Novartis Investor Relations

Novartis Oncology Update

Post-ASCO investor presentation
June 8, 2021

NOVARTIS | Reimagining Medicine

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Agenda

Novartis Oncology overview

ASCO 2021 readouts across platforms

Radioligand Therapy platform

Primary analysis of ^{177}Lu-PSMA-617 in mCRPC

Targeted Therapy platform

TNO155 program update

Q&A

Participants

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Global Head of Oncology Development, GDD

Samir Shah
Global Head Investor Relations

Sidonie Golombowski-Daffner
President, AAA

Susanne Schaffert

President of Novartis Oncology

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Leadership in Oncology based on innovation power and global scale

Past 5 years

4%
Net sales CAGR

6
First-in-class launches

2020

14.7bn
Oncology net sales (USD)

7
In-market blockbusters

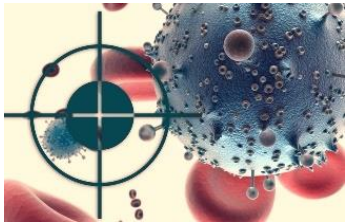
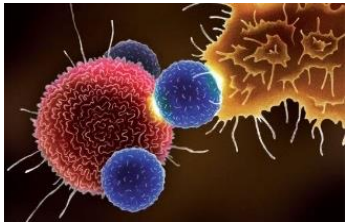
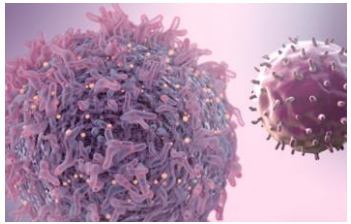
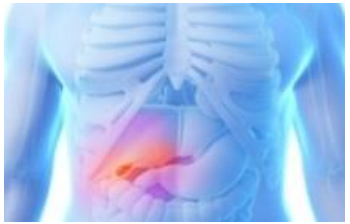
1.2m
Patients reached

2021 and beyond

2021 filings:	^{177}Lu-PSMA-617 Tislelizumab Asciminib	
2021 readouts:	Canakinumab Sabatolimab	
Key LCM programs:	Kisqali® adjuvant Asciminib 1L CML ^{177}Lu-PSMA-617 earlier lines of PC	
Next wave of priority assets:	TNO155 (SHP2) JDQ443 (KRAS) LXH254 (MAPK) NIS793 (TGF-b)	LAG525 (LAG-3) YTB323 (CD-19)[1] PHE885 (BCMA)[1]

1. Cell therapies using our Activated Rapid Manufacturing (ARM) platform

Uniquely positioned in four distinct therapeutic platforms, with potential to address significant unmet needs

	Targeted Therapy (TT)	Differentiated Immunotherapy (IO)	Cell & Gene (C&G)	Radioligand Therapy (RLT)
				
Key commercial assets	PROMACTA (eltrombopag) 25mg, 50mg, 75mg tablets; JAKAVI ruxolitinib; KISQALI ribociclib; Tafinlar (dabrafenib) + Mekinist (trametinib); PIQRAY; ADAKVEO crizanlizumab-tmca FOR IV INFUSION - 10 mg/mL; TABRECTA (capmatinib) tablets		KYMRIAH (tisagenlecleucel) Suspension for IV infusion	Advanced Accelerator Applications LUTATHERA (lutetium Lu 177 dotatate) injection, for intravenous use
Select pipeline assets[1] and opportunities	**MAPK** LXH254, LTT462 **STAMP** Asciminib **SHP2** TNO155 **KRAS** JDQ443	**PD-1** Tislelizumab **IL-1b** Canakinumab **TIM3** Sabatolimab **TGF-b** NIS793 **LAG-3** LAG525	**CAR-T CD-19** Kymriah **CAR-T CD-19** YTBB323[2] **CAR-T BCMA** PHE885[2]	**^{177}Lu-PSMA-617** **NeoB** **^{177}Lu-PSMA-R2** **Integrin** **FAPi**

Projects included are those with planned filings in US and/or EU. 1. All select pipeline assets are either investigational or being studied for (a) new use(s). Efficacy and safety have not been established. There is no guarantee that they will become commercially available for the use(s) under investigation. 2. Cell therapies using our Activated Rapid Manufacturing (ARM) platform

Leading scientific presence[1] at ASCO 2021

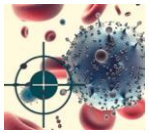
2021 ASCO® ANNUAL MEETING

71
Abstracts accepted

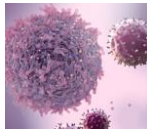
22
Novartis brands/ compounds with data being presented

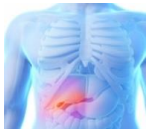
9
Oral presentations

Presented important data from each platform


Targeted Therapy

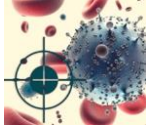

Differentiated Immunotherapy


Cell & Gene


Radioligand Therapy

1. Includes Novartis/partner sponsored, excludes IITs and independent

Building on our leadership in targeted therapy with a robust pipeline across tumor types


Targeted Therapy

Platform overview

Rich portfolio with 7 in-market blockbusters and 3 recent launches

Promising pipeline of combination-ready MoAs to fuel growth in the short- to mid-term

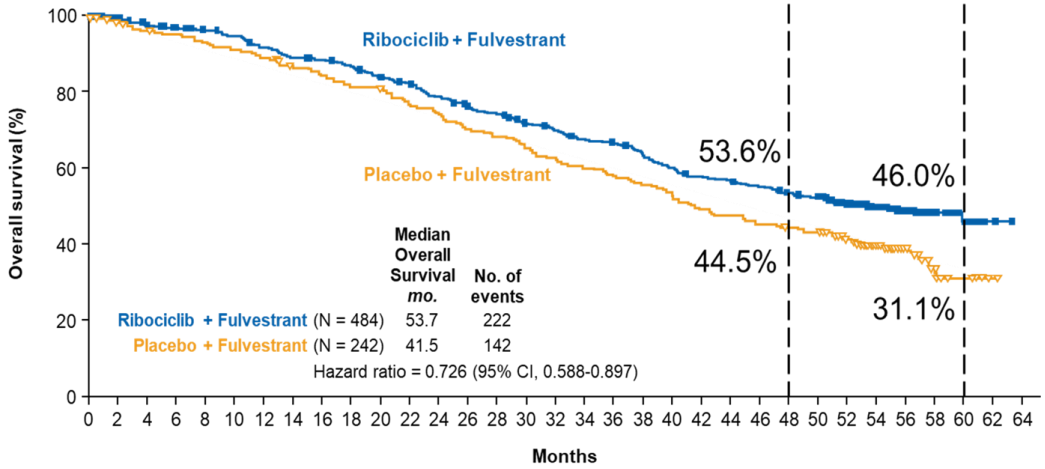
Key ASCO presentations include updated MONALEESA-3 OS data and first-in-human TNO155 data

Selected pipeline opportunities

Kisqali®	NATALEE Ph3 in adjuvant BC readout expected 2022
Asciminib	US/EU 3L CML submission expected H1 2021, 1L study starting H2 2021
LXH254	Ph1 combo in melanoma ongoing; Ph3 combo in planning
TNO155	Multiple combos across solid tumors ongoing & in planning
JDQ443	Ph1 combo ongoing; multiple Ph3 combos in NSCLC in planning

Kisqali®: MONALEESA-3 OS Update

2021 ASCO ANNUAL MEETING



Kisqali® continues to show prolonged and consistent OS benefit with a **median OS of ~4.5 years (ITT)**

Kisqali® demonstrated the **longest OS in post-menopausal patients** compared to other CDK4/6i and is the only CDK4/6i with data in 1L with fulvestrant

Advancing in immunotherapy with a strong PD-1 backbone for combination therapy

Differentiated Immunotherapy

Platform overview

Multiple assets, including 3 in late-stage development, with multi-blockbuster potential

Evaluating and prioritizing potential tislelizumab combinations across all Novartis Oncology platforms

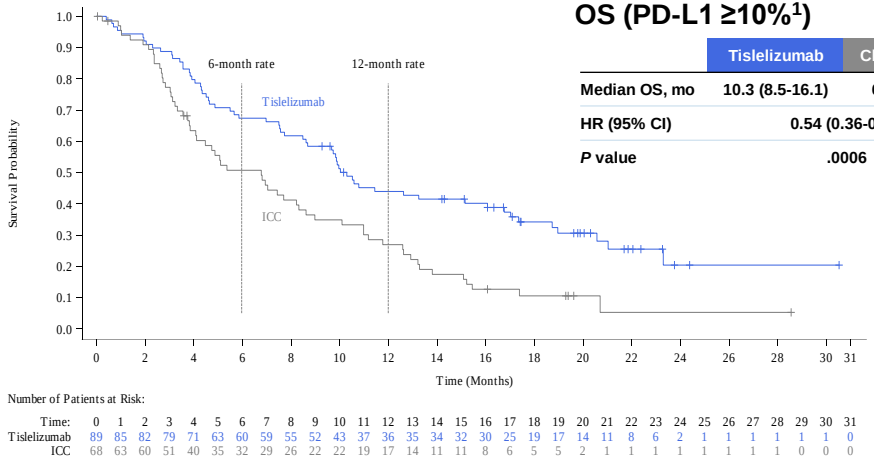
Key ASCO presentations include RATIONALE-302 in ESCC and -303 in NSCLC, and Ph1 data on NIS793

Selected pipeline opportunities

Tislelizumab	Submission in 2L NSCLC & 2L ESCC in H2 2021; multiple combos across solid tumors in planning
Canakinumab	CANOPY-1 Ph3 in 1L NSCLC readout in H2 2021; CANOPY-A Ph3 in adjuvant NSCLC ongoing
Sabatolimab	STIMULUS-MDS-2 Ph2 preliminary readout in MDS in H2 2021
NIS793	Ph2 combos in GI cancers ongoing; Ph3 combos in PDAC and CRC in planning

Tislelizumab: RATIONALE-302 in 2L ESCC

2021 ASCO ANNUAL MEETING



OS (PD-L1 ≥10%[1])

	Tislelizumab	Chemotherapy
Median OS, mo	10.3 (8.5-16.1)	6.8 (4.1-8.3)
HR (95% CI)	0.54 (0.36-0.79)	
P value	.0006	

Efficacy & safety of tislelizumab **comparable to nivolumab and pembrolizumab** (PD-L1+) monotherapy in 2L ESCC

These data will be used as the **basis for FDA & EMA registration** for tislelizumab in 2L ESCC

1. vCPS ≥ 10%, tested sequentially. vCPS: visually-estimated combined positive score.

