Final Results from a Phase 2 Study Using Off-the-shelf Activated Natural Killer (aNK) Cells in Combination with N-803, an IL-15 Superagonist, in Patients with Metastatic Merkel Cell Carcinoma (MCC)

*Shailender Bhatia**,[1,2] Candice D. Church[1], Kelly G. Paulson[1,2], Robert H. Pierce[2], Paul Nghiem[1,2], John H. Lee,[3] Bridget M. Adcock,[3] Patrick Soon-Shiong,[3] Sunandana Chandra[4]

**Presenting author*

[1]University of Washington, Seattle, WA
[2]Fred Hutchinson Cancer Research Center, Seattle, WA
[3]NantKwest, Inc, and ImmunityBio, Inc, Culver City, CA
[4]Northwestern University Feinberg School of Medicine, Chicago, IL

SITC 2019
November 8, 2019
Session 209: Virus-Driven Cancers

Disclosures

Shailender Bhatia has consulted for or advised Genentech, Bristol-Myers Squibb, EMD Serono, and Sanofi Genzyme. His institution has received research support from EMD Serono, Bristol-Myers Squibb, Merck, Oncosec, Immune Design, NantKwest, and Novartis.

Kelly G. Paulson has received research support from a SITC-Merck Fellowship award.

Robert H. Pierce has equity in OncoSec Medical and Sensei Biotherapeutics. He has consulted for or advised Immunomic Therapeutics, Pulse Biosciences, AbbVie, Calithera Biosciences, and Curis. He has received research support from Juno Therapeutics, Pulse Biosciences, Minerva Biosciences, AstraZeneca, Exicure, X4-Pharmaceuticals, and Incyte.

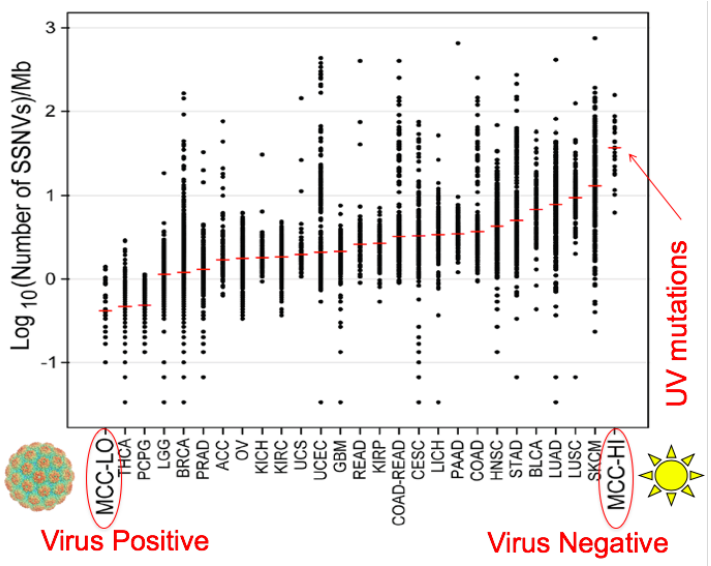
Paul Nghiem has consulted for EMD Serono, Pfizer, Merck, and 4SC. His institution has received research support from BMS and EMD Serono.

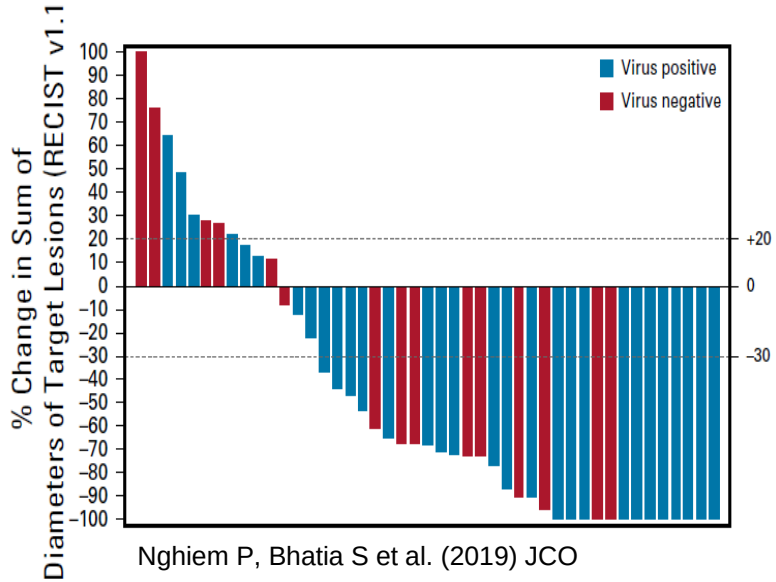
John H. Lee, Bridget M. Adcock, and **Patrick Soon-Shiong** are employees of NantKwest and ImmunityBio.

Sunandana Chandra has consulted for EMD Serono, BMS, Regeneron, and ArrayBioPharma.

Merkel Cell Carcinoma (MCC): An aggressive, virus-associated skin cancer that responds well to PD-1 blockade

- ~2500 cases annually in the US; **incidence** is increasing.
- **Aggressive course** with a disease mortality rate ~45%; 5-year OS for stage IV MCC is < 20%.
- **Pathogenesis**:
  - MCC polyoma virus (MCPyV) in ~80% of MCC tumors
  - UV-induced damage
- Both subsets, virus positive MCC (VP-MCC) and virus-negative (VN-MCC) are **highly immunogenic**
- **PD-1/PD-L1 blockade** associated with high response rates; responses are rapid-onset and generally durable.





Nghiem P, Bhatia S et al. (2019) JCO

{Paulson K *JAAD* 2017; Lemos BD *JAAD* 2010; Feng H *Science* 2008; Goh *Oncotarget* 2015; Nghiem P *NEJM* 2016; Kaufman H *Lancet Onc* 2016 }

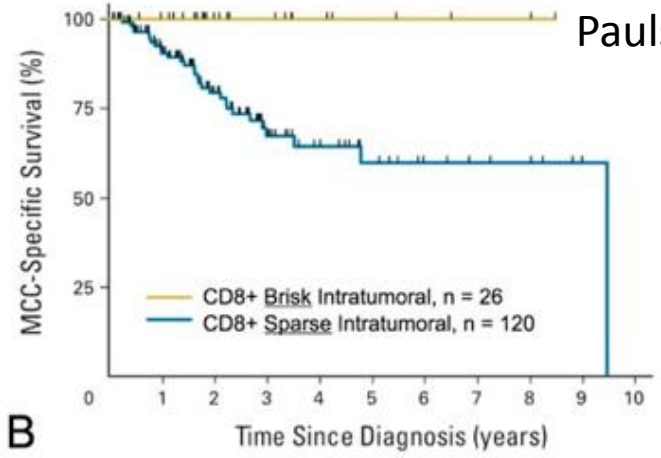
MCC: Unmets needs and Immune evasion mechanisms

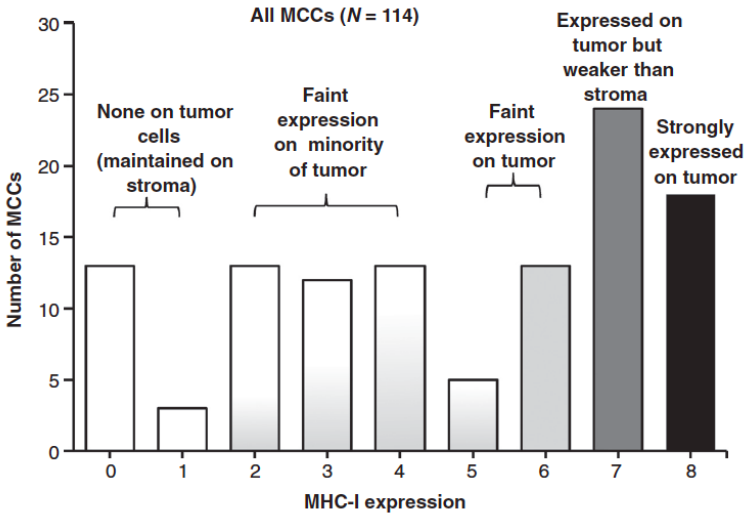
Kelly Paulson

- Still significant **unmet needs** in advanced MCC
  - Intrinsic or acquired resistance to ICI (~50% of MCC pts)
  - Ineligibility for ICI therapy (autoimmunity, immunosuppression etc).

