area of unmet need
- IO + VEGF targeting agents show some limited promise
- The presence of liver metastases is consistently associated with resistance to PD-1/PD-L1 inhibition in MSS CRC
  - Immunosuppressive Microenvironment (ISM) present in liver metastatic disease from colorectal cancer
- Tumor directed Oncolytic Immunotherapy may reverse local ISM in liver mets from MSS mCRC thus enhancing the role of IO in this disease.

Prasanna T et al . Acta Oncologica 2018; Wang C et al , JAMA ON 2021; Zeng D et al, Frontiers in Oncology 2021

Replimune®

Summary

Rob Coffin



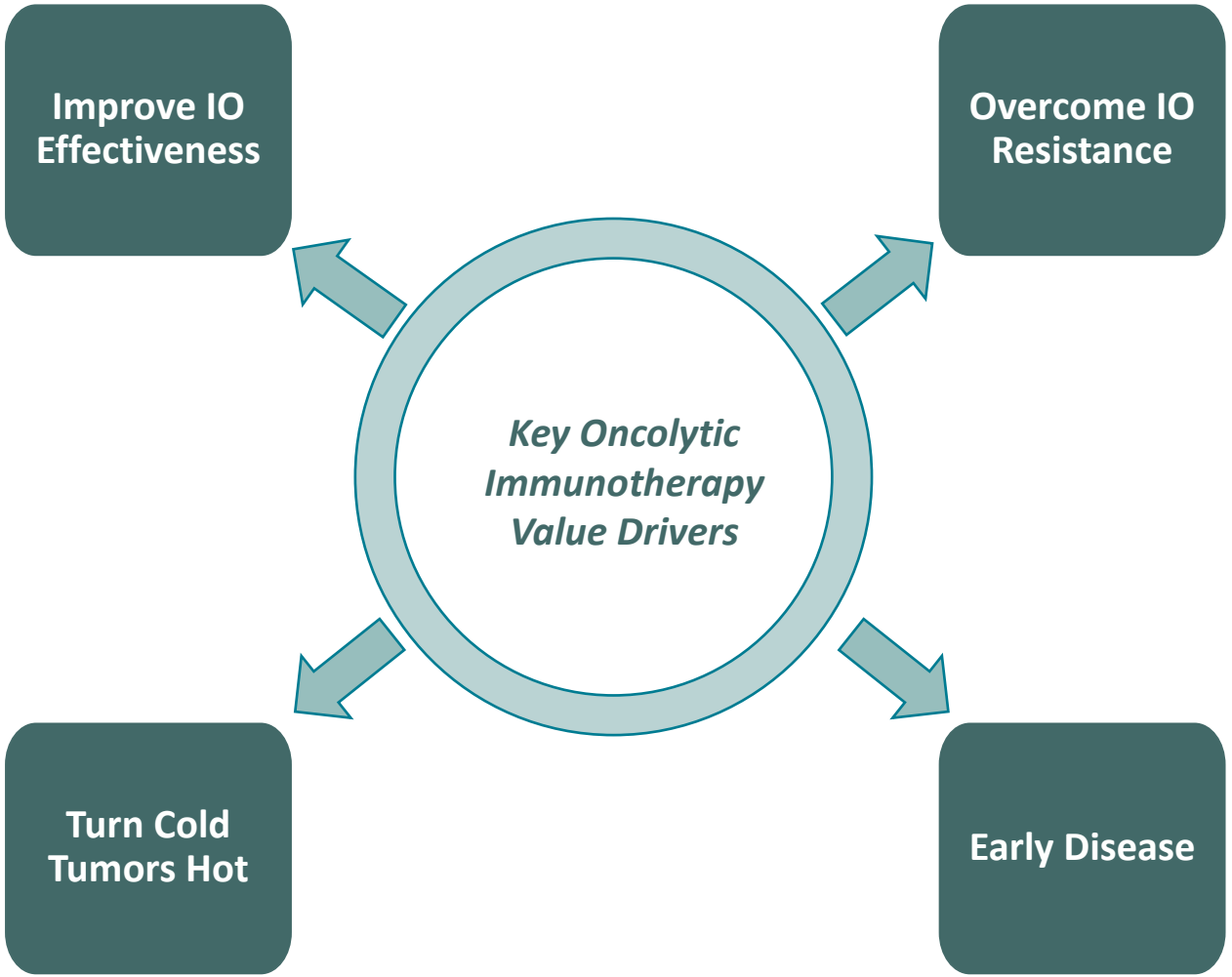
Development across the segments of interest

Build on IO to establish new combination SOC

- *Value: Gain/defend share in large, but increasingly competitive, markets with differentiated combination*
- *Example:*
  - ***RP1 + cemiplimab in adv CSCC (registrational study ongoing)***
  - ***RP2/3 + SOC IO in 1L HCC (Ph2 trial planned)***