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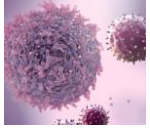
Continuing to improve our manufacturing capability in cell therapy, while we advance our ARM platform


Cell & Gene

Platform overview

Largest commercial presence with over 320 qualified centers across 28 countries

Largest global CAR-T manufacturing footprint with a robust and reliable manufacturing process

Advancing our next-generation Activated Rapid Manufacturing (ARM) platform to improve manufacturing reliability/simplicity, turnaround time, and potentially safety/efficacy

Selected pipeline opportunities

Kymriah®	BELINDA Ph3 readout 2L aNHL in H2 2021
YTB323[1]	Ph1 in hematological malignancies ongoing
PHE885[1]	Ph1 in r/r multiple myeloma ongoing

1. Cell therapies using our Activated Rapid Manufacturing (ARM) platform

Kymriah®: ELARA Primary Analysis

2021 ASCO ANNUAL MEETING

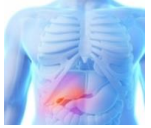
Efficacy Outcomes	N=94
CR, %	66
PR, %	20
ORR (CR + PR), %	86
6-month DOR, %	94
6-month PFS, %	76

Safety Outcomes	N=97
CRS	
Any Grade, %	49
Grade ≥3, %	0
NE	
Any Grade, %	9
Grade >3 / 4, n	0 / 1 pt

Kymriah® showed **consistent efficacy and favorable safety** in patients with r/r FL

These outcomes are particularly impressive given that ELARA included **high-risk patients** who were heavily pre-treated and relapsed early

Extending our leadership in radioligand therapy, which has the potential to become a new pillar of cancer care



Radioligand Therapy

Platform overview

Strong global expertise in commercializing RLTs in partnership with over 400 centers across 17 countries

Established scalable and reliable manufacturing network

Advancing 4 clinical programs and 11+ preclinical and discovery programs

Building rich pipeline of targets, isotopes and combinations

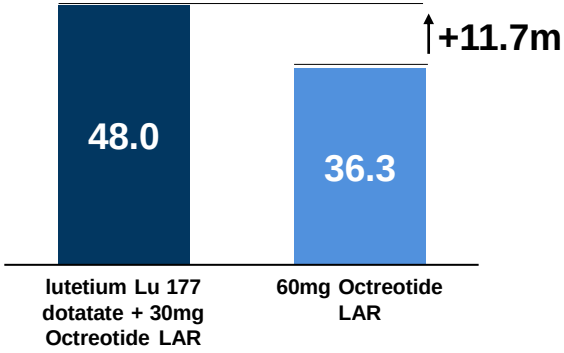
Selected pipeline opportunities

Lutathera®	NETTER-2 Ph3 in GEP-NET 1L G3 ongoing
^{177}Lu-PSMA-617	Submission (based on VISION) in H2 2021 Ph3 studies to start in mCRPC[1] pre-taxane & mHSPC[2]
^{225}Ac-PSMA-617	Ph1 study ongoing

Lutathera®: NETTER-1 Final Analysis

2021 ASCO ANNUAL MEETING

Median OS (95% CI), months



	lutetium Lu 177 dotatate + 30mg Octreotide LAR	60mg Octreotide LAR
Median OS (95% CI), months	48.0 (37.4, 55.2)	36.3 (25.9, 51.7)
Unstratified HR (95% CI)	0.84 (0.60, 1.17)	
Unstratified log-rank (2-sided)	P = 0.30	

Lutathera® significantly reduced the risk of progression or death by 82%[3] and demonstrated a clinically meaningful (but not statistically significant) trend towards **prolongation of median OS by 11.7 months**

These data support Lutathera®'s position as a valuable precision medicine option for advanced GEP-NETs

1. Metastatic castration resistant prostate cancer 2. Metastatic hormone sensitive prostate cancer 3. Per Lutathera® EU SmPC; 79% in Lutathera® USPI

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Sidonie Golombowski-Daffner

President, AAA

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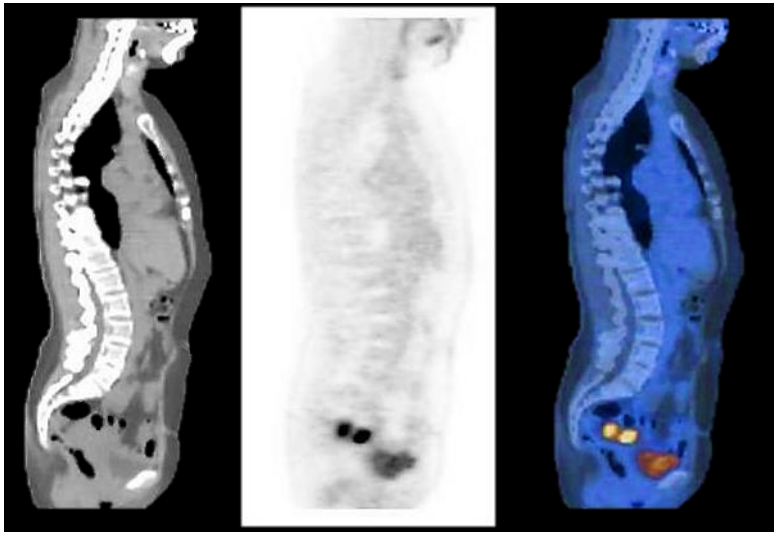
Reimagining cancer care with RLT: “Treat what you see”

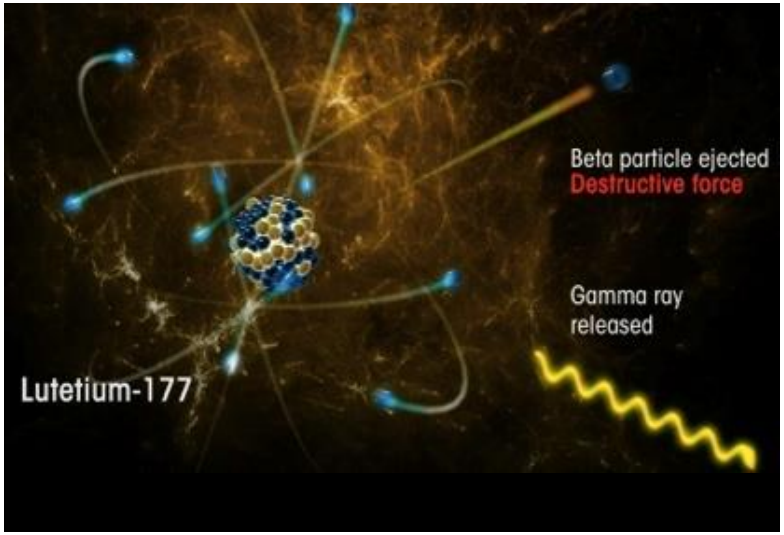
Precision Radioligand Imaging

Accurate diagnosis/assessment of complex diseases



Targeted Radioligand Therapy

Innovative therapeutic modality combining tumor targeting and radiation

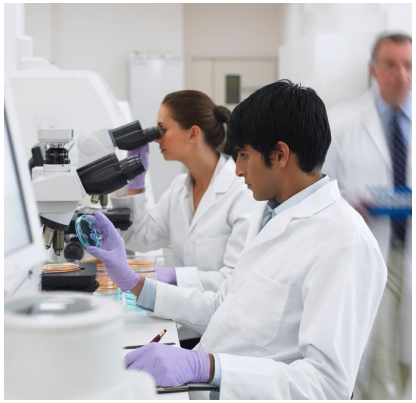


We are the first mover in this space, with a significant lead in three key areas

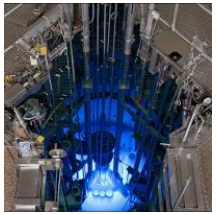
Manufacturing capabilities

Commercial expertise

R&D approach



Novartis built leadership in RLT with highly-complex, scaled, high quality and on-demand manufacturing

1 Week			1 Week		Infusion
					
Order irradiation of Lu-177 at reactor	Conversion of reactor produced Lu-177 to cGMP	Lu-177 shipment	Receive Lu-177 at factory	Lutathera® production and shipment	Time of administration
1 week prior to shipment to factory	6 days	1 day	1 day; or over the weekend	Production 1-5 days after receipt	Within 52 hours after end of production

Vertically integrated end-to-end value chain

- **On-demand manufacturing** with ability to deliver RLT within <2 weeks of order receipt; product shelf life ~2 days
- **Reliable and responsive** global supply chain; no doses missed despite COVID-19 restrictions
- Expanding existing sites and internalizing radioisotope supply to enhance **vertically integrated process**

Novartis is the only player in RLT with a globally commercialized product

Strong global commercial experience with Lutathera®

- Lutathera® Q1 sales of USD 122m, +6% cc vs. PY
- **>400 centers actively treating patients** globally, including ~220 in the US
- **>9k patients treated globally**, including >7k in the US
- **Strong relationships with customers** and key experts in the field
- Demand and delivery customer-facing teams with deep expertise in nuclear medicine and oncology

Levers to further strengthen commercial model ahead of future launches

1. Leverage expanded commercial footprint to **drive proper referrals** from community centers to RLT centers
2. **Expand disease awareness** campaign on PSMA[1] and Phenotypic Precision Medicine in advanced prostate cancer across relevant physician groups

