UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934
Date of Report (Date of earliest event reported): July 26, 2023

KRYSTAL BIOTECH, INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-38210**	**82-1080209**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification Number)**

2100 Wharton Street, Suite 701
Pittsburgh, Pennsylvania 15203
(Address of principal executive offices, including Zip Code)
Registrant's telephone number, including area code: (412) 586-5830

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock	**KRYS**	**Nasdaq Global Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On July 26, 2023, Krystal Biotech, Inc. (the "Company") announced it has expanded its R&D pipeline to oncology and that the U.S. Food and Drug Administration has accepted its Investigational New Drug application of its lead oncology drug candidate, KB707 for the treatment of locally advanced or metastatic solid tumor malignancies. In addition, the Company will host an investor conference call at 8:00 a.m. ET on July 27, 2023, to discuss the KB707 program. For purposes of the call, the Company will provide an investor slide presentation (the "Investor Slide Presentation"), which is available on the "Investors" section of the Company's website at www.krystalbio.com. Copies of the press release and the Investor Slide Presentation are attached hereto as Exhibit 99.1 and Exhibit 99.2, respectively, and are incorporated by reference herein. For those unable to listen to the live conference call, a replay will be available on the "Investors" section of the Company's website at www.krystalbio.com.

The information contained in Item 7.01 of this Current Report on Form 8-K, including Exhibit 99.1 and Exhibit 99.2, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that Section, or incorporated by reference in any filing with the Securities and Exchange Commission by the Company under the Exchange Act or the Securities Act of 1933, as amended, whether made before or after the date hereof, regardless of any general incorporation language in such filing, except as shall be expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Press Release, dated July 26,2023.
99.2	Investor Slide Presentation, dated July 2023.
104	Cover Page Interactive Data file (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: July 26, 2023

KRYSTAL BIOTECH, INC.

By: /s/ Krish S. Krishnan
Name: Krish S. Krishnan
Title: Chairman and Chief Executive Officer

Krystal Biotech Announces Pipeline Expansion into Oncology and FDA Acceptance of IND Application for Lead Oncology Candidate KB707

PITTSBURGH, July 26, 2023 (GLOBE NEWSWIRE) – Krystal Biotech, Inc. (the "Company") (NASDAQ: KRYS), a commercial-stage biotechnology company focused on the discovery, development and commercialization of genetic medicines to treat diseases with high unmet medical needs, announced today that it has expanded its R&D pipeline to oncology and that the US Food and Drug Administration (FDA) has accepted its Investigational New Drug (IND) application of its lead oncology drug candidate KB707 for the treatment of locally advanced or metastatic solid tumor malignancies. The Company will host an investor conference call and webcast, Thursday, July 27, 2023, at 8:00 am ET, to discuss the KB707 program. To join the investor conference call, please see the instructions below. The presentation for the investor conference call is attached to the Company's Form 8-K.

"The KB707 program leverages our learnings and clinical experience in two tissue areas, the skin and the lung, and underscores the broader potential of our HSV-1 platform to deliver all types of exogenous genetic material and improve outcomes for patients with debilitating diseases," said Krish S. Krishnan, Chairman and CEO of Krystal Biotech.

KB707 is a modified HSV-1 vector designed to deliver genes encoding both human IL-12 and IL-2 to the tumor microenvironment and promote systemic immune-mediated tumor clearance. Two formulations of KB707 are in development, a solution formulation for transcutaneous injection and an inhaled (nebulized) formulation for lung delivery.

"We believe KB707 is a unique and highly differentiated drug candidate with the potential to unlock the capabilities of cytokine-based immunotherapy," said Suma Krishnan, President of Research & Development at Krystal Biotech. "By enabling localized and sustained cytokine expression within a treated tumor, KB707 has the potential to maximize therapeutic efficacy while avoiding the tolerability challenges of systemic cytokine treatments."

