

# Real-world dosing patterns of patients with metastatic pancreatic cancer (mPC) treated with liposomal irinotecan (nal-IRI) in US oncology clinics

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## BACKGROUND

- Pancreatic cancer accounts for about 3% of all cancers and is the third leading cause of cancer related death in the United States, surpassing breast cancer.<sup>1</sup>
- Due to limited treatment options and the aggressive nature of the cancer, 5-year survival remains very low at 8.5%.<sup>2</sup>
- Liposomal irinotecan (nal-IRI) is a topoisomerase inhibitor indicated, in combination with 5-fluorouracil and leucovorin, for the treatment of metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy.<sup>3</sup>
- Used in combination with fluorouracil and folinic acid, nal-IRI has been proven to extend median overall survival to 6.1 months compared to 4.2 months in patients treated with fluorouracil and folinic acid.<sup>4</sup>
- Dose intensity over 6 weeks and duration of exposure for combination therapy with nal-IRI in the NAPOLI-1 trial was 167.5 mg/m<sup>2</sup> (SD 44.8) and 8.7 weeks (IQR: 5.4 – 22.0), respectively.<sup>4</sup>
  - Hazard ratios reported in NAPOLI-1 included overall survival [0.67 (95% CI 0.49 – 0.92)] and progression-free survival [0.56 (95% CI 0.41 – 0.75)].<sup>4</sup>

## OBJECTIVE

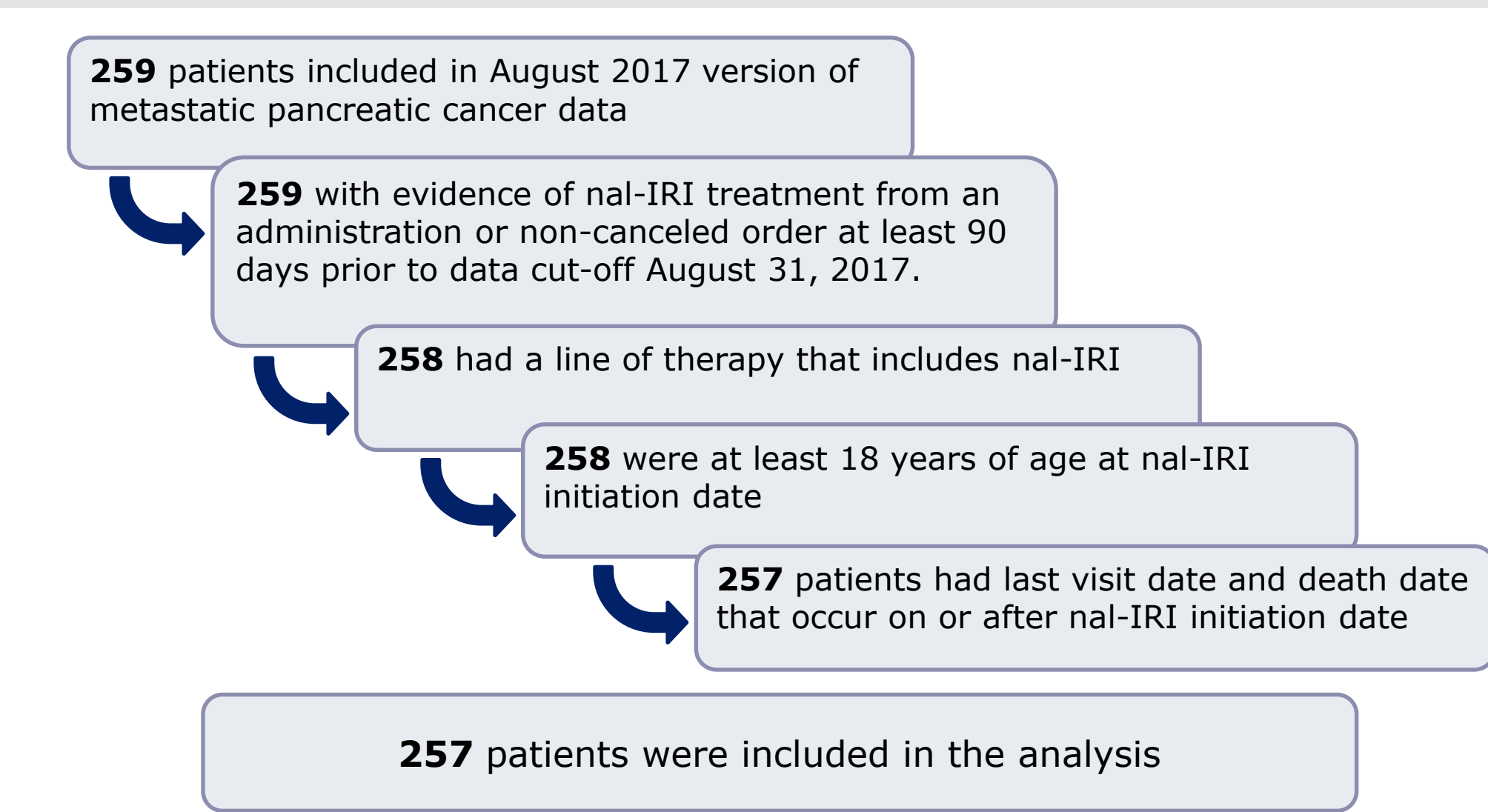
- To describe the real-world dosing patterns of patients with metastatic pancreatic cancer (mPC) treated with liposomal irinotecan (nal-IRI).

