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A Phase 1, First-in-human, Safety, Pharmacokinetic and Pharmacodynamic Study of Oral Dubermatinib (TP-0903) in Patients with Advanced Solid Tumors

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DISCLOSURE INFORMATION

All non-SDP Oncology employees declare institutional research funding from SDP Oncology (fka Tolero Pharmaceuticals) or Sumitomo Dainippon Pharma, Inc.

- J. Melear: Speakers Bureau: Janssen, AstraZeneca
- J. Thompson – Advisory: Pfizer
- J. Baranda: Research Funding: Exelixis, Astellas, Tolero, Xencor, Pfizer, Incyte, Eli Lilly, Sanofi, Nektar, SQZ. Stock: Forty-Seven, Inc, Moderna, Zymeworks, Morphosys AG. Travel: Sanofi
- B. Bastos: Speaker: Regeneron, Sanofi Genzyme
- A. Spira: Honoraria: Cytomx, Amgen, Novartis, Merck, Astrazeneca, BMS. Grants: EMD Serono, Turning Point
- Y. Lou: Advisory: Novocure, AstraZeneca, Clarion Healthcare. Research Funding: Merck Sharp & Dohme, Kyowa Hakko Kirin Pharma, MacroGenics, Tesaro, Blueprint Medicines Corporation, Vaccinex Inc, Harpoon Therapeutics, Sun Pharma Advanced Research Company Limited
- M. Seetharam –Advisory: Daiichi-Sankyo. Honorarium: CME Horizon
- M. Uemura: Advisory: Seattle Genetics. Stock: Abbott Laboratories (self), Regeneron (spouse)
- D. R. Camidge: Research Funding: Abbvie, AstraZeneca, BMS, GSK, Hansoh, Inhibrx, Lycera, Medimmune, Merck, Pfizer, Phosplatin, Psioxus, Rain, Roche/Genentech, Seattle Genetics, Symphogen, Takeda, Advisory: Anchiarno, Amgen, Takeda, Roche, EMD Serono, Sanofi, Pfizer, CBT Pharmaceuticals, Daiichi-Sankyo, G1 Therapeutics, Bio-Thera, Blueprint, Abbvie, Achilles, BeyondSpring, Apollomics, 14ner/Elevation, Archer, Helssin, BMS, Eli Lilly, Medtronic, Ribon, AstraZeneca, Arrys/Kyn, Regeneron, Hengrui, Hansoh, Blueprint, Roche/Genentech, Inivata
- N. Yamamoto: Research Funding: Astellas, Chugai, Eisai, Taiho, BMS, Pfizer, Novartis, Eli Lilly, AbbVie, Daiichi-Sankyo, Bayer, Boehringer Ingelheim, Kyowa-Hakko Kirin, Takeda, ONO, Janssen Pharma, MSD, MERCK, GSK. Advisory/ Consultancy: Eisai, Takeda, Otsuka, Boehringer Ingelheim, Cimic, Chugai. Speaker Bureau/Expert testimony: BMS, Pfizer, AstraZeneca, Eli Lilly, ONO, Chugai, Sysmex
- T. Doi: Research Funding: BMS, AbbVie, Taiho, Daiichi Sankyo, Novartis, Boehringer Ingelheim, MSD, Merck Serono, Lilly, Eisai, Kyowa Hakko Kirin, IQVIA, Pfizer. Honoraria: BMS, Astellas, AbbVie, Ono, Oncolys BioPharma, Taiho. Advisory: AbbVie, Taiho, Amgen, Sumitomo Dainippon, Rakuten Medical, Daiichi Sankyo, Takeda, Bayer, Novartis, Boehringer Ingelheim
- S. Anthony: Advisory: Exact Sciences. SDP Oncology Employee
- D. Bearss, M. Janát-Amsbury, M. Wade – SDP Oncology Employee