The FDA has accepted the Company's IND to evaluate intratumoral KB707 in patients with solid tumors accessible by transcutaneous injection, and the Company expects to initiate a Phase 1 study in the second half of 2023. The Company is planning to file an amendment to the KB707 IND in the second half of 2023 to evaluate inhaled KB707 in a clinical trial in the first half of 2024.

Interleukin-2 (IL-2) and interleukin-12 (IL-12) are secreted cytokines with complementary functions promoting cell-mediated immunity in humans. Both IL-2 and IL-12 have been shown to elicit anti-tumor immune responses in preclinical or clinical models and have been extensively studied for their potential in cancer immunotherapy. Despite promising signs of efficacy, it has proven difficult to effectively harness IL-2 and IL-12 for therapeutic benefit, as systemic administration is often poorly tolerated, and their inherently short half-lives necessitate high dose levels and extremely frequent dose intervals. KB707 leverages the Company's modified HSV-1 vector – and its ability to efficiently deliver a durable DNA payload without active replication and minimal cytotoxicity – to drive local and sustained cytokine expression within the tumor microenvironment and maximize the therapeutic window and benefit of IL-2 and IL-12.

"There remains an urgent unmet need for new therapies in cutaneous oncology, including for patients that do not respond to current first-line options and for the many who eventually progress on available therapy," said Jason Luke, MD, Associate Professor of Medicine in the Division of Hematology/Oncology and Director of the Cancer Immunotherapeutic Center within UPMC Hillman Cancer Center Immunology and Immunotherapy Program in Pittsburgh, PA. "As the lead investigator on multiple practice changing immunotherapy trials, I have seen first-hand the benefits that can be realized through effective immune

modulation and am excited about the potential of Krystal's approach for localized, sustained cytokine delivery."

In preclinical studies, KB707 has been shown to efficiently transduce mammalian cells *in vitro* leading to the secretion of bioactive IL-2 and IL-12 and can drive localized, durable cytokine expression in mouse skin after intradermal injection. Furthermore, in stringent checkpoint inhibitor refractory 'cold' syngeneic mouse models, HSV-1 vector based delivery of murine equivalent *IL2* and *IL12* elicited robust antitumor responses and survival benefits, including via intratumoral injection in single and dual flank B16F10 melanoma models, as well as via intratracheal delivery in a metastatic K7M2 osteosarcoma model, with evidence of protection from tumor rechallenge in both models suggestive of prolonged adaptive immunity.

The intratumoral KB707 Phase 1/Opal 1 study is an open-label, multi-center, monotherapy, dose escalation and expansion study, enrolling patients with locally advanced or metastatic solid tumors, who relapsed or are refractory to standard of care, with at least one measurable and injectable tumor accessible by transcutaneous route. The primary objective of the study is to evaluate safety and tolerability of KB707. Efficacy will also be assessed by multiple measures including overall response rate, progression free survival, and overall survival, and the immune effects of KB707 monotherapy will be assessed in tumor tissue, lymph nodes, and blood.

Investor Conference Call, Webcast and Presentation Information

The Company will host an investor conference call and webcast, Thursday, July 27, at 8:00 am ET, to discuss the KB707 program.

The conference call will include management's overview of the Company's expanded pipeline and research and development focus in oncology and discuss potential target indications as well as a summary of preclinical data and clinical development plans. External speakers will include Samuel Broder, M.D., former Director of the National Cancer Institute where he oversaw the development of numerous anti-cancer therapeutic agents, and Jason Luke, M.D., F.A.C.P., Associate Professor of Medicine in the Division of Hematology/Oncology and Director of the Cancer Immunotherapeutic Center within UPMC Hillman Cancer Center Immunology and Immunotherapy Program in Pittsburgh, PA.

To register and join the conference call, please go to: https://www.netroadshow.com/events/login?show=6a3175e6&confId=53637

For those unable to listen to the live conference call, a replay will be available on the Investor's section of the Company's website at www.krystalbio.com.

About Krystal Biotech, Inc.