- Several **mechanisms of immune evasion**:
  - Sparse T-cell infiltrates (~80% of MCC tumors)
  - Exhausted TILs
  - MHC-1 downregulation highly prevalent (84% of MCC)
  - MHC loss appears relevant to *acquired* resistance

- **NK-cells** should recognize MHC-1 deficient cells; unfortunately, cancer patients have dysfunctional NK cells





{Paulson K *JNCCN* 2018; Paulson K *JCO* 2010; Paulson K *CIR* 2014; Paulson K *Nat Comm* 2018}

QUILT-3.009: Phase 2 study of **aNK** (Activated NK-92 cells) in combination with **N-803** (IL-15 agonist) in patients with advanced MCC

Trial Number (NCT): 02465957

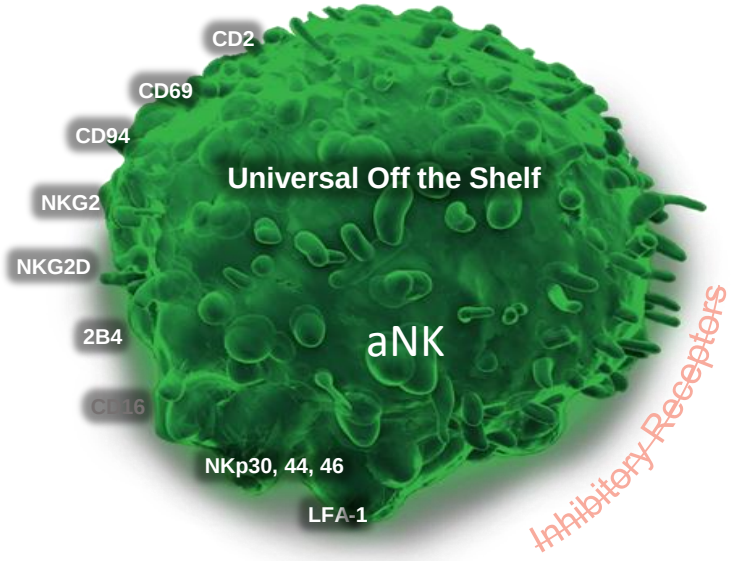
3 Sites: University of Washington, Seattle WA;
Northwestern University, Chicago IL
University of Pittsburgh, Pittsburgh PA;

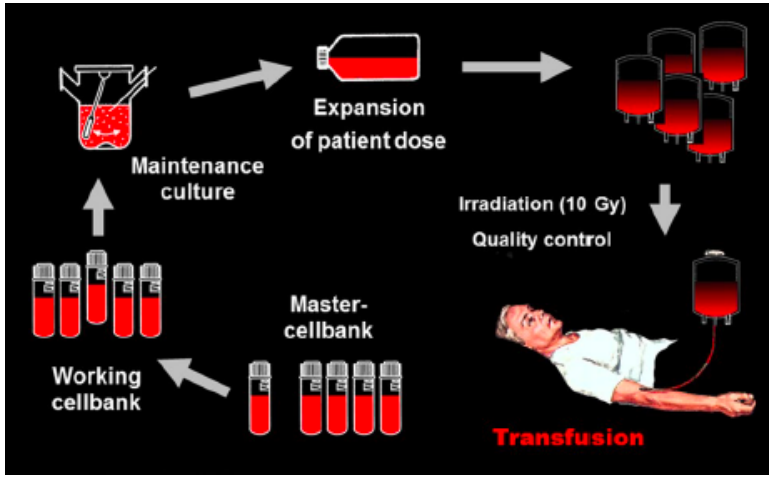
IND Sponsor: NantKwest, Inc

Study Population: Inoperable stage III or IV MCC, per AJCC 7th edition; prior systemic therapy allowed; good organ function; regardless of MCPyV status.

aNK (NK-92)

- **Established from a male patient with rare NK-cell lymphoma**
- IL-2 dependent NK cell line
  - **Lack expression of most killer cell inhibitor receptors (KIRs)**
  - Broad cytotoxic range
- Phase 1 trials of aNK demonstrated aNK to be **safe and active** in patients with hematologic and solid tumors
- (Allogeneic) aNK cells require **on-site expansion** and are irradiated before intravenous (IV) administration





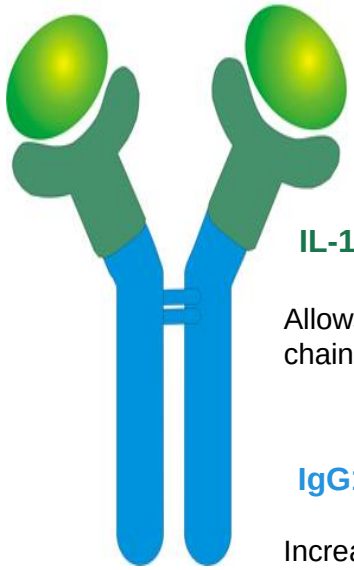
{Gong JH *Leukemia* 1994; Tonn *JHSCR* T 2001; Aria S *Cytotherapy* 2008; Tonn T *Cytotherapy* 2013}

N-803, an IL-15 Superagonist Fusion Complex

- N-803 has 30-fold greater activity and 10-fold longer half-life than rIL-15; administered subcutaneously (SC)

- Promotes NK and T cell expansion and activation without expanding immunosuppressive regulatory T cells; enhances NK-cell mediated ADCC.

- Several clinical trials have demonstrated safety and biologic activity



IL-15N72D

IL-15 N72D mutation enhances binding to IL-2Rβ, driving proliferation and activation of NK and T cells without expansion of Tregs

IL-15Rα

Allows transpresentation selectively to only IL-2Rβγ chain of NK and CD8+ T cells

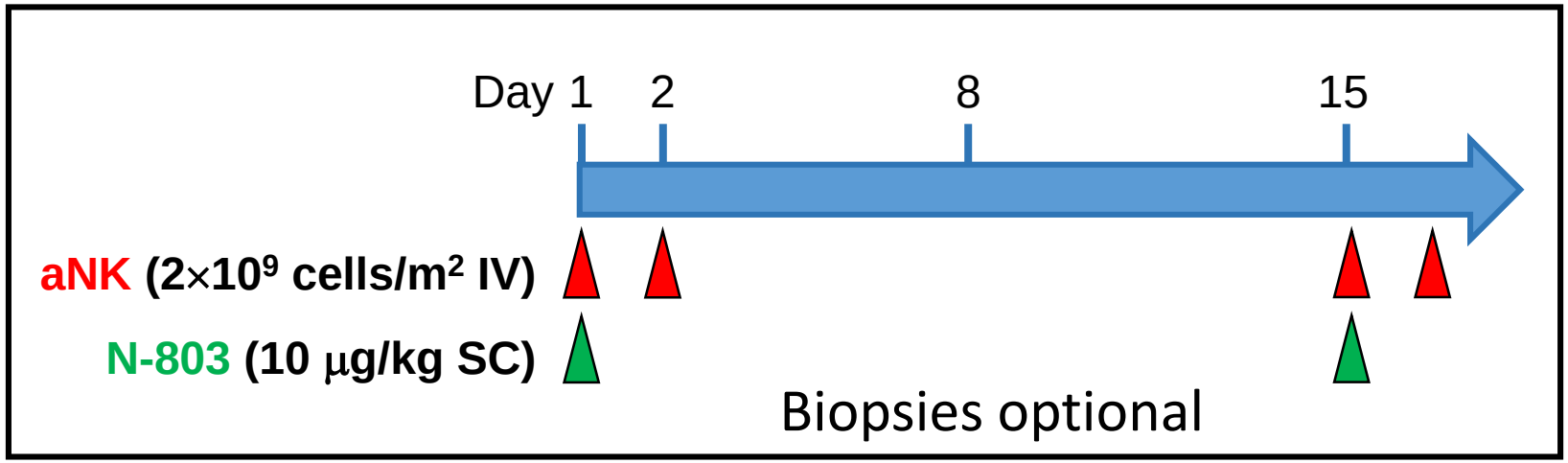
IgG1 Fc

Increases half-life and lymphoid recycling and distribution

{Han KP *Cytokine* 2011; Xu W *Can Res* 2013; Rhode PR *Can Immunol Res* 2016; Margolin K *CCR* 2018}

QUILT-3.009: Study Schema and Enrollment

2 week treatment cycles:



Enrollment: 7 patients total (Initial target N = 24)

3 patients received aNK monotherapy

4 patients received aNK + N-803

Trial was discontinued prematurely:

- **Proof-of-concept met** with convincing signal of safety and efficacy
- Logistical **challenges with on-site expansion** of aNK cells

Patient Demographics and Baseline Characteristics

	aNK (n=3)	aNK+N-803 (n=4)	All Subjects (n=7)
Age in years Median (Range)	76 (75, 81)	61 (60, 63)	63 (60, 81)
Sex			
Male	3 (100%)	3 (75%)	6 (86%)
Female	0	1 (25%)	1 (14%)
Ethnicity			
Not Hispanic or Latino	3 (100%)	4 (100%)	7 (100%)
Race			
White	3 (100%)	4 (100%)	7 (100%)
ECOG Score			
0	3 (100%)	2 (50%)	5 (71%)
1	0	2 (50%)	2 (29%)
Number of Prior Therapies [Median (Range)]			
All Prior Therapies	3 (0, 4)	3 (2, 12)	3 (0, 12)
Prior anti-PD-1 regimens*	1 (0, 1)	1 (1, 1)	1 (0, 1)

***6 of 7 patients had received prior anti-PD-1/PD-L1 containing regimens**

QUILT-3.009: Investigational Product Exposure

	aNK (n=3)	aNK+N-803 (n=4)	All Subjects (n=7)
Treatment cycles	4 (2, 14)	6.5 (1, 18)	4 (1, 18)
Time on treatment (days)	56 (27, 233)	80.5 (27, 239)	56 (27, 239)
Cumulative aNK exposure (cells $\times 10^9$)	16 (8, 56)	26 (4, 56)	16 (4, 56)
Cumulative N-803 exposure (micrograms)	-	8688 (1000, 15433)	8688 (1000, 15433)

NOTE: All measures show median (minimum, maximum).