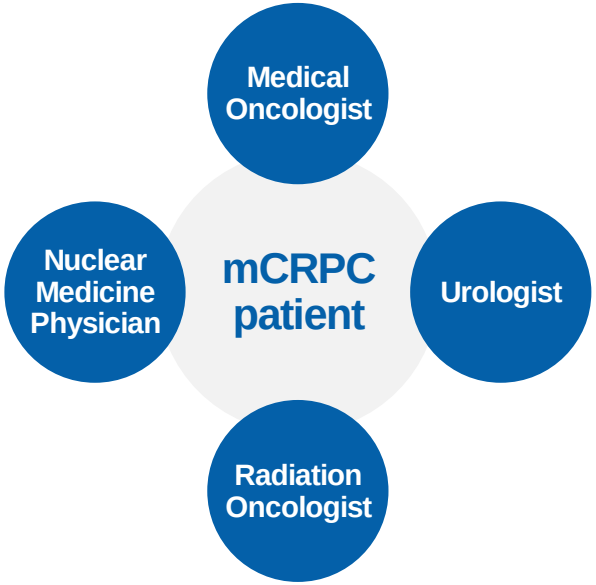
   Educate on the value of targeted RLT, and requirements for adoption in routine practice
3. Support top-tier centers to **expand RLT treatment capacity** and facilitate the coverage and reimbursement process[2]

1. Prostate specific membrane antigen 2. Hospital capacity is not a limiting factor for the ^{177}Lu-PSMA-617 launch – VISION indication will expand the overall patient population but not exceed existing RLT infrastructure, due to shorter infusion time (1/5 of Lutathera®) – but will support future launches in earlier lines in allowable jurisdictions as permitted by local law

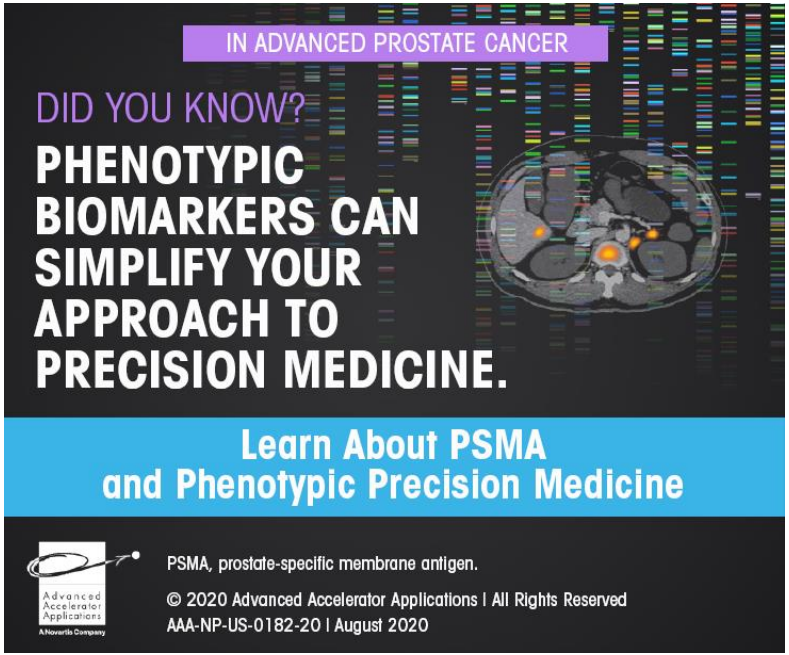
① Launching ^{177}Lu-PSMA-617 in mCRPC requires a multi-disciplinary approach

- Primary treatment decision-makers in prostate cancer vary by disease stage
- Urologist ownership in earlier stages transitions to oncologists as the disease advances
- In mCRPC, the medical oncologist is the primary treatment decision-maker and goals evolve to focus on extending survival and delaying progression without compromising QoL

Doubling down on medical education



② Pre-launch activities focused on raising awareness for PSMA as an important phenotypic biomarker…



PSMA is a diagnostic and therapeutic target, enabling a phenotypic precision medicine approach to managing advanced prostate cancer

- Precision medicine has traditionally relied on genotypic biomarkers
- The use of genotypic biomarkers in prostate cancer is complicated due to the heterogeneity of the disease
- PSMA is **overexpressed in >80% of men** with prostate cancer and can be detected by **noninvasive PET scan**
- Two PSMA PET imaging agents have been FDA approved in the last 6 months

③ ...and longer term, working with customers to expand RLT infrastructure in anticipation of earlier line launches

Our approach to build capacity[1]…

- Joint effort across Marketing, Value & Access and Medical to educate and support practices & stakeholders on becoming contracted RLT treatment sites
- Target goal of doubling contracted RLT treatment sites ahead of pre-taxane launch (~220 sites currently)
- Prioritizing sites that are already equipped with alpha hot labs

...building on growing interest in RLT following VISION readout

"RLT can be at the forefront of treating advanced prostate cancer, I want my practice to be a part of this"

Community Urologist

"I want our practice stakeholders [...] to understand all clinical, operational, and safe administrative practices for RLT post-ASCO"

National Ops Manager, Large Community Cancer/ Radiation Onc Network

"Whatever I can do now to prepare for the future of RLT in advanced prostate cancer, I want to get started today"

Community Radiation Oncologist

1. Hospital capacity is not a limiting factor for the ^{177}Lu-PSMA-617 launch – VISION indication will expand the overall patient population but not exceed existing RLT infrastructure, due to shorter infusion time (1/5 of Lutathera®) – but will support future launches in earlier lines in allowable jurisdictions as permitted by local law

To maintain our leadership position, we are expanding our RLT pipeline beyond prostate cancer

R&D focus areas

New targets

Acquired FAP[1]-targeting agents (SOFIE/iTheranostics)

New isotopes

Invested in biotech developing novel alpha-emitters (Aktis)

New combinations

Entered collaboration on novel combos with DDR[2] inhibitors (Artios)

Streamlined strategy and approach

Leveraging RLT-specific R&D advantages to strengthen PoS[3] and accelerate path to market

1. Fibroblast Activation Protein 2. DNA damage response 3. Probability of success

Growing RLT pipeline

Potential to address a range of solid tumors

Product	Disease (target)	Preclinical / Phase 1 / Phase 2 / Phase 3 / Filing / Marketed	Status
^{177}Lu PSMA-617	Prostate cancer (PSMA)	Phase 3	VISION study results reported
		Phase 3	Ph3 PSMAddition recruiting
		Phase 3	Ph3 PSMAfore to start H1 2021
		Phase 3	Earlier stage(s) in planning
^{225}Ac-PSMA-617		Phase 1	Ph1 study recruiting
^{177}Lu PSMA-R2		Phase 1	Ph1/2 study recruiting
^{68}Ga PSMA-R2		Phase 1	Ph1 study enrolled
^{18}F CTT1057		Phase 3	2 Ph3 studies to start H2 2021
^{177}Lu-Dotatate	Neuroendocrine tumors (SSTR)	Phase 3	Ph3 NETTER-2 in 1L GEP-NET enrolling
		Phase 1	Pediatric study in GEP-NET and PPGL planned H1 2021
	Other solid tumors (SSTR)	Phase 3	Other SSTR+ solid tumors in planning
^{177}Lu NeoB	Multiple solid tumors[1] (GRPR)	Phase 1	Ph1 basket study enrolling
^{68}Ga NeoB		Phase 2	IIT in GIST completed; Ph2 basket study completed
^{177}Lu FF-10158	Glioblastoma (integrin alphavbeta 3/5)	Phase 1	Study planned upon imaging results
^{68}Ga FF-10158		Phase 1	Ph1 study planned 2021
FAPi	Multiple solid tumors (FAP)	Phase 1	Deal closed with SOFIE Biosciences Q1 2021
FAPi		Phase 1	
Other (preclinical)	7 additional targets	Preclinical	Targets under investigation, across vector & linker technologies, with range of isotopes

1. Breast cancer, GIST, GBM, neuroblastoma, ovarian, head & neck, esophageal

Therapeutic Imaging / diagnostic

Our first-mover advantage creates high hurdles for competition

Manufacturing capabilities

Established access to raw materials

Proprietary insights regarding radioisotopes and stable RLT formulations

Capabilities to ensure patient administration before products lose activity due to radioactive decay

Commercial expertise

Strong customer and medical expert interfaces

Global commercial footprint with expertise in nuclear medicine and oncology

Strong patent protection for ^{177}Lu-PSMA-617 to at least 2034[1]

R&D approach

Expertise in conducting RLT clinical studies

Deep understanding of **radioligand imaging**, a key enabler for RLT

Bolstered capabilities in nuclear medicine and peptide discovery

1. We also have a robust portfolio of patents around our ^{177}Lu-PSMA-617 compound, with patent protection until at least 2034, plus possible patent extensions in major markets including the US and EU

Jeff Legos

Global Head of Oncology Development, GDD

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Prognosis remains poor for patients with mCRPC despite advances in treatments

2nd

most diagnosed cancer in men is prostate cancer[1]

>80%

patients metastatic at the time of CRPC diagnosis[2]

~30%

5-year survival prognosis for mCRPC patients[3]

~10

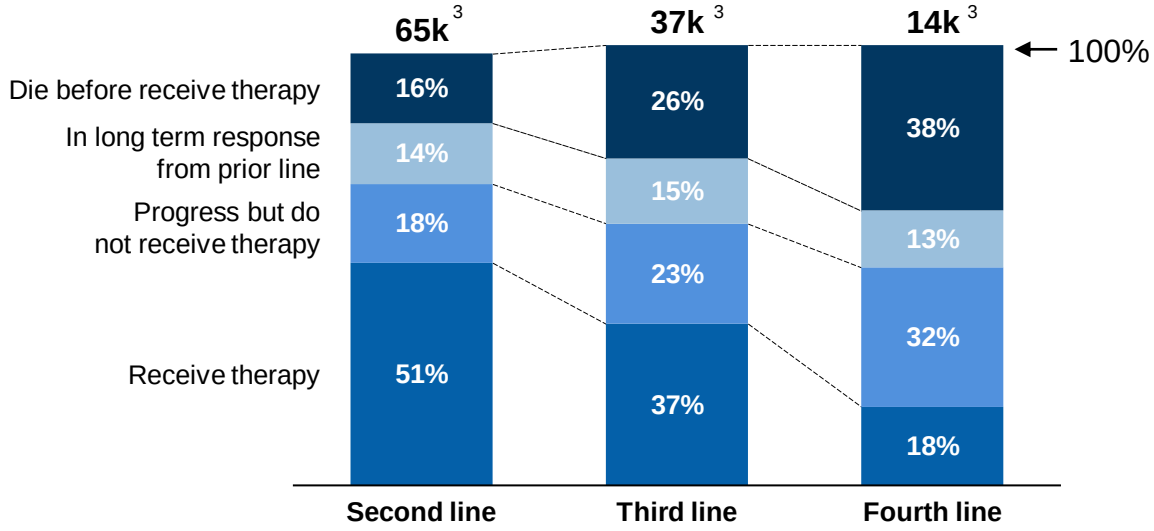
months median OS[4]