Expand IO into new tumor types

- *Value: Extend the value of IO to large underserved patient populations*
  - ***RP2/3 + nivo in 3L CRC (Ph2 trial planned)***
  - ***Uveal melanoma (signal confirming trial ongoing with RP2)***



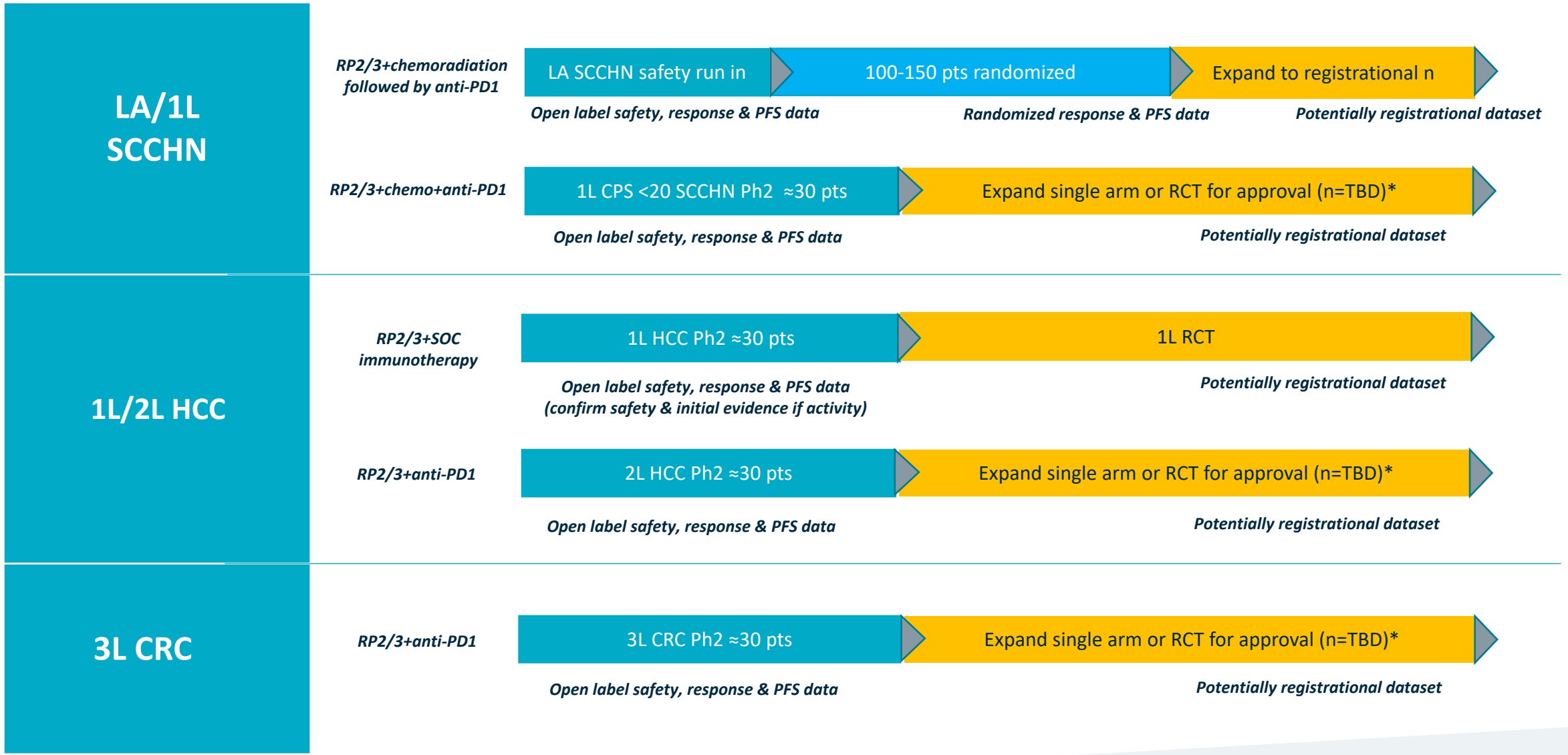
Reverse IO resistance in pts PD-L1 who have failed PD-(L)1 or have low

- *Value: Address large (and growing) patient populations with high unmet need*
- *Example:*
  - ***RP1 + nivo in CPI-experienced melanoma (registrational study ongoing)***
  - ***RP2/3 + nivo in 2L HCC; RP2/3+chemo/nivo CPS <20 recurrent SCCHN (Ph2 trial planned)***
  - ***Other e.g., esophageal cancer, breast cancer***

Ultimate Goal: Achieve Cure

- *Value: Provide a differentiated/better combination partner in an emerging and competitive space*
- *Examples:*
  - ***RP1 + PD-1 in neoadjuvant CSCC (study being planned)***
  - ***RP2/3 + chemoradiation in LA SCCHN (Ph2 trial planned)***