aNK + N-803 is Well-Tolerated as Outpatient Therapy

Treatment-Emergent AEs Occurring in > 1 Subject

	aNK (n=3)	aNK + N-803 (n=4)	All Subjects (n=7)
Subjects with at least 1 AE	2 (67%)	4 (100%)	6 (86%)
Endocrine disorders	1 (33%)	1 (25%)	2 (29%)
Hypothyroidism	1 (33%)	1 (25%)	2 (29%)
Gastrointestinal disorders	1 (33%)	2 (50%)	3 (43%)
Vomiting	0	2 (50%)	2 (29%)
General disorders, administration site conditions	2 (67%)	4 (100%)	6 (86%)
Chills	2 (67%)	3 (75%)	5 (71%)
Fatigue	1 (33%)	1 (25%)	2 (29%)
Injection site erythema	0	3 (75%)	3 (43%)
Injection site reaction	0	2 (50%)	2 (29%)
Pyrexia	0	2 (50%)	2 (29%)
Metabolism and nutrition disorders	0	4 (100%)	4 (57%)
Decreased appetite	0	2 (50%)	2 (29%)
Vascular disorders	0	2 (50%)	2 (29%)
Hypotension	0	2 (50%)	2 (29%)

No Grade 3 or higher Treatment-related Adverse Events (TRAE)

TRAEs by System Organ Class Occurring in > 1 Subject

	aNK (n=3)		aNK + N-803 (n=4)		All Subjects (n=7)	
Grade	Grade 0-2	Grade ≥ 3	Grade 0-2	Grade ≥ 3	Grade 0-2	Grade ≥ 3
Subjects With at Least 1 Treatment-Related AE	2 (67%)	0	4 (100%)	0	6 (86%)	0
General Disorders	2 (67%)	0	4 (100%)	0	6 (86%)	0
Chest discomfort	0	0	1 (25%)	0	1 (14%)	0
Chills	2 (67%)	0	3 (75%)	0	5 (71%)	0
Fatigue	0	0	1 (25%)	0	1 (14%)	0
Flushing	0	0	1 (25%)	0	1 (14%)	0
Injection site erythema	0	0	3 (75%)	0	3 (43%)	0
Injection site irritation	0	0	1 (25%)	0	1 (14%)	0
Injection site rash	0	0	1 (25%)	0	1 (14%)	0
Injection site reaction	0	0	2 (50%)	0	2 (29%)	0
Night sweats	0	0	1 (25%)	0	1 (14%)	0
Pyrexia	0	0	2 (50%)	0	2 (29%)	0
Infections	0	0	2 (50%)	0	2 (29%)	0
Oral candidiasis	0	0	1 (25%)	0	1 (14%)	0
Pharyngitis streptococcal	0	0	1 (25%)	0	1 (14%)	0
Upper respiratory tract infection	0	0	1 (25%)	0	1 (14%)	0
Investigations	0	0	2 (50%)	0	2 (29%)	0

5 grade ≥ 3 AEs (none treatment-related): Peripheral edema, sepsis, hydronephrosis, ureteric compression, ureteric obstruction.

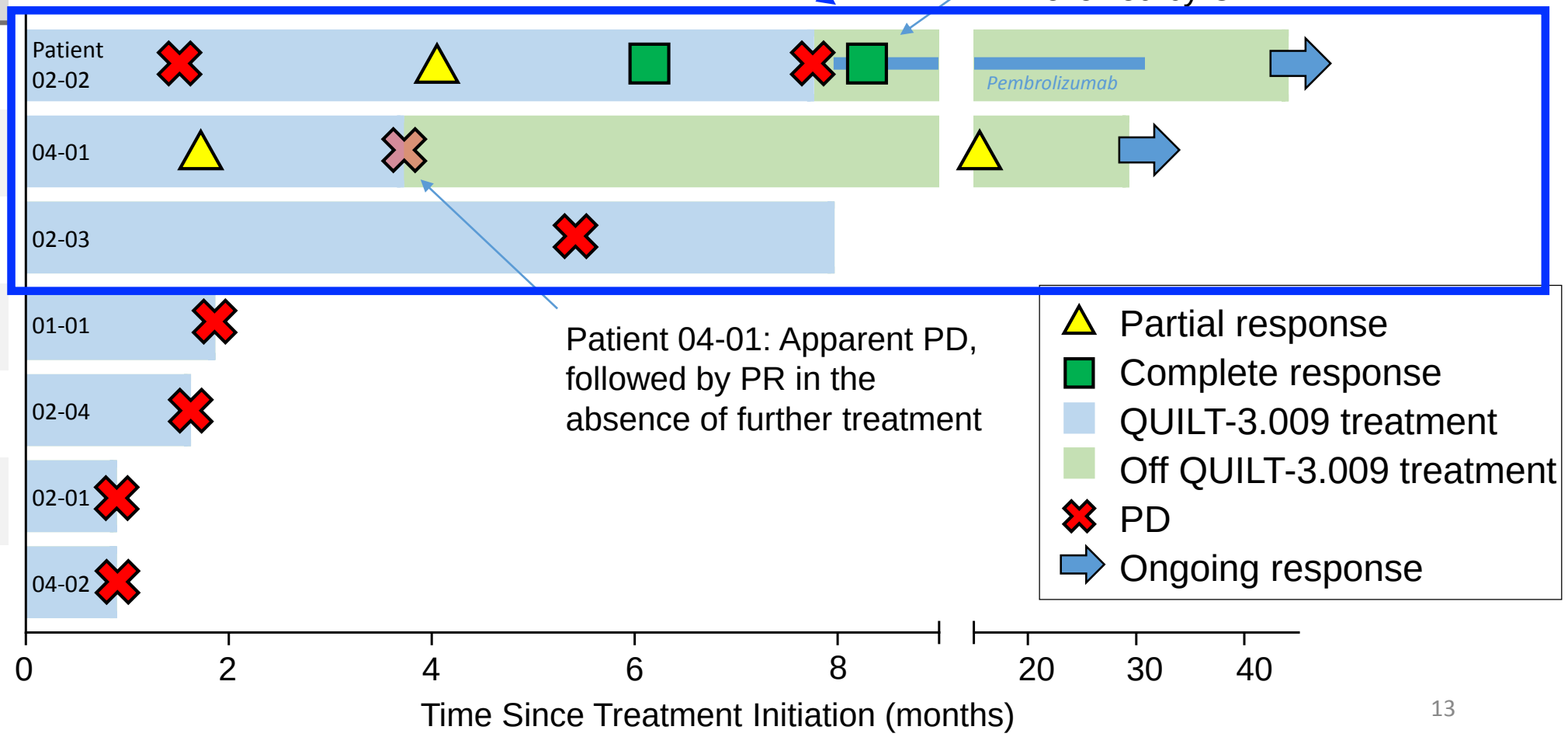
5 SAEs (none treatment-related): Peripheral edema, sepsis, encephalopathy, hydronephrosis, ureteric compression.

QUILT-3.009: Responses During and After Treatment

Sex	Age	Prev Ther	Prev ICI
M	81	4	Pem
M	61	3	Nivo
F	60	2	Pem
M	76	0	-
M	61	12	Pem
M	75	3	Pem
M	63	3	Pem

ORR for QUILT-3.009: 29% (2/7)
- 1 radiologic CR
- 1 PR

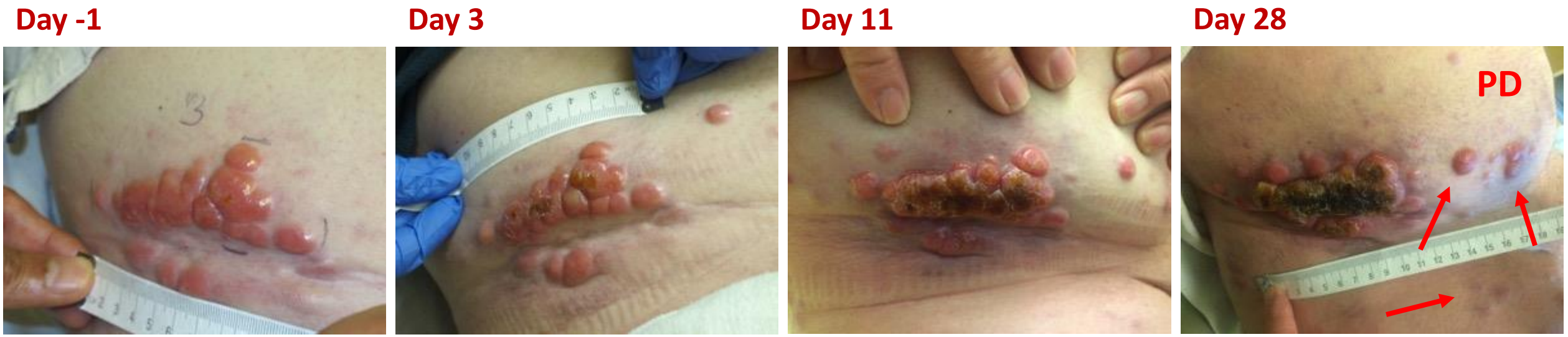
One patient also had SD (5.5 months)



