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# 医学信息速递
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# 抗PD-L1单克隆抗体Socazolimab治疗复发或转移性宫颈癌的疗效和安全性：一项单臂Ⅰ期+扩展研究

产品战略&医学与信息部

2022-12

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# 文献基本信息

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

**Efficacy and Safety of the Anti–PD-L1 mAb Socazolimab for Recurrent or Metastatic Cervical Cancer: a Phase I Dose-Escalation and Expansion Study**

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ABSTRACT

Purpose: This study (ClinicalTrials.gov identifier, NCT03476659) is an open, phase I dose-escalation and expansion study investigating the safety and efficacy of the recombinant, fully human anti–programmed death ligand 1 (PD-L1) mAb socazolimab in patients diagnosed with recurrent or metastatic cervical cancer.

Patients and Methods: Patients received socazolimab every 2 weeks until disease progression. The study was divided into a dose-escalation phase and a dose-expansion phase. Safety and tolerability were primary endpoints of the dose-escalation phase. The primary endpoints of the dose-expansion phase were safety and the objective response rate (ORR) of the 5 mg/kg dose. Efficacy was assessed by the third-party independent review committee (IRC) using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Results: 104 patients were successfully enrolled into the study. Twelve patients were included in the dose-escalation phase, with one complete response and two partial responses in the 5 mg/kg treatment group. Ninety-two patients (5mg/kg) were enrolled in the dose-expansion phase. Fifty-four patients (59.3%) had baseline PD-L1–positive tumor expression (combined positive score ≥1). ORR was 15.4% [95% confidence interval (CI), 8.7%–24.3%]. Median PFS was 4.44 months (95% CI, 2.37–5.75 months), and the median OS was 14.72 months (95% CI, 9.59–NE months). ORR of PD-L1–positive patients was 16.7%, and the ORR of PD-L1–negative patients was 13.9%. No treatment-related deaths occurred.

Conclusions: Our study demonstrates that socazolimab has durable safety and efficacy for the treatment of recurrent or metastatic cervical cancer and exhibits a safety profile similar to other anti–PD-1/PD-L1 mAbs.

**Introduction**

Cervical cancer is a common malignant tumor of the female reproductive system. Globally, it is ranked the fourth leading cause of cancer-related death among women (1). Despite the widespread adoption of human papillomavirus (HPV) vaccination and cervical cancer screening, mortality rates remain high. In contrast to patients with early-stage and locally advanced cervical cancer, the treatment options for recurrent or metastatic cervical cancer are limited, thus increasing the clinical need for new and innovative second-line and later treatment options (2).

Platinum-based chemotherapy is currently the standard first-line treatment for patients with recurrent or metastatic cervical cancer. Early studies of single-agent cisplatin treatments have reported objective response rates (ORR) ranging from 20% to 25% in advanced cervical cancer, which were often accompanied with poor responses due to cisplatin resistance (3). In contrast to first-line treatments, current second-line, single-agent treatments have demonstrated much lower ORRs. In a meta-analysis utilizing the results from different earlier clinical studies, including treatments such as bevacizumab, docetaxel, paclitaxel, gemcitabine, and epirubicin (4–12), the combined ORR was 12.8% [95% confidence interval (CI), 8.7% to 14.3%], with a median progression-free survival (PFS) of 3 months, and a median overall survival (OS) of 7 month upon meta-analysis. Cisplatin-combinations have also demonstrated improvements in responses and survival times, and more recently, the combination of cisplatin, paclitaxel, and bevacizumab was explored in the GOG-240 study for the treatment of advanced cervical cancer, resulting in an increase of 3.7 months for the median OS (13–15). High toxicities, however, have limited the safety and efficacy of these treatments, and therefore have accelerated the need for novel second-line treatments to treat patients with recurrent or metastatic cervical cancer.