## METHODS

### Study Design and Data Source

- A retrospective descriptive analysis was performed using the Flatiron Health longitudinal database, a demographically and geographically diverse database derived from electronic health record (EHR) data which includes data from over 265 cancer clinics representing more than 2 million active US cancer patients for analysis.<sup>5</sup>
  - Patient-level data include structured and unstructured data, curated via technology-enabled abstraction.
  - Data provided for study were de-identified with provisions in place to prevent re-identification and protect patients’ confidentiality.
- ### Patient Selection
- This analysis identified and evaluated adult patients diagnosed with mPC between 1/1/2014 and 8/31/2017 and treated with nal-IRI between 11/1/2015 and 8/31/2017.
  - Eligible patients were those who initiated nal-IRI treatment at least 90 days prior to 8/31/2017, were at least 18 years old, had last visit date and death date that occurred on or after nal-IRI initiation date.

**Figure 1. Cohort Attrition**



## Measures and Statistical Analyses

- Baseline demographics and clinical characteristics, dose intensity (DI), dose modification, and duration of exposure (DOE) (on or after index date), grade 3-4 adverse events (AE), growth factor usage, and reasons for discontinuation were determined.
- Dose intensity was the total dose (in mg/m<sup>2</sup>) of nal-IRI given to patients within the first 6 weeks of initiating a nal-IRI regimen.
- Dose modification was defined as a difference of ≥7 mg/m<sup>2</sup> amid consecutive administrations (or orders if missing administration).
- Grading of adverse events was only possible for lab values and used the NCI CTCAE grading scheme between nal-IRI initiation and discontinuation.
  - Grade 3 and 4 neutropenia was calculated as neutrophil counts <1000-500/μL and <500/μL, respectively.
- Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

### Patient Population

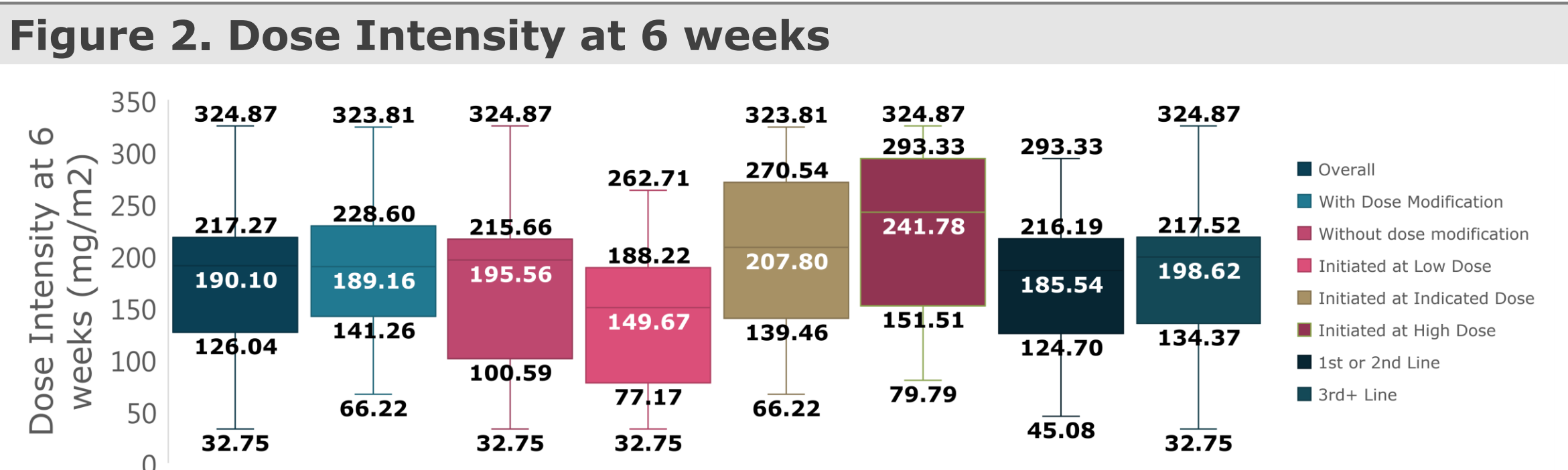
- The study sample included 257 patients; demographic and clinical characteristics are summarized in **Table 1**.