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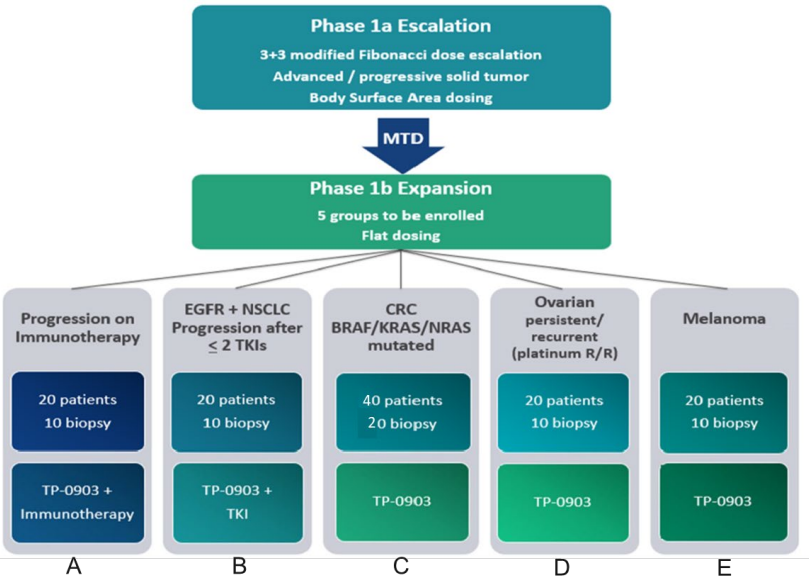
Study Design of TP-0903-101

Primary Objective: Determine the **maximum tolerated dose** and **dose limiting toxicities**



TP-0903-101 Amendment 5. For additional details on study design, please see https://clinicaltrials.gov/ct2/show/NCT02729298

Secondary Objectives:

- To establish the **pharmacokinetics** of orally administered dubermatinib
- To observe patients for any evidence of **antitumor activity** of dubermatinib by objective radiographic assessment by RECIST v1.1 and iRECIST
- To establish the **Recommended Phase 2 Dose (RP2D)** for future studies with dubermatinib (dose escalation)
- To determine early indications of clinical activity in subsets of patients for Phase 2 guidance (expansion cohorts)

Dose Level	Proposed Daily Dose	Increment from Previous Dose	No. of Patients In Cohort
1	1.5 mg/m^2	Starting Dose	3
2	3 mg/m^2	100%	3
3	6 mg/m^2	100%	3
4	9 mg/m^2	50%	3
5	12 mg/m^2	33%	3
6	16 mg/m^2	33%	5
7	21 mg/m^2	33%	3
8	28 mg/m^2	33%	6
9	37 mg/m^2	33%	6+4 (JPN)
10	50 mg*	-10%	3+3 (JPN)

*Moved to flat dose for ease of dosing

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Patient Characteristics

Cohort N	Dose escalation N = 45	Cohort A N = 21	Cohort B N = 22	Cohort C N = 47	Cohort D N = 22	Cohort E N = 20
Cancer type	Advanced solid tumors	Advanced solid tumors	EGFR+ NSCLC	BRAF-, KRAS-, or NRAS-Mutated CRC	Persistent/Recurrent Ovarian Cancer (Platinum R/R)	BRAF-WT, BRAF-Mutated Melanoma
Type of therapy	Single agent Dubermatinib	IO + Dubermatinib	EGFR TKI + Dubermatinib	Single agent Dubermatinib	Single agent Dubermatinib	Single agent Dubermatinib
Sex						
Female	21 (46.7%)	11 (52.4%)	14 (63.6%)	21 (44.7%)	22 (100%)	6 (30.0%)
Male	24 (53.3%)	10 (47.6%)	8 (36.4%)	26 (55.3%)	0	14 (70.0%)
Age (years), median (range)	65.8 (36.3, 81.6)	68.7 (43.7, 82.3)	63.8 (37.1, 85.1)	56.5 (39.4, 81.8)	61.7 (22.6, 80.8)	65.0 (29.6, 79.7)
ECOG PS						
0	23 (51.1%)	7 (33.3%)	8 (36.4%)	15 (31.9%)	11 (50.0%)	6 (30.0%)
1	21 (46.7%)	14 (66.7%)	14 (63.6%)	32 (68.1%)	11 (50.0%)	14 (70.0%)
2	1 (2.2%)	0	0	0	0	0
Race						
American Indian/ Alaska Native	0	0	0	1 (2.1%)	0	0
Asian	9 (20.0%)	0	7 (31.8%)	3 (6.4%)	2 (9.1%)	0
Black or African American	1 (2.3%)	0	1 (4.5%)	4 (8.5%)	2 (9.1%)	0
White	33 (73.3%)	21 (100%)	13 (59.1%)	38 (80.9%)	18 (81.8%)	19 (95.0%)
Multiracial	1 (2.2%)	0	0	0	0	1 (5.0%)
Not Reported	1 (2.2%)	0	1 (4.5%)	1 (2.1%)	0	0
Ethnicity						
Hispanic or Latino	11 (24.4%)	4 (19.0%)	0	6 (12.8%)	2 (9.1%)	3 (15.0%)
Not Hispanic or Latino	33 (73.3%)	17 (81.0%)	21 (95.5%)	40 (85.1%)	20 (90.9%)	16 (80.0%)
Not Reported	1 (2.2%)	0	1 (4.5%)	1 (2.1%)	0	1 (5.0%)

