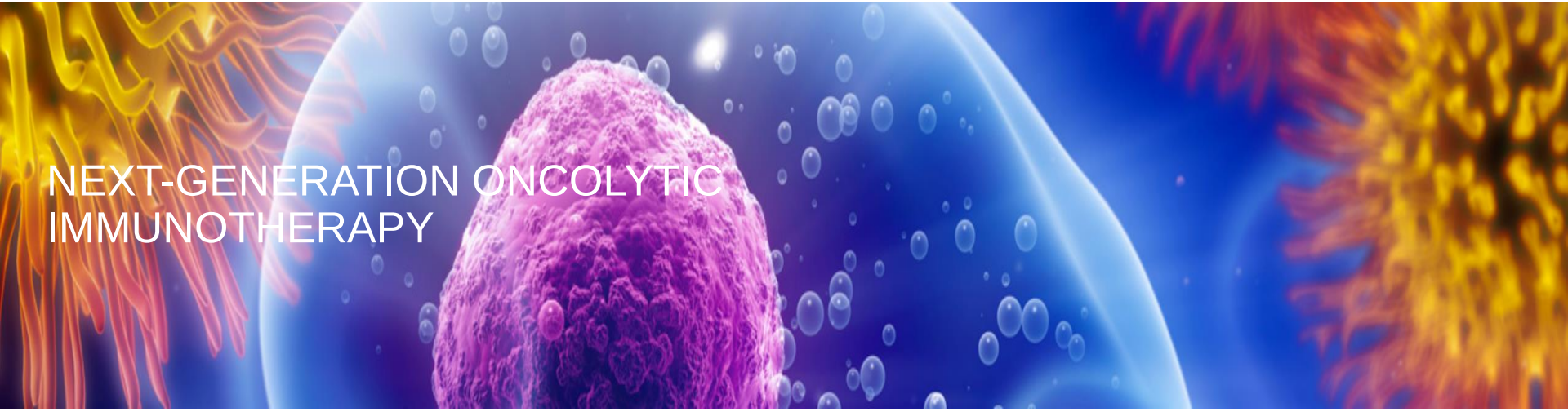
Replimune



Investor JP Morgan Presentation
January 2020

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 our cash runway, our advancement of our clinical trials, the results of our clinical trials, the timing and release of our clinical data, our goals to develop and commercialize our product candidates, our plans to operate our own in-house manufacturing facility, our expectations with respect to our in-house manufacturing capabilities, 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, and other risks set forth under the heading “Risk Factors” 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.

- Proprietary 'Immulytic' oncolytic immuno-gene therapy platform
  - Intended to maximally activate the immune system against a patient's cancer
  - Establish Replimune's products as the second cornerstone of immuno-oncology
- RP1 – in multiple clinical trials, with current focus on immuno-responsive tumors
  - Strong Phase 1/2 clinical data to date
  - Potential registration clinical trials underway or to initiate in first half
    - Ongoing 240 patient registration directed randomized Phase 2 clinical trial in CSCC in combination with cemiplimab – cost sharing collaboration with Regeneron
    - Single agent RP1 in CSCC in organ transplant recipients
    - 125 patient clinical trial in anti-PD1 refractory melanoma
  - RP2 & RP3 - intended to treat less immuno-responsive tumors
    - Ongoing Phase 1 clinical trial of RP2 alone & combined with nivolumab
    - RP3 intended to enter the clinic in 2020
- Well capitalized to deliver; ~$183 million in cash at December 31

Lead by the most experienced oncolytic immunotherapy team

PHILIP ASTLEY-SPARKE
CEO
Chairman at uniQure, CEO BioVex

ROBERT COFFIN
Founder, President & R&D Chief
Founder & CTO at BioVex, VP at Amgen

COLIN LOVE
Chief Operating Officer
SVP BioVex; VP at Amgen through T-Vec BLA filing

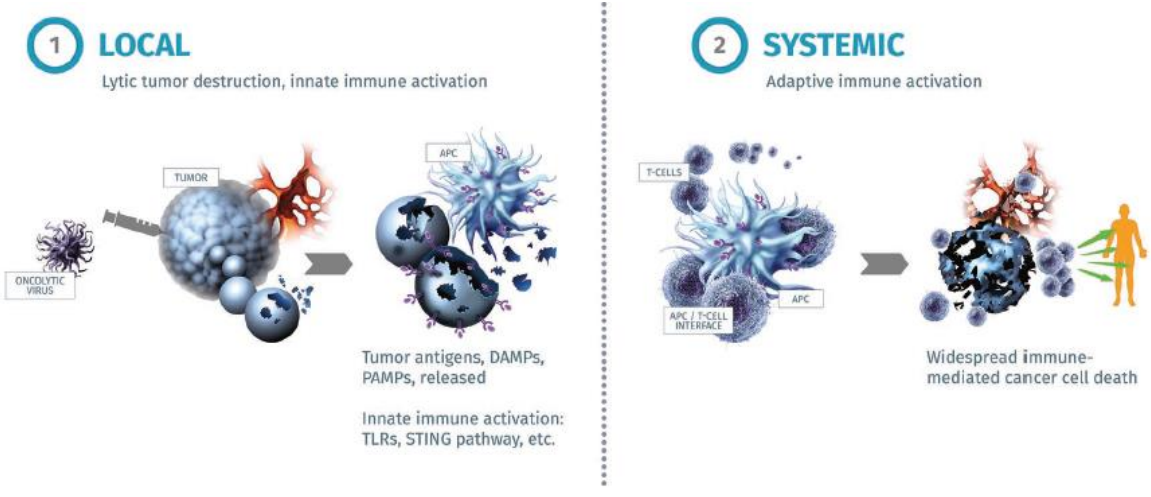
ANNE WOODLAND
SVP Regulatory & Quality
VP Regulatory at BioVex; led T-Vec BLA filing for Amgen post acquisition

PAMELA ESPOSITO
Chief Business Officer
VP BD at BioVex; CBO at Ra ***Pharmaceuticals***

JEAN FRANCHI
Chief Financial Officer
CFO at Merrimack Pharmaceuticals; CFO at Dimension Therapeutics; SVP Finance at Genzyme

Oncolytic immunotherapy

- The use of viruses that selectively replicate in & kill tumors to treat cancer
  - ✓ Highly inflammatory
  - ✓ Activates both innate and adaptive immunity
  - ✓ Releases the full array of tumor antigens into an inflamed environment
  - ✓ Systemically activates the immune system against the tumor & neo-antigens released
  - ✓ Can be ‘armed’ with additional genes to increase efficacy
- Single agent T-VEC is FDA approved for the treatment of advanced melanoma



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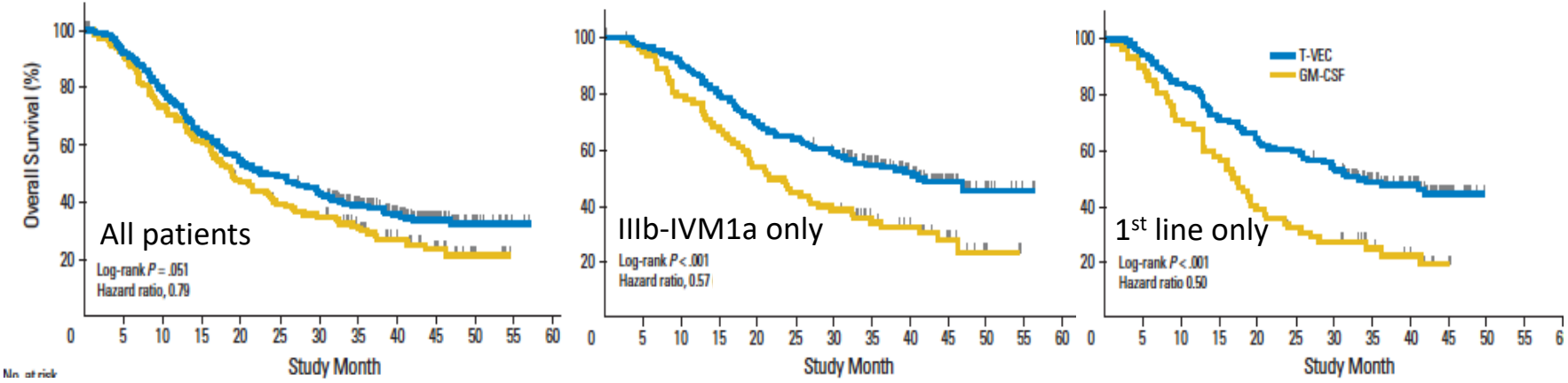
Single agent oncolytic immunotherapy works

- 436 patients randomized 2:1 to T-VEC or GM-CSF
- ORR **31.5%** vs. 6.4%, CR rate **19.9%** vs 0.7%
- Median OS 23.3 mo vs 18.9 months (P = 0.0494)
- Benefit increased in Stage IIIb-IVM1a & first line patients
  - Stage IIIb-IVM1a: **ORR 40.5%, OS HR 0.57**
  - First line: **ORR 37.7%, OS HR 0.50**
- Published post-approval real world data shows substantially further increased response rates