Patient 02-02: Pembrolizumab rechallenge after PD, followed by CR

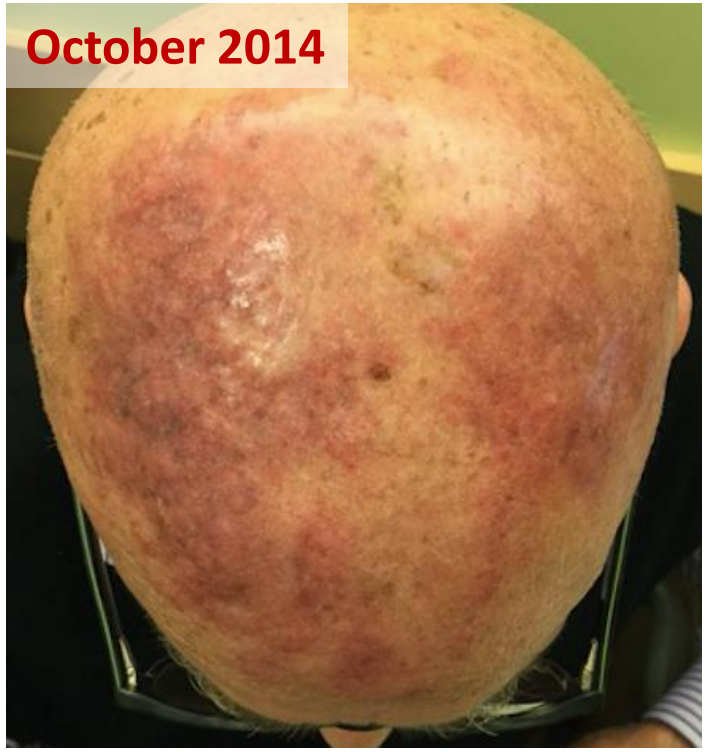
Patient 04-01: Apparent PD, followed by PR in the absence of further treatment

Patient 02-01: Intriguing biologic changes noticed in superficial tumors soon after 1st cycle of aNK monotherapy



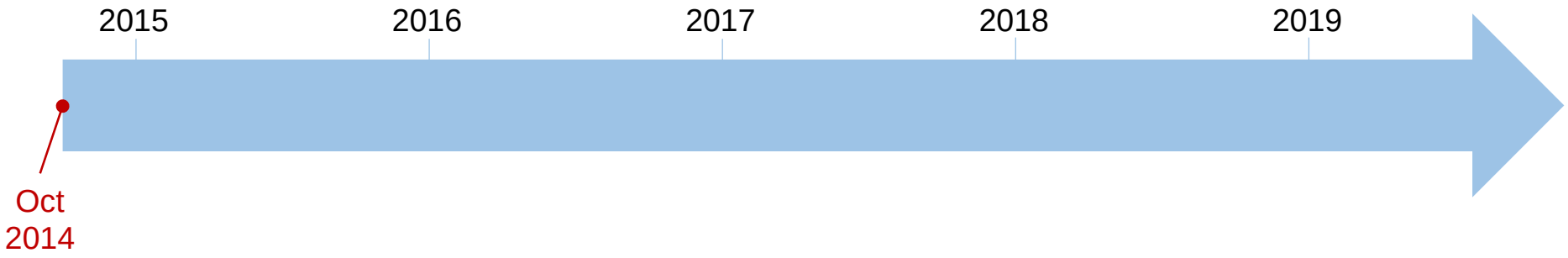
- Supports trafficking of aNK cells to the tumor microenvironment.
- Suggests rapid-onset *in vivo* cytotoxicity of aNK against MCC tumor cells.

Patient 02-02: aNK reverses refractoriness to PD-1 blockade

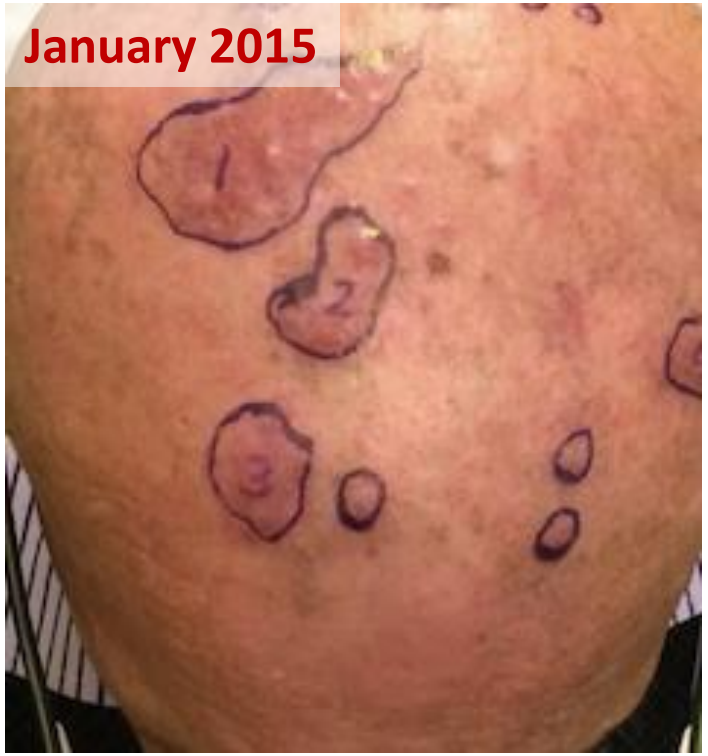


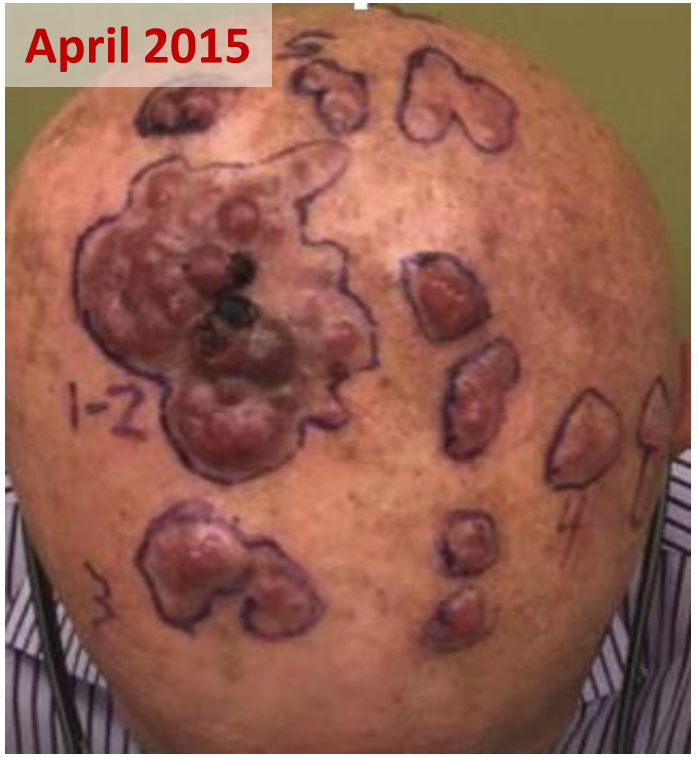
First consultation at the University of Washington

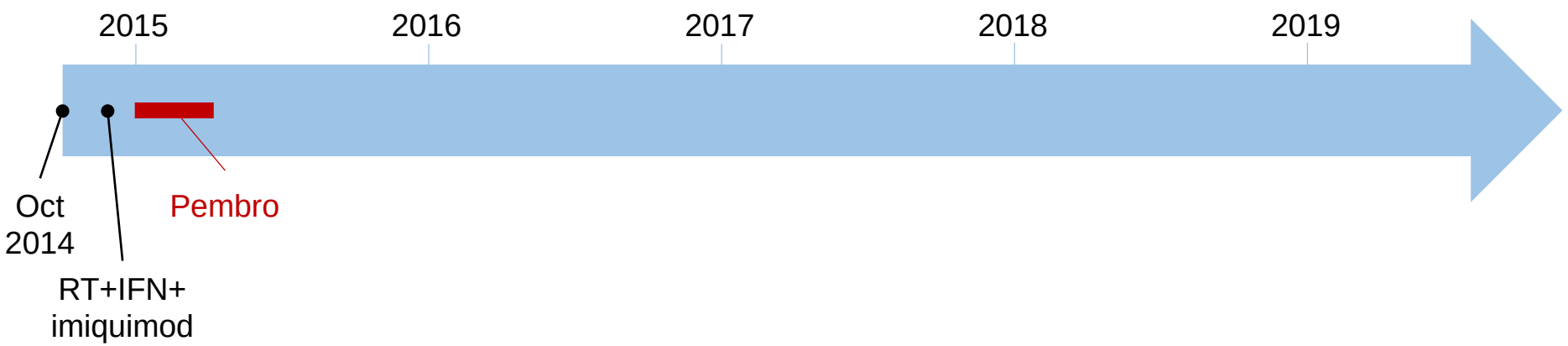
81 year-old man with VN-MCC; multifocal scalp tumors