For footnotes, please see slide 51

Treatments with new mechanisms of action are needed to improve outcomes beyond second line

Patients with mCRPC

US, EU5, Japan



Note: percentages do not add to 100% due to rounding

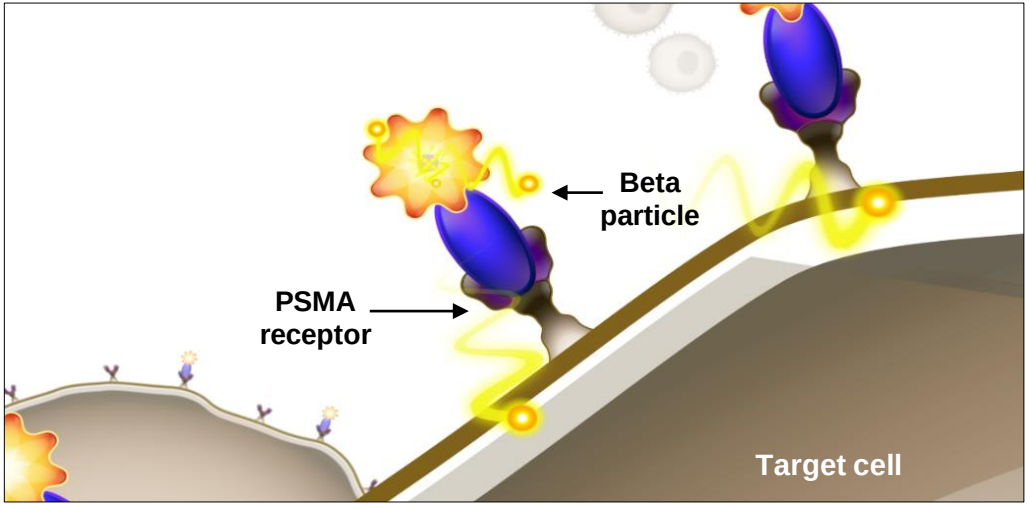
- Very limited set of treatment mechanisms available across lines in mCRPC: ARPI[1], ADT[2] and taxane
- Fewer patients receive each subsequent line of therapy, with no clear standard of care in late lines
- **High unmet need for new MoAs**, which can offer a new and potentially better option for patients in second line and beyond

1. Androgen receptor-pathway inhibitor 2. Androgen deprivation therapy 3. Number of patients and line outcome rates based on Kantar Health CancerMPact Treatment Architecture US, EU5, JP as of 2020 (report date Dec. 2019). Patient progression rates averaged between across geographies US, EU5, JP

^{177}Lu-PSMA-617 RLT enables targeted delivery of radiation to tumor while limiting damage to surrounding normal tissue

What makes PSMA RLT unique?

- Binds to PSMA, highly expressed on >80% prostate cancer cells[1-3]
- Once bound and internalized, the Lutetium-177 radioisotope releases an energetic beta particle
- This causes DNA breaks, disrupting target cell's ability to replicate and/or triggering cell death[4-6]
- Designed to deliver radiation to target cells; may also impact neighboring cells



For footnotes, please see slide 51

ASCO highlighted Phase 3 VISION study in plenary session on June 6

Eligible patients[1]

Previous treatment with both

- ≥ 1 androgen receptor pathway inhibitors
- 1 or 2 taxane regimens

Protocol-permitted standard of care (SoC) planned before randomization

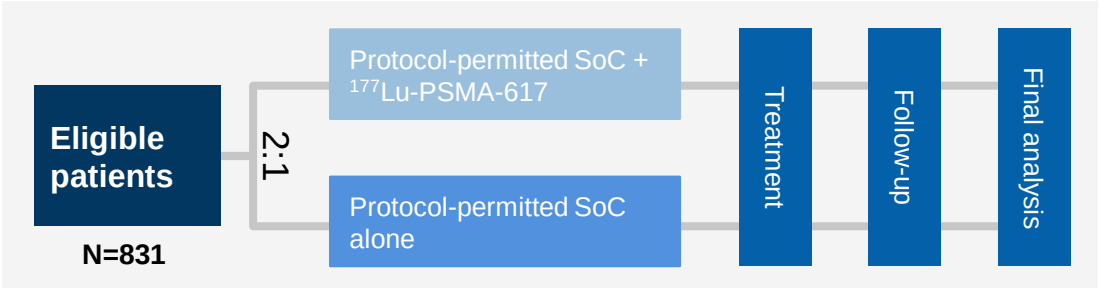
- Excluding chemotherapy, immunotherapy, Radium-223, investigational drugs

ECOG performance status 0–2

Life expectancy > 6 months

PSMA-positive mCRPC based on PET/CT scan with ^{68}Ga-PSMA-11

Study design[1]



Alternate primary endpoints	▪ Radiographic progression-free survival (rPFS) ▪ Overall survival (OS)
Key secondary endpoints	▪ Time to first symptomatic skeletal event (SSE)[3] ▪ RECIST v1.1 overall response rate (ORR) ▪ Disease control rate (DCR) ▪ Treatment emergent adverse events (TEAE)

For footnotes and abbreviations, please see slides 51 and 52, respectively

Baseline demographics and disease characteristics were well balanced across treatment arms (N = 831)

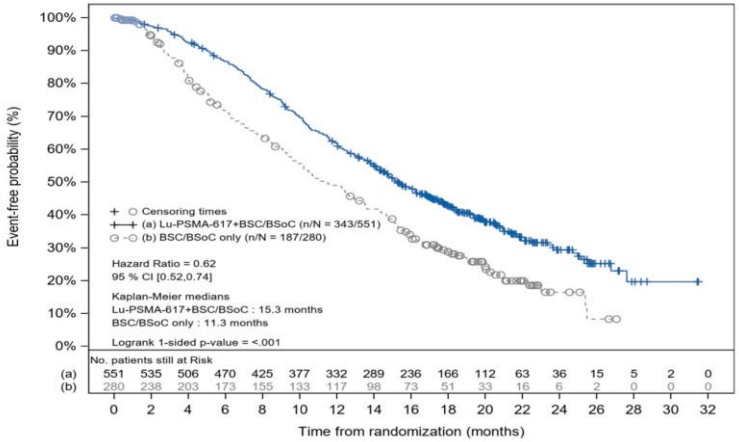
Baseline characteristic	^{177}Lu-PSMA-617 + SoC (n = 551)	SoC alone (n = 280)
Age, median (range)	70.0 (48–94)	71.5 (40–89)
Race, n (%)		
White	486 (88.2)	235 (83.9)
Black	34 (6.2)	21 (7.5)
Asian	9 (1.6)	11 (3.9)
ECOG status, n (%)		
0 or 1	510 (92.6)	258 (92.1)
2	41 (7.4)	22 (7.9)
Disease site, n (%)		
Lung	49 (8.9)	28 (10.0)
Liver	63 (11.4)	38 (13.6)
Lymph node	274 (49.7)	141 (50.4)
Bone	504 (91.5)	256 (91.4)

Previous prostate cancer treatment	^{177}Lu-PSMA-617 + SoC (n = 551)	SoC alone (n = 280)
Prostatectomy, n (%)	240 (43.6)	130 (46.4)
Radiotherapy, n (%)	415 (75.3)	217 (77.5)
Systemic therapy, n (%)	551 (100)	280 (100)
ARPI, n (%)		
1 regimen	298 (54.1)	128 (45.7)
2 regimens	213 (38.7)	128 (45.7)
> 2 regimens	40 (7.3)	24 (8.6)
Taxane, n (%)		
1 regimen	**325 (59.0)**	**156 (55.7)**
2 regimens	**220 (39.9)**	**122 (43.6)**
> 2 regimens	6 (1.1)	2 (0.7)
Docetaxel	534 (96.9)	273 (97.5)
Cabazitaxel	209 (37.9)	107 (38.2)

^{177}Lu-PSMA-617 met both primary endpoints of overall survival and radiographic progression free survival

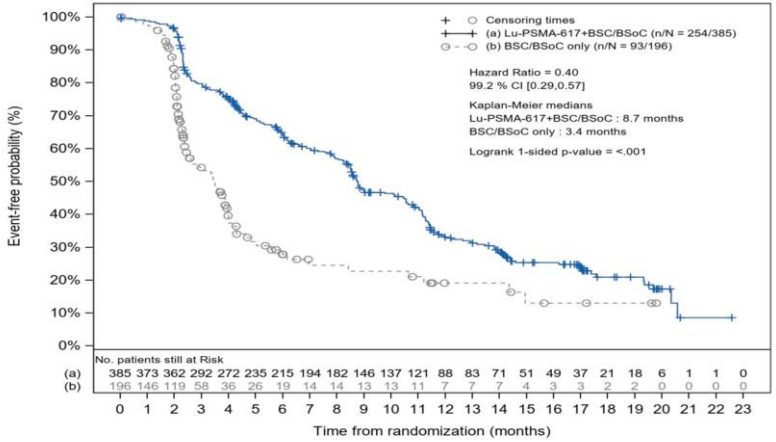
^{177}Lu-PSMA-617 significantly reduced the risk of death by 38%

OS HR[1]: **0.62** (95%CI: 0.52, 0.74)
Median OS: **15.3 months** (14.2, 16.9)[3] vs. **11.3** (9.8, 13.5)[3]