| Table 1. Demographics and Clinical Characteristics         |  |                  |
|--|--|------------------|
| Demographics   |  |                  |
| Total Cohort   |  | 257 (100%)       |
| Male (n=132)   |  | 132 (51.3%)      |
| Age at index, median (IQR) years (n=257)                   |  | 68 (61-74)       |
| Clinical Characteristics                                   |  |                  |
| BMI, median (IQR) kg/m <sup>2</sup> (n=225)                |  | 23.2 (20.7-26.5) |
| Tumor Location, n(%)                                       |  |                  |
| Head   |  | 132 (51.4%)      |
| Body   |  | 68 (26.5%)       |
| Tail   |  | 35 (13.6%)       |
| Overlapping  |  | 20 (7.8%)        |
| Pancreas, NOS  |  | 2 (0.8%)         |
| ECOG Score, n(%)   |  |                  |
| 0-1  |  | 128 (49.8%)      |
| 2-4  |  | 33 (12.8%)       |
| Missing  |  | 96 (37.4%)       |
| Charlson Comorbidity Index, n(%)                           |  |                  |
| 2 or more  |  | 257 (100%)       |
| Neutrophil to Lymphocyte Ratio (NLR), median (IQR) (n=160) |  | 3.9 (2.5-5.7)    |
| Number of lines prior to nal-IRI, n(%) <sup>a</sup>        |  |                  |
| 0 <sup>b</sup>   |  | 38 (14.8%)       |
| 1  |  | 107 (41.6%)      |
| 2  |  | 85 (33.1%)       |
| 3  |  | 21 (8.2%)        |
| 4+   |  | 6 (2.3%)         |
| Initial Dose, n(%)   |  |                  |
| Low (30 - <65 mg/m <sup>2</sup> )                          |  | 67 (26.1%)       |
| Indicated (65 - <75 mg/m <sup>2</sup> )                    |  | 152 (59.1%)      |
| High (≥70 mg/m <sup>2</sup> )                              |  | 11 (4.3%)        |
| Missing  |  | 27 (10.5%)       |

<sup>a</sup> 94.1% of patients received prior gemcitabine  
<sup>b</sup> Patients received neoadjuvant, adjuvant, or locally advanced treatment, but no previous therapy for metastatic disease

### Dose Intensity

- Overall mean DI was 177.8 mg/m<sup>2</sup> (SD 74.9 mg/m<sup>2</sup>) with median DI for subgroups indicated in **Figure 2**.
- Stratified into groups based on median DI (190 mg/m<sup>2</sup>), more patients below (<) median DI initiated at a low dose compared to those at or above (≥) median DI (44.4% vs 13.8%, respectively).