Krystal Biotech, Inc. (NASDAQ: KRYS) is a commercial-stage biotechnology company focused on the discovery, development and commercialization of genetic medicines to treat diseases with high unmet medical needs. VYJUVEK™ is the Company's first commercial product, the first-ever redosable gene therapy, and the only medicine approved by the FDA for the treatment of dystrophic epidermolysis bullosa. The Company is rapidly advancing a robust preclinical and clinical pipeline of investigational genetic medicines in respiratory, oncology, dermatology, ophthalmology, and aesthetics. Krystal Biotech is headquartered in Pittsburgh, Pennsylvania. For more information, please visit http://www.krystalbio.com, and follow @KrystalBiotech on LinkedIn and Twitter.

Forward Looking Statements

Any statements in this press release about future expectations, plans and prospects for Krystal Biotech, Inc., including statements about the potential of the Company's proprietary HSV-1 platform, the Company's beliefs about the clinical utility of KB707 and its potential therapeutic capabilities, the Company expectations regarding the timing of a Phase 1 study of the transcutaneous injection formulation of KB707, the Company's plans to file an amendment to the KB707 IND in the second half of 2023 to evaluate inhaled KB707 in a clinical trial in the first half of 2024, and other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "likely," "will," "would," "could," "should," "continue," and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: uncertainties associated with regulatory review of clinical trials and applications for marketing approvals, the availability or commercial potential of product candidates including KB707, the sufficiency of cash resources and need for additional financing and such other important factors as are set forth under the caption "Risk Factors" in the Company's annual and quarterly reports on file with the U.S. Securities and Exchange Commission. In addition, the forward-looking statements included in this press release represent the Company's views as of the date of this release. The Company anticipates that subsequent events and developments will cause its views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date of this release.

Disclosures

Dr. Jason Luke is a consultant for Krystal Biotech, Inc.

CONTACT
Investors and Media:
Meg Dodge
Krystal Biotech
mdodge@krystalbio.com

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.

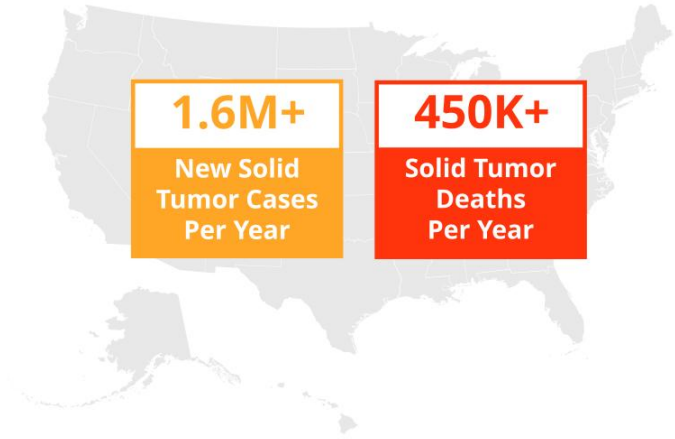
ARCI, autosomal recessive congenital ichthyosis; DEB, dystrophic epidermolysis bullosa; GLP, good laboratory practices; NHP, non human primates

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]



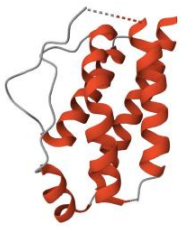
1. NCI SEER. 2023; https://seer.cancer.gov/statfacts/html/common.html [accessed July 20, 2023], combined estimates for incident cases and deaths from cancers of the anus, bladder, bone and joint, brain and nervous system, breast, cervix uteri, colon and rectum, eosophagus, kidney and renal pelvis, larynx, 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

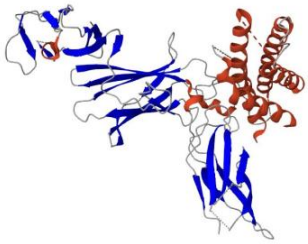
Cytokines with synergistic functions and therapeutic potential