Safety: TEAEs Related to Dubermatinib by Investigators' Judgement

- Most common TEAEs **at least possibly related** to dubermatinib were nausea, vomiting, and diarrhea
- GI-based AEs were manageable and improved with supportive care. 3 pts discontinued due to GI-based AE
- Patients discontinued (MTD population) d/t AE: 6/131 (4.6%)

MedDRA[a] Preferred Term	Dose escalation N=45		Cohort A N = 21		Cohort B N = 22		Cohort C N = 47		Cohort D N = 22		Cohort E N = 20	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Nausea	25 (55.6%)	1 (2.2%)	16 (76.2%)	0	13 (59.1%)	0	30 (63.8%)	1 (2.1%)	14 (63.6%)	1 (4.5%)	11 (55.0%)	0
Vomiting	27 (60.0%)	2 (4.4%)	13 (61.9%)	0	6 (27.3%)	0	32 (68.1%)	1 (2.1%)	14 (63.6%)	1 (4.5%)	10 (50.0%)	0
Diarrhoea	19 (42.2%)	1 (2.2%)	12 (57.1%)	1 (4.8%)	15 (68.2%)	3 (13.6%)	30 (63.8%)	3 (6.4%)	9 (40.9%)	1 (4.5%)	13 (65.0%)	1 (5.0%)
Fatigue	6 (13.3%)	1 (2.2%)	6 (28.6%)	0	5 (22.7%)	1 (4.5%)	15 (31.9%)	3 (6.4%)	6 (27.3%)	0	8 (40.0%)	1 (5.0%)
Decreased appetite	2 (4.4%)	0	2 (9.5%)	0	2 (9.1%)	0	8 (17.0%)	1 (2.1%)	5 (22.7%)	0	3 (15.0%)	0
Anaemia	6 (13.3%)	1 (2.2%)	2 (9.5%)	0	4 (18.2%)	1 (4.5%)	1 (2.1%)	1 (2.1%)	3 (13.6%)	0	3 (15.0%)	0
Thrombocytopenia	6 (13.3%)	3 (6.7%)	1 (4.8%)	0	1 (4.5%)	0	3 (6.4%)	0	2 (9.1%)	0	1 (5.0%)	1 (5.0%)
Abdominal pain	3 (6.7%)	0	4 (19.0%)	0	0	0	4 (8.5%)	0	0	0	2 (10.0%)	0
ALT increased	4 (8.9%)	0	1 (4.8%)	0	1 (4.5%)	0	3 (6.4%)	0	1 (4.5%)	0	2 (10.0%)	0
Dizziness	4 (8.9%)	0	5 (23.8%)	0	0	0	1 (2.1%)	0	1 (4.5%)	0	1 (5.0%)	0
Hypomagnesaemia	1 (2.2%)	0	4 (19.0%)	0	2 (9.1%)	0	1 (2.1%)	0	1 (4.5%)	0	2 (10.0%)	0
Constipation	2 (4.4%)	0	2 (9.5%)	0	1 (4.5%)	1 (4.5%)	0	0	1 (4.5%)	0	4 (20.0%)	0
Dehydration	2 (4.4%)	0	2 (9.5%)	0	0	0	3 (6.4%)	0	1 (4.5%)	0	1 (5.0%)	0

- Grade 4 Thrombocytopenia was DLT at 28 mg/m^2 (Escalation Cohort 8); expanded out to n=6, no additional thrombocytopenia
- Grade 3 Thrombocytopenia was observed in 2 patients at 37 mg/m^2 (Escalation Cohort 9)
- MTD was determined as 50mg flat dose.

Clinical Data cut-off: July 15, 2020

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Overall Clinical Activity

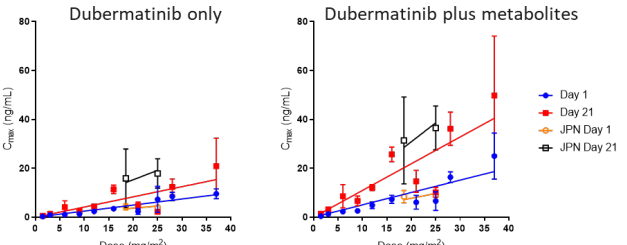
- 4 PRs observed; 2 in Dose Escalation (metastatic melanoma, intrahepatic cholangiocarcinoma), 1 in Cohort A (NSCLC + pembrolizumab) and 1 in Cohort B (NSCLC + osimertinib).