T-VEC phase 3 data in melanoma



Andtbacka et al JCO 2015, Amgen ODAC presentation 2015, Andtbacka et al. JITC 2019

Oncolytic immunotherapy + checkpoint blockade

Immune response to neo-antigens, inflamed tumor

- Oncolytic and immune-based efficacy in its own right
- Patient-specific neo-antigen vaccine generated in situ

'Brakes removed' from the immune response generated

- Without a pre-existing neo-antigen response, nothing to remove the brakes from
- Only some patients respond

Oncolytic immunotherapy is expected to be an ideal combination partner for checkpoint blockade therapies

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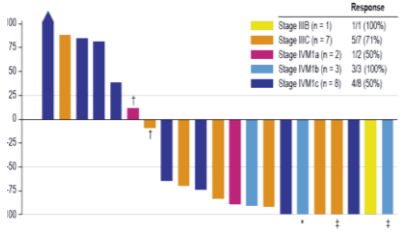
Oncolytic immunotherapy is synergistic with immune checkpoint blockade

- Randomized controlled 198 patient phase 2 study of T-VEC + ipilimumab vs. ipilimumab alone in advanced melanoma
- Response rates more than doubled in combination (38% vs. 18%)
- No additional toxicity as compared to ipilumumab alone Chesney et al JCO, 2017

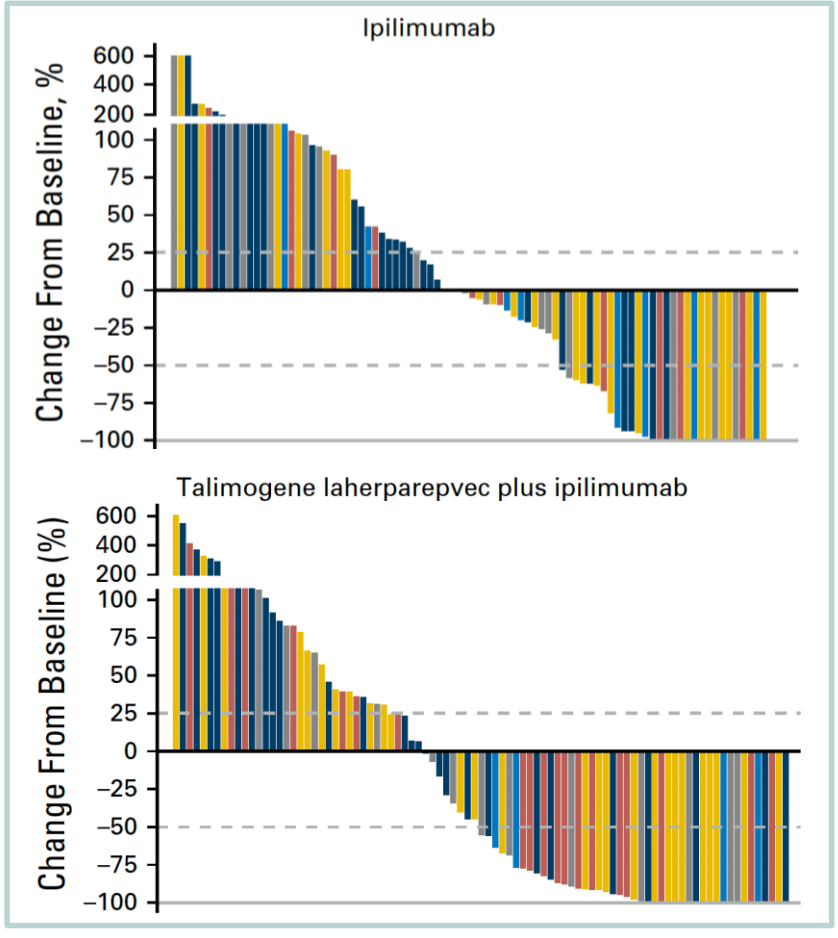
T-VEC+pembrolizumab ph1b study

Ribas *et al* Cell 2017 170: 1109-1119



67%* response rate; 43% CR rate*

Pembrolizumab+T-VEC currently in a >700 patient phase 3 study *longer term follow up presented at SMR 2018



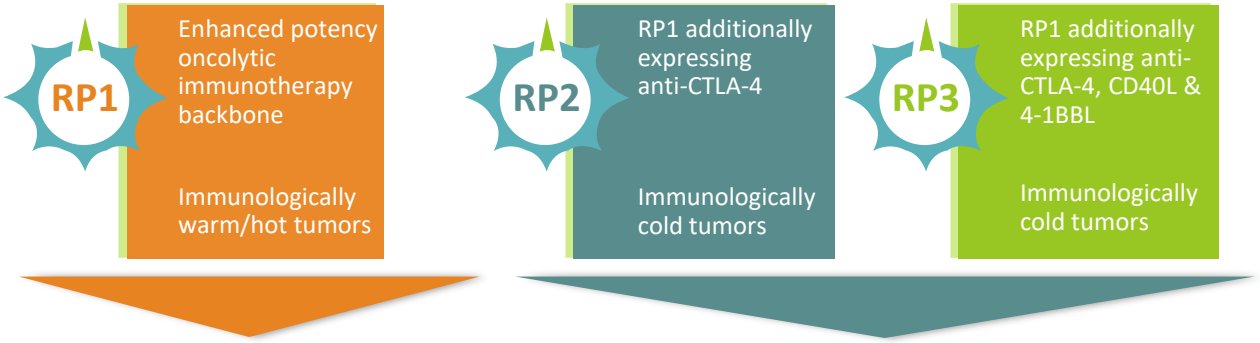
Replimune's Immulytic platform

1. A potent underlying HSV-1 strain

There is great diversity among clinical HSV strains

29 new clinical strains were tested & the most effective selected & engineered for oncolytic use

Our product candidates were then armed with two to four genes to augment tumor killing & the potency of immune activation



2. Increased tumor killing & spread

Armed with GM-CSF & a potent fusogenic protein (GALV-GP R-)

Provides a substantial increase in direct & immunogenic tumor killing*

Intended for immune responsive tumor types

3. Delivery of potent immune stimulatory proteins

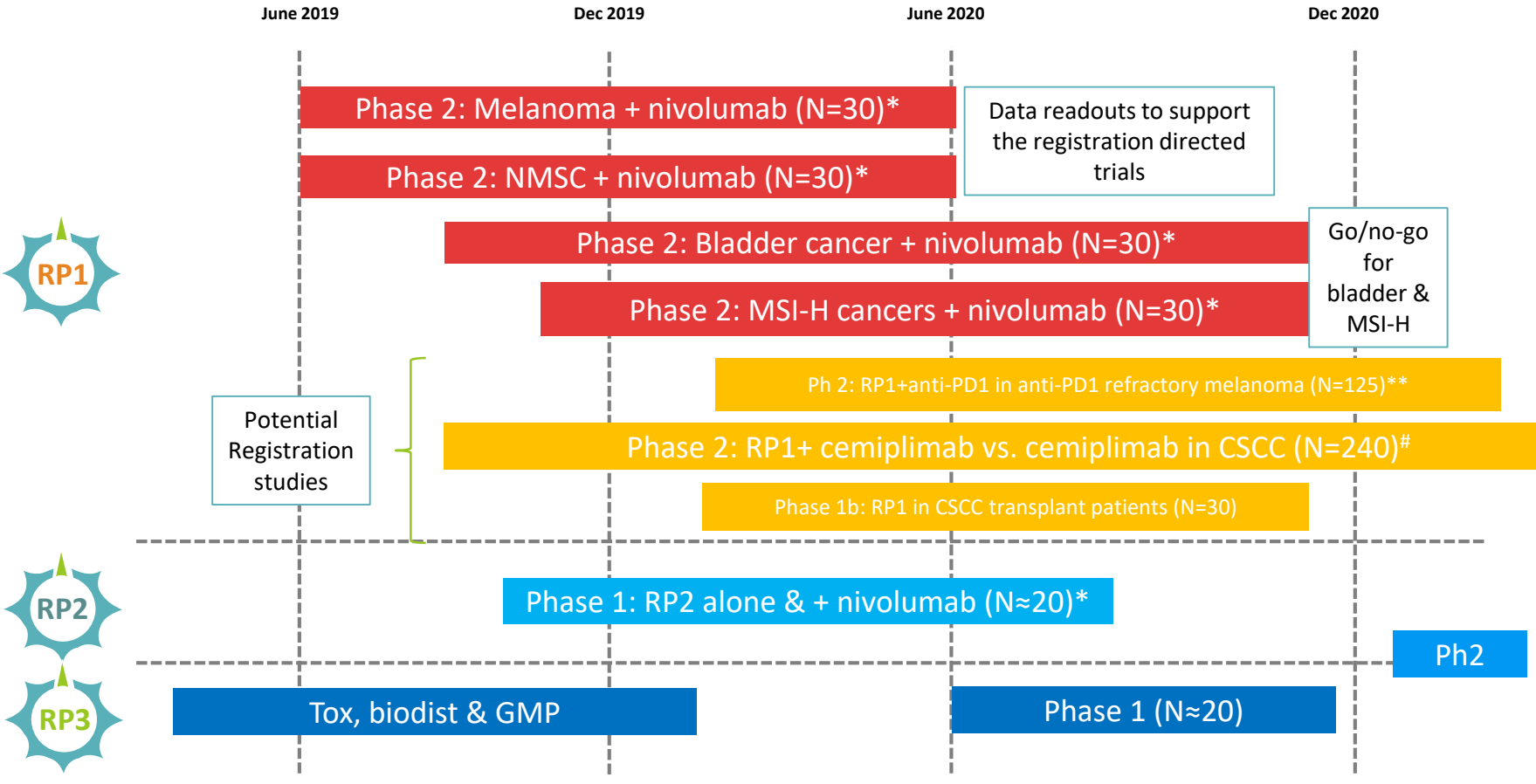
Focus on *clinically validated* pathways which function at the time & place of immune response initiation, but where systemic engagement is sub-optimal

