



再鼎医药首次亮相AACR! 公布中国首个尼拉帕利期临床试验结果

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美国东部时间) 2019年4月2日, 再鼎医药 (纳斯达克代码: ZLAB) 在2019年美国癌症研究协会 (AACR) 年会上, 以海报形式公布了中国卵巢癌患者中开展的首个尼拉帕利 (ZL-2306) 的期临床试验结果。这一研究由复旦大学附属肿瘤医院吴小华教授和张剑教授牵头, 联合国内多家医院进行。

A Phase I Study to Evaluate the Pharmacokinetics (PK) and Safety of Niraparib in Chinese Patients with Epithelial Ovarian Cancer (OC)

Poster #3891

Jian Zhang¹, Yu-Nong Gao¹, Ge Lou¹, Ru-Tie Yin¹, Jian-Mei Hou¹, James Yan¹, Yong-Jiang He¹, Zhi-Yi Zhang¹, Ashley Milton², Xiao-Hua Wu¹

1. Shanghai Cancer Center, Fudan University, Shanghai, China; 2. Beijing Cancer Hospital, Beijing University, Beijing, China; 3. Hainan Medical University Cancer Hospital, Hainan, China; 4. West China Second University Hospital, Sichuan University, Chengdu, China; 5. Research and Development, Zai Lab, Shanghai, China; 6. Tesaro, Inc., Waltham, MA, USA

PURPOSES

Niraparib is a highly selective PARP1/2 inhibitor approved by FDA and EMA for maintenance treatment of patients with recurrent platinum-sensitive OC. The objectives of this study were to characterize the PK and safety of niraparib as a maintenance therapy in Chinese OC patients.

METHODS

Eligible patients were randomized 1:1:1 to 100, 200, or 300 mg once daily cohort. Plasma samples were collected following single and multiple dosing and analyzed using a validated LC/MS/MS method. PK parameters were analyzed by standard non-compartmental approach with WinNonlin. A population PK (Pop-PK) model was derived from pooled PK data of current study and two previous PK studies predominantly in Caucasian patients: dose escalation and expansion study (PADO1), and the ENGOT-OV1/NINOVA sub-study. Non-linear mixed effect modeling was carried out with NONMEM®.

STUDY DESIGN

RESULTS

Thirty-six patients were randomized and included in the PK and safety analysis set. Niraparib was rapidly absorbed after dosing with $t_{1/2} \approx 3h$. The exposure of niraparib was dose proportional, while other PK parameters such as $t_{1/2}$, accumulation ratio were dose independent (Table 2). The Pop-PK analysis model was established using PK data from 144 Caucasians and 35 Chinese. Chinese patients had a slightly higher C_{max} than Caucasian patients but similar total exposure ($AUC_{0-\infty}$) after a single dose (Figure 1). Simulation by final Pop-PK model indicated comparable total exposure ($AUC_{0-\infty}$) and C_{max} between Chinese and Caucasian patients at the steady-state following multiple daily doses (Figure 2). There was no effect of race on niraparib AUC and a negligible effect on C_{max} . The effects of body weight on niraparib exposure were relatively modest, except for extreme weights (Figure 3,4).

Treatment emergent AEs (TEAEs) occurred in 97.2% of all patients treated with niraparib. The most frequent (>20%) TEAEs were consistent with the known safety profile of PARP inhibitors (Table 3). TEAEs of Grade 3/4 reported in 5% patients included decreased platelet count (13.9%), decreased neutrophil count (11.1%), anemia (8.3%) and increased gamma-glutamyl transferase (5.6%).