IL-2



+

IL-12



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

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*

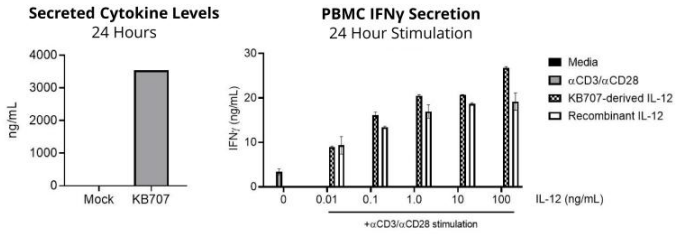
Vector-derived, secreted IL-12 and IL-2 equivalently bioactive to commercial recombinant proteins

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

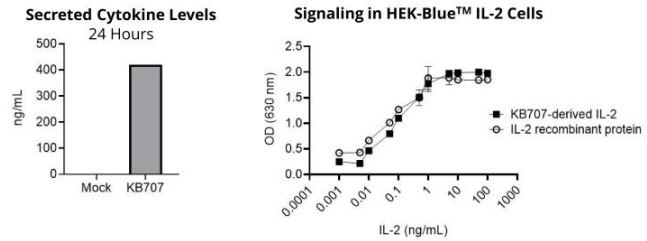
- IL-2 and IL-12 detected in cell culture supernatants 24 hours after transduction at MOI of 1
  - IL-12: Over 3,000 ng / mL
  - IL-2: Over 400 ng / mL
- KB707-derived IL-12 shown to elicit comparable IFNγ response from PBMCs as commercially available recombinant IL-12 after 24-hour *in vitro* co-stimulation 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



IL-2



Krystal Biotech, Data on File.

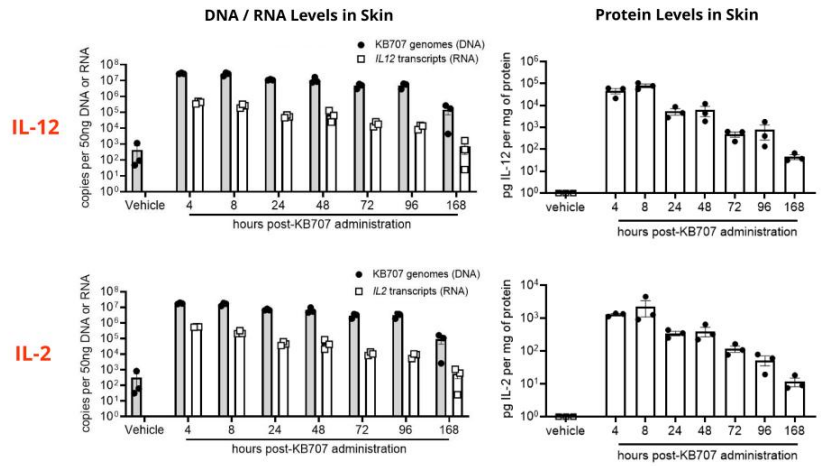
CD3, cluster of differentiation 3; CD8, cluster of differentiation 8; HEK, human embryonic kidney; IFNγ, interferon gamma; IL-12, interleukin-12; IL-2, interleukin-2; MOI, multiplicity of infection; PBMC, peripheral blood mononuclear cell; SEAP, secreted embryonic alkaline phosphatase

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



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

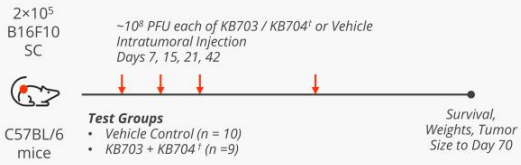
Intratumoral IL-12 and IL-2 Effective in Cold Syngeneic Mouse Tumor Model

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



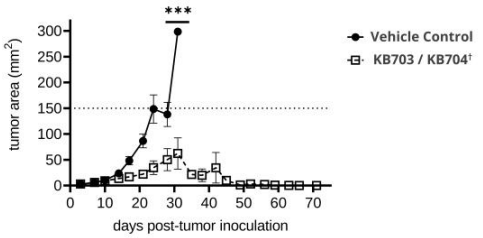
Krystal Biotech, Data on File.