- Anti-CTLA-4
- Immune-costimulatory pathway activators
- Aims to *increase efficacy* while *reducing toxicity*

Intended for less & non-immune responsive tumor types

* Replimune pre-clinical data published in Thomas et at JITC 2019

Replimune's development plan



* Under clinical trial collaboration & supply agreement with BMS for the supply of nivolumab – full commercial rights retained by Replimune

Under clinical trial collaboration agreement with Regeneron; 50:50 sharing of clinical trial costs – full commercial rights retained by Replimune

** Intended additional 125 pt cohort in the Phase 1/2 clinical trial in combination with nivolumab

Lead indication: CSCC

- 700,000 new cases/year in the US; 10% have ‘high risk’ disease (recurs following initial surgery)
- Approximately 7,000 US deaths annually (most conservative addressable population)
- Anti-PD-1 therapy active: Cemiplimab (Regeneron) gave 46% response rate, but low CR rate
- 80% of patients die from locoregional progression, not metastatic disease
- Registration-directed randomized controlled Phase 2 trial in collaboration with Regeneron
  - 240 patients randomized 2:1 (RP1+ cemiplimab vs cemiplimab alone)
  - Primary endpoint ORR, secondary endpoints including CR rate, duration of response, PFS, OS
- 30 patient clinical trial of single agent RP1 in solid organ transplant recipients with CSCC*
  - Organ transplant recipients are at increased risk of malignancy, with CSCC most prevalent
  - 70% of patients develop CSCC within 20 years
  - Anti-PD1 therapy contra-indicated due to the risk of organ rejection
  - Clinical data indicates that RP1 has single agent activity in CSCC
- Intend expansion of the CSCC program to also include testing for neoadjuvant use

* see additional data in the Appendix

Second indication: anti-PD1 refractory melanoma

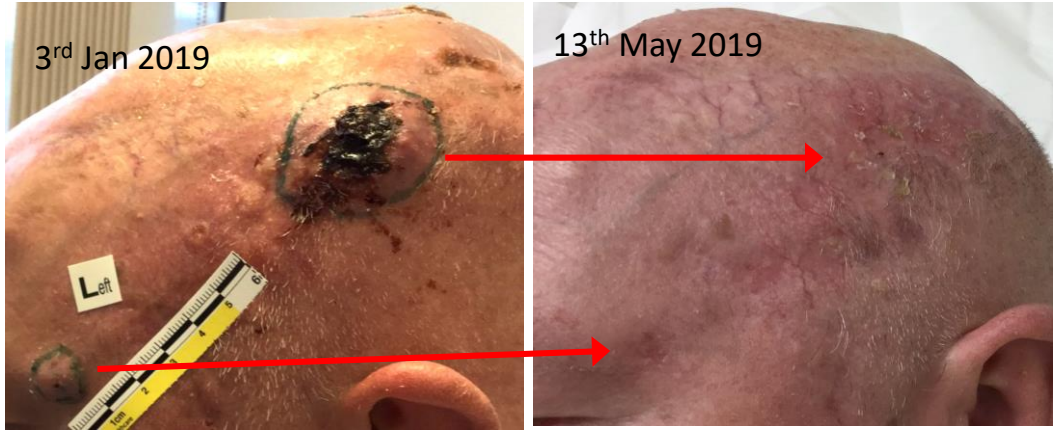
- Approximately half of advanced melanoma patients still die of their disease, despite multiple approved therapies now being available
  - anti-PD1, anti-CTLA-4, combined anti-CTLA-4/anti-PD1, BRAF targeted agents
- Approximately 8,000 US deaths annually (most conservative addressable population)
- Targeting patients with primary resistance to anti-PD1 therapy
  - No response following ≥12 weeks of therapy & with confirmed progression
  - Includes patients failing anti-PD1 adjuvant therapy
  - Very unlikely to respond to further treatment with single agent anti-PD1
  - Significant un-met medical need

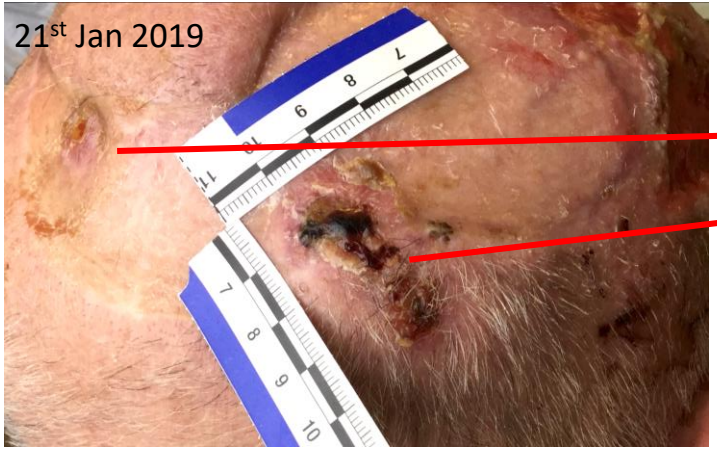
Current clinical focus based on compelling clinical data

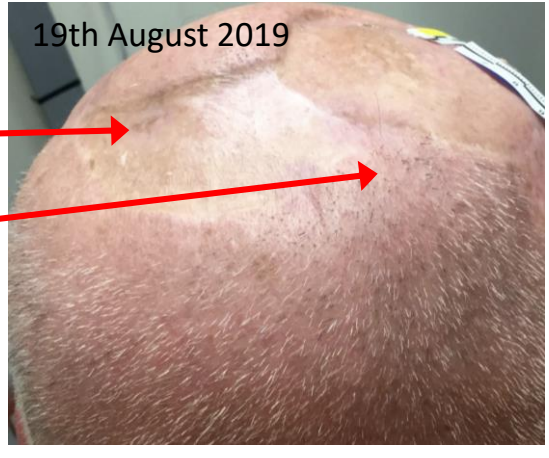
- Data from ongoing Phase 1/2 clinical trial of RP1 alone & combined with nivolumab*
  - Single agent RP1 clinical activity seen; clear abscopal effects
  - Four of five CSCC patients enrolled in combination with nivolumab responding to treatment
    - *Update on 30 patient NMSC Phase 2 cohort intended to be presented mid-year*
  - Three of the four anti-PD1 refractory cutaneous melanoma patients with follow up scans responding to treatment, in addition to responses seen in anti-PD1 naïve
    - *30 patient Phase 2 cohort fully enrolled; data intended to be presented mid-year*
  - Tumor reductions seen after just the first dose of RP1, prior to the first dose of nivolumab
  - Biomarkers indicated robust virus replication & immune activation
  - Indications of clinical activity in additional tumor types
- Phase 2 data in bladder cancer & MSI-H tumors is currently pending

* Data presented at SITC in November

CSCC Example Patient 1 – Ongoing CR



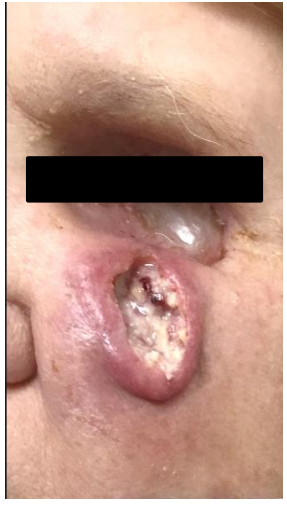




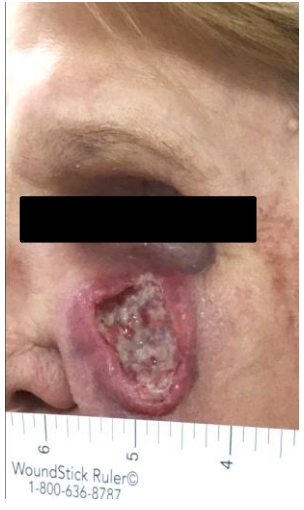
- Patient with extensive recurrent CSCC previously treated with surgery (including skin grafts), radiotherapy, cisplatin/5FU, then electrochemotherapy
- Now CR with residual areas tumor free by multiple biopsy & continuing to heal
- In addition to the complete tumor response, the patients' quality of life has been dramatically improved