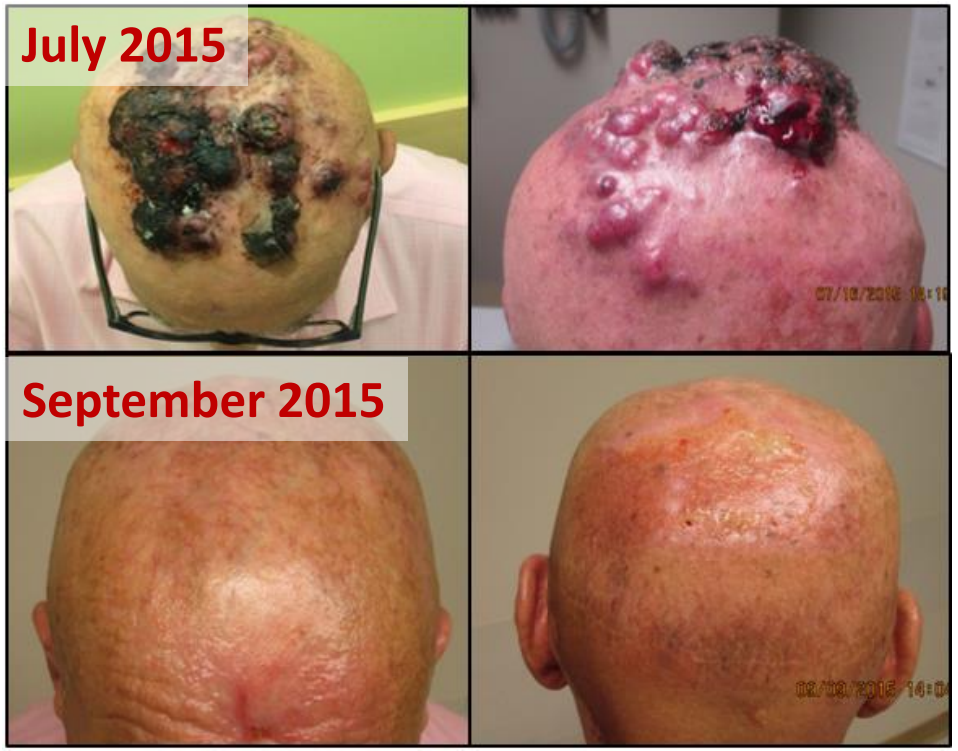
Patient 02-02: Non-responder to prior Pembrolizumab



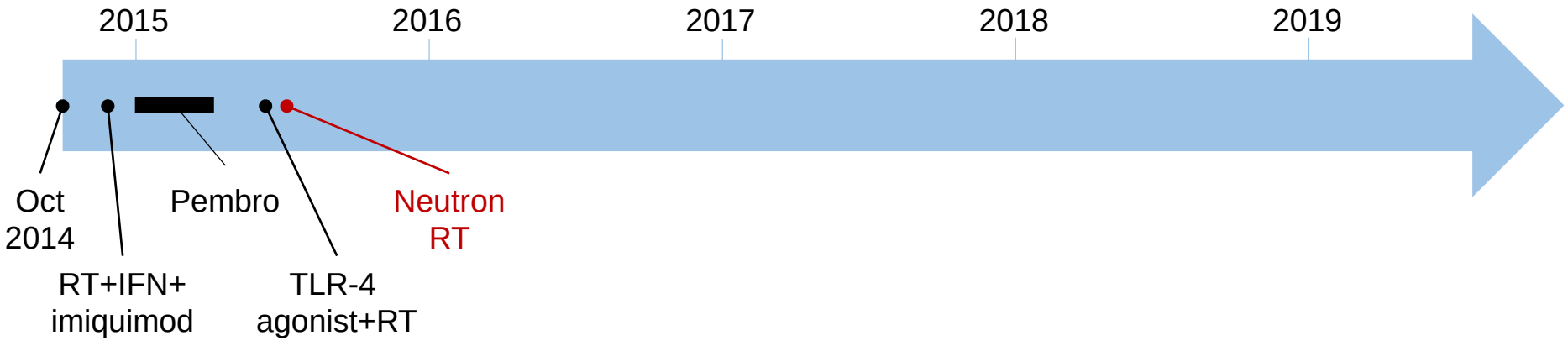




Robust palliative response from Neutron radiation therapy

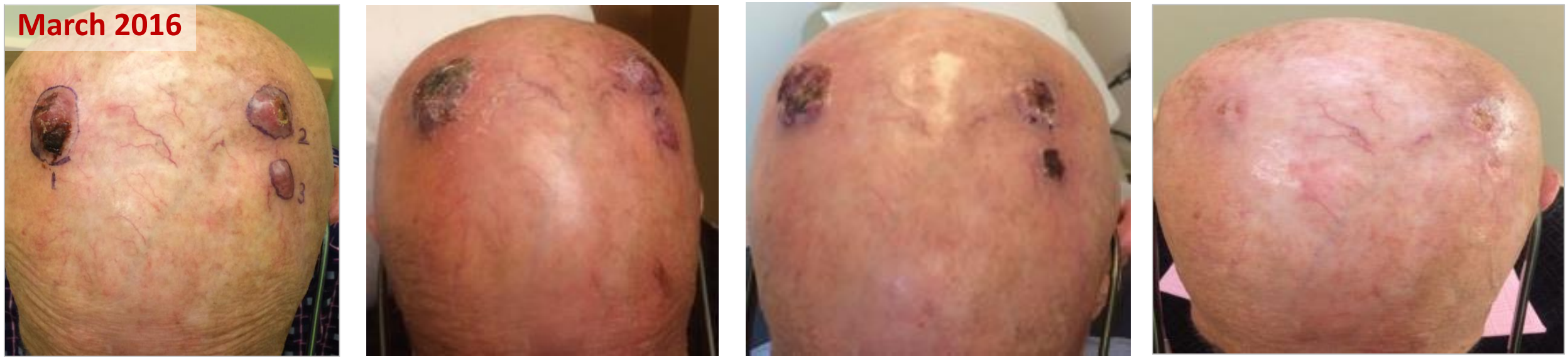


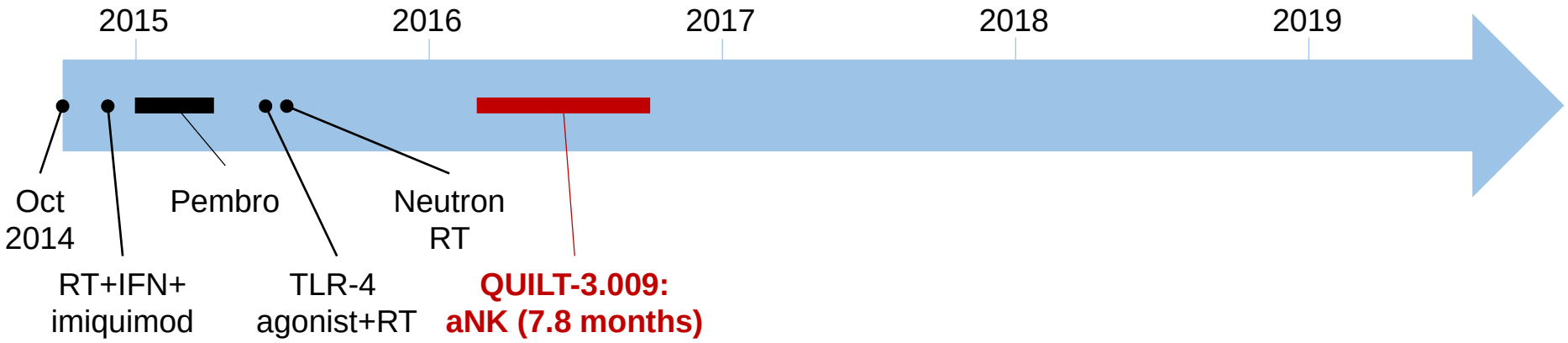
Upendra Parvathaneni
Rad Onc, UW



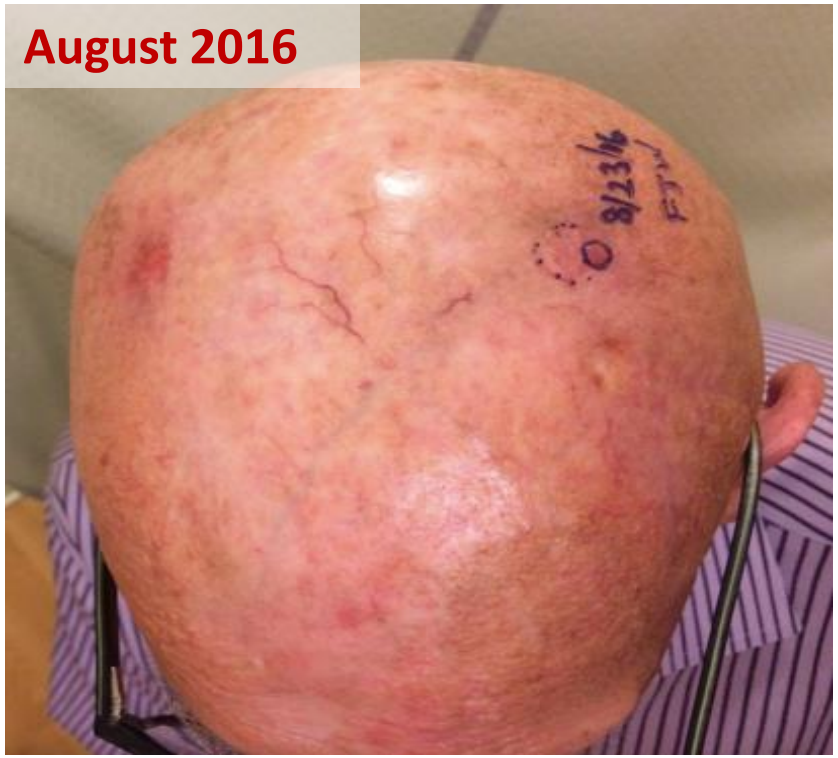
Recurrent MCC at RT field edge; received aNK for >6 months with radiologic CR

