Krystal

Research & Development
Oncology Program Announcement

July 2023

Speakers

Krystal R&D Leadership

Suma Krishnan

President, Research & Development

David Chien, MD

SVP, Clinical Development – Oncology

Trevor Parry, PhD

VP, Research and Scientific Affairs

Samuel Broder, MD

- Former Director of the National Cancer Institute where he oversaw the development of numerous anti-cancer therapeutic agents, such as TAXOL® and helped launch a number of large-scale clinical trials related to the prevention, diagnosis, and treatment of cancer, and he inaugurated the highly successful SPORE Program
- Authored over 340 scientific publications and is an inventor on many patents
- Elected to the National Academy of Medicine in 1991

Jason J. Luke, MD, FACP

- Associate Professor of Medicine in the Division of Hematology/Oncology at the University of Pittsburgh and UPMC Hillman Cancer Center
- Associate Director for Clinical Research and the Director of the Immunotherapy and Drug Development Center (Phase I) at UPMC
- Leading investigator in immunotherapeutics, having led trials of checkpoint inhibitors, bispecifics, metabolism modifiers, innate agonists, oncolytic viruses, and cellular therapies; over 150 publications
- Leadership roles for the Melanoma Committees of ASCO, Society for Melanoma Research, AACR and Board Member at SITC

Forward-Looking Statements and Disclosures

Forward-Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties and are based on the current expectations and beliefs of Krystal Biotech, Inc. (the "Company"). Any statements in this presentation about future expectations, plans and prospects for the Company, including but not limited to statements about the Company's technology platform; the Company's oncology program, including the therapeutic approach, target indications for KB707, market opportunities, preclinical safety and efficacy of KB707, the design, conduct, and timeline of the planned KB707 clinical program, and the clinical utility of KB707 and expected timing of clinical updates constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Words such as "anticipate", "believe", "estimate", "expect", "intend", "may", "plan", "predict", "project", "target", "potential", "likely", "will", "would", "could", "should", "continue" and similar expressions or the negative of these terms or other comparable terminology are intended to identify forward-looking statements, though not all forward-looking statements necessarily contain these identifying words. These forward-looking statements are neither forecasts, promises nor guarantees, and are based on the beliefs of the Company's management as well as assumptions made by and information currently available to the Company. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, risks and uncertainties, including: the content and timing of decisions made by regulatory authorities; the uncertainties inherent in the initiation and conduct of clinical trials; availability and timing of data from clinical trials; whether results of early clinical trials or studies in different disease indications will be indicative of the results of ongoing or future trials; uncertainties associated with regulatory review of clinical trials and applications for marketing approvals; the availability or commercial potential of product candidates; the ability to retain and hire key personnel; the sufficiency of cash resources and need for additional financing; and such other important factors as are set forth in the Company's annual and quarterly reports and other filings on file with the U.S. Securities and Exchange Commission. You are cautioned not to place undue reliance on these forward-looking statements, which speak to the Company's current beliefs and expectations only as of the date this presentation is given. Except as required by law, the Company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation in the event of new information, future developments or otherwise. No representation is made as to the safety or effectiveness of the product candidates for the therapeutic use for which such product candidates are being studied.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company's own internal estimates and research. While the Company believes these third-party sources to be reliable as of the date of this presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while the Company believes its own internal research is reliable, such research has not been verified by any independent source.

Disclosures

Dr. Jason Luke is a paid consultant of Krystal Biotech, Inc. The views expressed by Dr. Jason Luke in this presentation are his own views and not those of the University of Pittsburgh or UPMC.

Agenda

Introduction	Krish Krishnan; Chairman and CEO
Krystal Oncology Program	
Therapeutic Approach & Target Indications	Suma Krishnan, MS, MBA; President, Research & Development
	Samuel Broder, MD
Preclinical Overview	Trevor Parry, PhD; VP, Research and Scientific Affairs
Clinical Program	David Chien, MD; SVP, Clinical Development
Lead Investigator's Perspective	Jason J. Luke, MD, FACP
Q&A	All Speakers
Closing	Krish Krishnan, Chairman and CEO

Krystal Oncology Program

Therapeutic Approach & Target Indications

Oncology Program is Building on Our Foundation in Gene Delivery

Success and clinical experience in skin and lung gene delivery provides opportunity to target solid tumors of these tissues

Skin

- Krystal's lead product, VYJUVEK™, is the first approved topically applied gene therapy for DEB, a debilitating skin disease[1-3]
- Topical and intradermal product candidates for ARCI and aesthetic indications currently in clinical trials[4,5]
- Clear molecular evidence of gene delivery in humans via either route of delivery[3-5]
- Well tolerated in all studies to date[1-5]
- Safety, efficacy, redosability and payload delivery demonstrated in clinical trials[1-5]

Lung

- First Patient Dosed in cystic fibrosis clinical trial[6]
- Multiple inhaled delivery programs in or entering clinic in 2023
- Demonstrated in multiple animal models, including NHPs, that local delivery results in broad payload distribution in cells lining conducting airways of the lung[7]
- Clean toxicology profile in GLP studies[7]

1. Krystal Biotech. 2023; Vyjuvek™ (beremagene geperpavec-svdt) FDA Label; 2. Guide SV, et al. *N Engl J Med*. 2022; 387(24):2211 9; 3. Gurevich I et al. *Nat Med* 2022; 28:780 788; 4. Krishnan S, et al. Poster #169 at 2021 SID Annual Meeting (Virtual); 5. Paller A. Presentation at 2020 SID Annual Meeting (Virtual); 6. Krystal Biotech. Press Release July 3, 2023; 7. Parry T, et al. Poster #541 at 2021 NACFC (Virtual)

Krystal Biotech, Data on File.

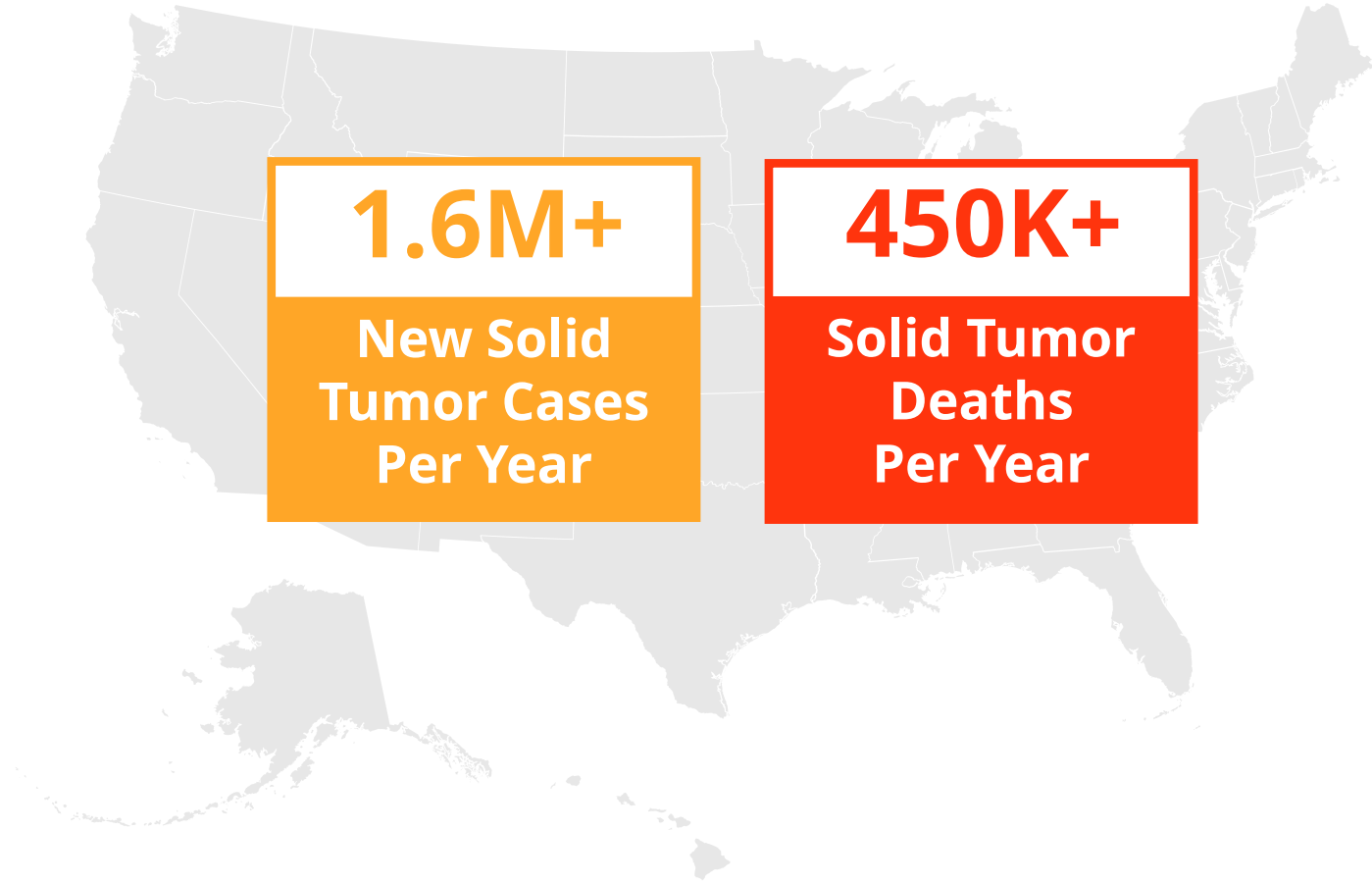
ARCI, autosomal recessive congenital ichthyosis; DEB, dystrophic epidermolysis bullosa; GLP, good laboratory practices; NHP, non human primates

Other than VYJUVEK, all products described in this presentation are investigational therapies

Major Unmet Needs in Checkpoint Inhibitor (CPI) Refractory Solid Tumors

Solid Tumor Incidence and Mortality in US

2023 SEER Estimates[1]



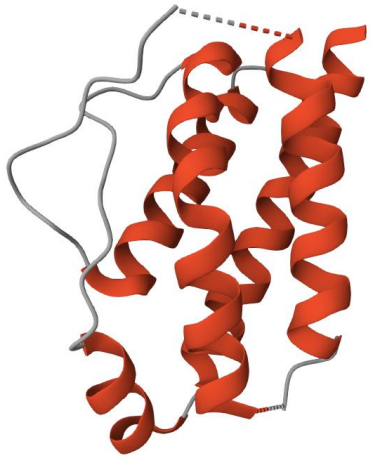
1. NCI SEER. 2023; https://seer.cancer.gov/statfacts/html/common.html [accessed July 20, 2023], combined estimates for incident cases and deaths from cancers of the anus, bladder, bone and joint, brain and nervous system, breast, cervix uteri, colon and rectum, eosophagus, kidney and renal pelvis, larynx, liver and intrahepatic bile duct, lung and bronchus, melanoma, oral cavity and pharynx, ovary, pancreas, prostate, small intestine, stomach, testis, thyroid, uterus, and vulva

SEER; Surveillance, Epidemiology, and End Results Program; US, United States

HSV-1 Based Vector Coded for the Local Delivery of Both IL-2 and IL-12

Cytokines with synergistic functions and therapeutic potential

IL-2

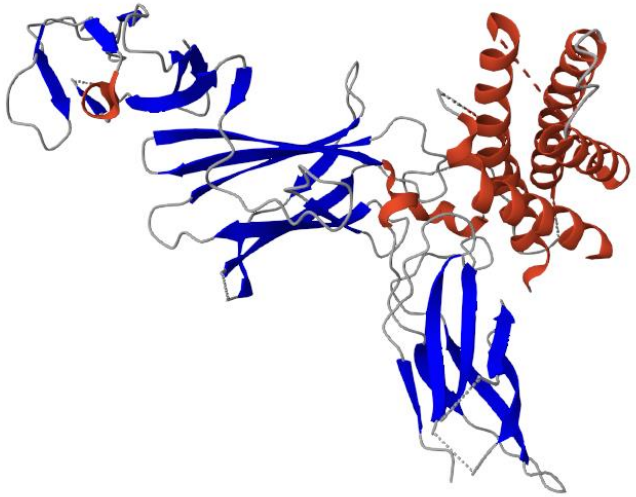


Expand and Activate Lymphocyte Population[1-3]