CSCC Example Patient 2 - Ongoing CR

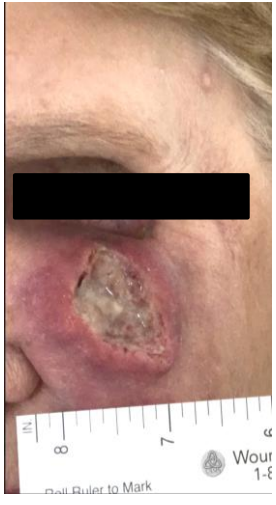
25th September 2019 (Baseline)



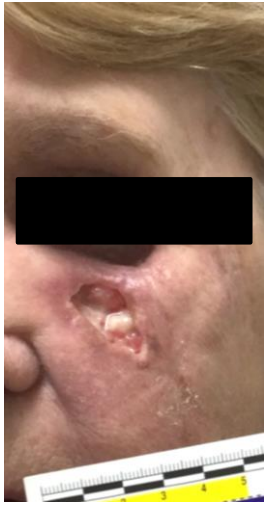
9th October 2019 (pre nivolumab)



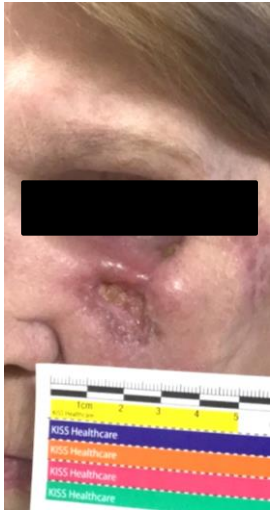
23rd Oct 2019



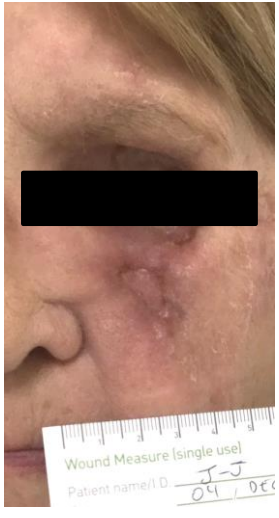
6th Nov 2019



20th Nov 2019



4th Dec 2019



- Recurrent, rapidly progressing CSCC of the left cheek with bone invasion through the maxillary region, previously treated with surgery & radiation before trial entry
- The lesion flattened considerably after the first dose of RP1, and continued to reduce & resolve thereafter – recent biopsy (December) demonstrates tumor free
- In addition to the ongoing CR, quality of life has dramatically improved

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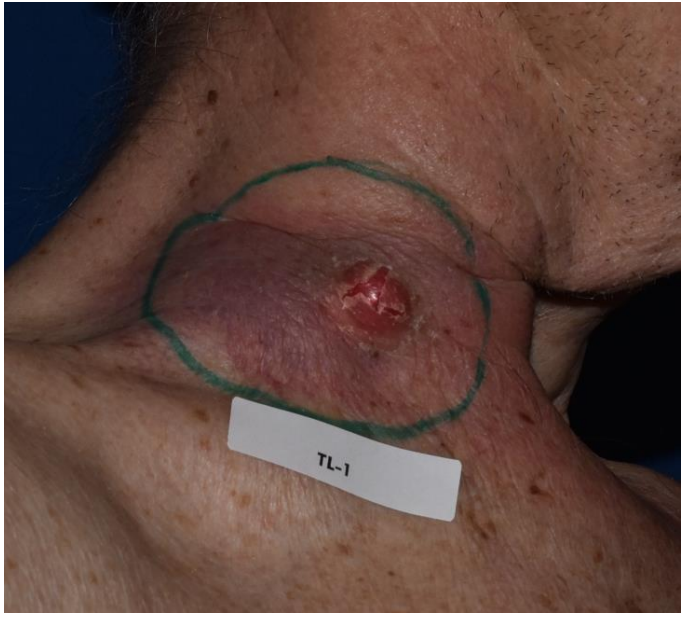
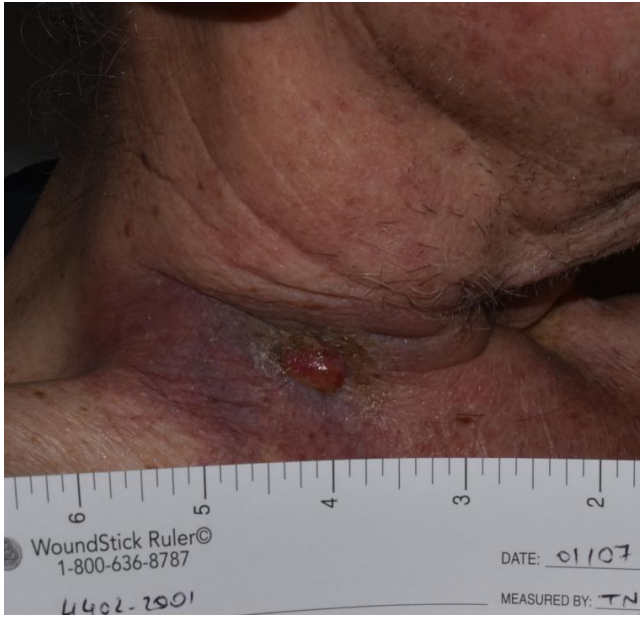
CSCC Example Patient 3

Patient close to CR – the only remaining lesions are a number of non-measurable bone metastases which are increasingly sclerotic

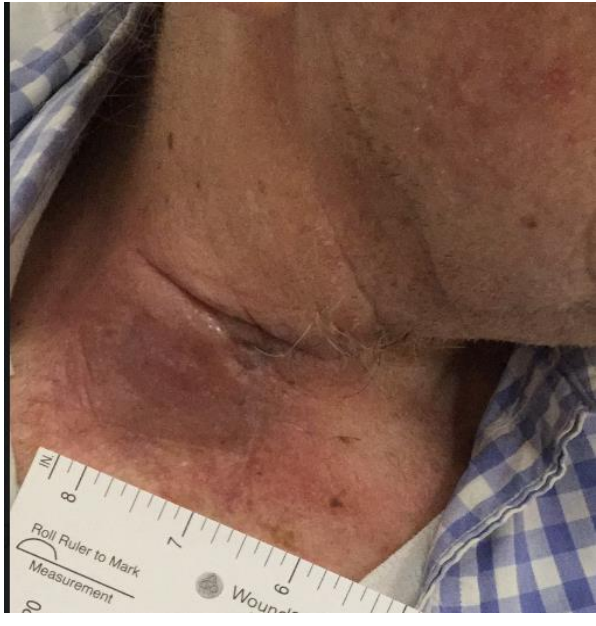
16th June 2019 (baseline)



1st July 2019 (post one dose of RP1, no nivolumab)



16th July 2019 (post 2 doses of RP1 & 1 dose of nivolumab)

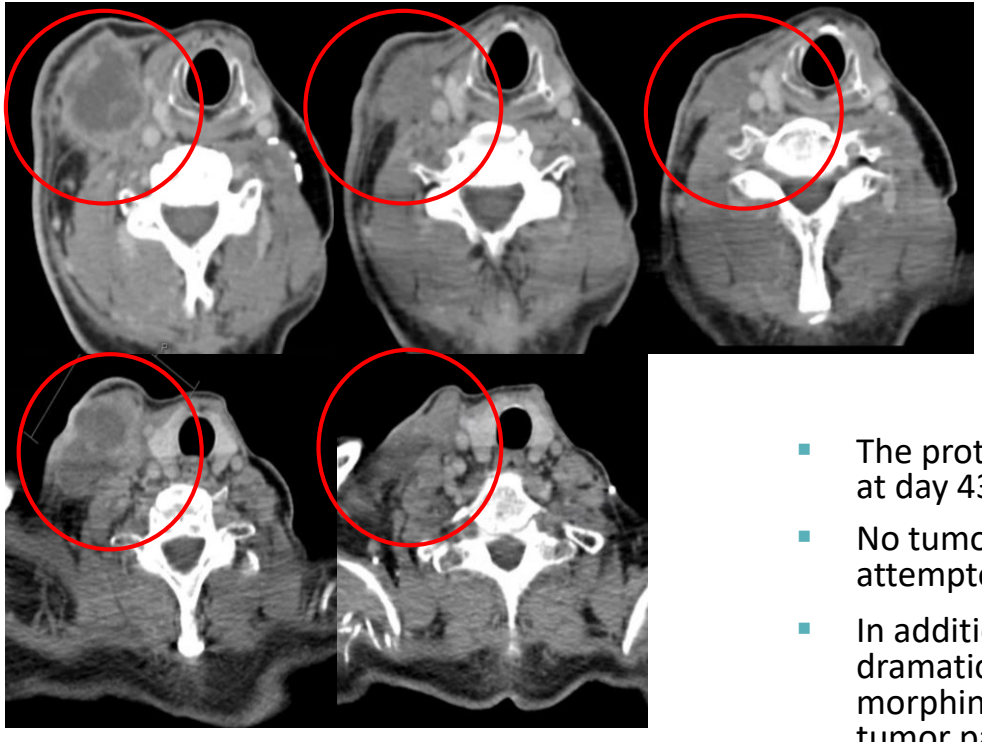


- Patient with recurrent CSCC of the neck (bilateral), previously treated with cisplatin-based chemoradiation & six cycles of carboplatin/5-FU, prior to entering the clinical trial
- Both the large injected tumor & the smaller contralateral uninjected tumor in the neck reduced considerably before the first nivolumab dose, i.e. after the first dose of RP1