^{177}Lu-PSMA-617 significantly reduced the risk of radiographic progression or death by 60%

rPFS HR[1]: **0.40** (99.2%CI: 0.29, 0.57)
Median rPFS: **8.7 months** (7.9, 10.8)[2] vs. **3.4** (2.4, 4.0)[2]



1. p<0.001, stratified log-rank test 1-sided 2. 99.2% CI, in line with hypothesis testing strategy 3. 95% CI

^{177}Lu-PSMA-617 met all key secondary endpoints as well…

Key secondary endpoints

Overall response rate (ORR)

^{177}Lu-PSMA-617 **significantly increased** the rate of objective tumor response (RECIST v1.1)

ORR: 29.8% vs. 1.7%

Odds ratio 24.99

(95%CI: 6.05,103.24)

Time to 1st symptomatic skeletal event (SSE)[1]

^{177}Lu-PSMA-617 **significantly reduced** the risk of SSE or deaths

SSE: 11.5m vs. 6.8m

HR: 0.5

(95%CI: 0.40, 0.62)

1. SSE denotes time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first

...and was well tolerated, in line with previous experience

Safety profile

^{177}Lu-PSMA-617 treatment discontinuation rates associated with TEAEs:

- ^{177}Lu-PSMA-617+SoC arm: 11.9% discontinued ^{177}Lu-PSMA-617, 8.5% discontinued SoC
- SoC arm: 7.8% discontinued

Higher rate of drug-related treatment emergent adverse events reported in the ^{177}Lu-PSMA-617 treatment arm (85.3%) compared to standard of care alone (28.8%)

Most Frequent Grade ≥3 treatment emergent adverse events (TEAEs) regardless of drug relatedness (>3.5% in either arm)

TEAEs	^{177}Lu-PSMA-617 + SoC	SoC only
Anemia	12.9%	4.9%
Thrombocytopenia	7.9%	1.0%
Lymphopenia	7.8%	0.5%
Fatigue	5.9%	1.5%
Urinary Tract Infection	3.8%	0.5%

VISION results support regulatory filings, on track for H2 2021, and advancing ^{177}Lu-PSMA-617 into earlier lines of therapy

- The combination of ^{177}Lu-PSMA-617 with standard of care resulted in:

  38% reduction in risk of death

  60% reduction in the risk of radiographic disease progression or death compared to standard of care alone

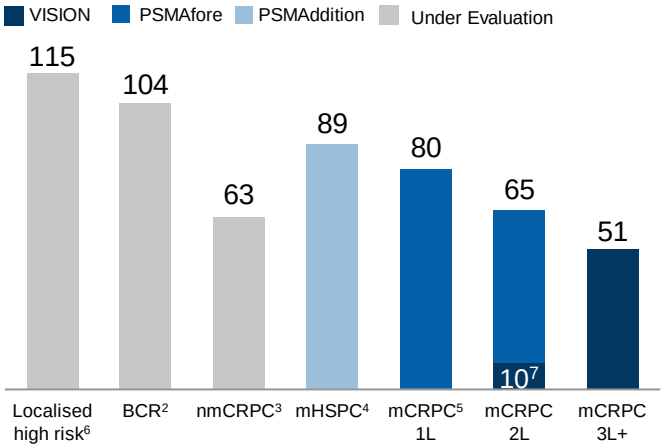
- Regulatory submissions in US and EU are on track for **H2 2021**
- These data further support investigating ^{177}Lu-PSMA-617 in earlier lines of therapy, and potentially earlier stages of disease

Significant unmet need in earlier lines and stages of prostate cancer; two additional Phase 3 studies starting in H1 2021

Prostate cancer incidence

US, EU5, JP[1] ('000)

>80% of patients express PSMA



Aim to expand in earlier lines of prostate cancer treatment

Setting	Study	Status	Opportunity (USD)	Expected filing
mCPRC 3/4L (post-taxane)	VISION	Completed	<500m - 1bn	H2 2021
mCRPC 1L/2L (pre-taxane)	PSMAfore	To start H1 21	>1bn	2023
mHSPC	PSMAddition	Recruiting	>1bn	2024
Earlier stages	Multiple further studies under evaluation in 2021			

For footnotes and abbreviations, please see slides 51 and 52, respectively

Alice Shaw

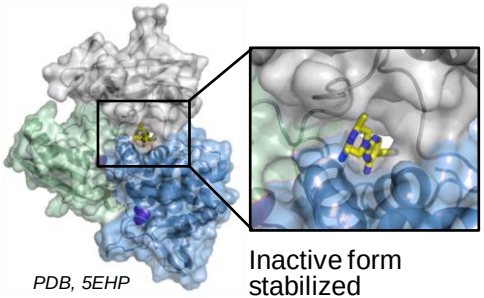
Global Head of Translational Clinical Oncology, NIBR

NOVARTIS | Reimagining Medicine

TNO155: A first-in-class inhibitor of SHP2 and ideal combination partner for targeted and checkpoint therapies

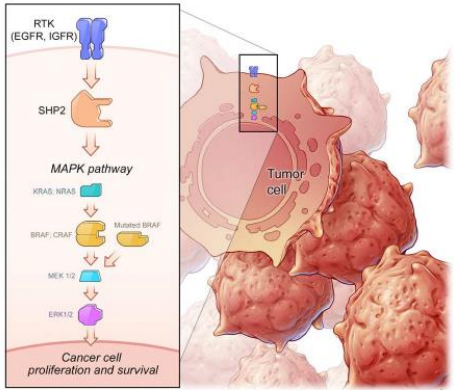
AACR American Association for Cancer Research

First SHP2i to enter the clinic



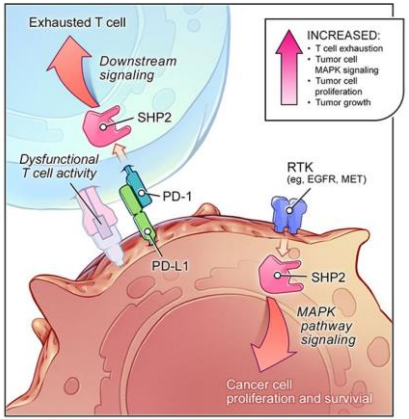
Ideal drug-like properties (e.g. high permeability, solubility, no CYP450 inhibition, ideal preclinical PK profile)

Required for RTK signaling



RTK-SHP2-RAS-MAPK pathway activation has been implicated across the majority of human cancers

Downstream transducer of PD-1



SHP2 is a downstream transducer of PD-1 signaling, a critical immune checkpoint in human malignancies

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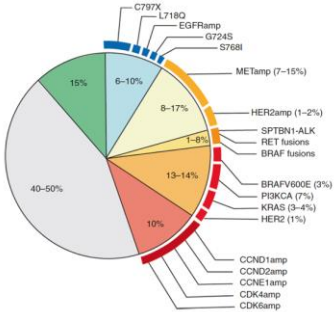
Almost all patients develop resistance to targeted therapies

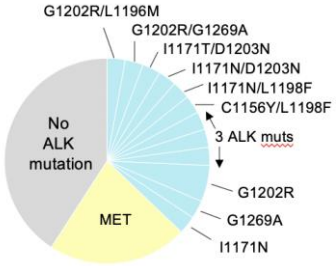
Role of SHP2 phosphatase

Multiple resistance mechanisms arise during targeted therapy treatment

1L Tagrisso® in EGFR[1]



2L+ Lorbrena® in ALK[2]



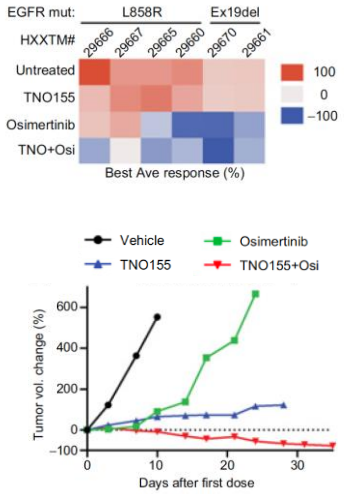
Multiple and diverse resistance mechanisms can develop in patients treated with targeted therapies, leading to clinical relapse

For highly selective, next-generation targeted agents, resistance is often mediated by off-target mechanisms that lead to MAPK reactivation

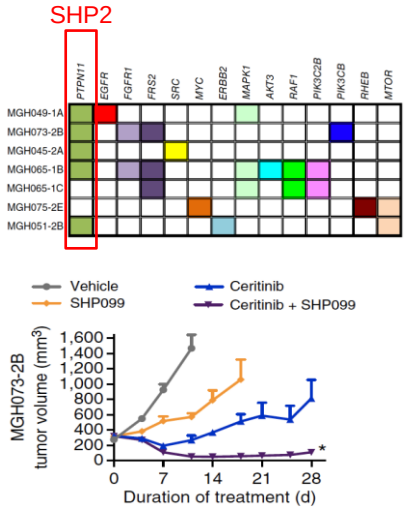
Combination strategies that target both the oncogenic driver and downstream signaling pathways are urgently needed

SHP2 inhibition overcomes resistance mechanisms in pre-clinical models

EGFR mutant NSCLC[3]



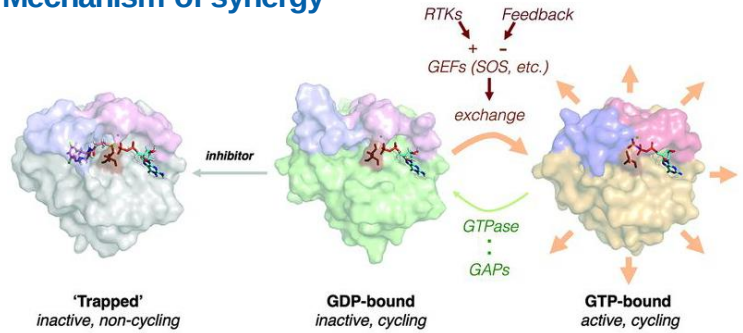
ALK+ NSCLC[4]



1. Leonetti Br J Cancer 2019 2. Dagogo-Jack, Clin Canc Res, 2020 3. Liu Clin Canc Res. 2021 4. Dardaei Nat Med 2018 Tagrisso® is a registered trademark of the AstraZeneca group of companies. Lorbrena® is a registered trademark of Pfizer, Inc.