Well-characterized NK and T cell activator with known roles inducing T cell proliferation and promoting NK and T cell cytotoxic functions

+

IL-12



Reinforce Cytotoxic Effector Functions[4,5]

Complementary cytokine known to promote lymphocyte effector functions and IFN-gamma secretion

1. IL-2 image from the RCSB PDB (RCSB.org) of PDB ID 1M47 [image generated July 20 2023]; 2. Jiang T, et al. *OncoImmnuology*. 2016; 5(6):e1163462; 3. Morgan DA, et al. *Science*. 1976; 193(4257):1007-1008; 4. IL-12 image from the RCSB PDB (RCSB.org) of PDB ID 1F45 [image generated July 20 2023]; 5. Lasek W, et al. *Cancer Immunol Immunother*. 2014; 63:419-35

IL-12, interleukin-12; IL-2, interleukin-2; NK, natural killer

Other than VYJUVEK, all products described in this presentation are investigational therapies

Advantages of Replication-Defective HSV-1 Based Cytokine Delivery

Platform well suited to accomplish dual goals of targeted but sustained delivery of IL-2 and IL-12 to the tumor

Optimal vector platform to maximize cytokine expression and immune activation

- ✓ Efficiently transduces a wide variety of cell types maximizing reach within tumor
- ✓ DNA payload persists in transduced cells extending the window of cytokine expression
- ✓ Lack of replication avoids premature lytic cell death or host cell shutdown
- ✓ Redosability to further boost local cytokine expression
- ✓ Safety profile suitable for both **inhaled** or **intratumoral** administration

Krystal Biotech, Data on File.

Other than VYJUVEK, all products described in this presentation are investigational therapies

Potential KB707 Target Indications for the Skin

8K

Estimated 2023 US Melanoma Deaths[1]

10K+

Estimated Gorlin Pts in US[5]

2.4 Years

Median Survival RDEB-SCC[9*]

CPI Refractory Melanoma

- Over 97K new US melanoma cases expected in 2023; 14K classified as regional or distant at diagnosis[1]
- CPI combos often used first-line, overall response rates (ORR) roughly 40-60%[2]
- Most patients either non-responsive or eventually progress to chemotherapy[2,3]
- Prognosis on chemotherapy is poor; ORR 10% or less, median survival < 1 year[4]

Basal Cell Carcinoma (BCC) and Gorlin

- Often addressed with surgery but Gorlin patients predisposed to recurrent BCC[5,6]
- Can have hundreds of BCCs over their lifetime with frequent surgeries[6]
- Systemic therapies either too toxic for regular use or have modest efficacy[7,8]
- ***No specific therapy FDA approved for patients with Gorlin***

Squamous Cell Carcinoma (SCC) and RDEB-SCC

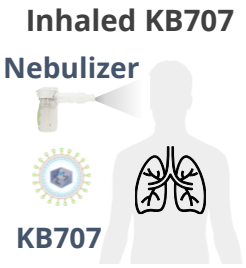
- Over 1M new cases in US each year, metastasis rates estimated at 2-6%[10-13]
- Treatment options limited to CPI with ORR of 30-50% or chemotherapy[8,14]
- Acute unmet need in RDEB patients with SCC, aggressive and lethal[9]

1. NCI SEER. 2023; https://seer.cancer.gov/statfacts/html/common.html [accessed July 20, 2023], advanced = regional or distant; 2. Larkin J, et al. *N Engl J Med*. 2019; 17;381(16):1535-1546; 3. Atkins MB, et al. *J Clin Oncol*. 2023; 41(2): 186-197; 4. Goldfinger SM, et al. *Eur J Cancer*. 2022; 162: 22-33; 5. Based on 1:31K prevalence estimate from Evans DG, et al. *GeneReviews* 201, https://www.ncbi.nlm.nih.gov/books/NBK1151/ [accessed July 20, 2023]; 6. Solis DC, et al. *JAMA Dermatol.* 2017; 153: 189-192; 7. Tang JY, et al. *N Engl J Med.* 2012; 366: 2180-2188; 8. Sanofi. 2021; Libtayo® (cemiplimab-rwlc) FDA Label; 9. Median survival for patients classified as having severe RDEB from Robertson SJ, et al. *Acta Derm Venereol.* 2021; 101(8): 100; 10. Skin Cancer Foundation. 2021. Our New Approach to a Challenging Skin Cancer Statistic - The Skin Cancer Foundation [accessed July 20, 2023]; 11. Rogers JW, et al. *JAMA Dermatol.* 2015; 151(10): 1081-1086; 12. Patel VA, et al. *Cancer Med* . 2022; 11: 94-103; 13. Tokez S, et al. *J Am Acad Dermatol*. 2022; 86: 331-338; 14. Merck, 2023; Keytruda® (pembrolizumab) FDA Label

CPI, checkpoint inhibitor; RDEB, recessive dystrophic epidermolysis bullosa; US, United States;

Other than VYJUVEK, all products described in this presentation are investigational therapies

Potential KB707 Target Indications for the Lung



Two Year Survival Rates on PD-1 Targeting CPI + Chemotherapy
Nonsquamous NSCLC, Split by PD-L1 TPS[1]*

39.3%	44.3%	52.2%
PD-L1 Low	PD-L1 Mid	PD-L1 High

- **Over 238K** new lung cancer cases and **over 127K** deaths estimated in US in 2023[2]
- CPI are increasingly used first-line but benefits from CPI transient and vary by PD-L1 expression level[2-4]
- In patients with low to mid PD-L1 expression, combination regimens with chemotherapy often used[2-4]
- New agents needed to improve patient outcomes in front-line and CPI refractory setting as well as reduce reliance on chemotherapy

1. Garassinio MC, et al. *J Clin Oncol.* 2023; 41(11): 1992-1998; 2. NCI SEER. 2023; https://seer.cancer.gov/statfacts/html/common.html [accessed July 20, 2023]; 3. Bodor JN, et al. *J Oncol Pract.* 2018; 14(9): 529-535; 4. Singh N, et al. *J Clin Oncol.* 2022; 40(28): 3323-3343

*PD-L1 Low = TPS < 1%,PD-L1 Mid = TPS 1%-49%, PD-L1 High = TPS ≥ 50%

CPI, checkpoint inhibitor; NSCLC, non small cell lung cancer; PD-L1, programmed death-ligand 1; TPS, tumor proportion score; US, United States

Other than VYJUVEK, all products described in this presentation are investigational therapies

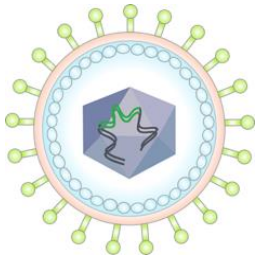
Oncology Program KB707

Preclinical Update

Preclinical Research Objectives

Research program built on stringent preclinical models to support clinical development

KB707



Replication-defective HSV-1 vector containing functional human *IL2* and *IL12*

- **Confirm expression, secretion, and bioactivity of vector-produced cytokines**
- **Assess durability of expression following local delivery in healthy immunocompetent animals**
- **Demonstrate safety and efficacy of repeated dosing of cytokine-expressing vectors in checkpoint refractory 'cold' syngeneic murine models of solid tumors**

IL-12/*IL12*, interleukin-12; IL-2/*IL2*, interleukin-2

Other than VYJUVEK, all products described in this presentation are investigational therapies

KB707 Transduction and Cytokine Secretion by Mammalian Cells *In Vitro*

Vector-derived, secreted IL-12 and IL-2 equivalently bioactive to commercial recombinant proteins

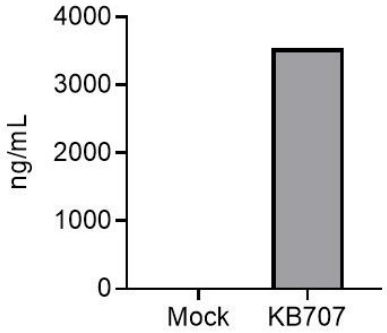
Initial studies conducted in HEK293FT cells demonstrated that KB707 efficiently transduced mammalian cells, resulting in production and secretion of bioactive IL-2 and IL-12

- IL-2 and IL-12 detected in cell culture supernatants 24 hours after transduction at MOI of 1
  - IL-12: Over 3,000 ng / mL
  - IL-2: Over 400 ng / mL
- KB707-derived IL-12 shown to elicit comparable IFNγ response from PBMCs as commercially available recombinant IL-12 after 24-hour *in vitro* co-stimulation with anti-CD3 / anti-CD28
- KB707-derived IL-2 elicited equivalent SEAP activity as commercially available recombinant cytokine in HEK-Blue-IL-2 cells, a proxy for IL-2 signaling,

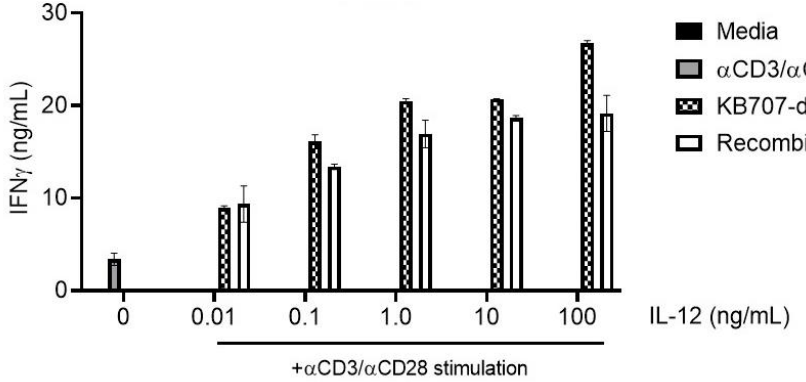
Cytokine production and secretion also confirmed in KB707-transduced primary human dermal fibroblasts and small airway epithelial cells, with evidence of cytokine accumulation in supernatants from 24 to 48 hours

IL-12

Secreted Cytokine Levels
24 Hours

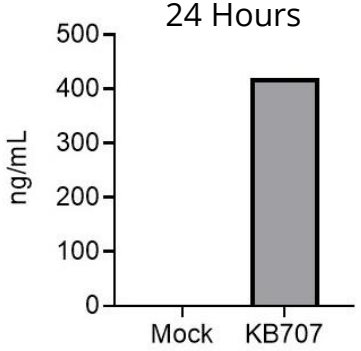


PBMC IFNγ Secretion
24 Hour Stimulation

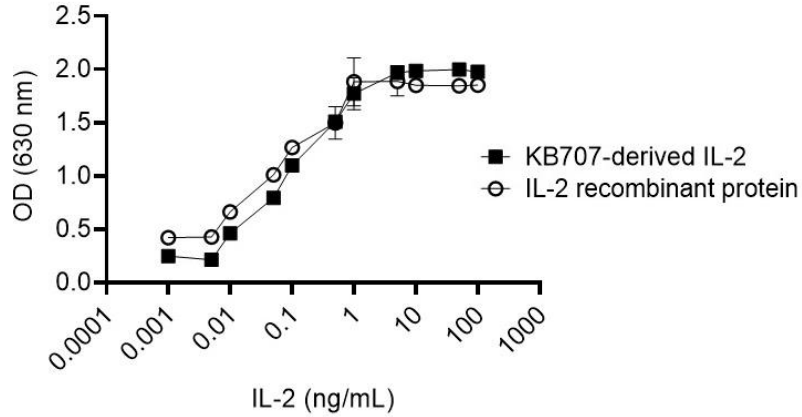


IL-2

Secreted Cytokine Levels
24 Hours



Signaling in HEK-Blue™ IL-2 Cells



Krystal Biotech, Data on File.