CSCC Example Patient 3 – Ongoing PR

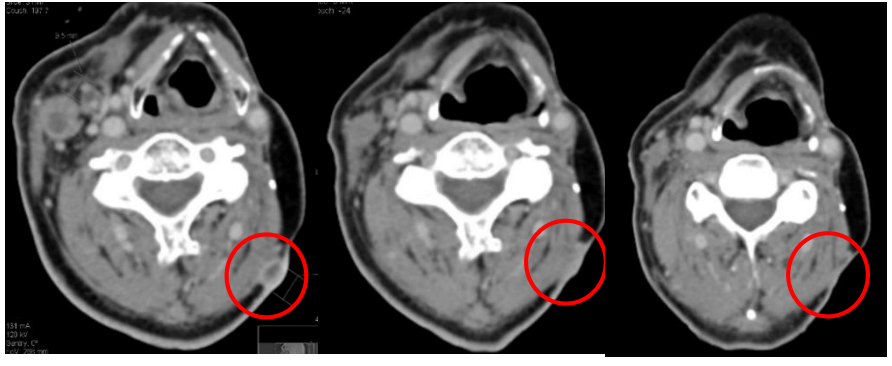
Right neck (injected)

Baseline 8 weeks 16 weeks



Left neck (not injected)

Baseline 8 weeks 16 weeks



- The protocol mandated biopsy of the injected tumor taken at day 43 was tumor free
- No tumor was found to remain when a biopsy was attempted from the left neck
- In addition to the tumor response, this patient has had a dramatic improvement in quality of life & is now off morphine which was previously necessary for substantial tumor pain

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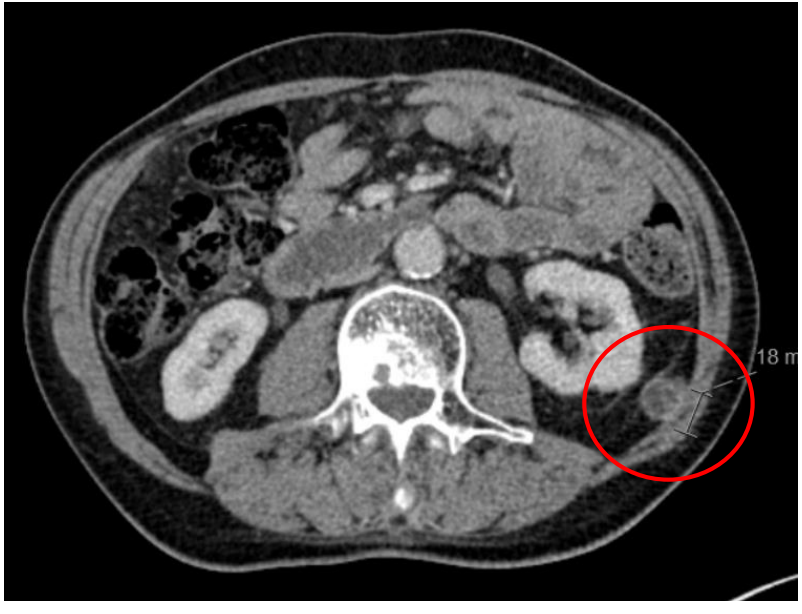
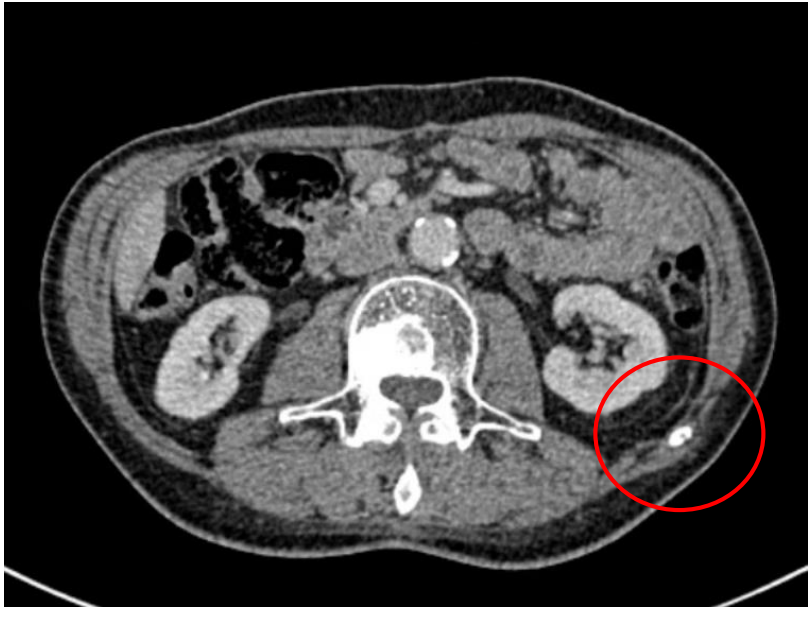
CSCC Example Patient 3 – Ongoing PR

Baseline

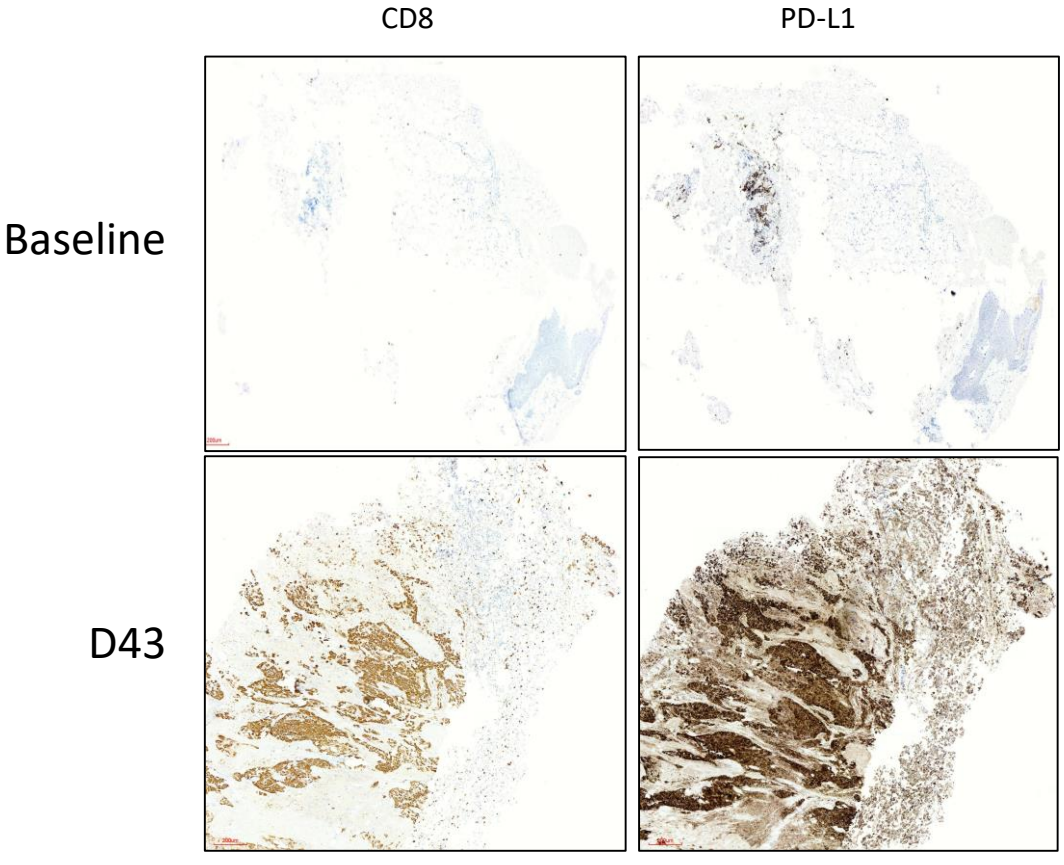


16 weeks



- The patient also had baseline retroperitoneal tumors (uninjected) which have completely resolved
- The only remaining disease are a number of non-measurable bone metastases, which were the main source of the cancer pain which has now resolved
- The bone lesions are increasingly sclerotic by CT scan, also indicative of a treatment response, with Zometa (stimulates bone formation) also now having been withdrawn