Strong pre-clinical synergy between SHP2i and KRAS^{G12C}i supports TNO155 + G12Ci combination approach

Mechanism of synergy

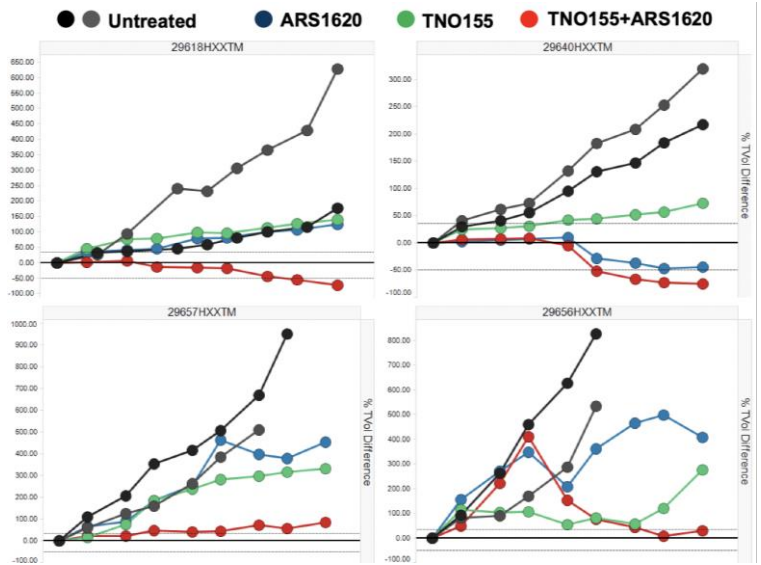


Science. 2016 Feb 5;351(6273):604-8.

KRAS^{G12C} still cycles between GTP- and GDP-bound states and SHP2i enriches the GDP-bound KRAS^{G12C}, which G12Ci binds (**enhances target engagement**)

SHP2i suppresses feedback activation of wildtype KRAS, NRAS, HRAS post ERK inhibition by G12Ci (**prevents pathway re-activation**)

TNO155 + KRAS^{G12C}i shrink tumors in KRAS^{G12C} NSCLC PDX pre-clinical models



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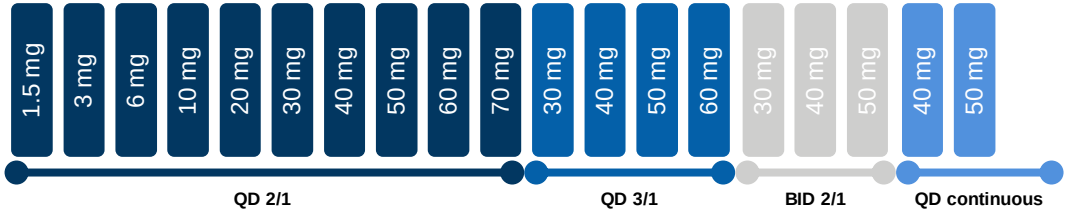
Phase 1 first-in-human study of TNO155: Optimizing dose and schedule to enable combinations

TNO155 dose escalation[1]

RAS/BRAF WT or KRAS G12C CRC
EGFR-mutant NSCLC
KRAS G12-mutant NSCLC

HNSCC
Esophageal SCC
GIST

BRAF/NRAS WT cutaneous melanoma
(N=125)



Data cut-off: February 8, 2021
Primary objective: DLTs, safety, tolerability
Secondary objective: ORR, DCR, PFS, DOR, PK, pharmacodynamics
Treatment until unacceptable toxicity, disease progression, or patient/physician decision

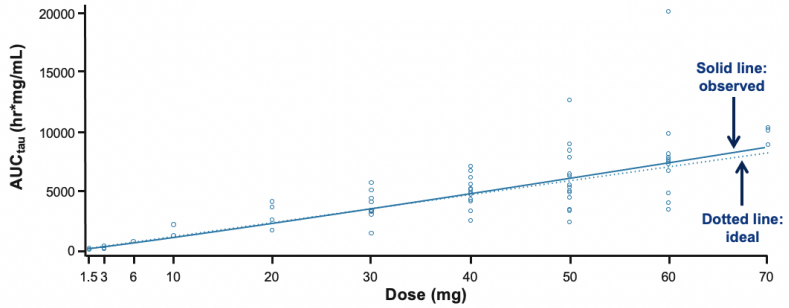
Characteristic	All patients, N=125
Median age, years (range)	59 (18-80)
Sex (male), n (%)	73 (58.4)
ECOG PS, n (%)	
0	56 (44.8)
1	68 (54.4)
2	1 (0.8)
Primary tumor type, n (%)	
CRC	66 (52.8)
KRAS G12C	4 (3.2)
GIST	21 (16.8)
NSCLC	15 (12.0)
EGFR-mutant	12 (9.6)
KRAS G12-mutant	3 (2.4)
HNSCC	11 (8.8)
Esophageal SCC	8 (6.4)
Melanoma	3 (2.4)
Cholangiocarcinoma	1 (0.8)
Prior therapy, n (%)	
Median number of prior systemic therapies, (range)	4 (1-10)

Enrolled patients had advanced solid tumors for which standard treatment has failed
For abbreviations, please see slide 52

1. CRC was removed and KRAS G12-mutant NSCLC and BRAF/NRAS WT melanoma added during a protocol amendment filed in 2020

TNO155 shows favorable PK and evidence of target engagement

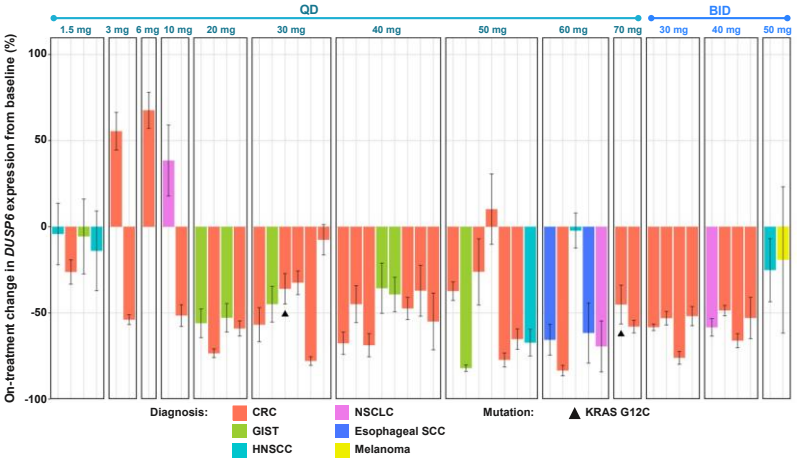
Dose proportionality for TNO155, QD dosing regiments, C1D14



Drug exposure increased nearly proportionally with dose level and moderate interpatient PK variability was observed; similar trends were seen with BID dosing

Based on non-clinical data, TNO155 is primarily metabolized by UGT1A3 and is not an inducer or inhibitor of major metabolic enzymes; drug–drug interactions are unlikely

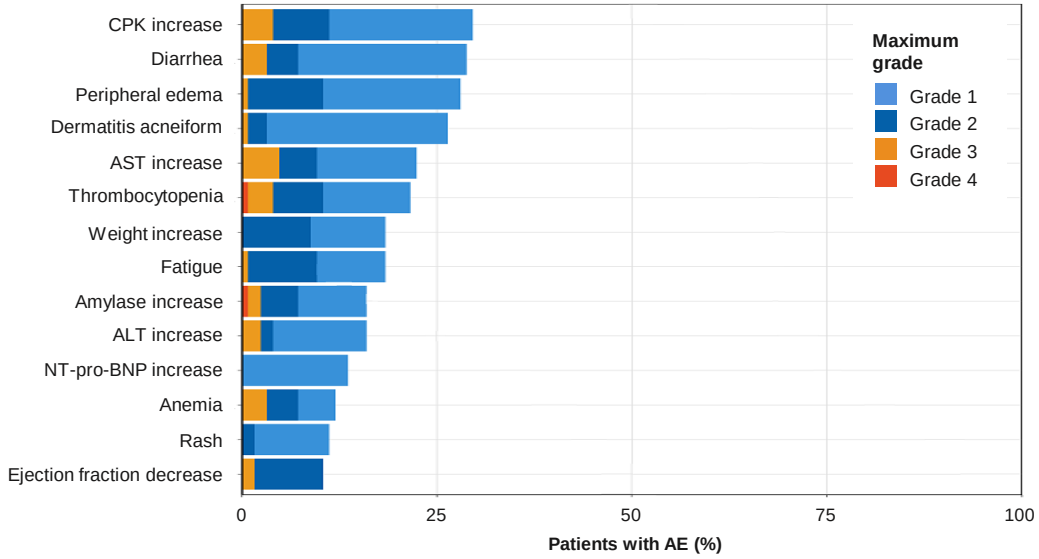
On-treatment percentage change from baseline in *DUSP6* expression



DUSP6 expression is a marker of MAPK pathway activity downstream of SHP2. Change in *DUSP6* expression by qPCR was assessed in paired pre- vs. on-treatment tumor samples

TNO155 was generally well tolerated with treatment-related AEs consistent with on-target SHP2 inhibition