CD3, cluster of differentiation 3; CD8, cluster of differentiation 8; HEK, human embryonic kidney; IFNγ, interferon gamma; IL-12, interleukin-12; IL-2, interleukin-2; MOI, multiplicity of infection; PBMC, peripheral blood mononuclear cell; SEAP, secreted embryonic alkaline phosphatase

Other than VYJUVEK, all products described in this presentation are investigational therapies

Sustained Cytokine Expression After Intradermal Delivery to Mice

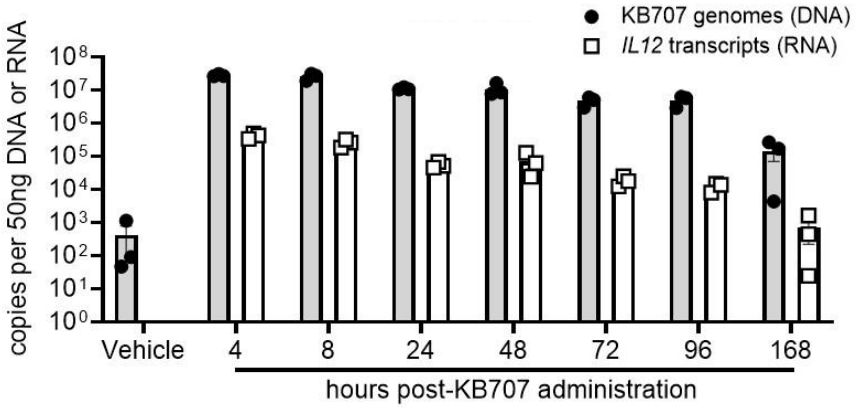
Vector genomes, cytokine transcripts, and protein detected out to seven days after single administration

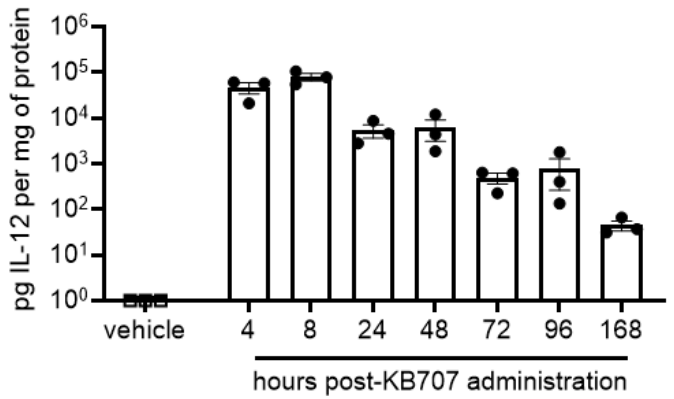
- Short half life of cytokines has limited clinical utility; FDA approved treatment regimen with recombinant IL-2 requires dosing three times daily[1]
- BALB/c mice administered 8×10^8 PFU of KB707 by intradermal injection
- Tissues collected for assessment of IL-2 and IL-12 expression at nucleic acid and protein levels, n = 3 samples per time point
- Peak cytokine protein levels observed at 8 hours post injection, remained detectable through Day 7
- Both DNA and RNA detectable through Day 7, potential for accumulation with repeat dosing
- Intradermal administration well tolerated with low systemic cytokine exposure

DNA / RNA Levels in Skin

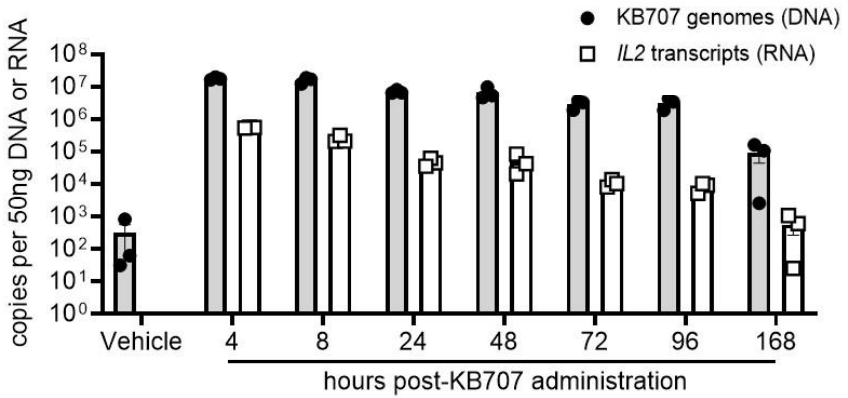
Protein Levels in Skin

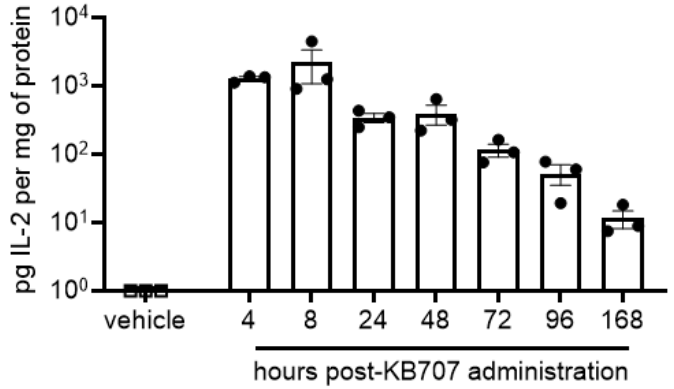
IL-12





IL-2





1. Clinigen, 2019, Proleukin® (aldesleukin) FDA Label

Krystal Biotech, Data on File.

DNA, deoxyribonucleic acid; IL-12, interleukin-12; IL-2, interleukin-2; PFU, plaque forming unit; RNA, ribonucleic acid

Other than VYJUVEK, all products described in this presentation are investigational therapies

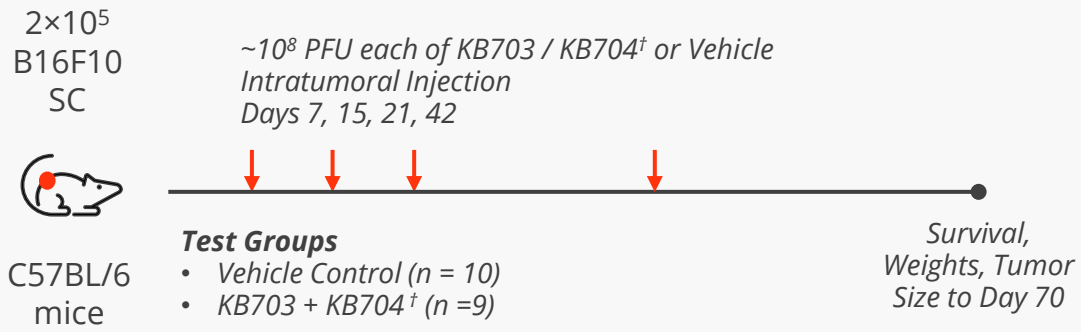
Intratumoral IL-12 and IL-2 Effective in Cold Syngeneic Mouse Tumor Model

Clear antitumor effect and survival benefit in checkpoint inhibitor refractory B16F10 tumor model

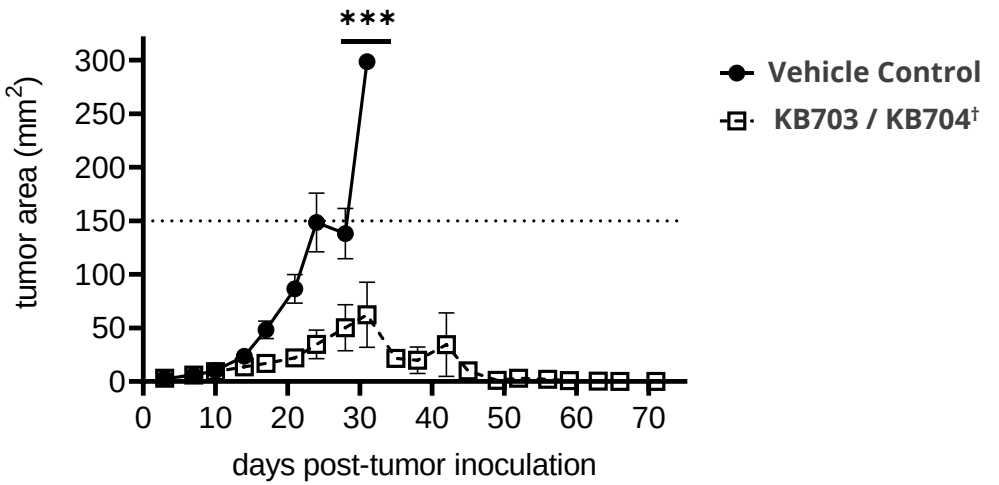
Single Flank B16F10 Melanoma Model

- B16F10 is a subclone of the B16 cancer cell line originally derived from the skin of a C57BL/6 mouse with melanoma
- B16F10 tumors are highly aggressive and minimally responsive to immunotherapy, including refractory to PD-1 targeting CPI
- Among the most stringent melanoma cell lines for the evaluation of candidate immunotherapeutics

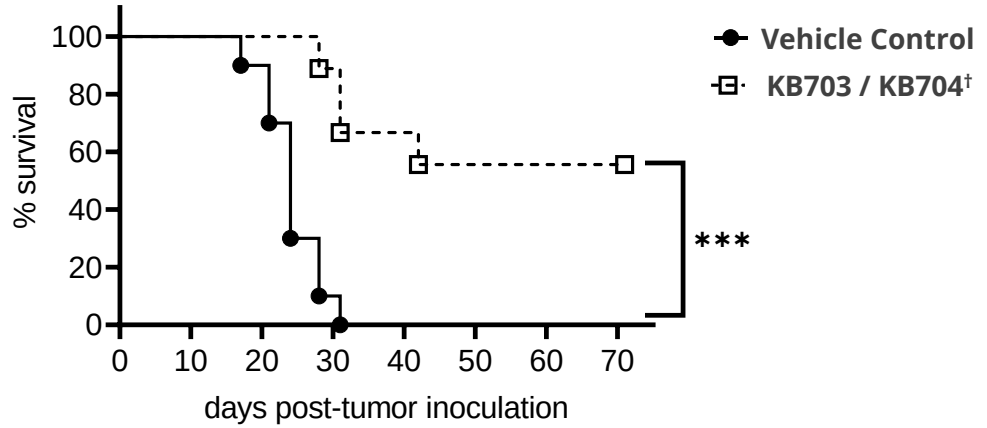
Study Design



Injected Tumor Size



Survival



Krystal Biotech, Data on File.