Immunotherapy has been gaining significant relevance as an alternate treatment method for cancer (16). Programmed cell death

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## Efficacy and Safety of the Anti–PD-L1 mAb Socazolimab for Recurrent or Metastatic Cervical Cancer: a Phase I Dose-Escalation and Expansion Study

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# 文献摘要

## 研究目的

一项开放的 I 期剂量递增和剂量扩展研究（NCT03676959），研究PD-L1单抗socazolimab在复发或转移性宫颈癌患者中的安全性和有效性。

## 研究方法

该研究分为剂量递增阶段和剂量扩展阶段。安全性和耐受性是剂量递增阶段的主要终点。剂量扩展阶段的主要终点是 5mg/kg 剂量的安全性和客观缓解率(ORR)。

## 研究结果

招募了 104 名患者。12 名患者被纳入剂量递增阶段，在 5mg/kg 治疗组中有 1 例完全缓解和 2 例部分缓解。92 名患者 (5mg/kg) 被纳入剂量扩展阶段，ORR 为 15.4%。中位 PFS 为 4.44 个月，中位 OS 为 14.72 个月。PD-L1 阳性和 PD-L1 阴性患者的 ORR 分别为 16.7% 和 17.9%。≥3级治疗相关不良事件发生率为 7.7% 。没有发生与治疗相关的死亡。

## 研究结论

我们的研究表明，**socazolimab对复发或转移性宫颈癌的治疗具有持久的安全性和有效性，其安全性与其他抗PD -1/PD-L1单抗相似。**

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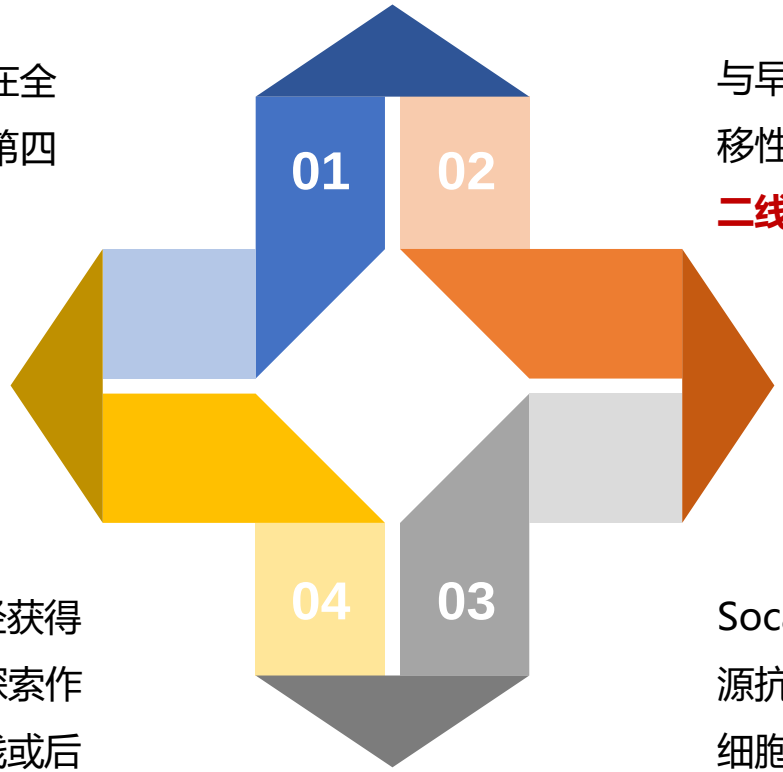
# 研究背景

宫颈癌是女性生殖系统常见的恶性肿瘤。在全球范围内，它是导致女性癌症相关死亡的第四大原因。




与早期和局部晚期宫颈癌患者相比，复发性或转移性宫颈癌的治疗方案有限，因此**临床对创新的二线和晚期治疗方案的需求巨大。**

免疫疗法作为癌症的一种替代治疗方法已经获得了普遍认可， PD-1/PD-L1免疫疗法已被探索作为一线失败后晚期复发的宫颈癌患者的二线或后期治疗方法。

Socazolimab是一种新型的、高特异性的、全人源抗PD-L1单抗，具有PD-L1抑制剂/抗体依赖的细胞介导的细胞毒性作用（ADCC）**两种协同作用的抗肿瘤活性机制。**

# - Efficacy and Safety of the Anti–PD-L1 mAb Socazolimab for Recurrent or Metastatic Cervical Cancer: a Phase I Dose-Escalation and Expansion Study -

1 研究背景

2 研究方法

3 研究结果

4 研究结论

# 研究方法



多中心、单臂I期+扩展研究以评估索卡佐利单抗在复发或转移性宫颈癌患者中的有效性和安全性。

- 年龄≥18岁；
- 经组织病理学或细胞学诊断，接受过一线含铂方案失败或者不能耐受的复发或转移性宫颈癌。一线失败的定义：辅助治疗期间或治疗结束后6个月内进展，姑息治疗后首次进展。
- ECOG评分0-1分；
- 至少有一个可测量病灶（根据RECIST v1.1）
- 脏器功能符合