CSCC Example Patient 3 - CD8 T cell & PD-L1 staining



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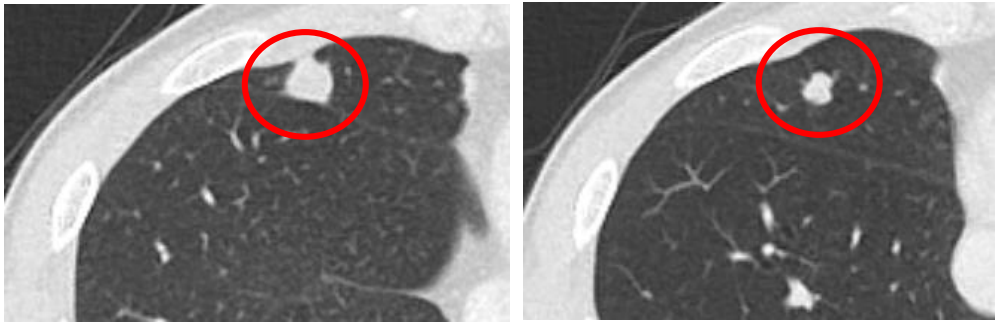
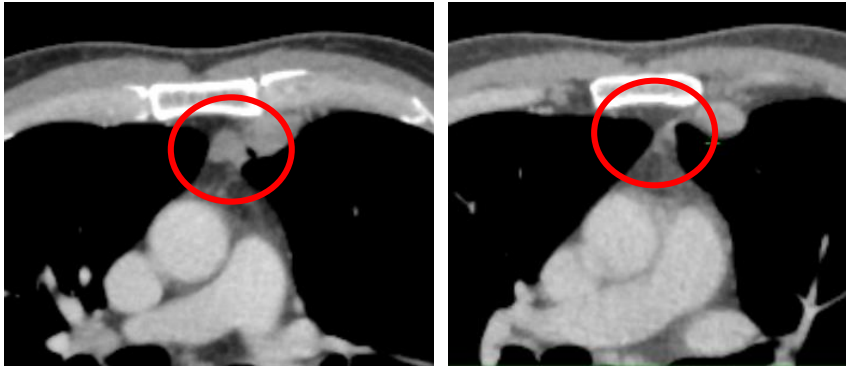
Example Patient 1 (ipilimumab & pembrolizumab refractory melanoma)

- Disease sites: Breast, lung, mediastinal and peritoneal anterior to the spleen
- RP1 injection site: Lesion behind the left ear

Lung



Anterior mediastinum



Baseline 10 months

- Confirmed progression on prior immune checkpoint blockade, where two sequential PET scans demonstrated new lesions while also concurrently being treated with local therapy for the lesion behind the ear, then entry into the RP1 clinical trial
- Ongoing PR
- Patient remains on treatment at 11 months

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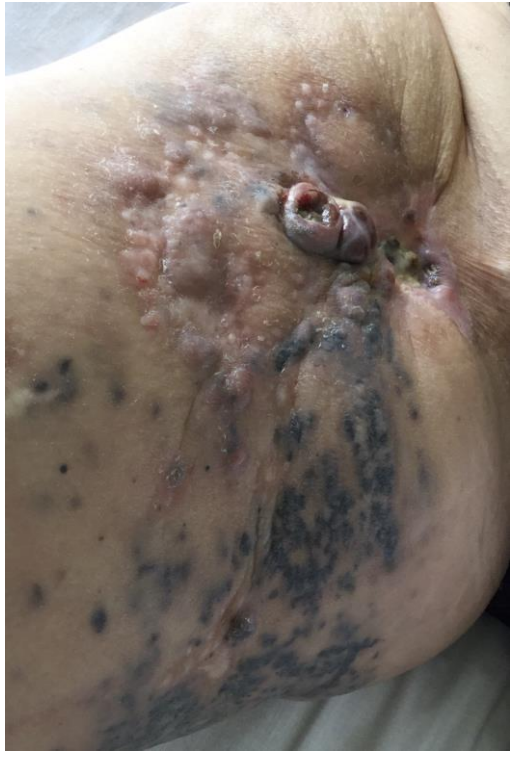
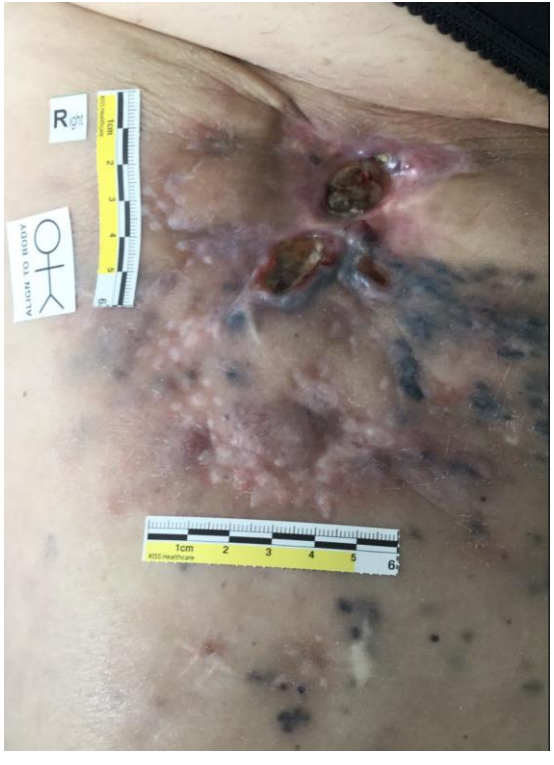
Example Patient 2 (ipilimumab/nivolumab refractory melanoma)

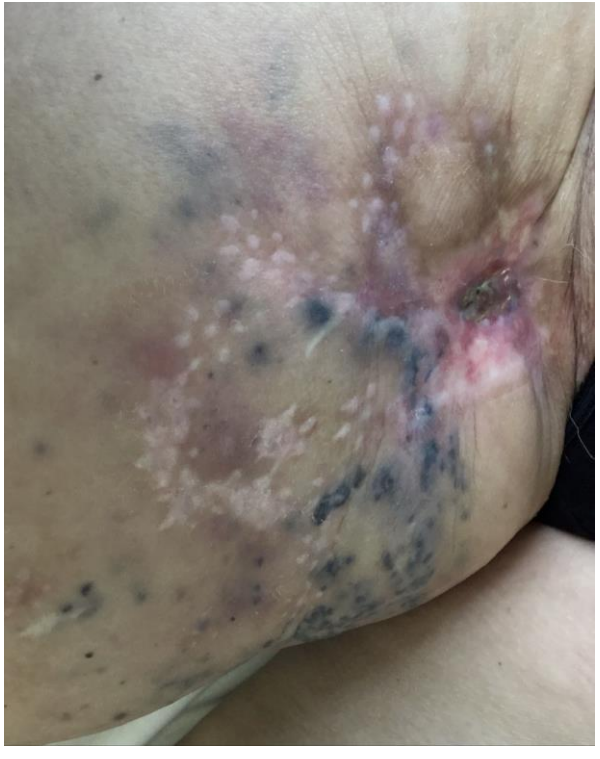
10th June 2019



24th June 2019 (pre nivolumab)



2nd September 2019



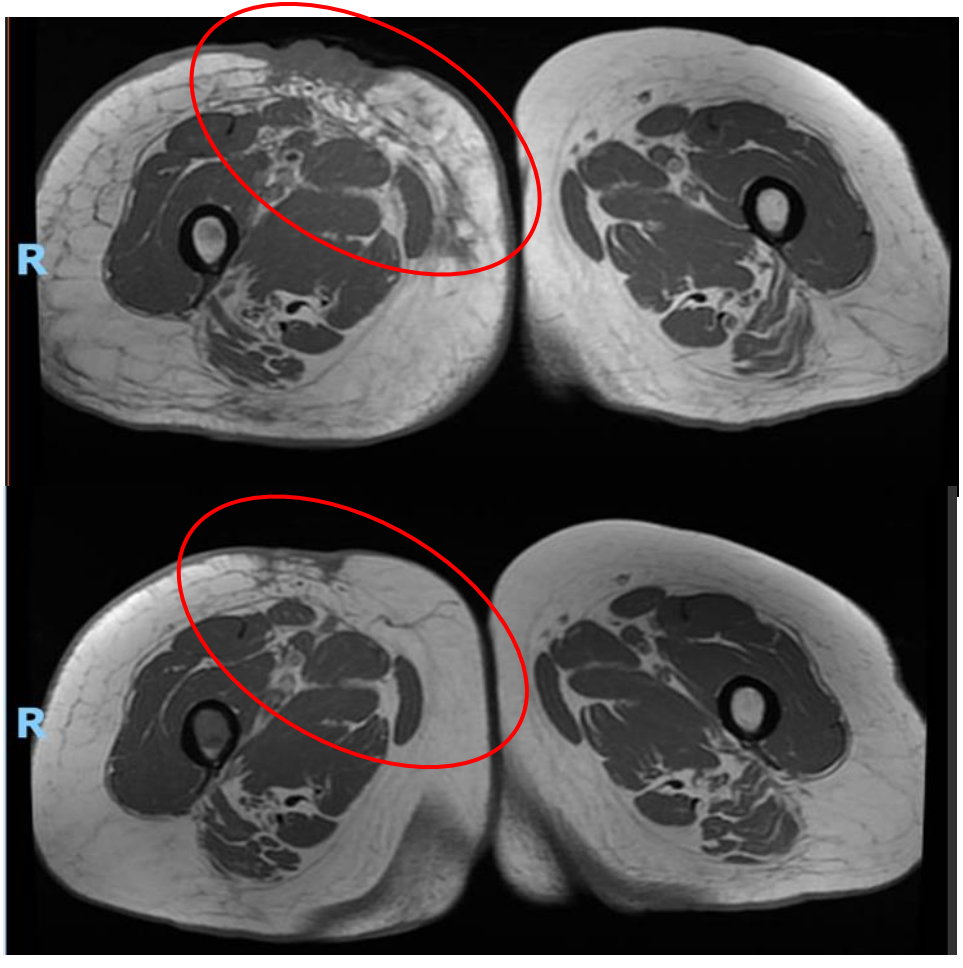
Patient history: Metastatic disease initially treated with ipili/nivo with best response of SD, then clear progression in the groin & thigh when radiotherapy followed by electrochemotherapy was added to continued nivolumab; following further clear progression, enrolled into the current trial