† KB703 encodes murine IL-12, KB704 encodes murine IL-2, and KB703 + KB704 is murine equivalent to KB707

IL-12, interleukin-12; IL-2, interleukin-2; PFU, plaque forming unit; SC, subcutaneous

Other than VYJUVEK, all products described in this presentation are investigational therapies

***p<0.001

Evidence of Systemic Immune Response with Intratumoral IL-12 and IL-2

Antitumor effect and survival benefit in dual flank B16F10 tumor model

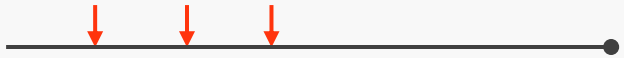
Dual Flank B16F10 Melanoma Model

- Dual flank model mimics metastatic, checkpoint refractory melanoma seen in late line clinical treatment setting
- Only tumor in first flank is injected to evaluate impact of systemic response on secondary tumor outgrowth

Study Design

Day 0
2×10^5 B16F10
First Flank SC

~10^8 PFU each of KB703 / KB704† or Vehicle
Intratumoral Injection First Flank Only
Days 7, 15, 21



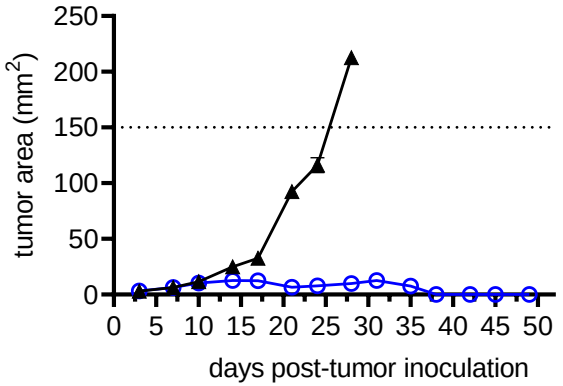
Survival, Weights, Tumor Size to Day 49

Day 4
1×10^5 B16F10
Second Flank SC

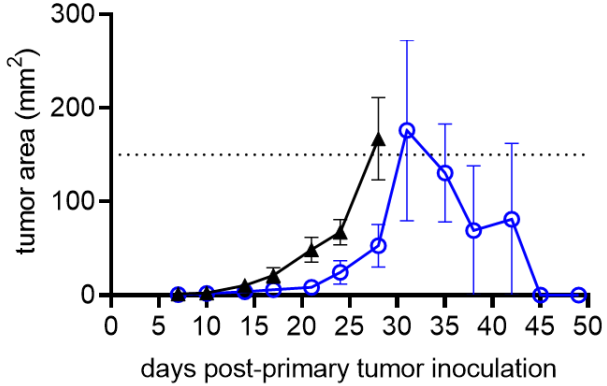
C57BL/6 Mice

Test Groups
- *Vehicle Control (n = 5)*
- *KB703 + KB704† (n =5)*

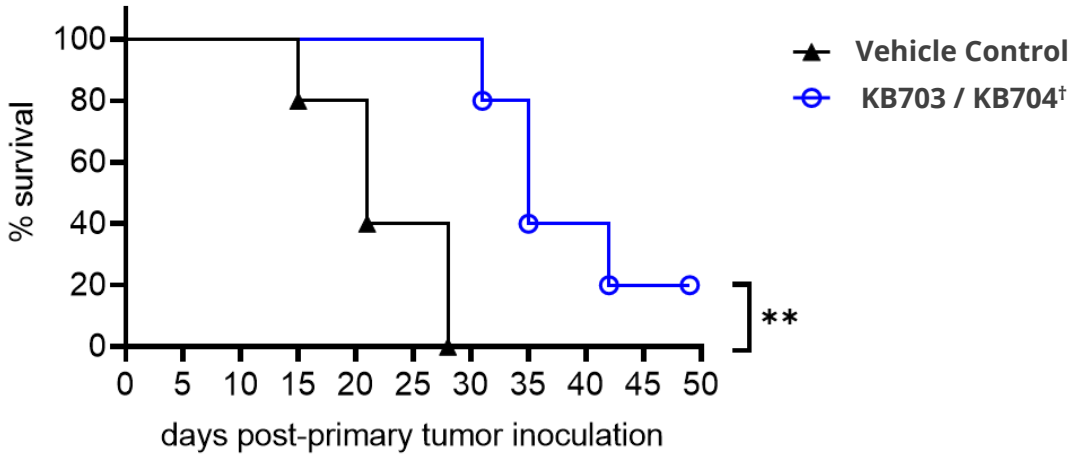
Injected Tumor Size



Secondary Tumor Size



Survival



Krystal Biotech, Data on File.

† KB703 encodes murine IL-12, KB704 encodes murine IL-2, and KB703 + KB704 is murine equivalent to KB707

IL-12, interleukin-12; IL-2, interleukin-2; PFU, plaque forming unit; SC, subcutaneous

Other than VYJUVEK, all products described in this presentation are investigational therapies

**p<0.01

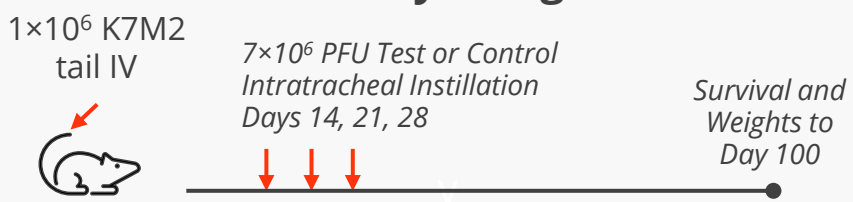
Lung Delivery Effective in Metastatic Osteosarcoma Model

Local delivery of IL-12 and IL-2 confers clear survival benefit in otherwise lethal, metastatic osteosarcoma

Metastatic K7M2 Osteosarcoma Model

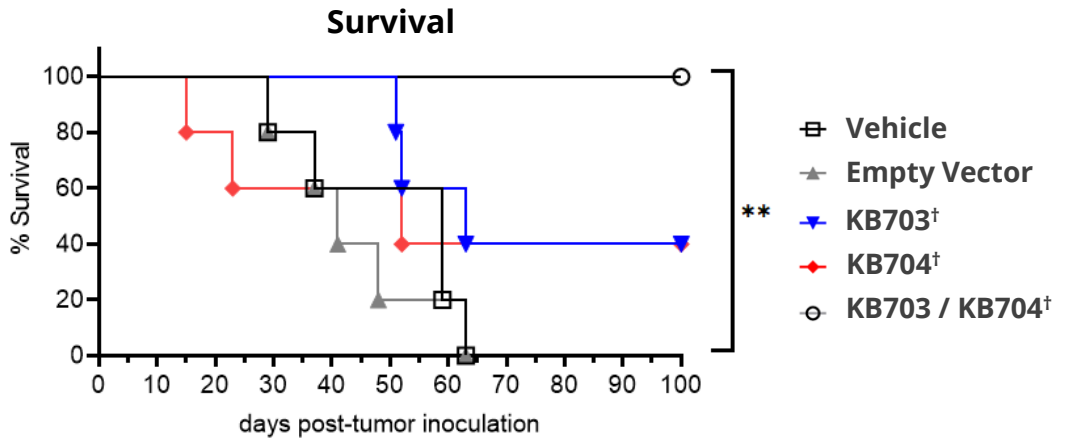
- K7M2 is an osteoblast cell line derived from bone of mouse with spontaneous osteosarcoma[1]
- Considered highly aggressive with pulmonary metastatic rate of over 90% in mice[1]
- Previously shown to be non-responsive to PD-1/PD-L1 targeting therapies, partial benefit from combo therapies[2]

Study Design

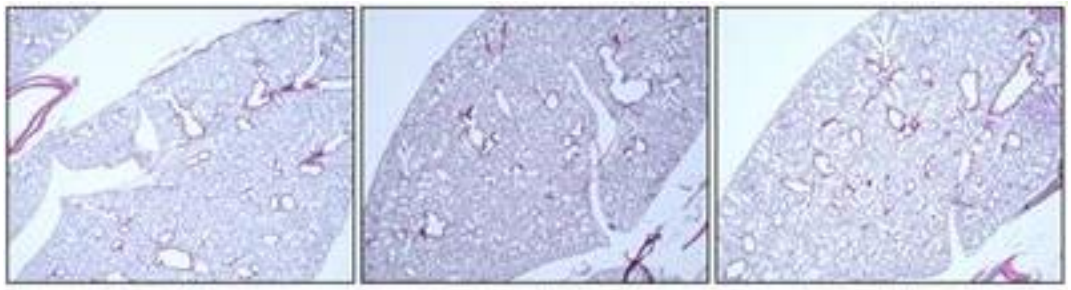


Test Groups

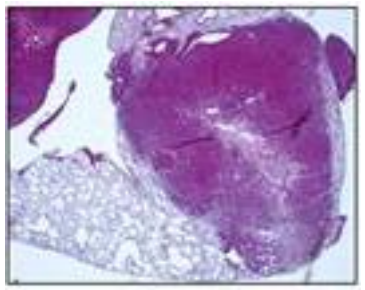
- *KB703 Alone† (n = 5)*
- *KB704 Alone† (n = 5)*
- *KB703 + KB704† (n = 5)*
- *Vehicle Control (n = 5)*
- *Naïve Control (n = 5)*



Lung H&E, Day 100



KB703 / KB704†
Representative images
from n = 3 of 5 survivors



KB703 Alone†
Representative image
from n = 1 of 2 survivors

1. Khanna C, et al., *Clin Exp Metastasis*. 2000;18(3):261-271; 2. Lussier DM et al. *J Immunother Cancer* 2015;3(21)

Krystal Biotech, Data on File.

† KB703 encodes murine IL-12, KB704 encodes murine IL-2, and KB703 + KB704 is murine equivalent to KB707

H&E, hematoxylin and eosin; IV, intravenous; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFU, plaque forming unit

Other than VYJUVEK, all products described in this presentation are investigational therapies

**p<0.01

Lung Delivery Also Confers Durable Protection from Tumor Rechallenge

Suggestive of memory adaptive immune response

K7M2 Osteosarcoma Rechallenge Model

Initial Challenge

1×10⁶ K7M2 tail IV

7×10⁶ PFU Test or Control Intratracheal Instillation Days 14, 21, 28

Survival and Weights to Day 70

BALB/c Mice

Test Groups
- *KB703 + KB704† (n = 5)*
- *Vehicle Controls (n = 4)*

Rechallenge

1×10⁶ K7M2 tail IV

Day 75

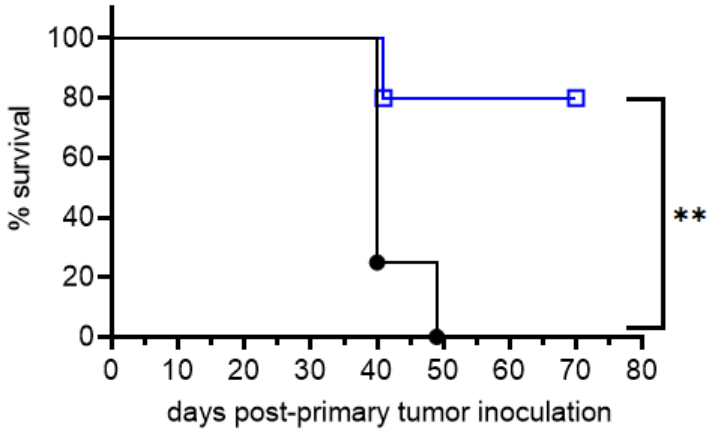
No additional treatment

Survival and Weights to Day 150

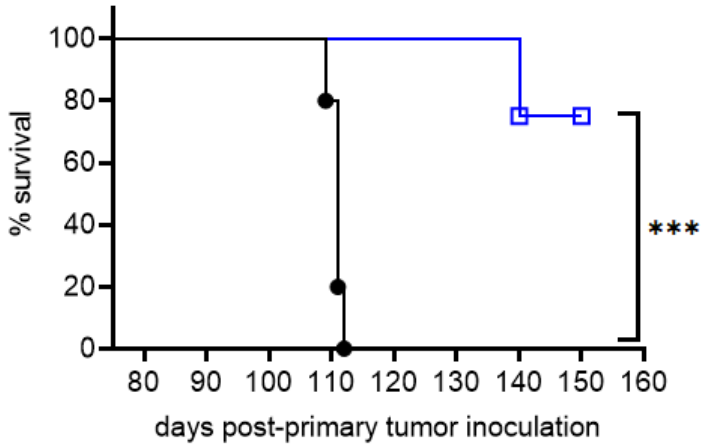
BALB/c Mice

Test Groups
- ***Survivors From Initial Challenge*** *KB703 + KB704† (n = 4)*
- ***New, Naïve*** *Vehicle Controls (n = 5)*

Survival
After Initial Challenge



Survival
After Rechallenge



Vehicle Control

KB703 / KB704†

Krystal Biotech, Data on File.