Table 1. Demographic and Baseline Disease Characteristics

Variables	Niraparib 100mg (Q1)(n=12)	Niraparib 200mg (Q2)(n=12)	Niraparib 300mg (Q3)(n=12)	Overall (N=36)
Age				
Mean (SD)	57.4 (7.8)	52.2 (7.3)	57.8 (9.8)	55.8 (8.0)
Median	56.5	49.5	56.5	55.5
Min-Max	46-74	43-64	49-72	43-74
Weight (kg)				
Mean (SD)	61.4 (8.6)	62.1 (11.3)	57.7 (8.6)	60.4 (8.6)
Median	62.3	64.0	59.0	61.5
Min-Max	46.0-75.3	50.0-90.0	38.4-65.0	38.4-93.0
BSA (m²)				
Mean (SD)	24.9 (3.8)	24.87 (3.0)	22.7 (3.3)	24.0 (3.0)
Median	24.5	25.0	22.8	24.1
Min-Max	18.8-32.3	18.8-32.0	16.40-27.9	16.4-33.0
ECOG performance status, n (%)				
0	6 (50.0)	5 (41.7)	4 (33.3)	15 (41.7)
1	6 (50.0)	7 (58.3)	6 (50.0)	19 (51.9)
Site of primary tumor, n (%)				
Ovary	11 (91.7)	12 (100.0)	11 (91.7)	34 (94.4)
Fallopian tube	1 (8.3)	0 (0.0)	1 (8.3)	2 (5.6)
Mixed epithelial, n (%)				
High grade serous	10 (83.3)	11 (91.7)	11 (91.7)	32 (88.9)
Others	2 (16.7)	1 (8.3)	1 (8.3)	4 (11.1)
BRCA mutations, n (%)				
Positive for a deleterious mutation	4 (50.0)	6 (50.0)	2 (16.7)	14 (38.9)
Genetic variant, suspected deleterious	0	0	1 (8.3)	1 (2.8)
Genetic variant, favor polymorphism	1 (8.3)	1 (8.3)	1 (8.3)	3 (8.3)

Table 2. Summary of pharmacokinetic parameters of niraparib

Cohort	N	AUC _{0-∞} (MHP)				C _{max} (MHP)			
		Day 1	Day 1	Day 22	Day 22	Day 1	Day 1	Day 22	Day 22
100 mg	Green	468	1202	3274	2214	35.1%	27.5%	58.5%	40.7%
	Orange	1304	4024	3985	5810				
200 mg	Green	32.4%	30.7%	31.2%	25.4%				
	Orange	1004	4024	3985	5810				
300 mg	Green	32.1%	32.5%	33.5%	34.3%				
	Orange	1004	4024	3985	5810				

Table 3. Most frequent (>20%) TEAEs during the study

Preferred Term (PT)	100mg Q1 (N=12)	200mg Q2 (N=12)	300mg Q3 (N=12)	Overall (N=36)
TEAE	91.7	100.0	100.0	97.2
Neutrophil count decreased	41.7	41.7	75.0	52.8
White blood cell count decreased	41.7	33.3	75.0	50.0
Nausea	8.3	33.3	75.0	38.9
Platelet count decreased	25.0	8.3	66.7	33.3
Anemia	8.3	16.7	66.7	30.6
Arthralgia	16.7	25.0	41.7	27.8
Vomiting	8.3	16.7	58.3	27.8
Altered transaminase increased	25.0	33.3	16.7	25.0
Abnormal creatinine	16.7	33.3	25.0	22.2
Decreased appetite	8.3	16.7	41.7	22.2

CONCLUSIONS

The PK profile of niraparib in Chinese patients was consistent with its known profile in Caucasians. Niraparib demonstrated an expected safety profile and was well tolerated in Chinese OC patients.

REFERENCES

- Sandhu SK, Schwman WR, Wilding G, Moreno V, Baird RC, Miranda S, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. *The Lancet Oncology*. 2015;16(9):882-892.
- Mirza MR, Monk BJ, Herrstedt J, Cira AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *The New England Journal of Medicine*. 2018;379(22):2494-2504.
- Moon K, Zhang ZY, Agreus S, Sun H, Patel MR, Kamra V. The effect of food on the pharmacokinetics of niraparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, in patients with recurrent ovarian cancer. *Cancer chemotherapy and pharmacology*. 2018;61(3):497-503.
- Papadopoulos C. Limitations to the use of catapaptin-based therapy in advanced ovarian cancer. *ECJ supplements: ECJ: official journal of EORTC, European Organization for Research and Treatment of Cancer*. [et al.]; 2014. 2021;13:6.
- Administration USFDA. Approval Details and History, Letters, Labels, Reviews for NDA 208447. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/208447Orig1s01.pdf
- Chenra A, Yachika S. Current status of poly(ADP-ribose) polymerase inhibitors and future directions. *Oncotargets and therapy*. 2017;10:1516-208.