Baseline | **Day 14** | **3 months** | **4 months**

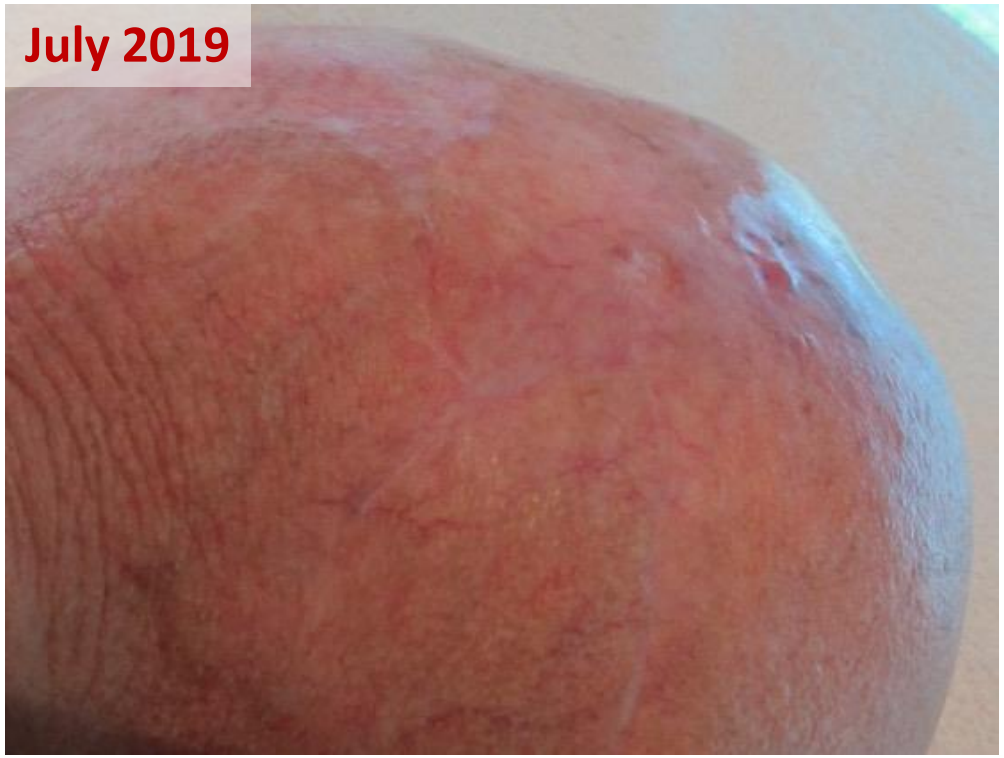


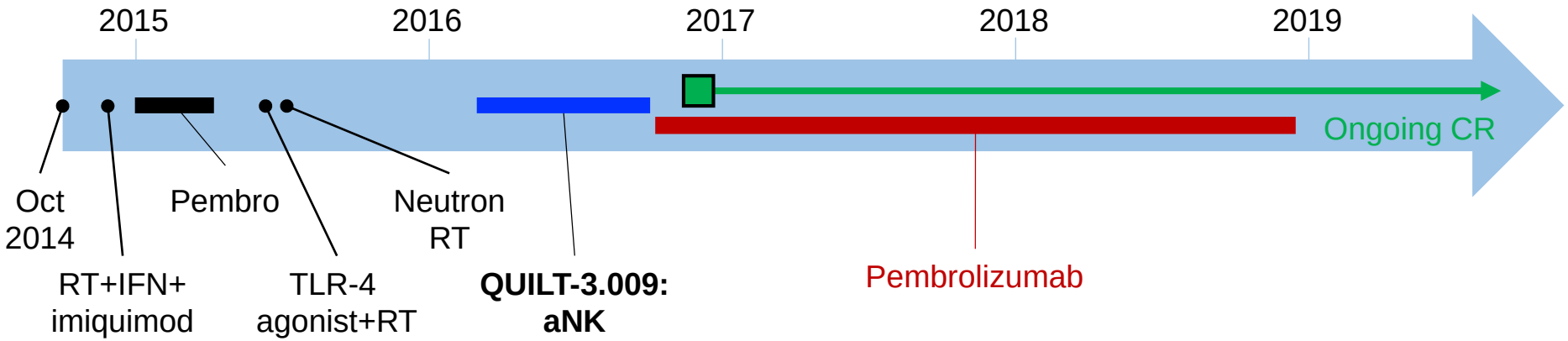


Despite radiologic CR, residual MCC was detected on biopsy. Pembrolizumab re-challenge led to durable CR, ongoing at 3 yrs



Pembrolizumab

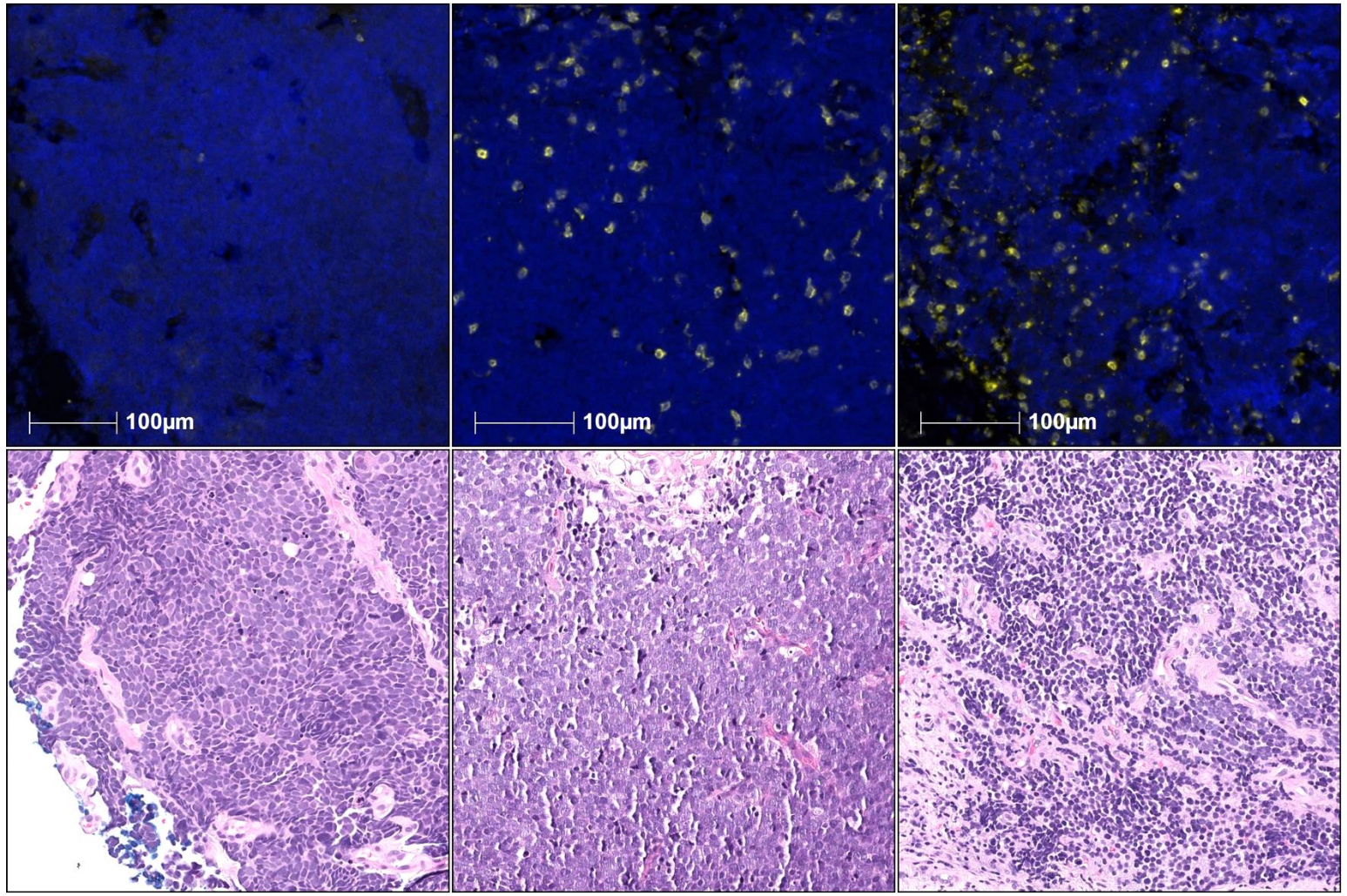




Patient 02-02: Immune cell infiltration in the TME is increased after aNK Monotherapy