† KB703 encodes murine IL-12, KB704 encodes murine IL-2, and KB703 + KB704 is murine equivalent to KB707

IV, intravenous; PFU, plaque forming unit

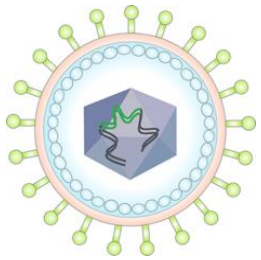
Other than VYJUVEK, all products described in this presentation are investigational therapies

**p<0.01, ***p<0.001

Preclinical Summary

Robust efficacy in stringent, CPI-refractory preclinical models supports clinical development

KB707



Replication-defective HSV-1 vector containing functional human *IL2* and *IL12*

- ✓ **Transduces human cells *in vitro* leading to secretion of bioactive IL-2 and IL-12**
- ✓ **Localized, durable cytokine expression in mouse skin after intradermal delivery**
- ✓ **Clear antitumor effects and survival benefits after intratumoral delivery in stringent, checkpoint refractory single and dual flank B16F10 melanoma models**
- ✓ **Lung delivery led to tumor clearance and significant survival benefit in immunotherapy resistant, metastatic K7M2 osteosarcoma model**
- ✓ **Evidence of protection from tumor rechallenge suggestive of adaptive memory**

Krystal Biotech, Data on File.

IL-12/*IL12,* interleukin-12; IL-2/*IL2*, interleukin-2

Other than VYJUVEK, all products described in this presentation are investigational therapies

Oncology Program KB707

Clinical Program

KB707 Clinical Program

Overall Phase 1/2 Approach

Deliver response to all solid tumor patients with immunotherapy

Phase 1 first-in-human study with intratumoral administration

- Evaluate the safety and tolerability of monotherapy in ascending dose
- Demonstrate single agent anti-tumor activity
- Patients with solid tumors that progressed on SOC
- Data will support further assessment in disease-specific indications

Inhaled administration

- Advantage in delivery to respiratory tract cancers (e.g., Lung, H&N), cancer metastasized to the lungs
- Staggered start to intratumoral administration leverages safety, tolerability, and pharmacodynamic data

H&N, head and neck; IL-12/*IL12,* interleukin-12; IL-2/*IL2*, interleukin-2; SOC, standard of care

Other than VYJUVEK, all products described in this presentation are investigational therapies

KB707-01 Intratumoral Phase 1 Study

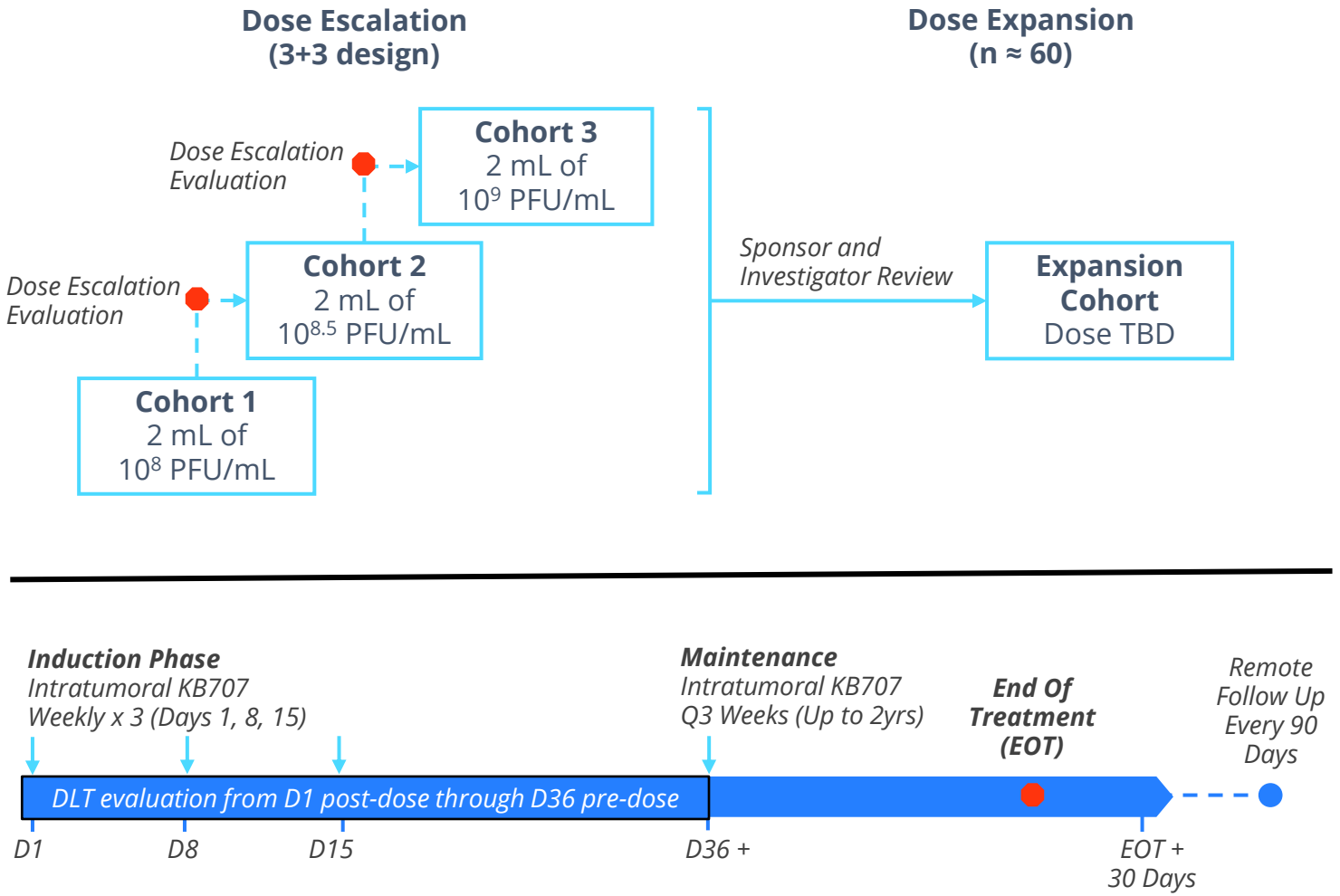
Open-label study to assess safety, tolerability, and preliminary efficacy

Study Objectives

- Evaluate the safety and tolerability
- Evaluate for maximum tolerated dose (MTD)
- Evaluate preliminary efficacy as assessed by multiple measures including
  - Objective response rate (ORR)
  - Progression free survival (PFS)
  - Overall survival (OS)
- Assess immunological effect of KB707 in blood and tumor

Key Enrollment Criteria

- Age ≥ 18 years with histologically confirmed locally advanced or metastatic solid tumor who has relapsed on or are refractory to standard of care.
- At least one measurable and injectable tumor accessible by transcutaneous route, including but not limited to
  - Melanoma
  - Cutaneous Squamous Cell Carcinoma
  - Basal Cell Carcinoma

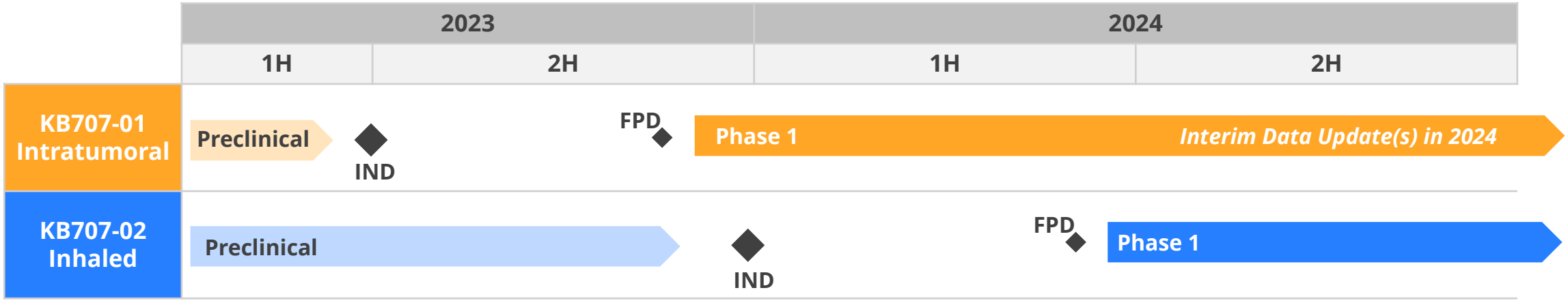


DLT, dose limiting toxicity; EOT, end of treatment; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PFU, plaque forming unit; TBD, to be determined

Other than VYJUVEK, all products described in this presentation are investigational therapies

KB707 Clinical Timeline

Both routes of administration under evaluation in Phase 1 by 1H 2024



Recent and Upcoming Milestones

KB707-01 Intratumoral

- ☑ IND accepted by US FDA in 1H 2023
- ❑ First patient dosed with KB707 in 2H 2023

KB707-02 Inhaled

- ❑ IND amendment in 2H 2023
- ❑ First patient dosed with inhaled KB707 in 1H 2024

First clinical update from KB707-01 expected in 2024

FDA, US Food and Drug Administration; FPD, first patient dosed; IND, investigational new drug; US, United States

Other than VYJUVEK, all products described in this presentation are investigational therapies