**剂量爬坡阶段（n=12）**
5mg/kg组3例，10mg/kg组3例，
15mg/kg组6例，每2周给药1次

**索卡佐利单抗注射液**

**剂量扩增阶段(n=92)**
扩增剂量组：5mg/kg
每2周给药1次

**（一）剂量爬坡阶段**
主要终点：最大耐受剂量（MTD），剂量限制性毒性（DLT），推荐剂量
次要终点：ORR，OS，初步有效性

**（二）剂量扩增阶段**
主要终点：客观缓解率（ORR）
次要终点：无进展生存期（PFS），缓解持续时间（DOR），总生存期（OS），最佳总体疗效（BOR）

最长用药24周期或1年，如仍能获益可以继续用药，直至毒性不能耐受或确定的疾病进展或自愿退出

# - Association Between Depression and Clinical Outcomes in Patients With Hypertrophic Cardiomyopathy -

1 文献简介

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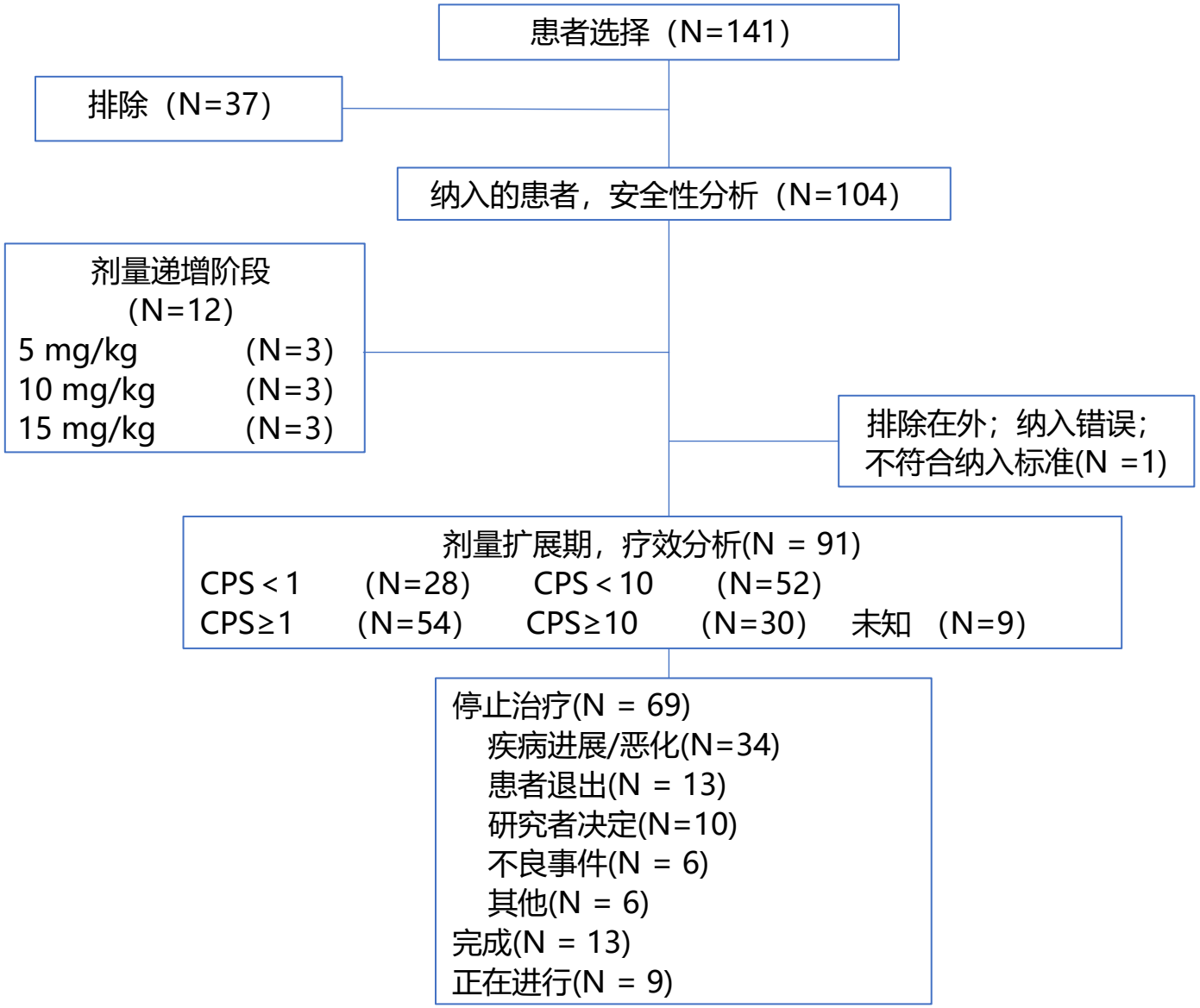
4 研究结论