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

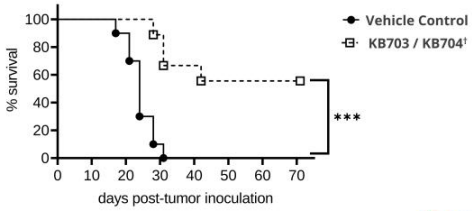
IL-12, interleukin-12; IL-2, interleukin-2; PFU, plaque forming unit; SC, subcutaneous

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

Injected Tumor Size



Survival



***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

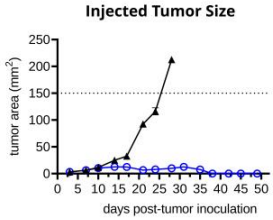
~10^8 PFU each of KB703 / KB704† or Vehicle Intratumoral Injection First Flank Only Days 7, 15, 21

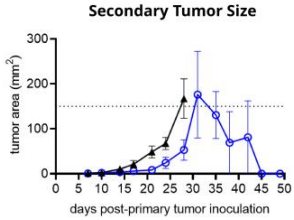
Day 4
1×10^5 B16F10
Second Flank SC

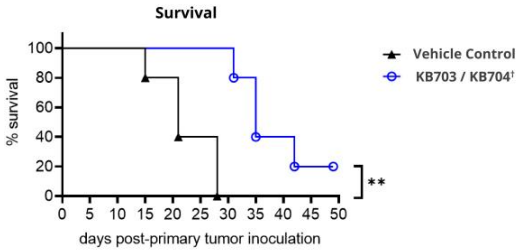
C57BL/6 Mice

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

Survival, Weights, Tumor Size to Day 49







Krystal Biotech, Data on File.

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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

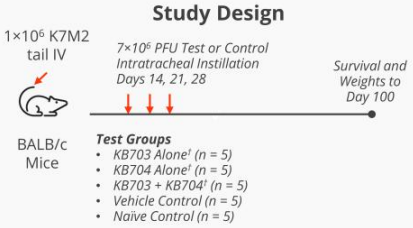
Lung Delivery Effective in Metastatic Osteosarcoma Model

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

Metastatic K7M2 Osteosarcoma Model

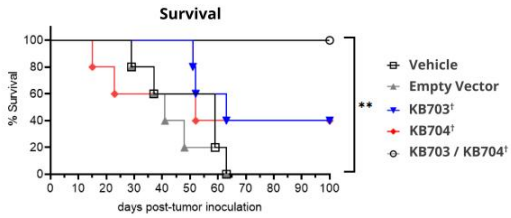
- K7M2 is an osteoblast cell line derived from bone of mouse with spontaneous osteosarcoma[1]
- Considered highly aggressive with pulmonary metastatic rate of over 90% in mice[1]
- Previously shown to be non-responsive to PD-1/PD-L1 targeting therapies, partial benefit from combo therapies[2]

Study Design

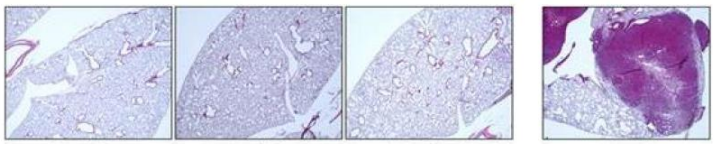


Test Groups

- *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

1×10^6 K7M2 tail IV

7×10^6 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

1×10^6 K7M2 tail IV

Day 75

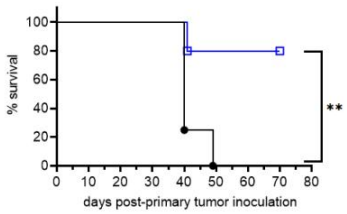
No additional treatment

Survival and Weights to Day 150

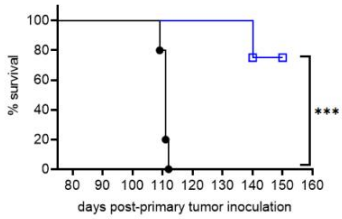
BALB/c Mice

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

Survival
After Initial Challenge



Survival
After Rechallenge



Krystal Biotech, Data on File.