RP2/3 prioritized indications

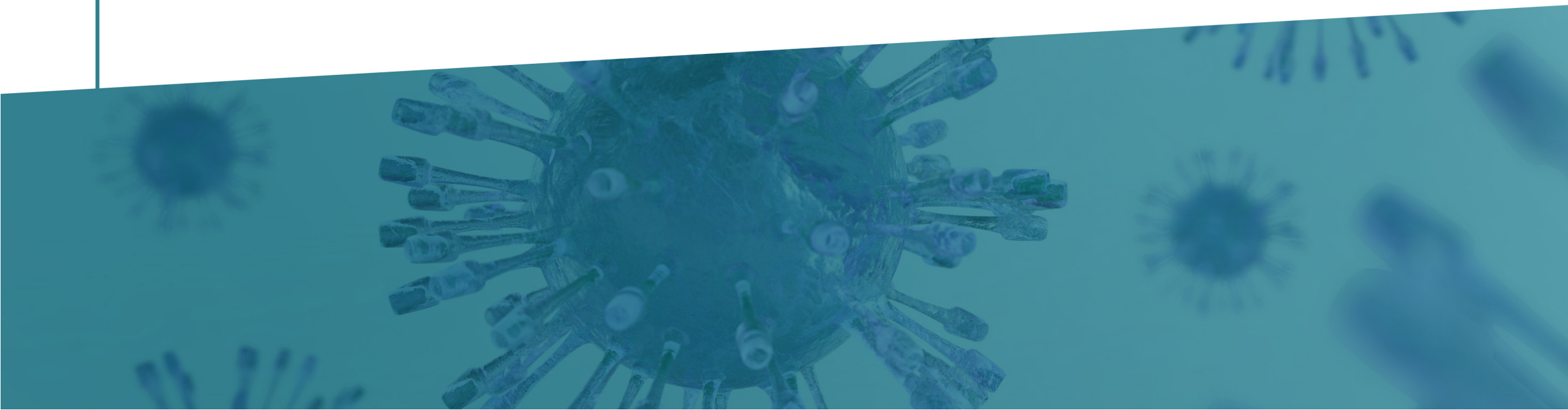


*Pending FDA buy in

Replimune has a clinical trial collaboration & supply agreement with BMS for the supply of Opdivo in its clinical trial program with RP2/3

Closing Remarks

Philip Astley-Sparke

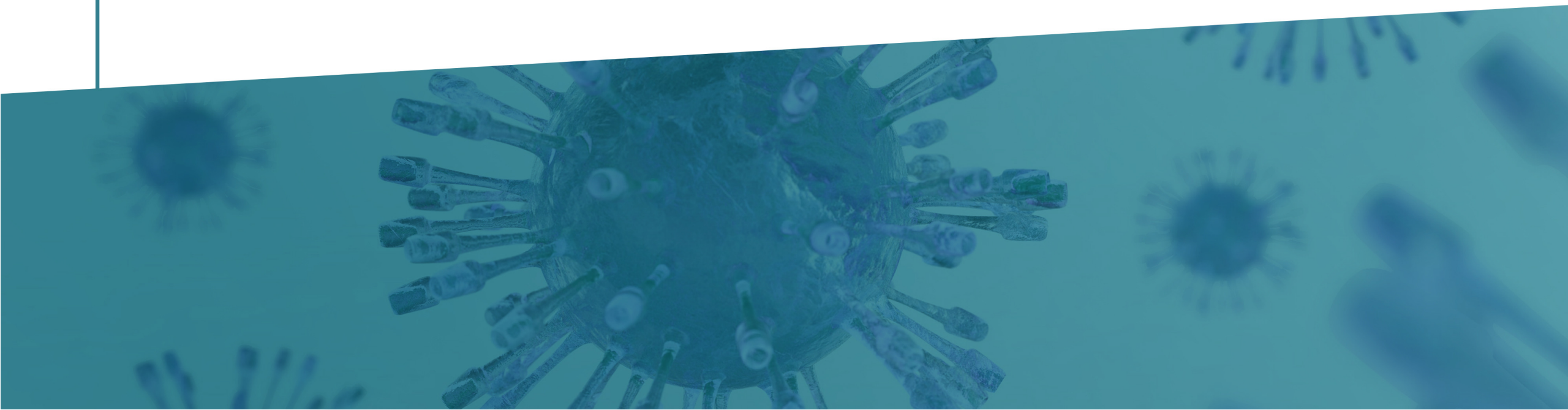


Summary

- Major skin cancer franchise planned with RP1
  - Strong data to date in multiple skin cancers in both the PD1 naïve and failed setting
  - Registrational data sets in late 22/early 23
  - Scale Manufacturing in place
    - To serve WW market at attractive COGS
  - Commercial planning ramping for US launch
- RP2/3 mid-stage pipeline
  - Focused on easily injected diseases with high commercial value
    - H&N
    - HCC
    - CRC
  - Fast routes to RCT or expansion for single arm approvals
- Strong cash position to execute vision

Replimune®

Q&A

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THANK YOU