# 结果：患者入组情况




- 入选的141名患者中，有104名患者接受了至少一剂socazolimab治疗。
- **12名**患者被纳入剂量递增阶段，并相应分配到5 mg/kg、10 mg/kg和15 mg/kg治疗组。
- **92例**患者被纳入5 mg/kg组进行剂量扩展期，其中1例患者未达到目标人群标准。
- 12例患者在剂量扩展期进行了PD-1受体占有率的检测。所有104例患者均纳入安全性分析。

# 结果：安全性

- Socazolimab耐受性良好，**安全性与其他抗PD-L1/PD-L1单克隆抗体相似**。
- 104例患者被纳入安全性分析。101例患者(97.1%)报告了AE，**66例患者(63.5%) 发生治疗相关的不良事件(TRAE)。所有TRAE均在其他抗PD-L1/PD-L1单克隆抗体中有过报道。**最常见的为甲减(17.3%)、白细胞减少(11.5%)、谷丙转氨酶和天冬氨酸转氨酶水平升高(各占9.6%)和贫血(8.7%)。**大多数TRAE为1-2级**，仅在5mg /kg组中有8例患者(8.4%)报告了≥3级TRAE，无治疗相关死亡发生。
- 40例患者(38.5%)发生免疫相关不良事件。最常见的为甲减(17.3%)、类风湿因子升高(7.7%)、甲亢(5.8%)和白细胞减少(4.8%)。

**Table 2.** Summary of patient AEs (safety analysis set, $N = 104$).

| AEs | 5 mg/kg ($n = 95$) Any grade | 5 mg/kg ($n = 95$) Grade 3 or above | 10 mg/kg ($n = 3$) | 15 mg/kg ($n = 6$) | Total ($N = 104$) |
|---|---|---|---|---|---|
| TRAEs | 59 (62.1%) | 8 (8.4%) | 2 (66.7%) | 5 (83.3%) | 66 (63.5%) |
| TRAE-related treatment interruption | 19 (20.0%) | | 0 | 0 | 19 (18.3%) |
| TRAE-related dose discontinuation | 9 (9.5%) | | 0 | 0 | 9 (8.7%) |
| Hypothyroidism | 16 (16.8%) | 0 | 0 | 2 (33.3%) | 18 (17.3%) |
| Leukopenia | 9 (9.5%) | 0 | 1 (33.3%) | 2 (33.3%) | 12 (11.5%) |
| Elevated alanine aminotransferase | 9 (9.5%) | 1 (1.1%) | 1 (33.3%) | 0 | 10 (9.6%) |
| Elevated aspartate aminotransferase | 9 (9.5%) | 0 | 1 (33.3%) | 0 | 10 (9.6%) |
| Anemia | 7 (7.4%) | 0 | 1 (33.3%) | 1 (16.7%) | 9 (8.7%) |
| Elevated rheumatoid factor | 5 (5.3%) | 0 | 1 (33.3%) | 2 (33.3%) | 8 (7.7%) |
| Nausea | 5 (5.3%) | 1 (1.1%) | 2 (66.7%) | 1 (16.7%) | 8 (7.7%) |
| Hyperthyroidism | 5 (5.3%) | 0 | 0 | 1 (16.7%) | 6 (5.8%) |
| Intestinal obstruction | 1 (1.1%) | 1 (1.1%) | 0 | 0 | 1 (1.0%) |
| Elevated γ-glutamyltransferase | 1 (1.1%) | 1 (1.1%) | 0 | 0 | 3 (2.9%) |
| Abnormal liver function | 1 (1.1%) | 1 (1.1%) | 0 | 0 | 3 (2.9%) |
| Pharyngitis | 1 (1.1%) | 1 (1.1%) | 0 | 0 | 1 (1.0%) |
| Elevated conjugated bilirubin | 1 (1.1%) | 1 (1.1%) | 0 | 0 | 1 (1.0%) |
| Immune-mediated myocarditis | 1 (1.1%) | 1 (1.1%) | 0 | 0 | 1 (1.0%) |
| Vomiting | 1 (1.1%) | 1 (1.1%) | 1 (33.3%) | 1 (16.7%) | 4 (3.8%) |
| Immune-mediated AEs | 34 (35.8%) | 4 (4.2%) | 1 (33.3%) | 5 (83.3%) | 40 (38.5%) |
| Hypothyroidism | 16 (16.8%) | 0 | 0 | 2 (33.3%) | 18 (17.3%) |
| Elevated rheumatoid factor | 5 (5.3%) | 0 | 1 (33.3%) | 2 (33.3%) | 8 (7.7%) |
| Hyperthyroidism | 5 (5.3%) | 0 | 0 | 1 (16.7%) | 6 (5.8%) |
| Leukopenia | 3 (3.2%) | 0 | 1 (33.3%) | 1 (16.7%) | 5 (4.8%) |
| Elevated alanine aminotransferase | 3 (3.2%) | 1 (1.1%) | 0 | 0 | 3 (2.9%) |
| Elevated aspartate aminotransferase | 3 (3.2%) | 1 (1.1%) | 0 | 0 | 3 (2.9%) |
| Elevated blood thyroid stimulating hormone | 3 (3.2%) | 0 | 0 | 0 | 3 (2.9%) |
| Abnormal liver function | 1 (1.1%) | 1 (1.1%) | 0 | 0 | 1 (1.0%) |
| Pharyngitis | 1 (1.1%) | 1 (1.1%) | 0 | 0 | 1 (1.0%) |
| Immune-mediated myocarditis | 1 (1.1%) | 1 (1.1%) | 0 | 0 | 1 (1.0%) |