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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

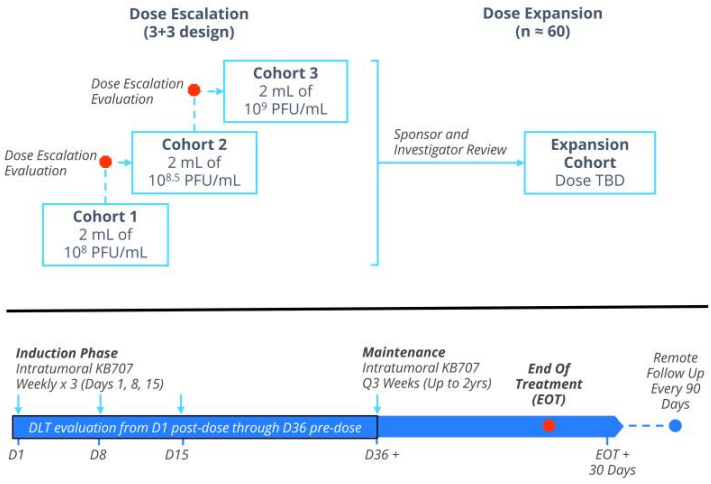
Open-label study to assess safety, tolerability, and preliminary efficacy

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

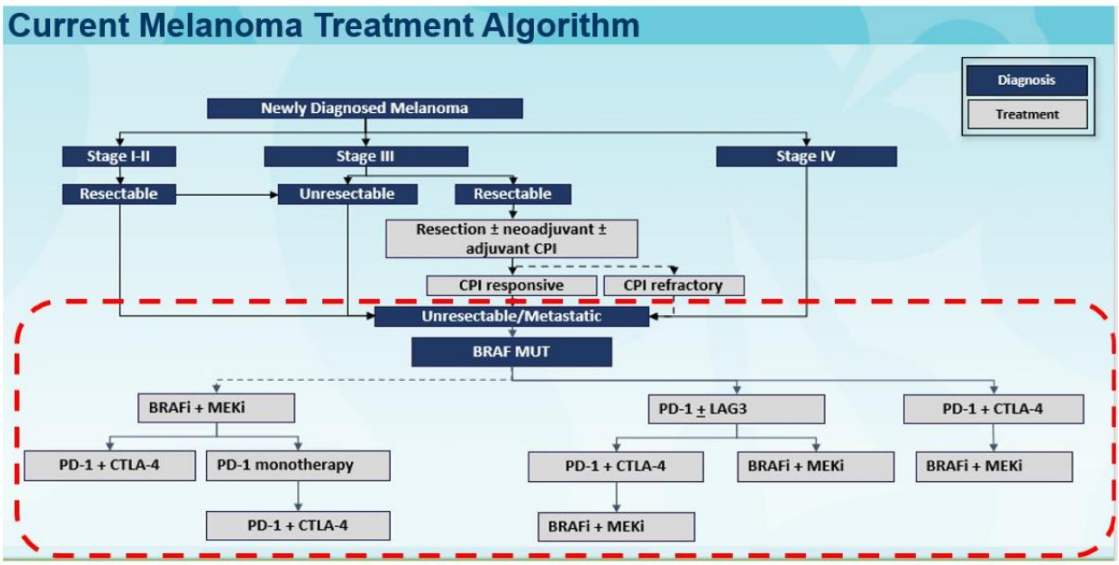
Cutaneous oncology landscape for refractory disease