	Dose escalation N=45	Cohort A N = 21	Cohort B N = 22	Cohort C N = 47	Cohort D N = 22	Cohort E N = 20
Cancer type	Advanced solid tumors	Advanced solid tumors	EGFR+ NSCLC	BRAF-, KRAS-, or NRAS-Mutated CRC	Persistent/Recurrent Ovarian Cancer (Platinum R/R)	BRAF-WT, BRAF-Mutated Melanoma
Type of therapy	Single agent Dubermatinib	IO + Dubermatinib	TKI + Dubermatinib	Single agent Dubermatinib	Single agent Dubermatinib	Single agent Dubermatinib
Number of prior line, n(%)						
1-2	9 (20%)	12 (57%)	14 (64%)	3 (6%)	1 (5%)	6 (30%)
3-4	17 (38%)	5 (24%)	4 (18%)	28 (60%)	6 (27%)	8 (40%)
>4	19 (42%)	4 (9%)	4 (18%)	16 (34%)	15 (68%)	6 (30%)
Prior IO therapy, n(%)						
Yes	12 (27%)	21 (100%)	8 (36%)	24 (51%)	10 (45%)	19 (95%)
No	33 (73%)	0 (0%)	13 (59%)	23 (49%)	12 (55%)	1 (5%)
Best response to TP-0903						
PR	**2 (4.4%)**	**1 (4.8%)**	**1 (4.5%)**	0	0	0
SD	13 (28.9%)	10 (47.6%)	10 (45.5%)	9 (19.1%)	3 (13.6%)	5 (25%)
Disease Control Rate (SD+PR)	33.3%	52.4%	50.0%	19.1%	13.6%	25%
[95% Confidence Interval]	[19.5%, 48.0%]	[29.8%, 74.3%]	[28.2%, 71.8%]	[9.1%, 33.3%]	[2.9%, 34.9%]	[8.2%, 47.2%]
Not-Evaluated	12 (27%)	3 (14%)	4 (18%)	8 (17%)	5 (24%)	9 (45%)
Median weeks on TP-0903 (range)	8.1 (0.3, 50.1)	8.9 (0.3, 25.1)	9.0 (2.7, 16.1)	8.1 (0.1, 27.1)	8.1 (2.1, 32.1)	8.1 (1.1, 16.0)

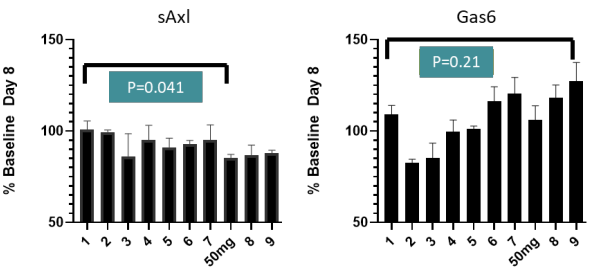
Clinical Data cut-off: July 15, 2020

Pharmacokinetics and Biomarkers

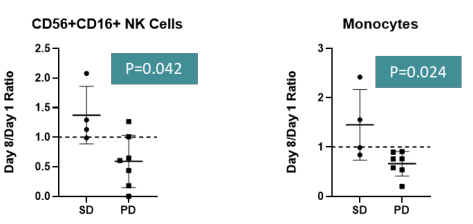
Dose Proportionality



Blood Markers Correlate with Drug Exposure

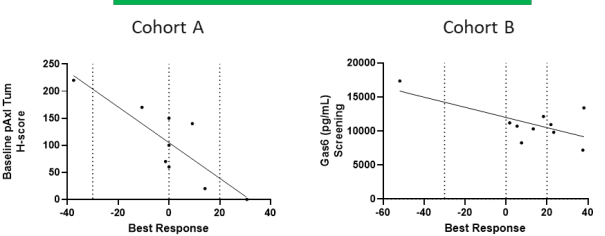


Immune Cell Regulation and Response (Cohort C)



Patients experiencing clinical activity appear to have a higher number of NK cells and monocytes at Day 8 versus Day 1, while those who progress do not

Markers Correlate with Response



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