### Duration of Exposure

- The median DOE for all patients was 7.3 weeks (IQR 3.4 – 17.1). **Table 3** contains a summary for each subgroup.
- In 1st or 2nd line patients, median DOE was 8.9 (IQR 3.1 – 19.0) weeks compared to 6.4 (IQR 3.4 – 12.1) weeks in 3rd+ line patients.
- Stratified by initial dose, patients initiated at the indicated dose had a median DOE of 8.1 weeks (IQR 3.4 – 18.3).
- Low dose and high dose DOE was 7.1 and 6.1 weeks, respectively.
- Patients with a dose modification experienced a longer DOE (13.1 weeks) compared to those without a dose modification (6.1 weeks).

| Table 3. Duration of Exposure |     |                     |
|-------------------------------|-----|---------------------|
| Characteristic                | n   | Median (IQR), weeks |
| Overall                       | 257 | 7.3 (3.4 – 17.1)    |
| Below Median Dose Intensity   | 115 | 3.1 (0.1 – 8.1)     |
| With Dose Modification        | 70  | 13.1 (7.1 – 24.9)   |
| Initiated at Low Dose         | 67  | 7.1 (2.1 – 13.4)    |
| Initiated at Indicated Dose   | 152 | 8.1 (3.4 – 18.3)    |
| Initiated at High Dose        | 11  | 6.1 (2.1 – 24.3)    |
| 1st or 2nd Line               | 145 | 8.9 (3.1 – 19.0)    |
| Below Median Dose Intensity   | 66  | 2.1 (0.1 – 8.9)     |
| With Dose Modification        | 47  | 14.1 (7.1 – 25.1)   |
| 3rd+ Line                     | 112 | 6.4 (3.4 – 12.1)    |
| Below Median Dose Intensity   | 49  | 3.4 (0.7 – 7.1)     |
| With Dose Modification        | 23  | 11.0 (7.1 – 24.1)   |

### Dose Modification

- Overall, 27.2% of patients experienced a dose modification (**Table 4**); when stratified by median DI similar rates were seen for below median DI and at or above median DI.
  - Across all subgroups, dose reductions were more common compared to dose escalations.

| Table 4. Dose Modifications |                    |                   |                   |
|-----------------------------|--------------------|-------------------|-------------------|
| Category                    | All Patients, n(%) | < Median DI, n(%) | ≥ Median DI, n(%) |
| Overall                     | 257 (100%)         | 115 (100%)        | 116 (100%)        |
| Modified Dose               | 70 (27.2%)         | 35 (30.4%)        | 35 (30.2%)        |
| Increased Dose              | 25 (9.7%)          | 11 (9.6%)         | 14 (12.1%)        |
| Decreased Dose              | 58 (22.6%)         | 29 (25.2%)        | 29 (25.0%)        |
| 1st or 2nd Line             | 145 (56.4%)        | 66 (57.4%)        | 65 (56.0%)        |
| Modified Dose               | 47 (32.4%)         | 24 (36.4%)        | 23 (35.4%)        |
| Increased Dose              | 18 (12.4%)         | 7 (10.6%)         | 11 (16.9%)        |
| Decreased Dose              | 37 (25.5%)         | 20 (30.3%)        | 17 (26.2%)        |
| 3rd+ Line                   | 112 (43.6%)        | 49 (42.6%)        | 51 (44.0%)        |
| Modified Dose               | 23 (20.5%)         | 11 (22.4%)        | 12 (23.5%)        |
| Increased Dose              | 7 (6.3%)           | 4 (8.2%)          | 3 (5.9%)          |
| Decreased Dose              | 21 (18.8%)         | 9 (18.4%)         | 12 (23.5%)        |

### Adverse Events

- Neutropenia was the only AE with labs to measure grading during and before the nal-IRI containing regimen.
  - Grade 3 and 4 neutropenia during baseline was observed in 21.4% and 8.2% of all patients, respectively (**Table 5**).