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

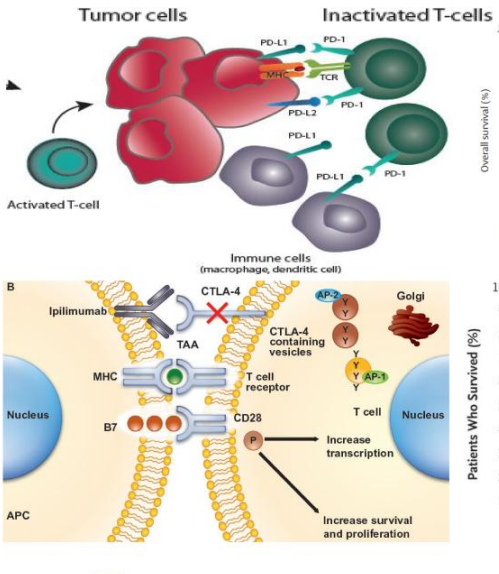
University of Pittsburgh

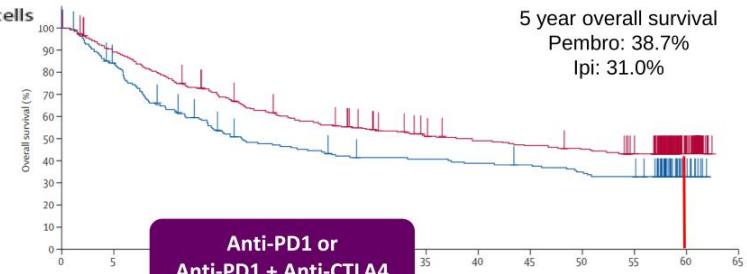
NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

UPMC LIFE CHANGING MEDICINE

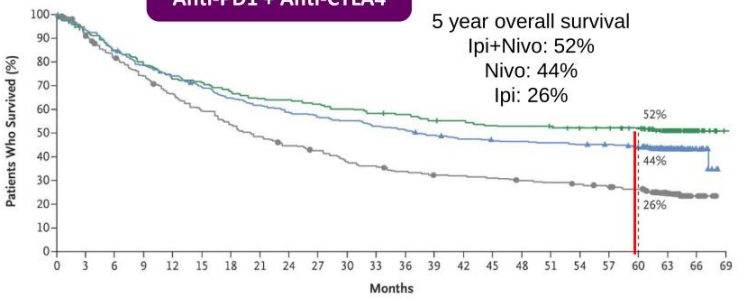


@jasonlukemd



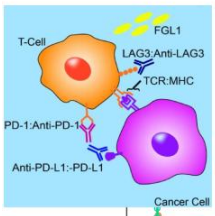


Anti-PD1 or Anti-PD1 + Anti-CTLA4



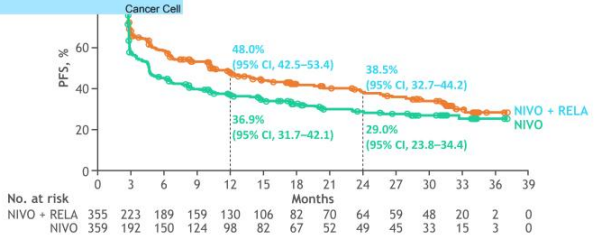
@jasonlukemd

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)	

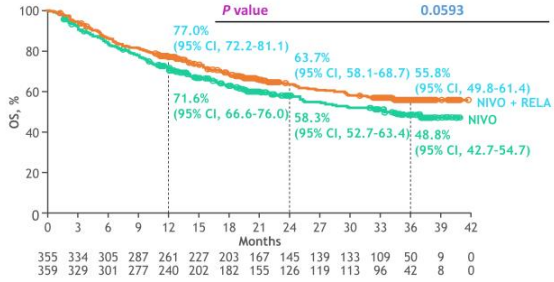


No. at risk

NIVO + RELA	355	223	189	159	130	106	82	70	64	59	48	20	2	0
NIVO	359	192	150	124	98	82	67	52	49	45	33	15	3	0

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	



	355	334	305	287	261	227	203	167	145	139	133	109	50	9	0
	359	329	301	277	240	202	182	155	126	119	113	96	42	8	0

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

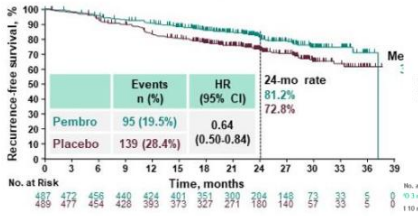
Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients; OS boundary for statistical significance 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.