Nuclei
CD8

H&E



Pre **1.8** **4.5**

Months from Start of Therapy

Kimberly Smythe
FHCRC

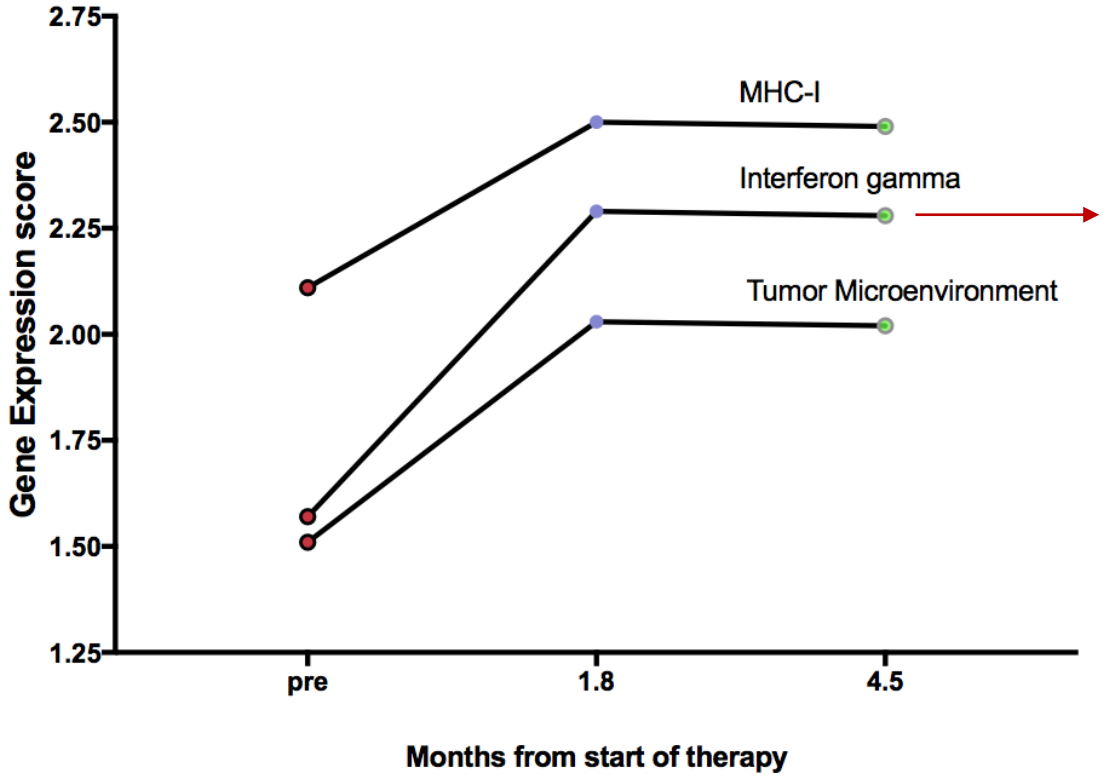
Candice Church
UW

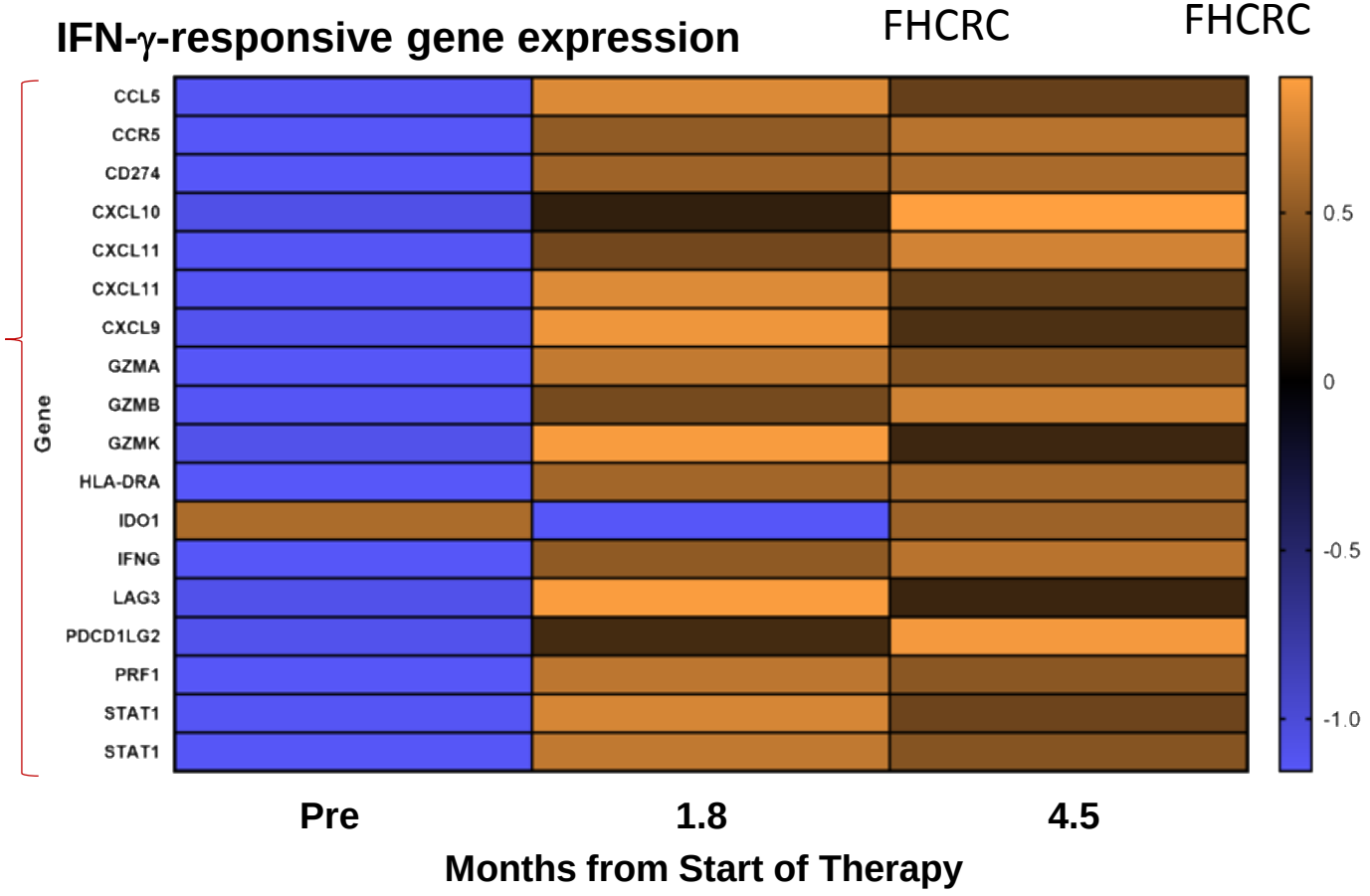
Jean Campbell
FHCRC

Patient 02-02: Immune response-related gene expression is increased in the TME after aNK monotherapy

Lauri Aicher
FHCRC

Jean Campbell
FHCRC

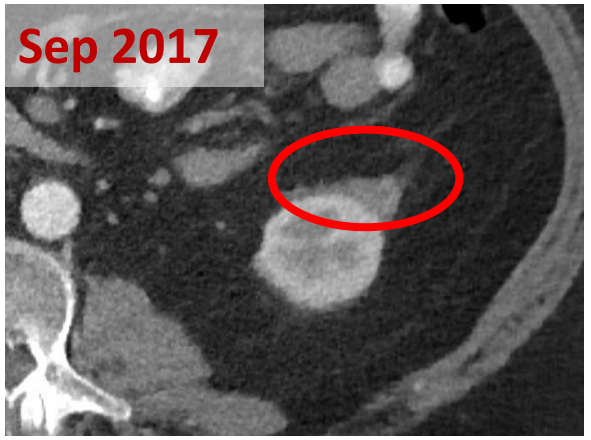




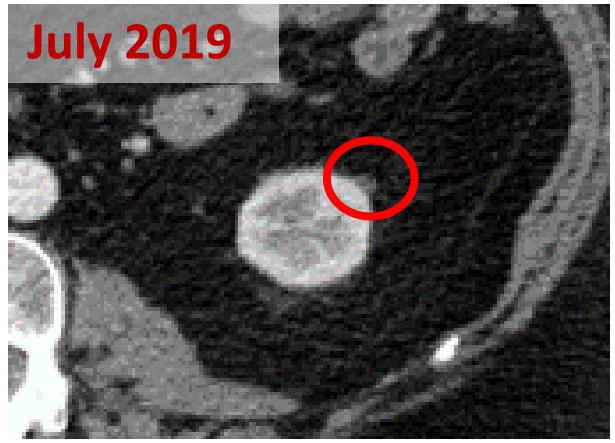
Patient 04-01: aNK+N-803 resulted in apparent PD, followed by PR (>75% regression) ongoing at 15+ months

Progressed after previous nivolumab treatment. Target lesion 2 is 41mm.

Partial response after 4 cycles of aNK+N-803. 13 mm.