治疗相关的不良事件

甲状腺功能减退
白细胞减少
谷丙转氨酶水平升高
天冬氨酸转氨酶水平升高
贫血

免疫相关不良事件
甲状腺功能减退
类风湿因子升高
甲状腺功能亢进
白细胞减少

Note: Data noted as *n* (%) unless stated otherwise. TRAEs (with ≥ 5% incidence rates); immune-related AEs (with ≥ 2% incidence rates).

# 结果：疗效

- 在剂量递增阶段，5 mg/kg组有1例患者出现CR（完全缓解），2例PR（部分缓解）。10mg /kg组和15mg /kg组均未见CR和PR。此外，由于在第二个治疗周期之前，5 mg/kg剂量的受体占有率(88.03%)已经达到，因此选择5 mg/kg剂量作为推荐目标剂量。
- 在剂量扩展期(5 mg/kg)，客观缓解率(ORR)为15.4%，疾病控制率(DCR)为49.5%，mPFS为4.44，mOS为14.72。
- PD-L1 阳性患者的ORR为16.7%， PD-L1 阴性患者的ORR为17.9%。CPS≥10和1≤CPS < 10亚组的ORR分别为20.0%和12.5%，这**进一步证明Socazolimab对不同PD-L1表达水平的患者有效。**
- 由于目前已知的几种抗PD -1/PD-L1单克隆抗体仅在PD-L1阳性患者中表现出疗效，socazolimab将增加患者获得宫颈癌**PD-L1阴性患者**免疫治疗的机会。

客观缓解率

疾病控制率

**Table 3.** Antitumor efficacy assessment by IRC evaluation (efficacy analysis set, *N* = 91).

| | | PD-L1 expression | | | |
|---|---|---|---|---|---|
| Efficacy | 5 mg/kg dose expansion (*N* = 91) | CPS < 1 (*N* = 28) | 1 ≤ CPS < 10 (*N* = 24) | CPS ≥ 10 (*N* = 30) |
| ORR | 14 (15.4%) | 5 (17.9%) | 3 (12.5%) | 6 (20%) |
| 95% CI | 8.7%–24.5% | 6.1%–36.9% | 2.7%–32.4% | 7.71%–38.57% |
| DCR | 45 (49.5%) | 12 (42.9%) | 11 (45.8%) | 21 (70.00%) |
| 95% CI | 38.8%–60.1% | 24.5%–62.8% | 25.6%–67.2% | 50.60%–85.27% |
| PFS, months | | | | |
| Median duration (95% CI) | 4.44 (2.37–5.75) | 2.79 (1.81–5.72) | 3.58 (2.00–7.66) | 7.56 (2.56–NE) |
| OS, months | | | | |
| Median duration (95% CI) | 14.72 (9.59–NE) | 15.84 (7.10–NE) | NE (8.54–NE) | NE (13.34–NE) |
| OS (%) | | | | |
| 6 months (95% CI) | 78.6% (68.5–85.8) | 74.7% (54.1–87.1) | 74.2% (51.3–87.5) | 93.3% (75.9–98.3) |
| 12 months (95% CI) | 58.2% (45.4–69.0) | 59.3% (36.6–76.3) | 53.0% (23.3–75.8) | 77.0% (55.3–89.1) |
| DOR, months | | | | |
| Median duration (range) | NE (3.32–14.92) | NE (3.81–12.88) | NE (3.32–14.92) | NE (3.32–14.92) |

Note: Data noted as *n* (%) unless stated otherwise.