| Table 5. Grade 3 or 4 Neutropenia |                 |                              |                                |
|-----------------------------------|-----------------|------------------------------|--------------------------------|
|                                   | Baseline*, n(%) | During 90-day baseline, n(%) | During nal-IRI treatment, n(%) |
| <b>Grade 3</b>                    |                 |                              |                                |
| All Patients                      | 55 (21.4%)      | 17 (6.6%)                    | 18 (7.0%)                      |
| 1st or 2nd line                   | 26 (17.9%)      | 11 (7.6%)                    | 8 (5.5%)                       |
| 3rd+ line                         | 29 (25.9%)      | 6 (5.7%)                     | 10 (8.9%)                      |
| Below Median DI                   | 22 (19.1%)      | 8 (7.0%)                     | 8 (7.0%)                       |
| At or above Median DI             | 27 (23.3%)      | 7 (6.0%)                     | 7 (6.0%)                       |
| <b>Grade 4</b>                    |                 |                              |                                |
| All Patients                      | 21 (8.2%)       | 5 (2.0%)                     | 5 (2.0%)                       |
| 1st or 2nd line                   | 8 (5.5%)        | 1 (0.7%)                     | 3 (2.1%)                       |
| 3rd+ line                         | 13 (11.6%)      | 4 (3.6%)                     | 2 (1.8%)                       |
| Below Median DI                   | 9 (7.8%)        | 2 (1.7%)                     | 2 (1.7%)                       |
| At or above Median DI             | 10 (8.6%)       | 3 (2.6%)                     | 3 (2.6%)                       |

\*Time period for baseline was from mPC diagnosis to nal-IRI initiation

### Growth Factor Usage

- For all groups, a higher proportion of patients were on growth factors prior to nal-IRI treatment compared with during treatment.

### Reasons for Discontinuation

- Progression was the most common reason for discontinuation across all groups and was followed by disease-related symptoms not due to therapy (**Table 6**).

| Table 6. Reasons for Discontinuation*       |               |                   |                   |
|---|---------------|-------------------|-------------------|
| End Reason                                  | Overall, n(%) | < Median DI, n(%) | ≥ Median DI, n(%) |
| Completed treatment                         | 3 (1.17%)     | 1 (0.87%)         | 2 (1.72%)         |
| Death                                       | 14 (5.45%)    | 5 (4.35%)         | 6 (5.17%)         |
| Disease-related symptoms not due to therapy | 32 (12.45%)   | 19 (16.52%)       | 12 (10.34%)       |
| Other                                       | 3 (1.17%)     | 2 (1.74%)         | 1 (0.86%)         |
| Patient request                             | 14 (5.45%)    | 12 (10.43%)       | 1 (0.86%)         |
| Progression                                 | 106 (41.25%)  | 34 (29.57%)       | 60 (51.72%)       |
| Toxic effect of therapy                     | 27 (10.51%)   | 17 (14.78%)       | 8 (6.90%)         |
| Missing                                     | 66 (25.68%)   | 29 (25.22%)       | 31 (26.72%)       |
| Total Unique Patients                       | 257 (100.00%) | 115 (100.00%)     | 116 (100.00%)     |

\*Patients may have multiple end reasons, categories are not mutually exclusive, and therefore percentages in each column may sum to more than 100%.

## LIMITATIONS

- EHR data are subject to possible entry errors and missing information which could have led to extreme or incorrect values.
- Age was limited to 85 years and younger for de-identification reasons therefore the true age of the older patients of the population and true average age of the overall population is unknown.
- Diagnosis codes from the structured data were captured at the oncology clinic. Conditions not relevant to cancer may not have been captured, potentially leading to an underestimate of the true comorbidity burden.

## CONCLUSIONS

- Compared to the NAPOLI-1 trial, this real-world analysis demonstrated similar DI results, however patients had fewer dose modifications and were slightly older, with worse performance status than those in the trial.
  - Similarly, rates of treatment related reasons for discontinuation were comparable: 10.5% in this analysis vs. 11.1% in NAPOLI-1.
- Below median DI was associated with an increased proportion of patient discontinuation due to side effects and patient request, as opposed to progression in the ≥ median DI group, suggesting that median DI reflect tolerability.
- Larger patient cohort analyses will further elucidate dosing patterns and outcomes in patients treated with nal-IRI.

## References

1. American Cancer Society. Cancer Facts and Figures 2017. Atlanta: American Cancer Society; 2018. <https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics.html>
2. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, [https://seer.cancer.gov/csr/1975\\_2014/](https://seer.cancer.gov/csr/1975_2014/), based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
3. Zhang, H. (2016). Onivyde for the therapy of multiple solid tumors. OncoTargets and Therapy, 9, 3001–3007.
4. Wang-Gillam, A., Li, C. P., Bodoky, G., Dean, A., Shan, Y. S., Jameson, G., ... & Hubner, R. A. (2016). Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. The Lancet, 387(10018), 545-557.
5. Flatiron Health database (<https://flatiron.com/real-world-evidence/>), October 2017

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