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Dear Dr. Grinienko,

Below are my responses to the questions you asked me to address regarding the lymphoma cases which occurred in patients receiving Elidel cream.

As you may know, I am a pathologist with a special interest in lymphomas. Therefore, my comments will focus on the pathology of these lymphomas. In addition, I have had the opportunity to study and publish on lymphomas that occur as a result of low-dose, long-term methotrexate therapy for dermatomyositis and rheumatoid arthritis. I will provide some of the information that has been used to show the causal relationship between lymphoma and methotrexate in that setting.

**1. Would additional information be useful in the evaluation of these cases?**

- 1) PHEH2004US01380 – Histiocytic lymphoma

The tumor immunophenotype and the EBV-status of the tumor cells.

- 2) PHEH2004US07674 – Lymphoblastic lymphoma

No additional information needed. (This morning, I received the e-mail detailing the clinical history, pathology and immunophenotype of this case)

- 3) PHBS2004CA12158 – Lymphoma

There is no information provided for this case. Clinical, pathologic, immunophenotypic and EBV data would be required to evaluate if this lymphoma occurred as a result of therapy related immune system modulation.

- 4) PHEH2004US10204 – Subcutaneous panniculitis like T-cell lymphoma

No additional information is needed.

**2. Case Comments**

- 1) PHEH2004US01380 – Histiocytic lymphoma

Diffuse large cell lymphoma is one of the most common non-Hodgkin's lymphomas in adults. While data regarding immunophenotype and EBV status are not provided, there do not appear to be unusual features (i.e. unusual site, unusual morphology, spontaneous regression).

2) PHEH2004US07674 – Lymphoblastic lymphoma

This appears to be a standard case of pediatric lymphoblastic lymphoma.

3) PHBS2004CA12158 – Lymphoma

No comments will be provided since there is no information given on this case.

4) PHEH2004US10204 – Subcutaneous panniculitis like T-cell lymphoma

This is a rare subtype of non-Hodgkin's lymphoma which to my knowledge has not been associated with iatrogenic immune modulation.

### **3. Features that Characterize Lymphomas Occurring in the Setting of Immunomodulatory Therapy**

The literature which first described characteristics of lymphomas occurring as a result of therapy-related immunosuppression was that describing lymphomas in solid organ transplant recipients. In the last decade or so, another body of literature has emerged that describes iatrogenic lymphomas associated with immunomodulatory therapy for rheumatologic diseases, in particular rheumatoid arthritis and dermatomyositis (see references below).

There are several features which must be present to show a link between immunomodulatory therapy and the development of lymphoma. This is true for immunosuppression associated lymphomas in solid organ transplants and in iatrogenic lymphomas in patients who receive immunomodulatory therapy for rheumatic diseases. These features are:

1. Frequent occurrence in unusual sites, including soft tissue, joint spaces, lungs.
2. Polymorphous, pleomorphic large cell or Hodgkin's – like morphology.
3. Presence of Epstein-Barr virus genome in lymphoma cells.
4. Lymphomas develop weeks, months or less commonly up to several years of receiving immunomodulatory therapy.
5. In a significant percentage of cases (one-third to one-half), the lymphomas spontaneously regress following withdrawal of immunomodulatory therapy without the need for chemotherapy or radiation therapy.

These features, when present in aggregate, implicate therapy as contributing to or causing lymphoma. Spontaneous regression following discontinuation of therapy is obviously a very important piece of clinical information and was important in linking methotrexate to lymphomas despite the fact that this is an uncommon event.

#### **4. Lack of Causal Relationship between administration of Elidel and Lymphoma**

None of the information provided indicates or suggests a causal relationship between Elidel and lymphoma.

PHEH2004US01380 – Histiocytic lymphoma

I interpret this “histiocytic lymphoma” as representing a diffuse large cell lymphoma using current terminology. While it would be useful to have data regarding the immunophenotype and EBV status, the description that is provided does not suggest that this lymphoma is immunosuppression related. This is a relatively common type of lymphoma in older adults. Its location is not unusual. No mention is made of an unusual morphology (pleomorphic or Hodgkin’s cell-like). While the additional data would allow me to be more definitive about this case, none of the information provided indicates a link to immunosuppression.

PHEH2004US07674 – Lymphoblastic lymphoma

This is a straightforward case of pediatric T-lymphoblastic lymphoma. The additional information provided by e-mail today gives a clinical history typical for this neoplasm, including the mediastinal location. The T-cell phenotype is typical for this lymphoma in this location in this age group.

PHBS2004CA12158 – Lymphoma

No comments will be provided since there is no information given on this case.

PHEH2004US10204 – Subcutaneous panniculitis like T-cell lymphoma

This is a rare type of non-Hodgkin’s lymphoma that to my knowledge has not been associated with iatrogenic immune modulation. The clinical, pathologic, and immunophenotypic data that is provided is complete and consistent with a usual presentation, morphology and immunophenotype of this rare type of lymphoma.

#### **5. References**

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Respectfully submitted,

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