Cutaneous oncology landscape for refractory disease

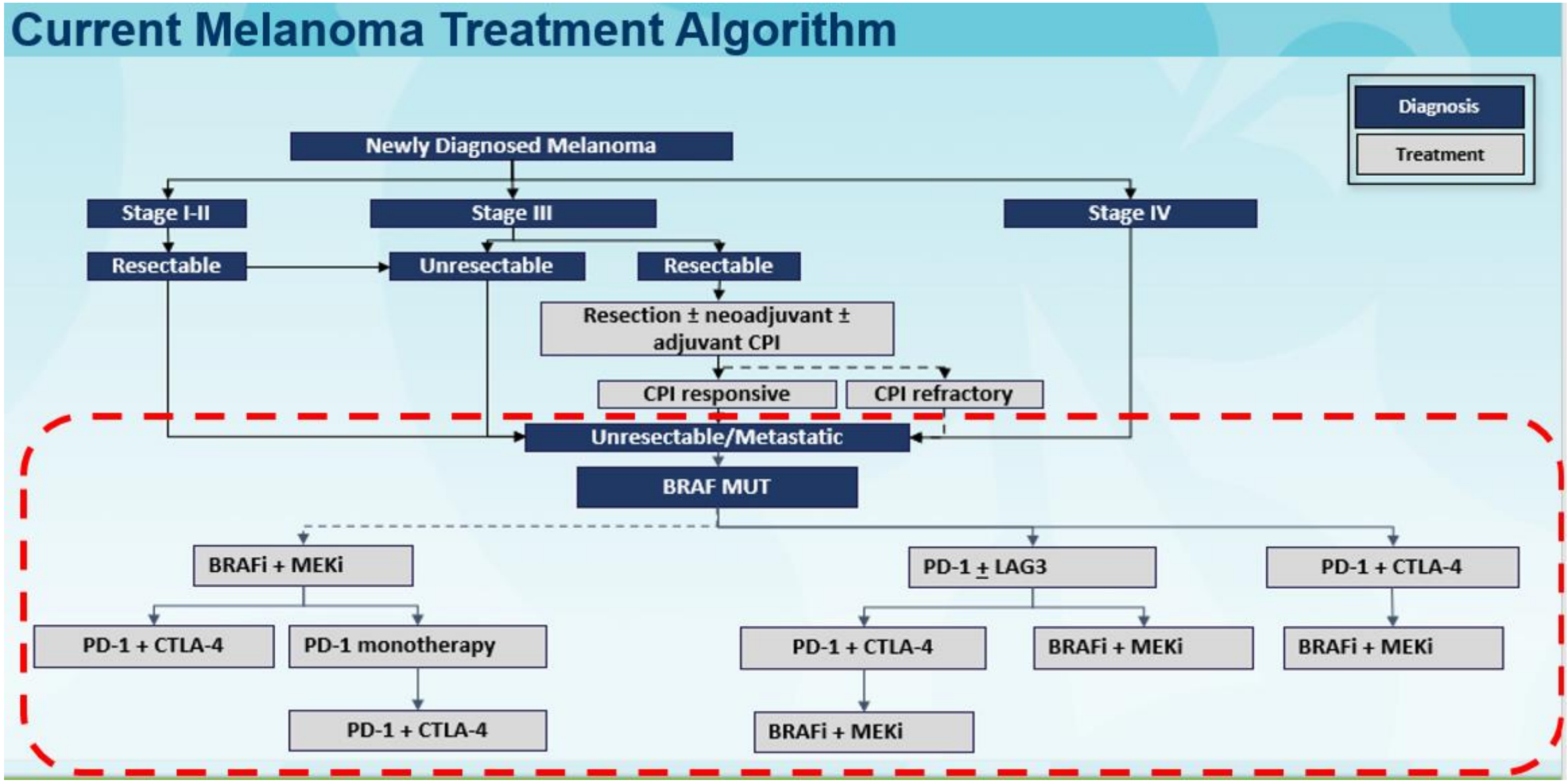
Jason J. Luke, MD, FACP
Associate Professor
Director of the Immunotherapy and Drug Development Center
Associate Director for Clinical Research

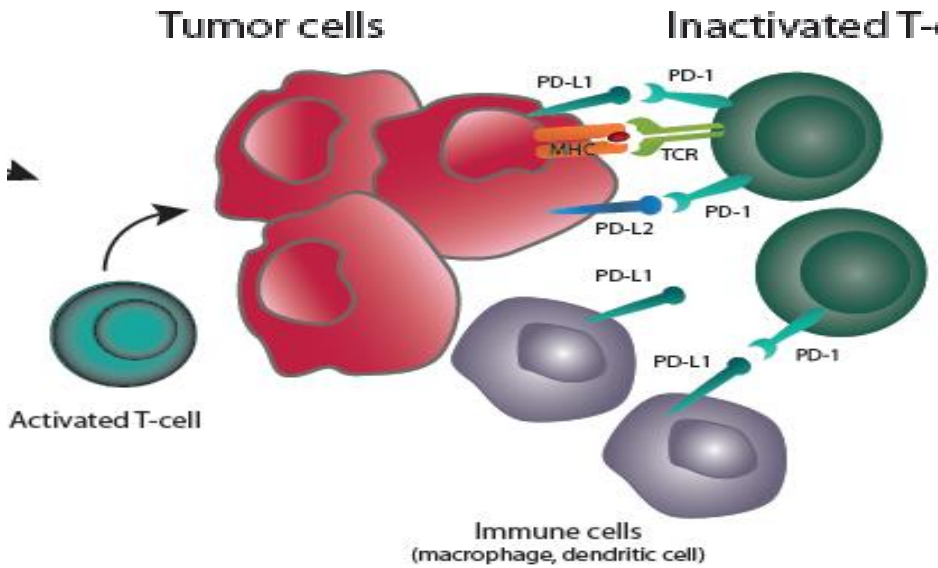
University of Pittsburgh

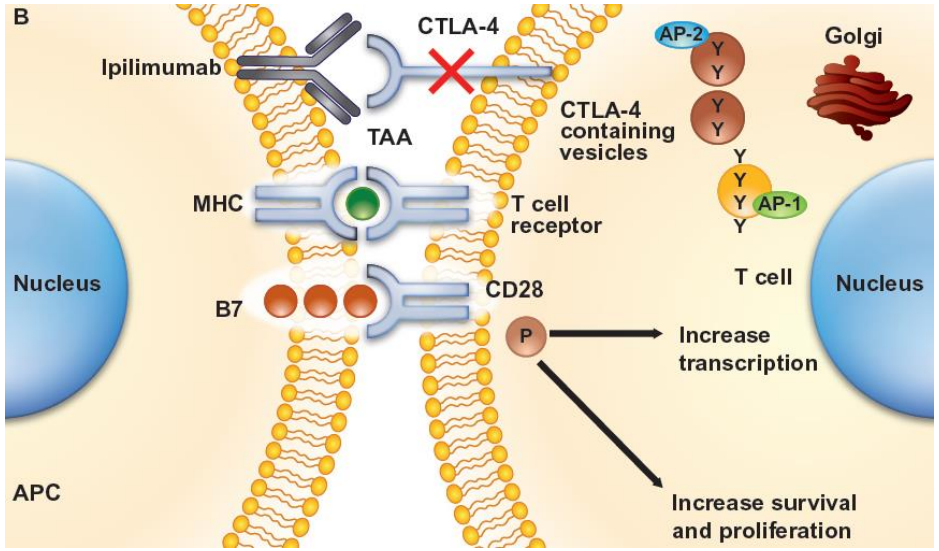
NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

