# Risk of Malignancy and Hemophagocytic Lymphohistiocytosis (HLH) in Pediatric IBD: Results from the DEVELOP Registry

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# BACKGROUND

- As part of post-marketing surveillance, the DEVELOP Registry (initiated in 2007) is an international, multicenter, prospective registry of long-term safety in pediatric patients with IBD treated with (REMICADE®) and/or other medical therapies
- Within this framework the incidences of malignancy and hemophagocytic lymphohistiocytosis (HLH) per patient years exposure were compared
- Patients categorized into 3 exposure cohorts (meaning ever-exposed):
  - IFX: IFX as only biologic ± non- biologics
  - Biologics: All biologics, including IFX, ± non-biologics
  - Non-biologics: 5-ASA's, steroids, thiopurines, MTX, antibiotics, and other IBD therapies in the absence of biologics

# Malignancy and HLH events

- As of March 18, 2016 among **5691** patients (71% CD; 23637 patient years followup; median **4.5 years per patient** follow-up) there were **14 malignancy events** (12 exposed to thiopurines (8 with infliximab; 4 thiopurine only); 1 only to infliximab; 1 to neither biologics nor thiopurines)
  - 2 basal cell carcinomas; 1 malignant melanoma;
  - 1 parotid gland adenocarcinoma; 1 renal papillary cell carcinoma
  - 1 Hodgkin disease; 1 acute monocytic leukemia; 1 acute lymphocytic leukemia; 4 B-cell lymphomas; 1 mycosis fungoides; 1 chronic myeloid leukemia
- **5 HLH occurrences**
  - All thiopurine exposure; none biologic exposure
  - 4 associated with primary EBV infection (1 CMV)

# Results: Lymphoid Malignancies (n=9)

| | Diagnosis | Age, Gender, IBD dx | Duration of IBD prior to malignancy dx (y) | Duration of IBD therapy prior to malignancy dx (y) | | | | Infectious Exposures |
|---|---|---|---|---|---|---|---|---|
| | | | | IFX | ADA | 6MP/ AZA | MTX | |
| 1 | Acute monocytic leukemia | 17 y M CD | 9.2 | 4 | <1 | 6 | 3 | unknown |
| 2 | Acute lymphocytic leukemia* | 16 y M UC | 4.5 | 0 | 0 | 0 | 0 | EBV negative |
| 3 | B-cell lymphoma** | 16 y F CD | 1.6 | 0 | 0 | 2 | 0 | EBV positive |
| 4 | B-cell lymphoma | 14 y M CD | 7.3 | 5 | 3 | <1 | 6 | unknown |
| 5 | B-cell lymphoma | 18 y M UC | 5.1 | 2 | 0 | 0 | 0 | EBV negative |
| 6 | B-cell lymphoma | 22 y M CD | 14.1 | 13 | 8 | 6 | 6 | EBV positive |
| 7 | Chronic myeloid leukemia | 14 y M CD | 3.2 | 2 | 0 | 3 | <1 | EBV negative |
| 8 | Hodgkin's lymphoma | 16 y M CD | 4.1 | 0 | 0 | 4 | 0 | unknown |
| 9 | Mycosis Fungoides (Cutaneous T-cell Lymphoma) | 13 y M CD | 4.1 | 0 | 0 | 3 | 0 | EBV negative |

All patients received corticosteroids and/or 5-ASAs , and were not exposed to any other biologic therapies
* This patient was exposed only to 5-ASAs and steroids
**This patient was also diagnosed with HLH

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# Results: Solid Tumors and Skin Cancers (n=5)

| | Diagnosis | Age, Gender, IBD dx | Duration of IBD prior to malignancy dx (y) | Duration of IBD therapy prior to malignancy dx (y) | | | | Infectious Exposures |
|---|---|---|---|---|---|---|---|---|
| | | | | IFX | ADA | 6MP/ AZA | MTX | |
| | **Solid Tumors** | | | | | | | |
| 1 | Adenocarcinoma Parotid Gland | 17 y F CD | 3.6 | <1 | 2 | <1 | 0 | unknown |
| 2 | Renal papillary cell carcinoma * | 20 y M UC | 3.4 | 4 | 3 | 4 | 0 | unknown |
| | **Skin Cancers** | | | | | | | |
| 3 | Basal cell carcinoma | 13 y F CD | 1.1 | <1 | 0 | <1 | 0 | unknown |
| 4 | Basal cell carcinoma | 16 y F CD | 3.2 | 0 | 0 | 3 | 0 | unknown |
| 5 | Malignant Melanoma | 14 y M CD | 2.0 | 2 | 0 | 1 | 1 | unknown |

All received corticosteroids and/or 5-ASAs , and were not exposed to any other biologic therapies
*This patient is deceased

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# Results: HLH Cases (n=5)

| Age, Gender, IBD dx | Duration of IBD prior to HLH dx (y) | Duration of IBD therapy prior to HLH dx (y) | | | | Infectious Exposures |
|---|---|---|---|---|---|---|
| | | IFX | ADA | 6MP/ AZA | MTX | |
| 16 y F CD | 1.2 | 0 | 0 | 1 | 0 | Primary EBV |
| 16 y M CD | 11 | 0 | 0 | 11 | 0 | Primary EBV |
| 16 y F CD | 1.6 | 0 | 0 | 2 | 0 | Primary EBV* |
| 15 y F CD | 1.2 | 0 | 0 | 1 | 0 | CMV** |
| 19 y M CD | 7.0 | 0 | 0 | 7 | 0 | Primary EBV |

All patients received corticosteroids and/or 5-ASAs, and were not exposed to any other biologic therapies
*This patient was also diagnosed with B-cell lymphoma
** Unknown if primary infection or reactivation of CMV