Treatment-related AEs, ≥10% of patients

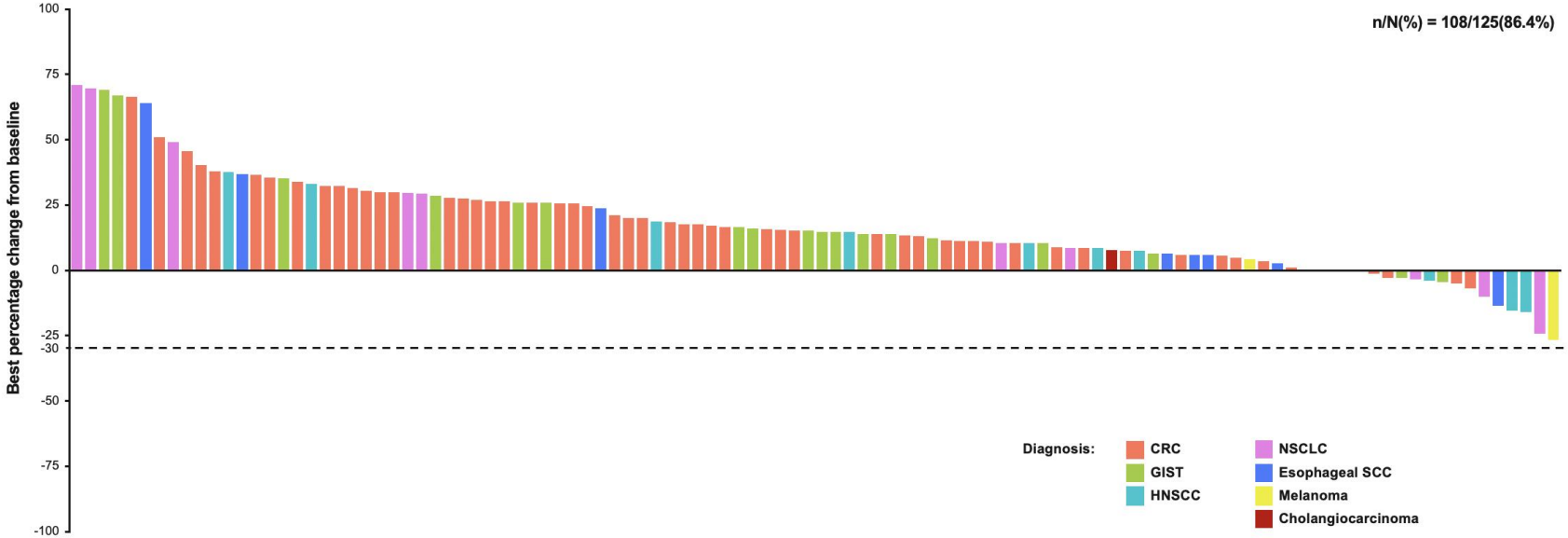


- Most AEs were Grade 1 or 2 in severity
- There were no treatment-related Grade 5 AEs
- Ejection fraction decreases/left ventricular dysfunction of any grade were reported in 13/125 (10%) patients, most of which were mild, reversible, and identified as a result of frequent monitoring[1]

AE terms which are equivalent are grouped for reporting: rash and maculopapular rash are reported as rash; platelet count decrease and thrombocytopenia are reported as thrombocytopenia; neutrophil count decrease and neutropenia are reported as neutropenia; ejection fraction decrease and left ventricular dysfunction are reported as ejection fraction decrease. 1. Cardiac imaging by echocardiogram or MUGA scan was required at baseline, C1D14 (2/1 schedule) or C1D21 (3/1 or continuous schedules), C2D1, C2D14 or C2D21, C3D1, then D1 of every even cycle through C8, then D1 of every third cycle. C: cycle; D: day For other abbreviations, please see slide 52

Limited clinical activity of single agent TNO155 in advanced solid tumors

Best percentage change from baseline in sum of target lesion diameters



CRC: colorectal cancer; GIST: gastrointestinal stromal tumor; HNSCC: head and neck squamous cell cancer; NSCLC: non-small cell lung cancer; SCC: squamous cell cancer

Multiple TNO155 combinations are being explored clinically

	Combination	Disease	Est. frequency	FPFV
	TNO155 + EGF816	EGFR mutant NSCLC, post osimertinib	10-40% of NSCLC	September 2020
MGH	**TNO155 + lorlatinib**	ALK+ NSCLC, post next generation ALK TKI	3-5% of NSCLC	March 2021
	TNO155 + dab/tram **TNO155 + dab/LTT462**	BRAF V600-mut CRC	~10% of CRC	Q2 2021
	TNO155 + PDR001	$KRAS^{G12C}$ NSCLC, ≥1% PD-L, post-chemo and aPD-(L)1	~13% of NSCLC	August 2019
	TNO155 + ribociclib	KRAS-mut CRC, post-SoC, per local standard	30-40% of CRC	August 2019
	TNO155 + JDQ443	$KRAS^{G12C}$ NSCLC and CRC	~13% of NSCLC ~4% of CRC	Q3 2021
MIRATI THERAPEUTICS	**TNO155 + MRTX849**	$KRAS^{G12C}$ NSCLC and CRC	~13% of NSCLC ~4% of CRC	April 2020

Early clinical activity with adagrasib + TNO155 in KRAS^{G12C} mutant cancers

Patient is a 53-year-old male current smoker diagnosed with metastatic NSCLC in April 2017

Patient had received several prior treatments:

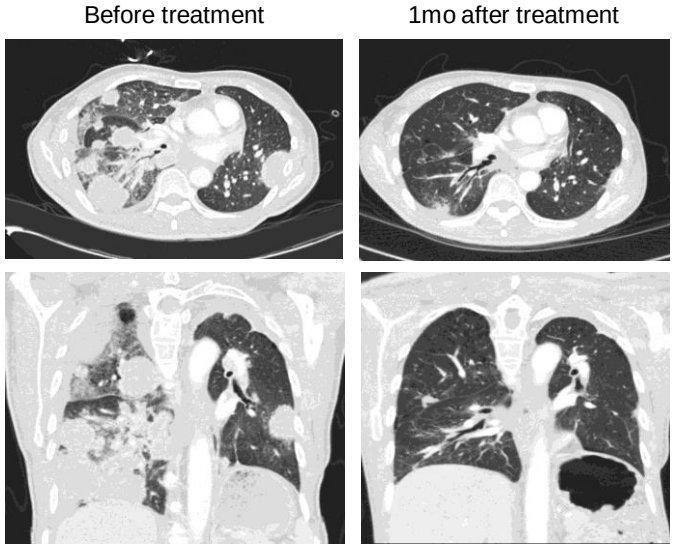
- Chemotherapy
- Immunotherapy
- Chemotherapy + immunotherapy
- AMG510 x 3 mos
- RMC4630 + cobimetinib x 1 cycle
- Experimental CDK4/6i

Patient enrolled in combination trial MRTX849 + TNO155 (initial dose level)

Patient showed rapid resolution of cancer symptoms, PR on first scans (shown on right panel)

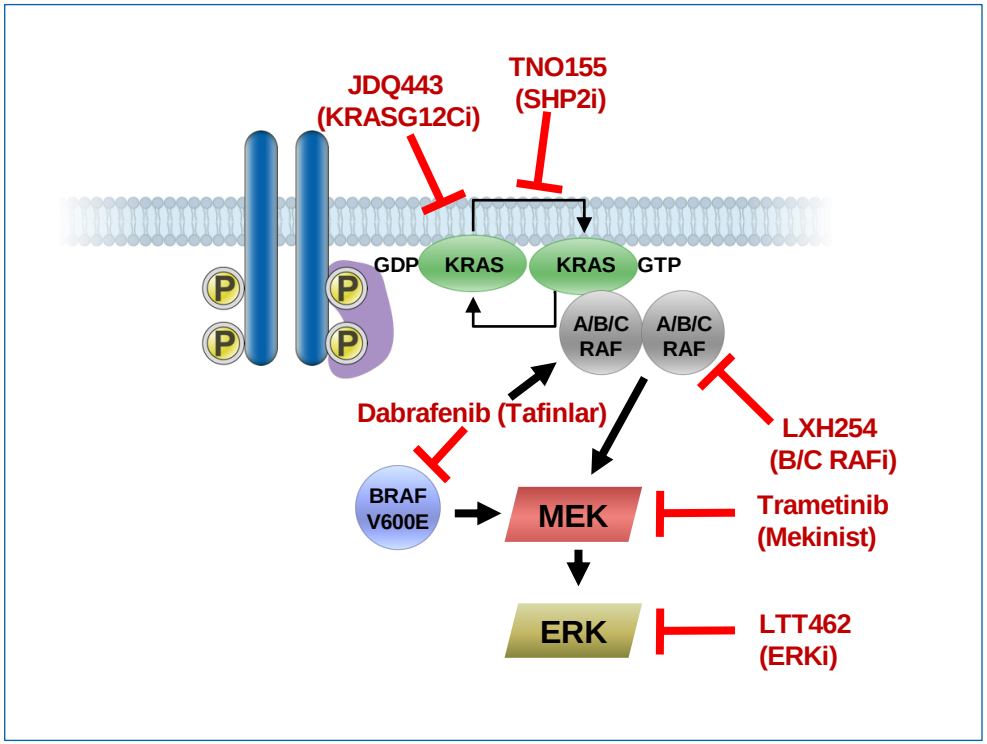
Mild grade 1 toxicities

CT scan of NSCLC patient before treatment and 1 month after treatment with MRTX849 + TNO155



Courtesy of Dr. Zhu (UCI)

Expanding the Novartis MAPK pipeline to enable innovative combination strategies



- KRAS-MAPK is one of the most highly validated oncogenic pathways in human cancer
- In addition to TNO155 combinations, Novartis is exploring multiple other combination therapies, including:
  - LXH-based combinations in NRAS mutant melanoma, BRAF mutant melanoma, KRAS mutant NSCLC, atypical BRAF mutant NSCLC
  - Dabrafenib/LTT462 and dabrafenib/trametinib triplet combinations in BRAF mutant CRC
  - Combinations of JDQ443 in KRASG12C mutant cancers
  - Ras/MAPK targeted therapies and checkpoint inhibitors

Conclusion

- Novartis is a global leader in Oncology, with a strong track record of pioneering innovation
- Only company with depth and expertise in four unique therapeutic platforms, which we believe will be critical for the future of cancer care
- VISION study demonstrates that RLT can dramatically improve patient outcomes, not only in a rare disease like NET, but also in prostate cancer, one of the most prevalent cancers in men
- Well positioned with our pipeline to tackle remaining unmet needs in cancer, including through combination approaches within/across our platforms