# 结果：药代动力学



- 在剂量递增阶段，在5 mg/kg至15 mg/kg剂量范围内观察到药代动力学特征(表4)。
- 对于5 mg/kg组，Socazolimab的血清浓度在1.98 h达到最大值，并以10.75 mL/h的清除率下降。观察到剂量依赖的线性药代动力学特征。4个治疗周期(8周)后，Socazolimab达到稳态浓度。Socazolimab的平均血清半衰期为317.0 h(13.2天)。
- 5例患者治疗前抗药物抗体阳性。治疗期间，在安全性分析组的104例可评估患者中，另外11例(10.6%)检测到抗药物抗体。大多数患者在第12个治疗周期后抗药物抗体检测呈阴性，仅1例(1.0%)患者仍然呈阳性。

**Table 4.** Pharmacokinetic characteristics of each treatment group in the dose-escalation phase ($N = 12$).

| Pharmacokinetic parameters | 5 mg/kg ($N = 3$) | 10 mg/kg ($N = 3$) | 15 mg/kg ($N = 3$) |
|---|---|---|---|
| $C_{max}$ (μg/mL) ($\times 10^2$) | 1.23 ± 0.07 | 2.22 ± 0.59 | 3.51 ± 0.53 |
| $T_{max}$ (h) | 1.98 ± 0.27 | 1.98 ± 1.04 | 2.67 ± 1.37 |
| $AUC_{0-t}$ (μg/mL/h) ($\times 10^4$) | 2.42 ± 0.04 | 4.15 ± 0.9 | 6.84 ± 1.39 |
| $AUC_{inf}$ (μg/mL/h) ($\times 10^4$) | 3.15 ± 0.08 | 4.92 ± 1.37 | 8.51 ± 1.81 |
| $t_{1/2}$ (h) ($\times 10^2$) | 3.17 ± 0.14 | 2.61 ± 0.31 | 2.98 ± 0.70 |
| $CL_t$ (mL/h) | 10.75 ± 2.20 | 12.40 ± 0.82 | 12.36 ± 3.56 |
| Vd (mL) ($\times 10^3$) | 4.88 ± 0.80 | 4.65 ± 0.50 | 5.27 ± 1.76 |

缩写：$AUC_{inf}$，浓度-时间曲线下面积(时间0到无穷)；$AUC_{0-t}$，浓度-时间曲线下面积(时间0到t)；Cmax，血液中药物的最大浓度；CLt，药物清除率；$T_{max}$，药浓度达最大值的时间；$_{t1}$/2半衰期；Vd，药物分布体积。

# 结果：药效学



- 所有患者在单次给药后均保持PD-1完全受体占有至少16周。在第2个治疗周期之前，平均受体占用率为88.03%，与第9个治疗周期第1天的88.44%水平保持一致。PD-1受体的完全占有率为80% ~ 120%。
- 总的来说，**药代动力学、药效学和安全性资料提供了很好的证据，说明5 mg/kg剂量是进一步临床研究的合适剂量。**

# 结果：小结



**01** 总体疗效好，单药ORR 15.4%；mOS 14.7个月；

**02** 单药对PD-L1表达阴性人群治疗有效，阴性ORR 17.9%

**03** 高度安全性，总相关AE发生率63.5%，≥3级7.7%

**04** 平均受体占用率为88.03%

**05** 平均血清半衰期为317.0 h(13.2天)

# - Association Between Depression and Clinical Outcomes in Patients With Hypertrophic Cardiomyopathy -

1 文献简介

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4 研究结论

## 结论

- 我们的研究表明，索卡佐利单抗在治疗复发性或转移性宫颈癌方面有显著的安全性和有效性，无论PD-L1的表达状态。同时药物使用剂量低，mOS长。

# 谢谢关注！

thanks for your attention.