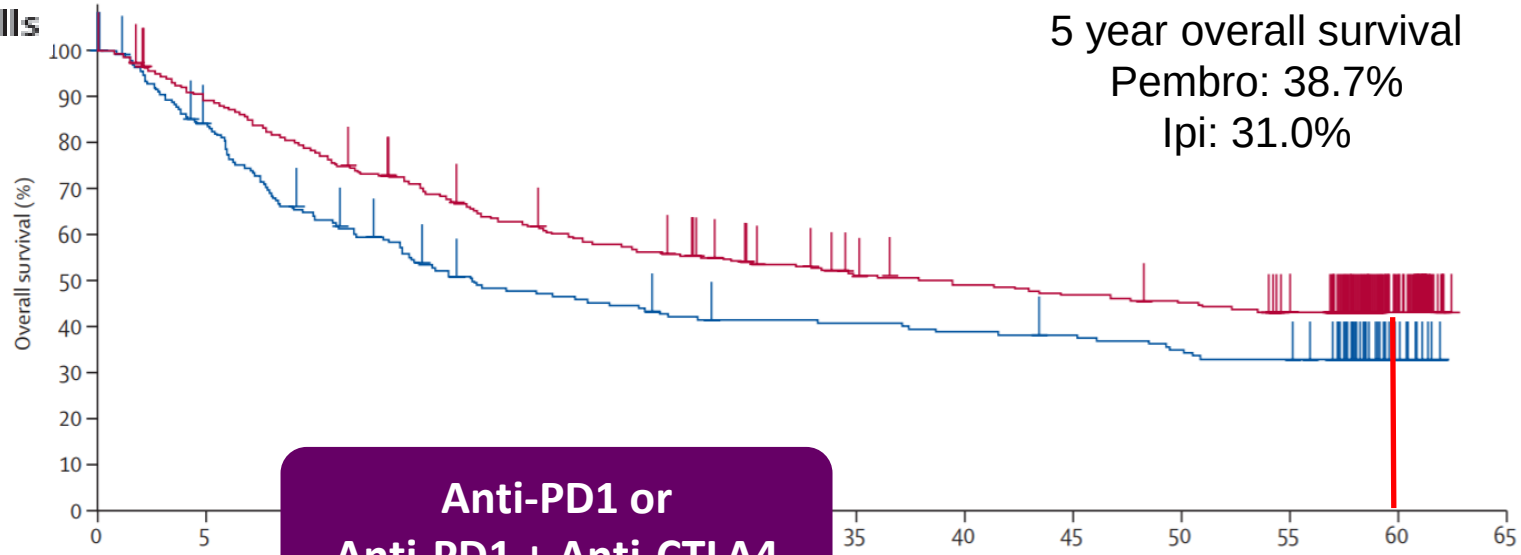
UPMC LIFE CHANGING MEDICINE

Current Melanoma Treatment Algorithm



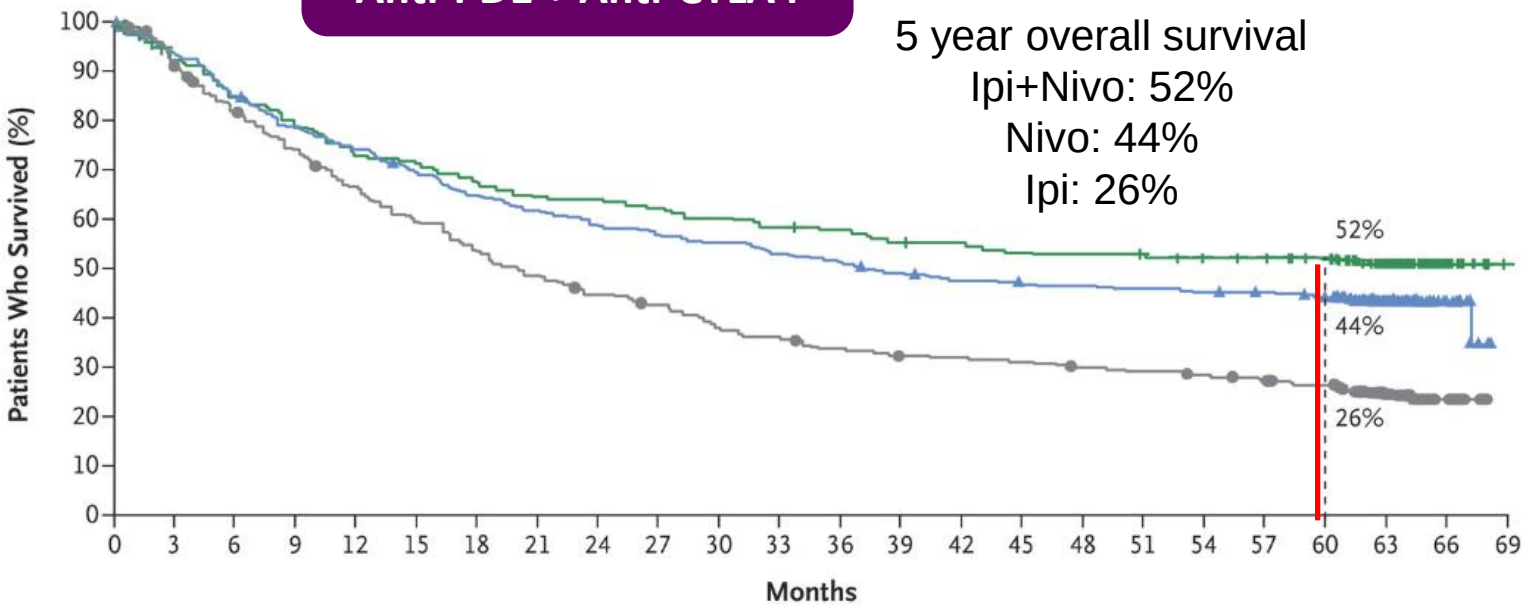






5 year overall survival
Pembro: 38.7%
Ipi: 31.0%

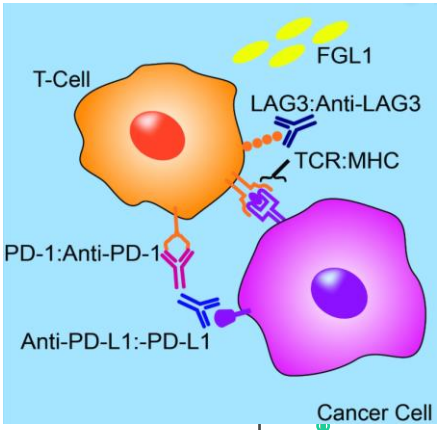
Anti-PD1 or
Anti-PD1 + Anti-CTLA4



5 year overall survival
Ipi+Nivo: 52%
Nivo: 44%
Ipi: 26%

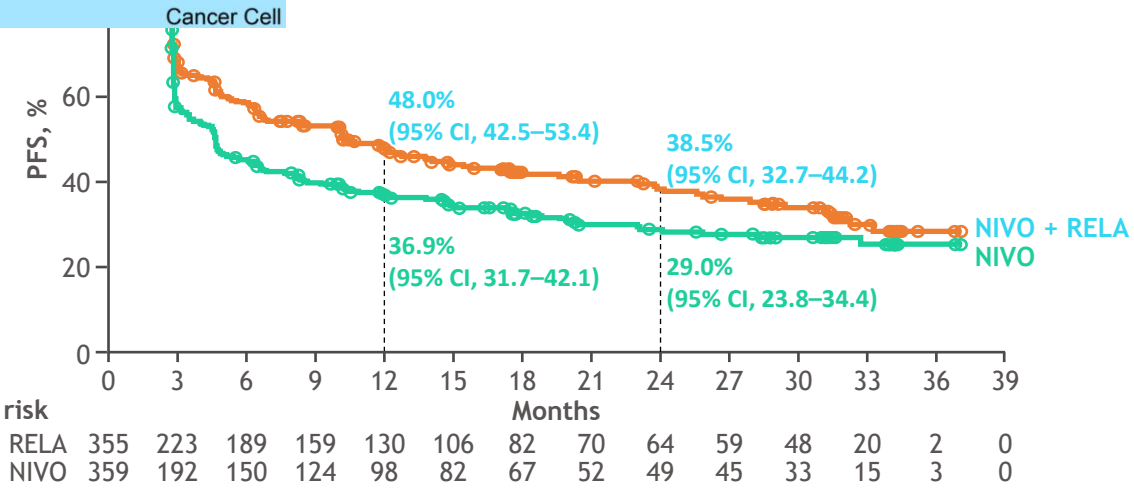
@jasonlukemd

Robert *et al*. *Lancet Onc.* 2019; Larkin *et al*. *N Engl J Med.* 2019; Luke and Hodi. *Oncologist*. 2013; Luke and Ott. *Oncotarget*. 2015



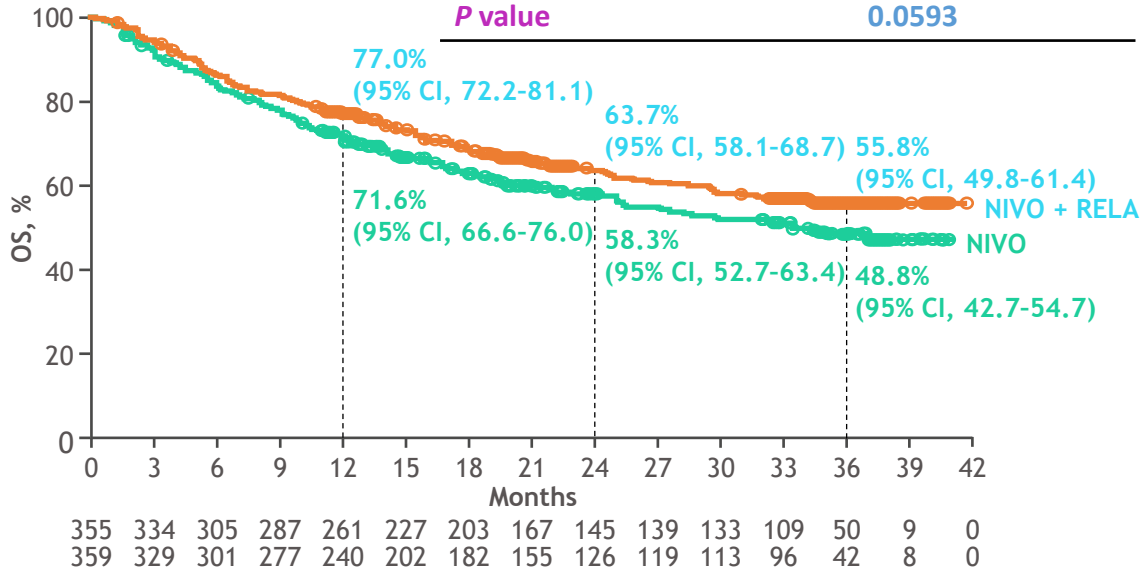
Updated PFS by BICR

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo (95% CI)	**10.22** (6.51–14.75)	**4.63** (3.48-6.44)
HR (95% CI)	0.78 (0.64–0.94)	



OS

	NIVO + RELA (n = 355)	NIVO (n = 359)
mOS, mo (95% CI)	**NR** (34.20–NR)	**34.10** (25.23–NR)
HR (95% CI)	0.80 (0.64–1.01)	
P value	0.0593	



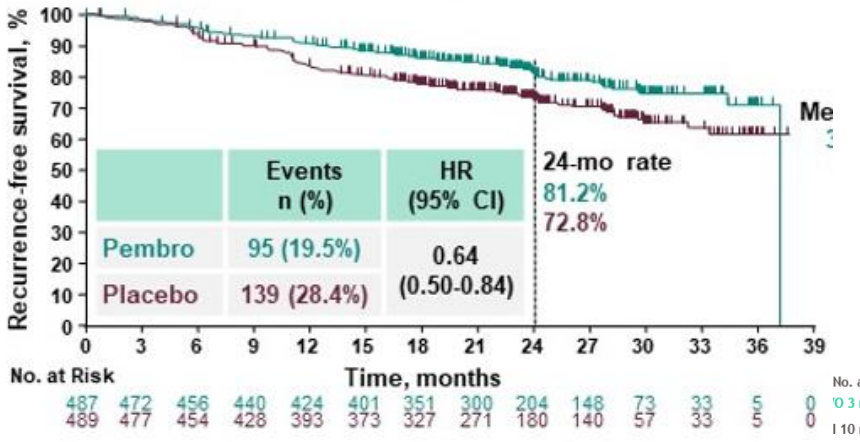
Confirmed ORR by BICR	NIVO + RELA (n = 355)	NIVO (n = 359)
ORR % (95% CI)	**43.1** (37.9-48.4)	**32.6** (27.8-37.7)

DBL date: October 28, 2021. Median follow-up: 19.3 mo

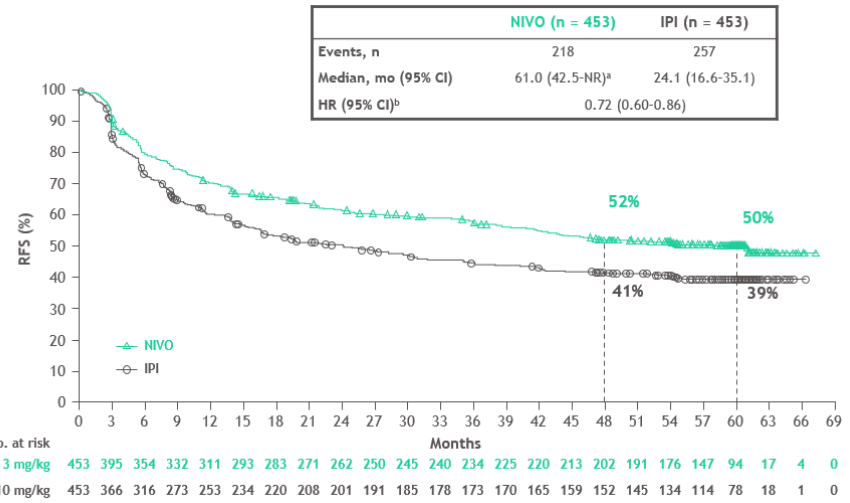
Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients; OS boundary for statistical significance was $P < 0.04302$ (2-sided) analyzed at 69% power; target HR, 0.75; ORR could not be formally tested and was descriptively analyzed. Minimum potential follow-up (time from last patient randomized to last patient last visit) was 8.7 mo.

Long GV, et al. Oral presentation at the American Society of Clinical Oncology (ASCO) 2022 March Plenary Series; March 15, 2022; Virtual. Abstract 360385.