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# Results: Unadjusted Malignancy and HLH Incidence Rates

| | Infliximab and thiopurines | Infliximab without thiopurines | Biologics and thiopurines | Biologics without thiopurines | Non-biologics and thiopurines | Non-biologics without thiopurines | All patients |
|---|---|---|---|---|---|---|---|
| Total patients, N | 1556 | 778 | 2655 | 1081 | 1159 | 796 | 5691 |
| Total PY F/U | 7334.5 | 3026.8 | 10977.1 | 3968.0 | 5669.3 | 3022.8 | 23637.2 |
| Malignancy events/ 1000 PY [n] 95% CI | 0.41 [3] 0.08, 1.20 | 0.33 [1] 0.01, 1.84 | 0.73 [8] 0.32, 1.43 | 0.25 [1] 0.01, 1.40 | 0.71 [4] 0.19, 1.80 | 0.33 [1] 0.01, 1.84 | 0.59[14] 0.32, 0.99 |
| HLH events/1000 PY [n] 95% CI | 0[0] 0.00, 0.41 | 0[0] 0.00, 0.99 | 0 [0] 0.00, 0.27 | 0 [0] 0.00, 0.76 | 0.88 [5] 0.29, 2.06 | 0 [0] 0.00, 0.99 | 0.21 [5] 0.07, 0.49 |

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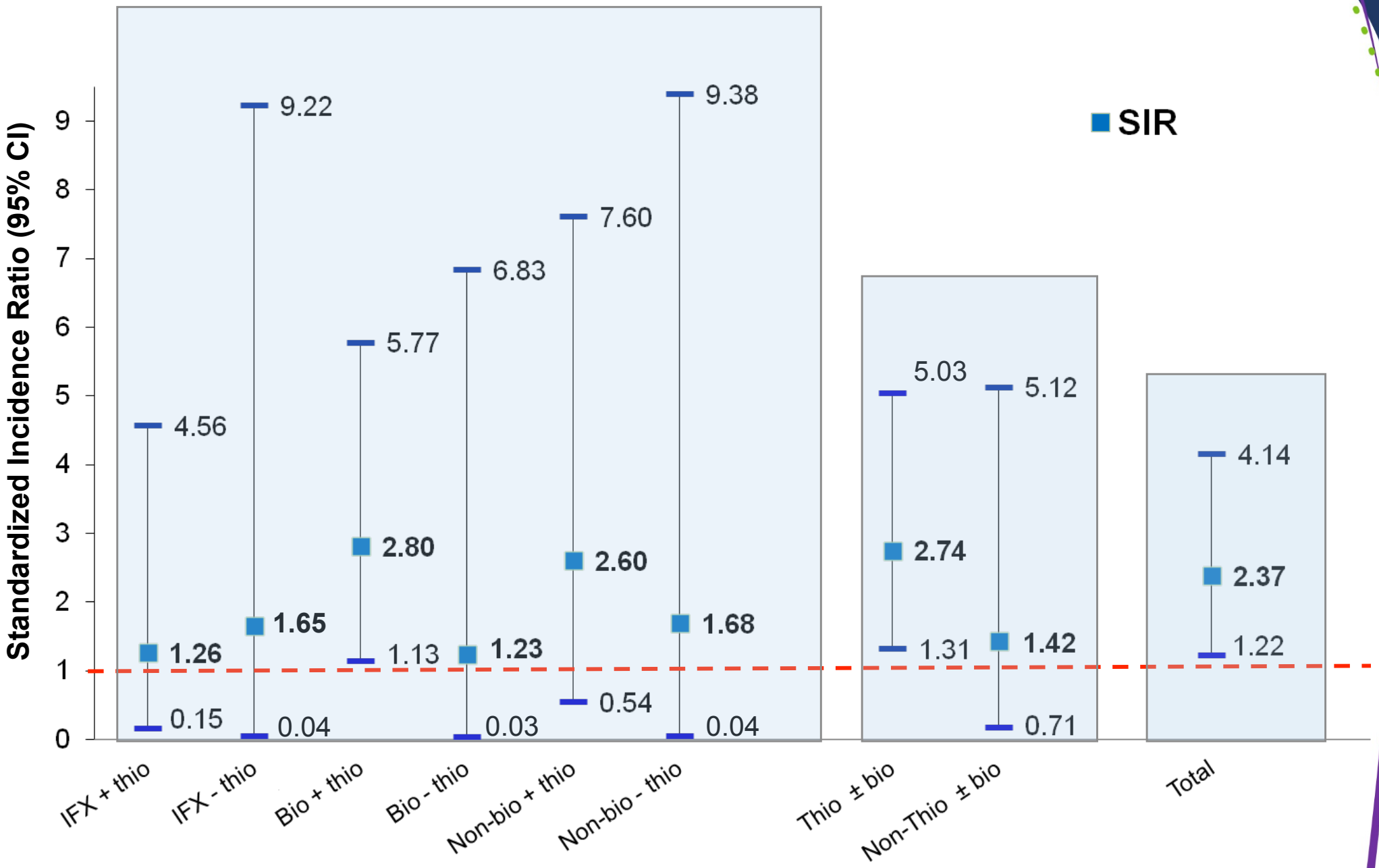
# Standardized Incidence Ratios (SIR) for malignancies (excluding basal cell carcinomas)

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# How will this change practice?

- Further support for the argument that benefit/risk ratio is more favorable for anti-TNF versus thiopurines
- Will raise awareness of HLH with primary EBV infection when thiopurines are used
- Overall more use of anti-TNF (or emerging biologics) in pediatric patients without trial of thiopurines