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美国癌症研究协会 (AACR) 成立于1907年, 是世界上创立最早、规模最大的专注于癌症研究的科学组织。AACR年会则是世界上规模最大的癌症研究会议之一, 每年都会吸引来自全球各地的近2万名专业人士出席会议。今年的AACR年会于3月29日至4月3日在美国亚特兰大举办。

此次再鼎医药公布的研究结果表明, 尼拉帕利在中国卵巢癌患者人群中的药代动力学特征与高加索人群基本相似。尼拉帕利呈线性药代动力学特征, 即药物暴露量随药物服用剂量增加而线性增大, 这为临床医生估算药物暴露量及调整药物剂量提供了便利。尼拉帕利的药物半衰期相比同类多个PARP抑制剂更长, 平均约36.4个小时, 为患者一天只服药一次提供了可能, 有助于药品上市后提高患者的依从性。群体药代动力学表明种族对尼拉帕利的药代动力学特征影响微弱, 而患者的基线体重可能是尼拉帕利的药物暴露量的一个协变量。在药物安全性方面, 尼拉帕利在中国卵巢癌患者的安全性与高加索人群相似, 患者耐受性总体良好, 不良反应可有效管控。患者的基线体重可能是尼拉帕利的药物暴露量的一个协变量, 良好的药代动力学性质为其更优的疗效奠定了基础, 同时也会临床医生有效管控药物不良反应提供了依据。

此外, 为了进一步探索尼拉帕利在中国卵巢癌患者中的疗效, 目前复旦大学附属肿瘤医院吴小华教授牵头, 联合国内多家医院正在开展一项尼拉帕利用于铂敏感复发 (PSR) 患者二线维持治疗的III期临床试验 (NORA研究, 已完成入组)。与此同时, 中国医学科学院肿瘤医院吴小华教授牵头, 联合国内多家医院正在开展一项尼拉帕利用于铂敏感患者一线维持治疗的III期临床试验 (PRIME研究)。相应的临床试验结果会陆续在国内外学术大会上披露。

尼拉帕利在中国卵巢癌患者中的III期临床试验是由国内多家医院协作完成的随机、开放、多中心研究。在此, 特别感谢复旦大学附属肿瘤医院妇科科吴小华教授和张剑教授、北京大学北京肿瘤医院高雨农教授、哈尔滨医科大学肿瘤医院姜国教授以及四川大学华西二院尹如铁教授等多位研究者们的共同努力!

关于尼拉帕利

尼拉帕利 (则乐® ZL2306) 是一种高效、选择性的每日一次口服小分子聚 (ADP-核糖) PARP 1/2抑制剂。尼拉帕利于2017年3月在美国获批, 同年11月在欧洲获批, 用于对含铂化疗完全或部分缓解的复发性上皮卵巢癌、输卵管癌或原发性腹膜癌患者的维持治疗。基于在美国和欧洲的获批, 尼拉帕利已于2018年10月在香港获批上市。尼拉帕利于2018年12月递交新药上市申请, 并于2019年1月被纳入优先审评审批名单。

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再鼎医药 (纳斯达克代码: ZLAB) 是一家立足中国、全球运营的创新型生物制药公司, 致力于为中国及全球的肿瘤、自身免疫性及传染性疾病患者提供创新药物。公司经验丰富的团队已与全球领先的生物制药公司建立了战略合作, 打造了一系列的候选创新药物, 以满足中国医药市场快速增长和全球范围内未满足的医疗需求。再鼎医药的远景是成为一家综合性的创新生物制药公司, 研发、生产并销售自主研发及合作伙伴的产品, 为促进全世界人类的健康福祉而努力。