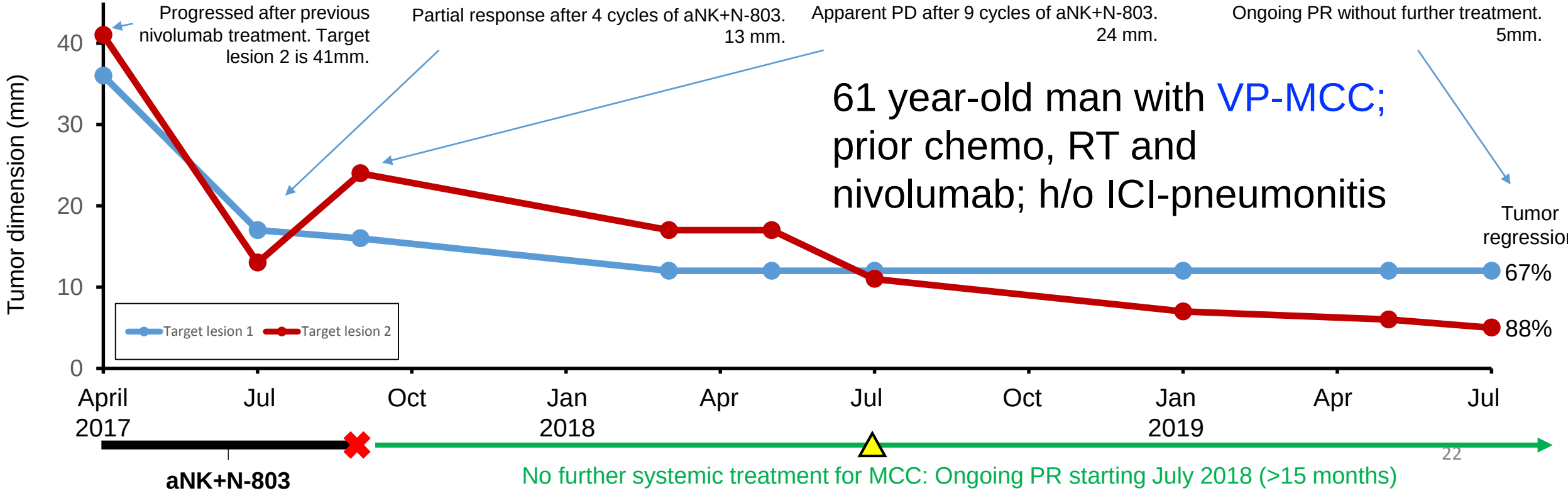


Apparent PD after 9 cycles of aNK+N-803. 24 mm.

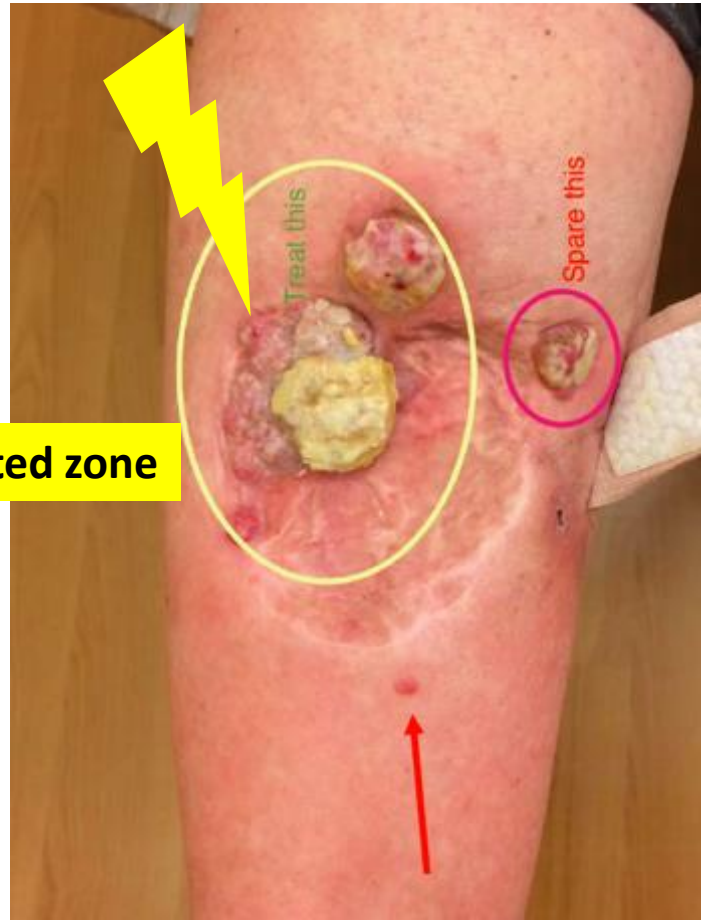


Ongoing PR without further treatment. 5mm.

61 year-old man with VP-MCC; prior chemo, RT and nivolumab; h/o ICI-pneumonitis

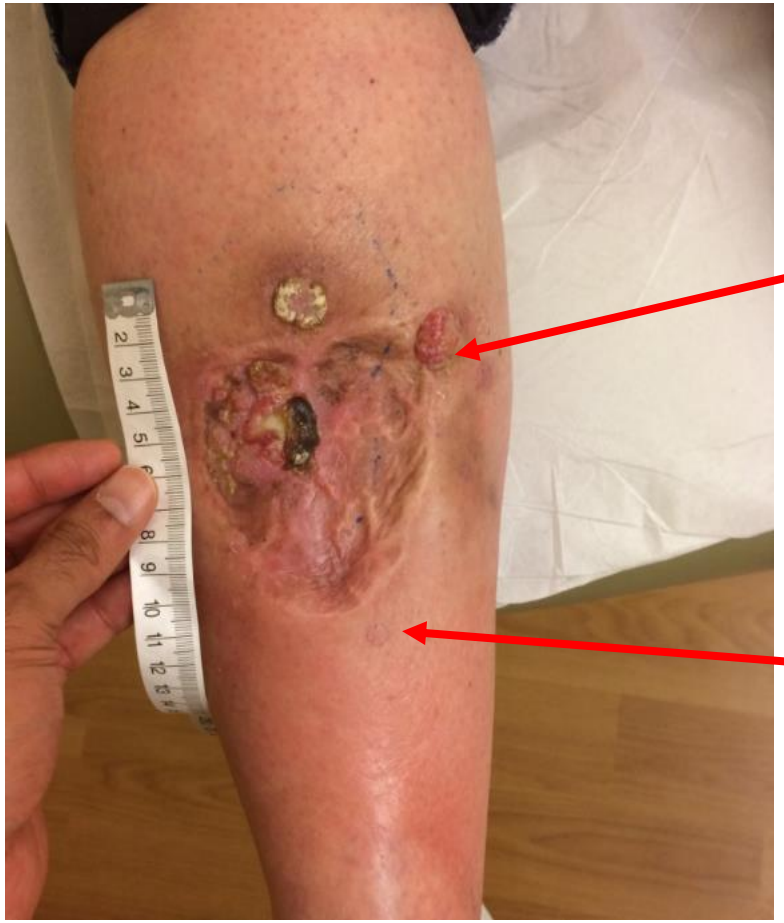


Patient 02-03: aNK+N-803 resulted in stable disease (SD) for 5.5 months in PD-1 refractory VP-MCC tumors



Radiated zone

Baseline



Regressed

Resolved

Post-treatment

QUILT-3.009: Conclusions

- aNK monotherapy and aNK+N-803 were **well-tolerated**, with no treatment-related SAEs or grade ≥3 AEs.

- Promising **clinical activity** was observed with aNK monotherapy and with aNK+N-803 [ORR of 29% (2 of 7 patients); 1 pt with SD].
  - 1 patient (aNK monotherapy) experienced a radiologic CR; evidence for reversal of ICI refractoriness after aNK.
  - 1 patient (aNK + N-803) experienced a PR (ongoing after pseudo-progression)
  - Biologic activity observed even in patients with PD.

- Evidence of increased TILs and immune response-related gene expression after aNK in available biopsy samples.

- aNK-based therapeutic regimens need to be investigated further in patients with advanced MCC .

QUILT-3.063: A Phase 2 Study of Combination Therapy with an IL-15 Superagonist (N-803), Off-the-Shelf CD16-Targeted Natural Killer Cells (haNK), and Avelumab Without Cytotoxic Chemotherapy In Subjects With Merkel Cell Carcinoma (MCC) That Has Progressed On Or After Treatment With A Checkpoint Inhibitor

Phase 2, single-arm combination therapy:

- Investigational Products
  - **N-803**
  - **haNK™ (Cryopreserved, thawed at bedside, on-site expansion is not needed)**
- FDA-approved product: **Avelumab** (BAVENCIO®)

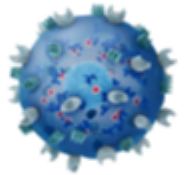
	8-week Treatment Cycle							
Week	1	2	3	4	5	6	7	8
Avelumab	▼		▼		▼		▼	
haNK	▼		▼		▼		▼	
N-803	▼			▼			▼	
Response Evaluation								◆

- Subjects must have progressed on or within 6 months of checkpoint inhibitor therapy with single-agent avelumab or pembrolizumab.
- **Up to 43 patients enrolled**
- NCT03853317

N-803 Combination with Checkpoint

N-803
(IL-15RαFc)

Anti-PD-1
(Avelumab)



haNK®
(Allogeneic NK)

QUILT-3.063

Metastatic Merkel Cell Carcinoma (MCC) That Has Progressed After Checkpoint Inhibitor Therapy

QUILT-3.063 trial sponsored by NantKwest, Inc.

Acknowledgements

UW/Hutch team

Vivian Nguyen, BS. Seattle Cancer Care Alliance, Seattle, WA

Rima Kulikauskas, BS. UW, Seattle, WA

Jean Campbell, PhD. Fred Hutch, Seattle, WA.

Kimberly Smythe, BS. Fred Hutch, Seattle, WA.

Lauri Aicher, MS. Fred Hutch, Seattle, WA.

Patients/Families

Steven Powell, MD. Sanford Health, Sioux Falls, SD.

NantKwest team

Sharif Taha, PhD. ImmunityBio, Inc, Culver City, CA.