Q&A session

Susanne Schaffert
President, Novartis Oncology

Alice Shaw
Global Head of Translational Clinical Oncology, NIBR

Jeff Legos
Head of Oncology Development, GDD

Samir Shah
Global Head Investor Relations

Sidonie Golombowski-Daffner
President, AAA

Appendix

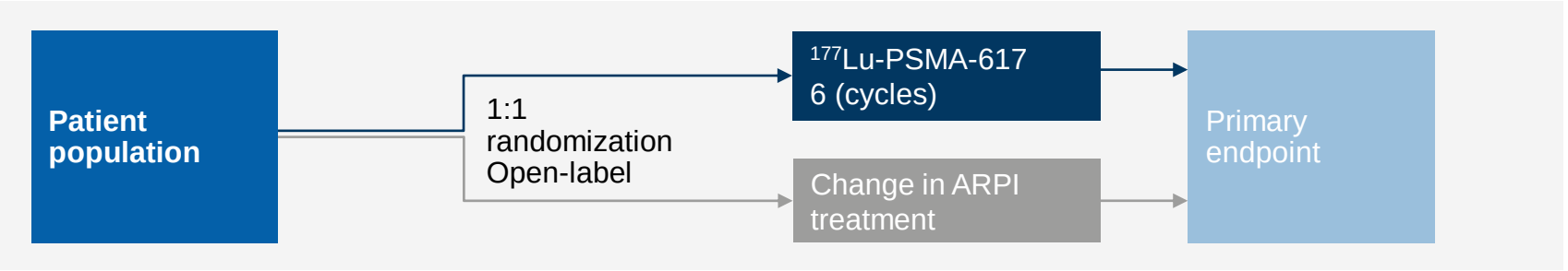
We have advanced our pipeline in each platform since our investor update at ASCO 2020

	Platform	Asset	Program	Milestone
Regulatory decisions & designations	TT	Adakveo®	Sickle cell disease	EU approval ✓
	TT	Tabrecta®	EGFR wt, ALK- NSCLC	US & Japan approval ✓
	TT	Tafinlar® + Mekinist®	BRAF+ adj melanoma	China approval ✓
	TT	Asciminib	CML 3L	FDA BTD & Fast Track ✓
	IO	Sabatolimab	MDS	FDA Fast Track ✓
	C&G	Kymriah®	r/r follicular lymphoma (FL)	FDA Orphan Drug designation ✓
Submissions	TT	Jakavi®	Acute & chronic GvHD	EU & Japan submission ✓
	TT	Afinitor®	ER+ BC 2/3L	China submission ✓
Trial readouts	RLT	^{177}Lu-PSMA-617	mCRPC 3/4L	VISION Ph3 FIR ✓
	RLT	Lutathera®	GEP NET 2/3L	NETTER-1 Ph3 OS ✓
	TT	Asciminib	CML 3L	ASCEMBL Ph3 FIR ✓
	TT	Jakavi®	Chronic GvHD	REACH-3 Ph3 FIR ✓
	IO	Canakinumab	NSCLC 2/3L	CANOPY-2 Ph3 FIR ✗
	C&G	Kymriah®	r/r FL	ELARA Ph2 primary analysis ✓
	C&G	Kymriah®	Adult r/r DLBCL	JULIET Ph2 follow-up efficacy results ✓

✓ **Achieved** ✗ **Missed**

PSMAfore: ^{177}Lu-PSMA-617 in pre-taxane mCRPC

Aiming to spare patients the need for chemotherapy

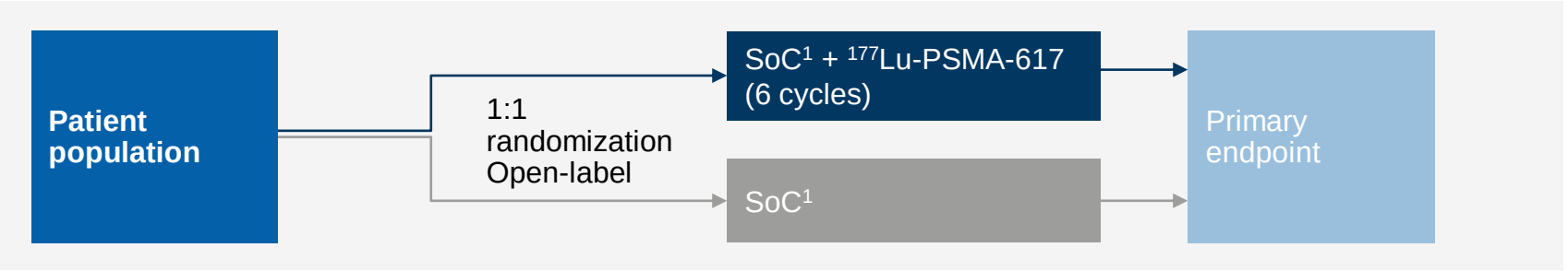


Patient population	mCRPC with disease progression on prior ARPI (in HSPC or CRPC setting)* No previous taxane in CRPC or HSPC setting PSMA+ as determined by central read on PET/CT scan
Primary endpoint	Radiographic progression free survival (rPFS)
Key secondary endpoint	Overall survival (OS)
Sample size	450 patients
Expected completion	2024

Stratification factor: Prior ARPI use in CRPC vs. HSPC; asymptomatic and mildly symptomatic vs. symptomatic patients *Candidates who are considered appropriate for delaying taxane-based chemotherapy

PSMAddition: ^{177}Lu-PSMA-617 in mHSPC

Expanding RLT into the hormone-sensitive space



Patient population	Untreated mHSPC (allow up to 42 days ADT) Appropriate for ARPI PS = 0-2 PSMA+ as determined by central read on PET/CT scan
Primary endpoint	Radiographic progression free survival (rPFS)
Key secondary endpoint	Overall survival (OS)
Sample size	1,126 patients
Expected completion	2024 (primary endpoint)

1. Standard of Care: Combination of ADT and ARPI is allowed; ARPI is as per SoC/guidelines, including abiraterone/prednisolone, enzalutamide, apalutamide

Footnotes

Unmet need in mCRPC	
1	Epidemiology of Prostate Cancer. Rawla P., World J Oncol. 2019;10(2):63-89
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^{177}Lu-PSMA-617 MoA	
1	Hupe MC, Philippi C, Roth D, et al. Expression of prostate-specific membrane antigen (PSMA) on biopsies is an independent risk stratifier of prostate cancer patients at time of initial diagnosis. Front Oncol 2018;8:623
2	Bostwick DG, Pacelli A, Blute M, et al. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer 1998;82(11):2256–61
3	Pomykala KL, Czernin J, Grogan TR, et al. Total-body 68Ga-PSMA-11 PET/CT for bone metastasis detection in prostate cancer patients: potential impact on bone scan guidelines. J Nucl Med 2020;61(3):405–11
4	Jurcic JG, Wong JYC, Knox SJ, et al. Targeted radionuclide therapy. In: Gunderson LL, Tepper JE, eds. Gunderson & Tepper's Clinical Radiation Oncology. 4th ed. Philadelphia, PA: Elsevier, Inc.; 2016:423-437.e19
5	Unak P. Targeted tumor radiotherapy. Braz Arch Biol Technol. 2002;45:97-110. doi:10.1590/S1516-89132002000500014
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VISION Study	
1	Endocyte. Study of ^{177}Lu-PSMA-617 In Metastatic Castrate-Resistant Prostate Cancer (VISION). U.S. National Library of Medicine: Clinical Trials. 2018; NCT03511664 [https://www.clinicaltrials.gov/ct2/show/NCT03511664?term=PSMA-617&draw=2&rank=4]
2	Morris M. et al, Phase 3 study of 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION); ASCO 2021 plenary
3	SSE denotes time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first

Unmet needs in earlier lines of prostate cancer	
1	2020 Incidence Based on Kantar Health CancerMPact Treatment Architecture US, EU5, JP (February 2021). Incidence incl. patients in long-term response from prior line, who die before receiving therapy, progress but do not receive therapy, and receive systemic therapy
2	Biochemically recurrent
3	Non-metastatic castration-resistant prostate cancer
4	Metastatic hormonal-sensitive prostate cancer
5	Metastatic castration-resistant prostate cancer
6	Localised high risk prostate cancer including adjuvant and neoadjuvant eligible
7	NVS estimation based on current treatment rates with 15% of 2L patients assumed to have progressed on both a fist ARDT and taxane treatment.

Abbreviations

2/1	2 weeks on/1 week off
3/1	3 weeks on/1 week off
ADT	Androgen deprivation therapy
ALT	Alanine amino transferase
ARM	Activated Rapid Manufacturing
ARPI	Androgen receptor-pathway inhibitor
AST	Aspartate amino transferase
BCR	Biochemically recurrent
BID	Twice daily
C&G	Cell & Gene
cGMP	Current Good Manufacturing Practice
CML	Chronic myeloid leukemia
CPK	BLood creatine phosphokinase
CR	Complete response
CRC	Colorectal cancer
CRS	Cytokine release syndrome
DCR	Disease control rate
DDR	DNA damage response
DLT	Dose-limiting toxicity
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group performance status
ESCC	Esophageal squamous cell carcinoma
FAP	Fibroblast activation protein
FIH	First in human
FL	Follicular lymphoma
GEP-NET	Gastroenteropancreatic neuroendocrine tumor
GIST	Gastrointestinal stromal tumor
HNSCC	Head and neck squamous cell carcinoma
IO	Immuno-oncology
ITT	Intent to treat
LCM	Lifecycle management
mCRPC	Metastatic castration-resistant prostate cancer
mHSPC	Metastatic hormone sensitive prostate cancer
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
NE	Neurological event
NHL	Non-Hodgkin's lymphoma
NSCLC	Non-small cell lung cancer
NT-pro-BNP	N-terminal prohormone brain natriuretic peptide
ORR	Overall response rate
OS	Overall survival
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PK	Pharmacokinetics
POS	Probability of success
PR	Partial response
PSMA	Prostate specific membrane antigen
QD	Once daily
QOL	Quality of Life
RD	Recommended dose
RLT	Radioligand therapy
rPFS	Radiographic progression-free survival
SCC	Squamous cell cancer
SoC	Standard of care
SSE	Symptomatic skeletal event
TEAE	Treatment emergent adverse events
TT	Targeted therapy
vCRS	Visually-estimated combined positive score
WT	Wild-type