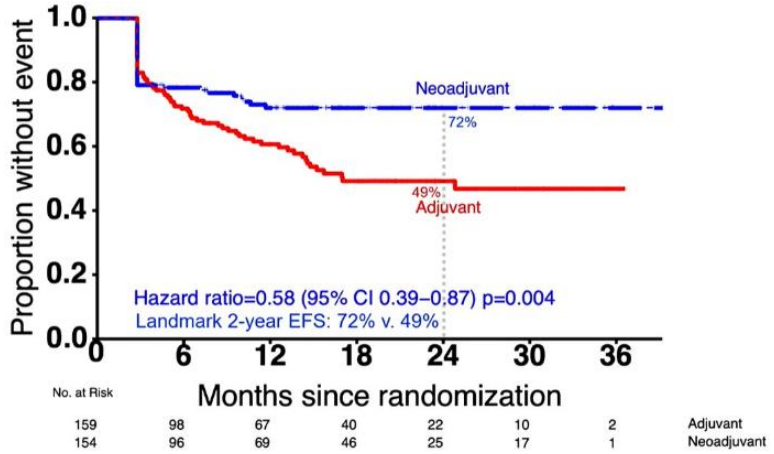
Stage IIB/C – anti-PD1



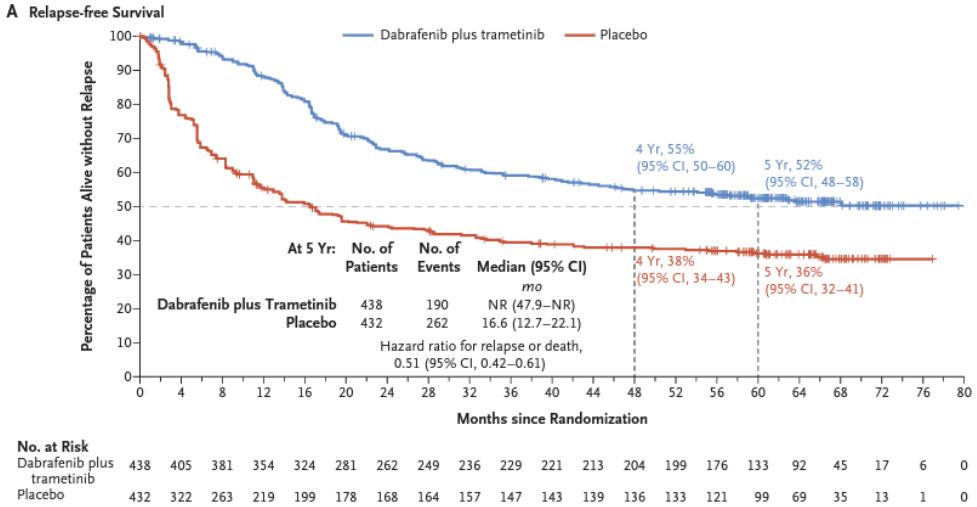
Stage III – anti-PD1



Stage IIIB/C/IV – anti-PD1



BRAF-MEK

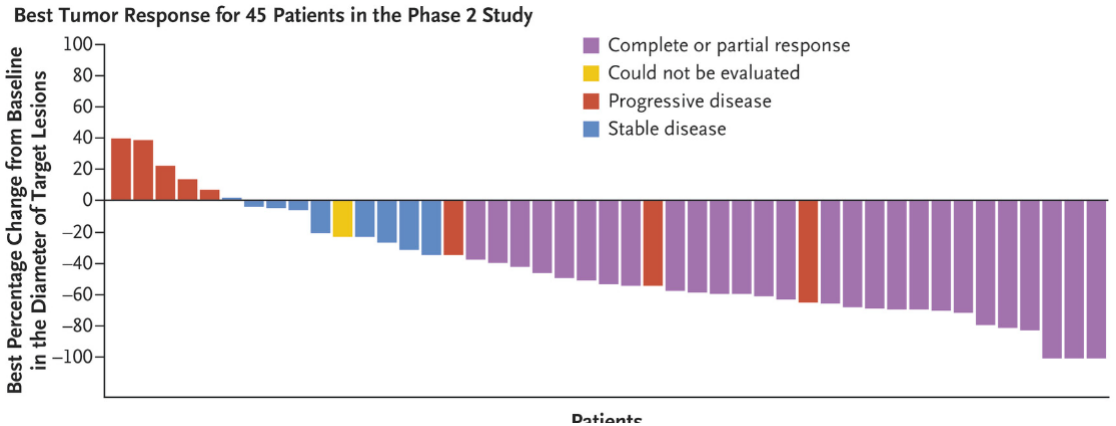


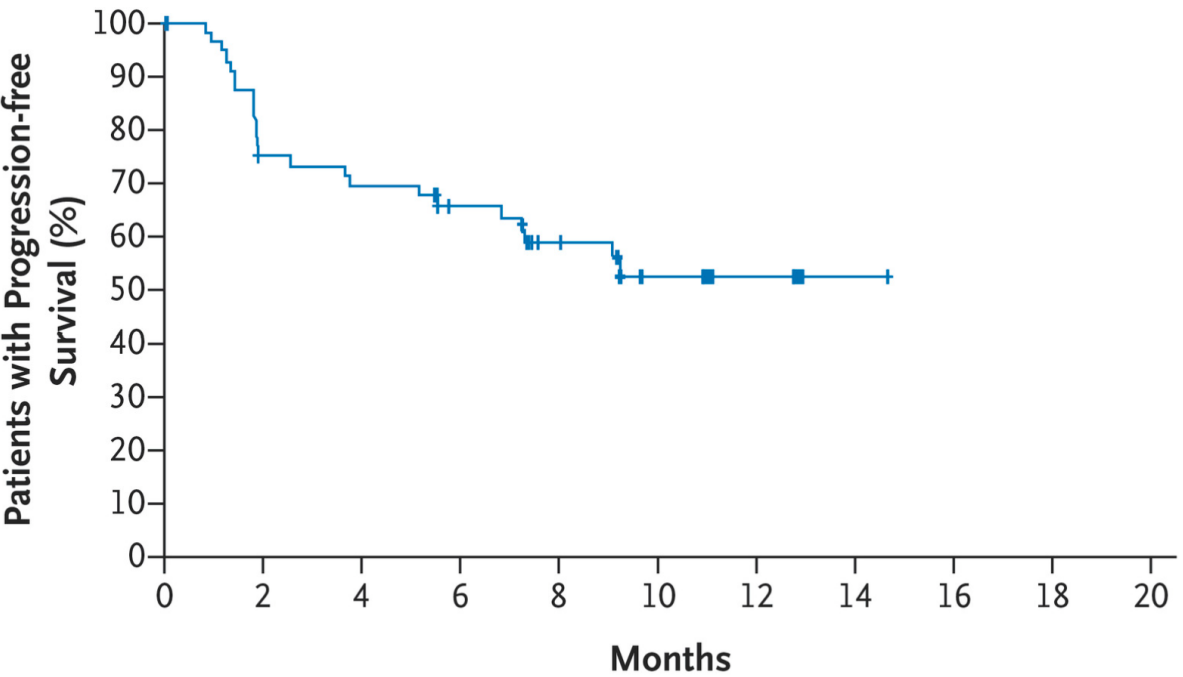
@jasonlukemd

Luke *et al. Lancet*. 2022; Weber *et al. NEJM* 2021; Long *et al. NEJM* 2021; Patel *et al. ESMO*. 2022

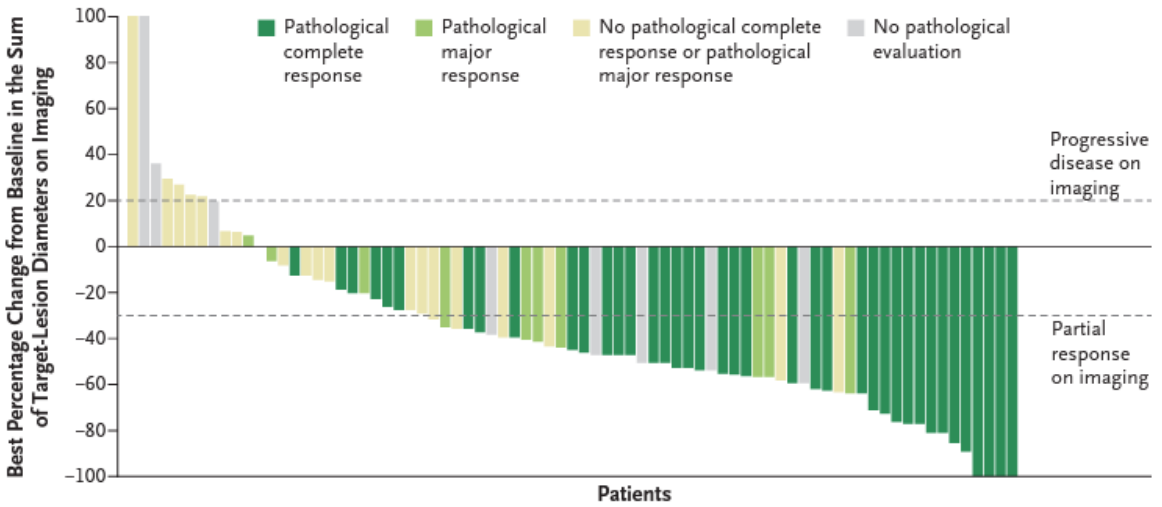
- **Patient with a 3.2 mm melanoma on the right leg undergoes resection and nodal evaluation identifying 2 nodes involved. Tumor is BRAF WT**
- **Adjuvant treatment with nivolumab is given for eight months with progression in new nodes and lung.**
- **Nivo + ipi vs Nivo + rela are considered but ipi combo is chosen.**
- **Patient has obvious new lesions within 1.5 months and rising LDH.**
- **What treatment to choose then?**

Anti-PD1 (cempilimab in locally advanced cSCC)





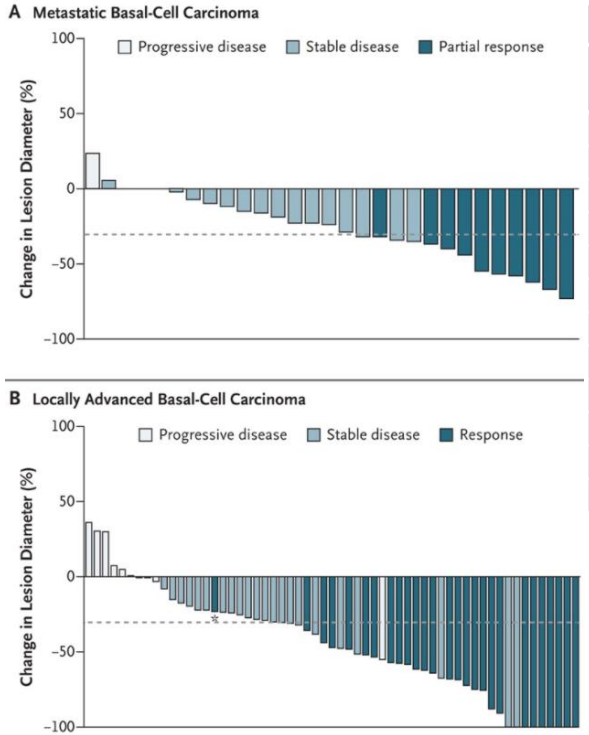
Neoadjuvant cempilimab in cSCC)



@jasonlukemd

Midgen et al. NEJM. 2018; Gross et al. NJEM. 2023

Hedgehog inhibitor efficacy and toxicity



Sonidegib Dose (daily)	200 mg (n = 79)		800 mg (n = 150)	
AEs in ≥ 20% of Patients, Any Grade, %; Grade 3/4, %[a]	Primary	12-Month	Primary	12-Month
All AEs	95; 30	98; 38	100; 56	100; 59
Muscle spasms	49; 3	52; 3	67; 5	69; 5
Alopecia	43; 1	49; 0	55; 0	57; 0
Dysgeusia	38; 0	41; 0	59; 1	60; 0
Nausea	33; 1	35; 1	45; 3	47; 3
CK increased	29; 6	30; 6	37; 13	37; 13
Fatigue	29; 0	29; 0	36; 2	36; 2
Weight decreased	27; 1	29; 3	38; 5	42; 6
Diarrhea	24; 0	30; 1	22; 0	23; 0
Appetite decreased	19; 0	23; 0	31; 4	32; 4
Myalgia	19; 0	19; 0	26; 2	26; 2
Vomiting	6; 1	8; 1	26; 1	27; 1

"Chronic grade 1-2 toxicity is worse for the patient than an episode of grade 3-4"
Len Saltz, MD - MSKCC

Anti-PD1 efficacy

	Patients (n=84)
Objective response	26 (31%; 21–42)*
Best overall response	
Complete response	5 (6%)
Partial response	21 (25%)
Stable disease	41 (49%)
Progressive disease	9 (11%)
Not evaluable†	8 (10%)
Disease control	67 (80%; 70–88)
Durable disease control	50 (60%; 48–70)
Median time to response, months‡	4·3 (4·2–7·2)
Observed duration of response‡	
Range, months	2–21
≥6 months	19 (79%)
≥12 months	11 (46%)
Kaplan-Meier estimation of duration response‡	
Median	Not reached
Remained in response at 6 months	91% (68–98)
Remained in response at 12 months	85% (61–95)

Sekulic *et al*. *N Engl J Med*. 2012; Midgen *et al*. *Lancet Oncology*. 2015

- **Patient with history of multiple early stage non-melanoma skin cancers develops a bleeding ulcer on the scalp.**
- **Moh's procedure removes the lesion but within 4 months the skin graft erodes and the ulcer returns**
- **A second resection attempt is considered but aborted when margins are positive**
- **Anti-PD1 with cemiplimab is initiated but the lesion continue to grow.**
- **What treatment to consider?**

- **In melanoma, unmet needs remains after progression on anti-PD1**
  - **KB707 has high upside potential for combinations with anti-PD1 in earlier lines of therapy given arming with IL2 and IL12**
- **Therapeutic landscape open in non-melanoma skin cancers**
  - **Anti-PD1 is SOC but 50% do not respond in cSCC**
  - **FDA has greenlighted development of therapeutics in BCC despite activity of HHi due to toxicity of those agents**
- **KB707 is well positioned to overcome previous cytokine therapy challenges by leveraging unique molecular biology and field leading cytokine combinations**

Q&A

Panelists

Jason J. Luke, MD, FACP

Samuel Broder, MD

Krish Krishnan

Chairman and CEO

Suma Krishnan

President, Research & Development

David Chien, MD

Senior Vice President, Clinical Development – Oncology

Trevor Parry, PhD

Vice President, Research and Scientific Affairs

Krystal