All tumors flattened after the first dose of RP1, i.e. prior to nivolumab & extensive oedema rapidly reduced

Example Patient 2 (ipilimumab/nivolumab refractory melanoma)

May 2019 (Baseline)

August 2019



- Patient also had nodes in the groin which increased and are now reducing and lung metastases which following no change for prior 18 months are now reducing
- Patient quality of life has also greatly improved, from being essentially immobile at baseline to now able to go on long country walks
- Patient remains on treatment at 6 months

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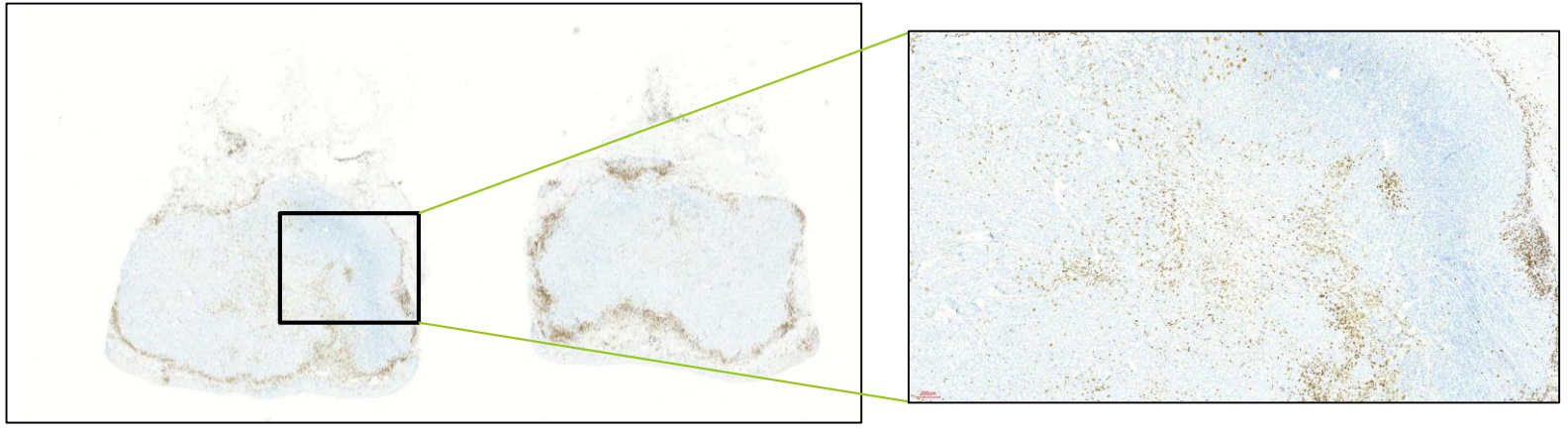
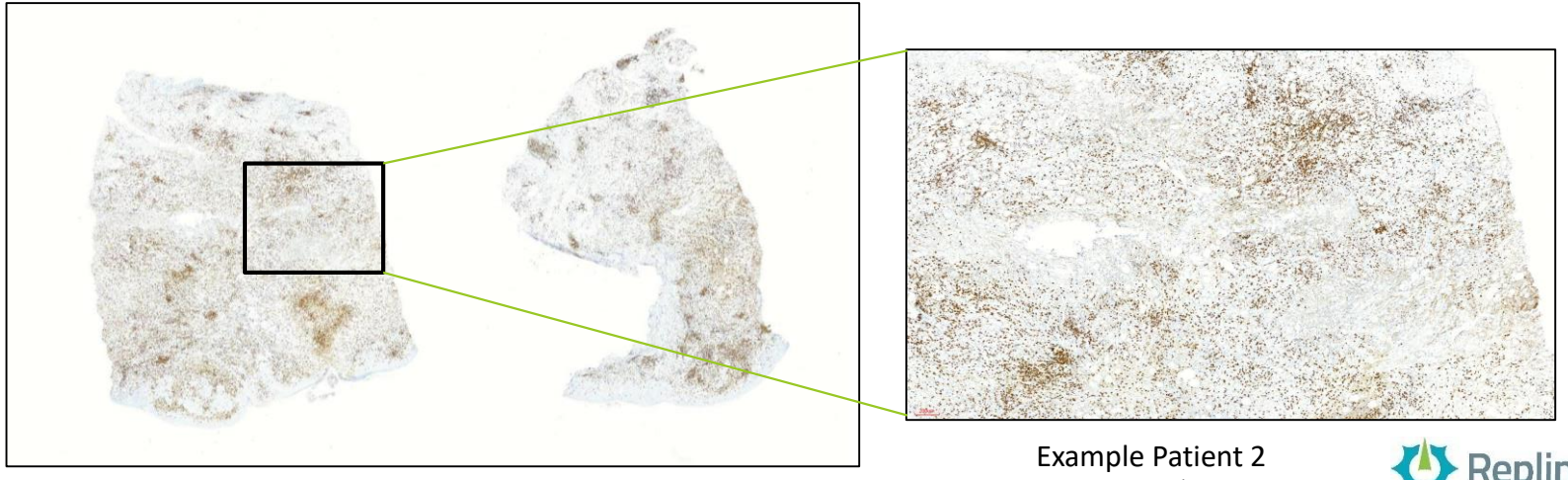
Reversal of T cell exclusion with RP1 combined with nivolumab

CD8
Baseline
biopsy



CD8
Day 43
biopsy



Example Patient 2
Cutaneous melanoma
(ipilimumab/nivolumab refractory)

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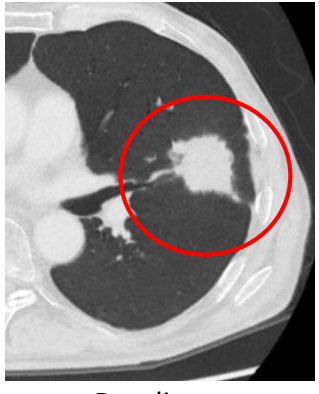
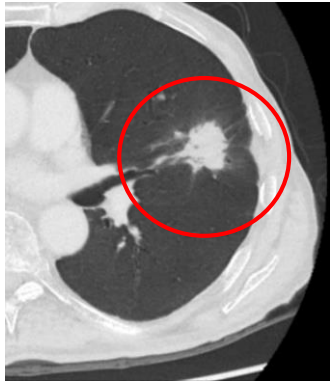
Example activity in other tumor types: Esophageal cancer

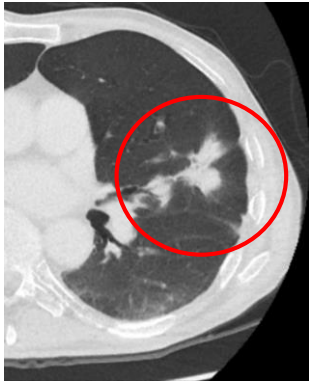
- Heavily pre-treated esophageal cancer (8 prior therapies)
- Lung lesions & lesions around the esophagus.
- Patient continues on treatment at 10 months
- Current status: Ongoing PR