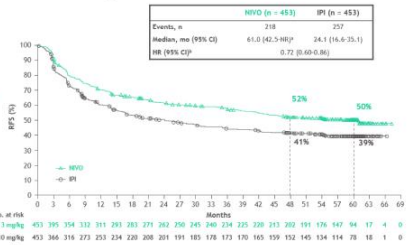
@jasonlukemd

Presented by Hussain Tawbi, MDACC - ASCO 2022

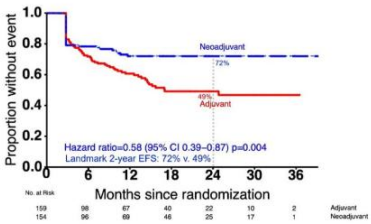
Stage IIB/C – anti-PD1



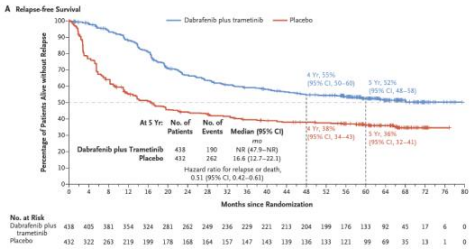
Stage III – anti-PD1



Stage IIIB/C/IV – anti-PD1



BRAF-MEK

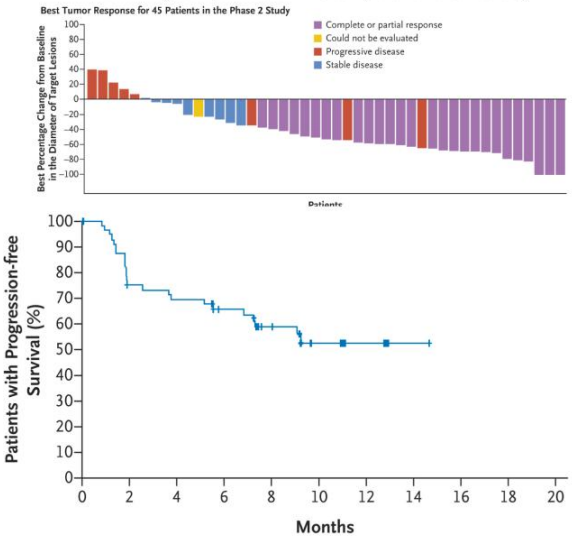


@jasonlukemd

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

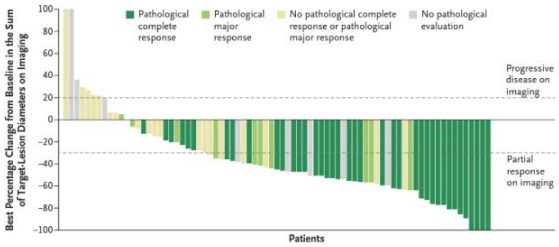
- **Patient with a 3.2 mm melanoma on the right leg undergoes resection and nodal evaluation identifying 2 nodes involved. Tumor is BRAF WT**
- **Adjuvant treatment with nivolumab is given for eight months with progression in new nodes and lung.**
- **Nivo + ipi vs Nivo + rela are considered but ipi 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)



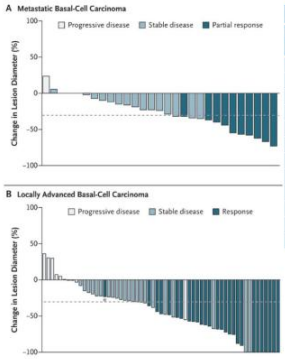
@jasonlukemd

Neoadjuvant cempilimab in cSCC)



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)

@jasonlukemd

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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