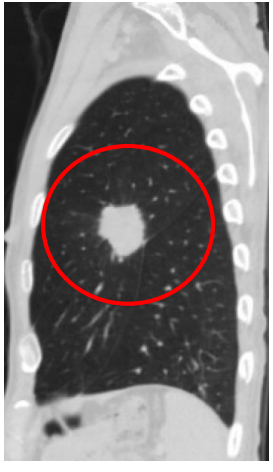
Baseline



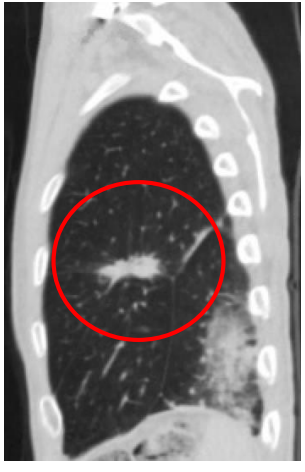
C5



C11



Baseline



C11

RP2/3: Target anti-PD1/L1 non-responsive or less responsive tumor types

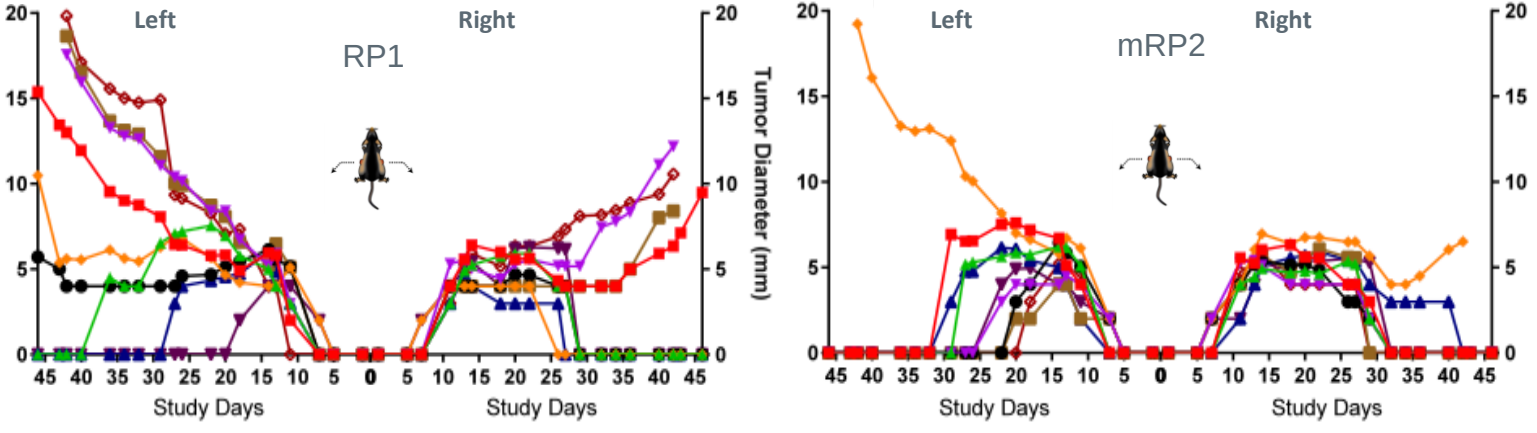
Replimune

Intratumoral anti-CTLA-4 & co-stimulatory pathway agonists

- Focus on delivery of proteins which act <u>as the immune response is being generated</u>
  - Systemic antibody approaches probably don't act at the right place or the right time
  - Potential for toxicity
- RP2
  - Delivery of anti-CTLA-4 directly into the tumor
  - Blocks Treg activation/inhibition of T cell activation at the site of immune response initiation
  - Retain the efficacy of ipilimumab alone & in combination with anti-PD1 but reduce toxicity
    - Potential for improved activity as compared to combination anti-CTLA-4/anti-PD1
- RP3
  - Delivery immune co-stimulatory pathway activating ligands
  - Antibody approaches have given indications of activity, but toxic
    - Considerable pharma interest in these pathways
  - RP3 encodes GALV-GP-R-, anti-CTLA-4, CD40L & 4-1BBL
    - CD40L: Broadly activates both innate & adaptive immunity
    - 4-1BBL: Promotes the expansion of cellular & memory immune responses

Replimune

Expression of anti-mCTLA4 enhances efficacy



Immune competent A20 mouse tumor model
Subtherapeutic dose for RP1 ($5x10^4$ pfu) injected 3x into the right tumor only

Critical focus on manufacturing

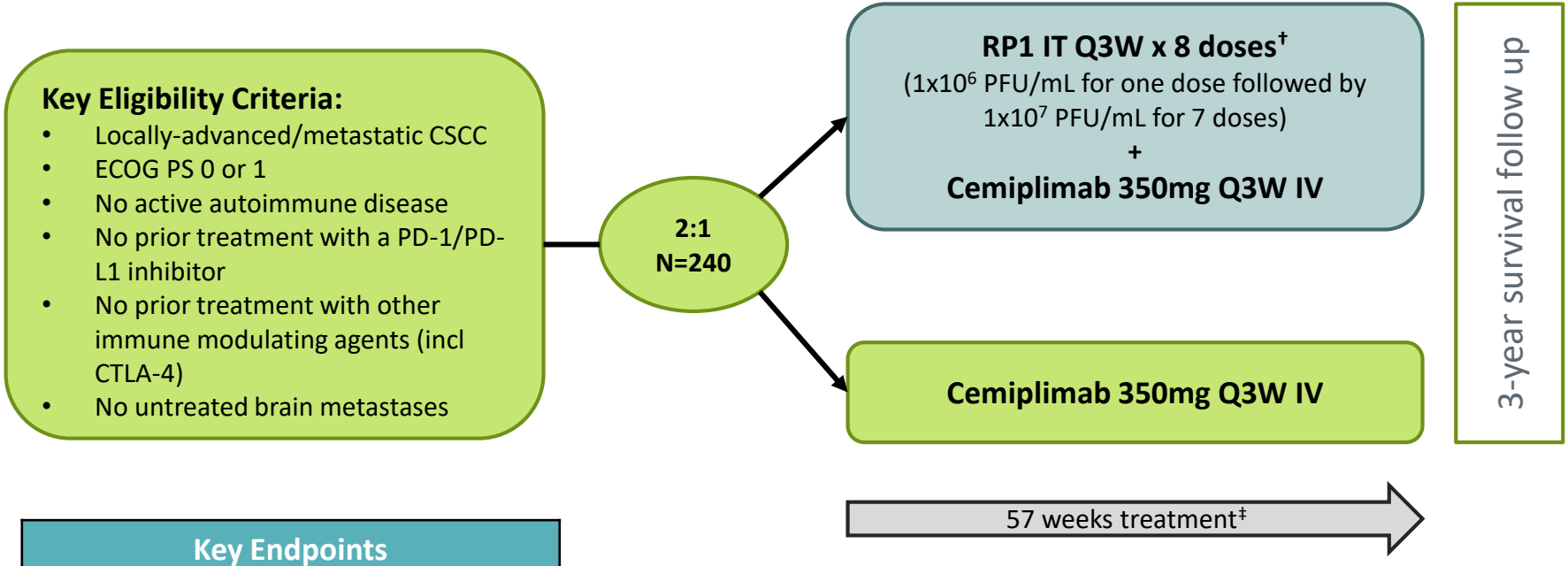
- RP1-RP3 currently manufactured by a CMO for ongoing clinical development
- For later stage development & commercialization, in-house manufacturing is preferred
- The team has extensive manufacturing experience
- 63,000 ft^2 manufacturing facility leased in July 2018 in Framingham, MA, appropriate for multi-product production
  - State of the art facility
  - Fully fitted out; first tech transfer run successfully completed
  - Scale sufficient to cover full global commercialization of Replimune's products at full capacity
- Expected to be on-line to produce clinical product in 2020

Milestones towards commercialization in 2020

- Initiate & complete accrual in the single agent RP1 potentially registrational clinical trial in organ transplant recipients with CSCC
  - Initial data read out H2 2020
  - Additional CSCC data from Phase 2 in combination with nivolumab expected mid-2020
- Initiate potentially registrational clinical trial in anti-PD1 refractory melanoma
  - Additional melanoma data from Phase 2 in combination with nivolumab expected; mid-2020
- Complete Phase 2 MSI-H and bladder cancer cohorts + nivo and determine go/no-go
- RP2 Phase 1 data
- RP3 to enter the clinic
- Well Capitalized to deliver
  - ~$183 million in cash at December 31, 2019 will be sufficient to fund its operating expenses into the 2H 2022

Appendix

Randomized controlled Phase 2 study in CSCC (CERPASS)



Key Endpoints

Primary: ORR (RECIST v1.1)
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

Phase 1b clinical trial in solid organ transplant recipients with CSCC

Key Eligibility Criteria:

- Locally-advanced/metastatic CSCC
- ECOG PS 0 or 1
- Renal or hepatic organ allograft recipients on stable immunosuppressive regimen for ≥12 mos
- No prior systemic anti-cancer treatment for CSCC
- No transplant-related viral infections (such as BK, EBV, CMV) within 3 months
- No untreated brain metastases

RP1 IT Q2W x 26 doses
($1x10^6$ PFU/mL for one dose followed by $1x10^7$ PFU/mL)

50 weeks treatment

3-year survival follow up

Key Endpoints

Primary: Safety and tolerability
Secondary: ORR (RECIST v1.1), DOR, Disease-Free Survival, incidence/severity of graft rejection

Replimune

CSCC in patients with solid organ transplants

- Approximately 30,000 lung & kidney transplants are conducted in the US each year
- Solid organ transplant recipients are at a 2-4 fold increased risk of cancer compared to the general population
- There is a particularly high risk of developing skin cancers
  - 2-8 fold increased risk of developing melanoma
  - 65-250 fold increased risk of developing CSCC
    - Up to 70% of patients develop CSCC within 20 years
- Clinical trials with immune checkpoint blockade drugs have excluded transplant patients due to the risk of transplanted organ rejection (41% kidney, 35% liver, 20% heart)
- However, response rates to immune checkpoint blockade seem to be similar to the general population
- There is therefore a substantial unmet need in solid organ transplant recipients with CSCC
- Single agent RP1 may be an attractive option for these patients